Cara Therapeutics, Inc.
Form S-1/A
December 31, 2013
Table of Contents

As filed with the Securities and Exchange Commission on December 31, 2013

Registration No. 333-192230

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

PRE-EFFECTIVE AMENDMENT NO. 1

TO

FORM S-1

REGISTRATION STATEMENT

UNDER

THE SECURITIES ACT OF 1933

CARA THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**2834**	**75-3175693**
(State or other jurisdiction of	*(Primary Standard Industrial*	*(I.R.S. Employer*

incorporation or organization) *Classification Code Number)* *Identification Number)*

1 Parrott Drive

Shelton, Connecticut 06484

(203) 567-1500

(Address, including zip code, and telephone number, including area code, of registrant s principal executive offices)

Derek Chalmers, Ph.D., D.Sc.

President and Chief Executive Officer

Cara Therapeutics, Inc.

1 Parrott Drive

Shelton, Connecticut 06484

(203) 567-1501

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

Babak Yaghmaie	**Peter N. Handrinos**
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(212) 479-6000	**(617) 948-6060**

Approximate date of commencement of proposed sale to the public:

As soon as practicable after the effective date of this registration statement.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, check the following box. ¨

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ¨

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration number of the earlier effective registration statement for the same offering. ¨

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 the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 under the Securities Exchange Act of 1934. (Check one):

Large Accelerated Filer ¨	Accelerated Filer ¨	Non-accelerated Filer x	Smaller Reporting Company ¨

The registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment that specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

Table of Contents

The information in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED DECEMBER 31, 2013

PRELIMINARY PROSPECTUS

Shares

Common Stock

$ per share

This is the initial public offering of Cara Therapeutics, Inc. We are offering shares of our common stock. Prior to this offering, there has been no public market for our common stock. We estimate that the initial public offering price will be between $ and $ per share.

We have applied to list our common stock on The NASDAQ Global Market under the symbol CARA.

We are an emerging growth company as defined by the Jumpstart Our Business Startups Act of 2012 and, as such, we have elected to comply with certain reduced public company reporting requirements for this prospectus and future filings.

Investing in our common stock involves a high degree of risk. See Risk Factors beginning on page 10.

	Per Share	Total
Initial public offering price	$	$
Underwriting discounts and commissions[(1)]	$	$
Proceeds, before expenses, to us	$	$

(1) We refer you to Underwriting beginning on page 134 of this prospectus for additional information regarding total underwriter compensation.

We have granted the underwriters a 30-day option to purchase a total of up to additional shares of common stock on the same terms and conditions set forth above.

The underwriters expect to deliver shares of common stock to purchasers on , 2014.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

Stifel **Piper Jaffray**

Canaccord Genuity

Needham & Company

Janney Montgomery Scott

The date of this prospectus is , 2014.

Table of Contents

TABLE OF CONTENTS

We have not authorized anyone to provide any information or to make any representations other than those contained in this prospectus or in any free writing prospectuses we have prepared. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus is an offer to sell only the shares offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information contained in this prospectus is current only as of its date.

For investors outside the United States: We have not and the underwriters have not done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons who come into possession of this prospectus and any applicable free writing prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus and any such free writing prospectus applicable to that jurisdiction.

Table of Contents

PROSPECTUS SUMMARY

This summary highlights information contained in other parts of this prospectus. Because it is only a summary, it does not contain all of the information that you should consider before investing in shares of our common stock and it is qualified in its entirety by, and should be read in conjunction with, the more detailed information appearing elsewhere in this prospectus. You should read the entire prospectus carefully, especially Risk Factors and our financial statements and the related notes, before deciding to buy shares of our common stock. Unless the context requires otherwise, references in this prospectus to Cara, we, us and our refer to Cara Therapeutics, Inc. and its subsidia taken as a whole.

Overview

Our Company

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 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.

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, would 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 and avoiding the abuse and addiction issues

associated with currently approved mu opioid analgesics.

Table of Contents

Our Product Candidates

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 Complete	Cara (worldwide, other than Japan and South Korea) Maruishi Pharmaceuticals (Japan) Chong Kun Dang Pharmaceutical (South Korea)
Oral CR845	Acute & Chronic Pain	Phase 1	Cara (worldwide, other than Japan and South Korea) Maruishi Pharmaceuticals (Japan for acute pain indication only) Chong Kun Dang Pharmaceutical (South Korea)
CR701	Neuropathic & Inflammatory Pain	Preclinical	Cara (worldwide)

Overview of CR845

CR845 is a peripherally-acting kappa opioid receptor agonist that we are developing for treatment of both acute and chronic pain. 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 opioid use and mu opioid-related adverse events 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; 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.

I.V. CR845

Our most advanced product candidate, I.V. CR845, is being developed for the treatment of acute pain in a hospital setting. I.V. CR845 has demonstrated tolerability and efficacy in three randomized, double-blind, placebo-controlled Phase 2 clinical trials as follows:

Phase 2b Laparoscopic Hysterectomy Trial (*CLIN2002*): *CLIN2002* was a multicenter, double randomized, double-blind placebo-controlled trial conducted in 203 patients at 22 sites in the United States. In this trial, patients received either I.V. CR845 or placebo prior to surgery and then

Table of Contents

I.V. CR845 or placebo after surgery. Compared to the group receiving only placebo, all groups that received I.V. CR845 exhibited a reduction in mean pain intensity relative to baseline for all time intervals measured in the trial. Importantly, in comparison to placebo, the two groups receiving postoperative I.V. CR845 exhibited a statistically significant improvement in mean 24-hour summed pain intensity differences, or SPID, a cumulative measure of pain reduction that has been recommended by the FDA as a primary endpoint in Phase 3 postoperative pain trials in support of a New Drug Application, or NDA. Patients receiving I.V. CR845 also used less morphine and had a statistically significant lower incidence of nausea and vomiting than those receiving only placebo. 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.

Phase 2 Bunionectomy Trial *(CLIN2003)*: *CLIN2003* was a randomized, double-blind, placebo-controlled trial conducted in 51 patients following bunionectomy surgery at a single site in the United States. Patients completing the trial who received multiple doses of I.V. CR845 exhibited a statistically significant improvement in SPID, compared to placebo, for both the 24 and 48 hour time periods following initiation of treatment. Patients receiving I.V. CR845 also exhibited a statistically significant reduction in nausea and vomiting compared to placebo, despite the use of similar amounts of fentanyl rescue medication, indicating a potential direct anti-vomiting and anti-nausea effect of CR845. Bunionectomy is considered a hard tissue surgery, in contrast to laparoscopic hysterectomy, which is considered a soft tissue surgery; efficacy in both types of surgery is desirable to demonstrate breadth of analgesic efficacy for regulatory approval.

Phase 2a Laparoscopic Hysterectomy Trial (*CLIN2001*): *CLIN2001* 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. Two cohorts were employed, with drug treatment beginning either 24 hours after surgery or immediately after randomization. In the first cohort, with a 24-hour delay in treatment, an insufficient number of patients exhibited moderate-to-severe pain to provide meaningful results. However, for the second cohort of 46 patients who received immediate postoperative treatment, CR845-treated patients exhibited statistically significantly greater reductions in pain intensity up to 6 hours following treatment compared to those receiving placebo. In addition, these CR845-treated patients used statistically significantly less morphine and exhibited a substantial reduction in nausea and vomiting, compared to patients receiving placebo. These findings provided the basis for the design of the larger Phase 2 trial noted above, *CLIN2002*.

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 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. Rescue medication is an additional analgesic drug (other than study drug), which is permitted to be administered to clinical trial subjects if they feel they are not receiving sufficient pain relief at any point during the trial protocol. We expect to commence these clinical trials in the second half of 2014.

Table of Contents

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, non-steroidal anti-inflammatory drugs, or NSAIDs, or CNS anticonvulsant agents for the treatment of moderate-to-severe chronic pain. In addition to its potential efficacy benefits, we believe a significant benefit of Oral CR845 in the chronic pain market would be its ability to avoid CNS side effects, including euphoria, which should preclude the misuse, abuse and addiction risks associated with currently approved mu opioids.

We have successfully completed a Phase 1 trial of an oral capsule version of CR845 to establish the degree to which the drug is absorbed into the circulation after swallowing, or oral bioavailability parameters. The single center, randomized, double-blind placebo-controlled, escalating single oral dose, sequential group Phase 1 trial was conducted in 50 male volunteers administered with an enteric-coated capsule of CR845 (0.5 mg, 1 mg, 3 mg, or 10 mg) or matched placebo. The level of exposure at all doses was sufficient to activate peripheral kappa receptors. Oral CR845 was well tolerated and considered safe across all doses tested. Adverse events were generally similar to those reported after I.V. administration, with the addition of mild abdominal discomfort. We subsequently developed a tablet version which we expect 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 the first half of 2014 and, if the results of these trials are favorable, initiate a Phase 2a proof-of-concept trial in acute pain in the second half of 2014.

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:

- continue to advance I.V. CR845 to approval for acute pain in the United States;
- build a sales and marketing organization to commercialize I.V. CR845 for acute pain in the hospital setting in the United States;
- establish partnerships for the development and commercialization of I.V. CR845 outside of the United States; and
- advance Oral CR845 to proof-of-concept and seek a global development and commercialization partner.

Intellectual Property

CR845 was discovered by our scientists. We own six U.S. patents with claims 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.

Our Collaboration Agreements

We have entered into collaboration agreements for both I.V. and Oral CR845 with Maruishi Pharmaceutical Co., Ltd., or Maruishi, in Japan and Chong Kun Dang Pharmaceutical Corp., or CKD, in South Korea, which provide them with the exclusive right to develop and market CR845 for certain

Table of Contents

indications within those territories. As of September 30, 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.

Financial Overview

Our revenue to date has been generated primarily through license transactions. We have not generated any commercial product revenue. As of September 30, 2013, we had $17.7 million of cash and cash equivalents and an accumulated deficit of $60.4 million.

Risks Associated with Our Business

Our ability to implement our business strategy is subject to numerous risks and uncertainties. As a clinical stage biopharmaceuticals company, we face many risks inherent in our business and our industry generally. You should carefully consider all of the information set forth in this prospectus and, in particular, the information under the heading Risk Factors, prior to making an investment in our common stock. These risks include, among others, the following:

- 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.
- Our short operating history makes it difficult to evaluate our business and prospects.
- 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.
- 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.
- 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 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 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.
- 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.
- 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.
- The collaboration arrangements that we are a party to, including in Japan with Maruishi, and in South Korea with CKD, or any other collaboration arrangements we may enter into in the future, may not be successful, which could adversely affect our ability to develop and commercialize our product candidates.
- We may not be able to manage our business effectively if we are unable to attract and retain key personnel.

Our Corporate Information

We were incorporated as Cara Therapeutics, Inc. in Delaware in July 2004. Our principal executive offices are located at 1 Parrott Drive, Shelton, Connecticut 06484, and our telephone number is (203) 567-1500. Our website address is www.caratherapeutics.com. The information contained on, or that

Table of Contents

can be accessed through, our website is not a part of this prospectus. Investors should not rely on any such information in deciding whether to purchase our common stock. We have included our website address in this prospectus solely as an inactive textual reference.

We use CARA THERAPEUTICS as a registered service mark in the United States. This prospectus also includes references to trademarks and service marks of other entities, and those trademarks and service marks are the property of their respective owners.

Implications of Being an Emerging Growth Company

As a company with less than $1 billion in revenue during our last fiscal year, we qualify as an emerging growth company as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from specified disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced Management s Discussion and Analysis of Financial Condition and Results of Operations disclosure;
- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor s report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We may take advantage of these provisions for up to five years or until such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company if we have more than $1 billion in annual revenues, have more than $700 million in market value of our capital stock held by non-affiliates or issue more than $1 billion of non-convertible debt over a three-year period. We may choose to take advantage of some, but not all, of the available exemptions. We have taken advantage of some reduced reporting burdens in this prospectus. Accordingly, the information contained herein may be different than the information you receive from other public companies in which you hold stock.

In addition, 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. This provision allows an emerging growth company to delay the adoption of some accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Table of Contents

THE OFFERING

Common stock offered by us	shares
Total common stock to be outstanding after this offering	shares
Underwriters option	The underwriters have an option for a period of 30 days to purchase up to additional shares of our common stock.
Use of proceeds	We intend to use the net proceeds of this offering to fund the clinical trials and other development activities for I.V. and Oral CR845 and for working capital and other general corporate purposes. See Use of Proceeds on page 48 for a description of the intended use of proceeds from this offering.
Risk Factors	You should read the Risk Factors section of this prospectus beginning on page 10 for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
Proposed Nasdaq Global Market symbol	CARA

The number of shares of our common stock to be outstanding after this offering is based on 42,106,178 shares of common stock (including preferred stock on an as-converted basis) outstanding as of September 30, 2013, and excludes:

- 49,628 shares of common stock issuable upon exercise of an outstanding warrant as of September 30, 2013 at an exercise price of $4.03 per share;
- 1,225,400 shares of common stock issuable upon exercise of stock options outstanding as of September 30, 2013 pursuant to our 2004 Stock Incentive Plan, as amended, or the 2004 Plan, at a weighted-average exercise price of $0.54 per share; and
- shares of common stock reserved for issuance under our 2014 Equity Incentive Plan, or the 2014 Plan, which will become effective upon the signing of the underwriting agreement for this offering.

Except as otherwise indicated herein, all information in this prospectus, including the number of shares that will be outstanding after this offering, assumes or gives effect to:

a - for - reverse stock split of our common stock expected to be completed prior to the completion of this offering;
the filing of our amended and restated certificate of incorporation and the adoption of our amended and restated bylaws immediately prior of the closing of this offering;
the conversion of all outstanding shares of our preferred stock into an aggregate of 31,385,554 shares of our common stock, which will occur automatically upon the closing of this offering, which we refer to as the automatic preferred stock conversion; and
no exercise of the underwriters option to purchase additional shares in this offering.

Table of Contents

SUMMARY FINANCIAL DATA

The following summary financial data for the years ended December 31, 2011 and December 31, 2012 have been derived from our audited financial statements included elsewhere in this prospectus. The following summary financial data for the nine months ended September 30, 2012 and 2013 and as of September 30, 2013 have been derived from our unaudited financial statements included elsewhere in this prospectus. Our unaudited financial statements have been prepared on the same basis as the audited financial statements and, in the opinion of our management, include all adjustments, consisting of normal recurring adjustments and accruals, necessary for a fair statement of the information for the interim periods. Our historical results for any prior periods are not necessarily indicative of results to be expected for a full year or for any future period.

You should read this information together with our financial statements and related notes included elsewhere in this prospectus and the information under Selected Financial Data and Management s Discussion and Analysis of Financial Condition and Results of Operations.

	Year Ended December 31,		Nine Months Ended September 30,	
	2011	2012	2012	2013
			(unaudited)	
	(in thousands, except share and per share data)			
Statement of Operations Data:				
Total revenue	$	$ 1,190	$ 1,190	$ 10,991
Operating expenses:				
Research and development	7,159	4,597	3,574	6,707
General and administrative	2,407	2,829	2,083	2,457
Total operating expenses	9,566	7,426	5,657	9,164
Operating income (loss)	(9,566)	(6,236)	(4,467)	1,827
Total other expense	(275)	(66)	(28)	(3,724)
Loss before benefit from income taxes	(9,841)	(6,302)	(4,495)	(1,897)
Benefit from income taxes	35	31	21	27
Net loss	$ (9,806)	$ (6,271)	$ (4,474)	$ (1,870)
Net loss available to common stockholders	$ (9,806)	$ (6,271)	$ (4,474)	$ (979)
Net loss per share:				
Basic	$ (1.21)	$ (0.76)	$ (0.54)	$ (0.10)
Diluted	$ (1.21)	$ (0.76)	$ (0.54)	$ (0.10)

Weighted average shares:				
Basic	8,089,370	8,249,996	8,225,901	10,202,188
Diluted	8,089,370	8,249,996	8,225,901	10,202,188

Table of Contents

The following table presents our summary balance sheet data:

- on an actual basis as of September 30, 2013;
- on a pro forma basis to give effect to the automatic preferred stock conversion, which will occur automatically upon the closing of this offering; and
- on a pro forma as adjusted basis to give further effect to our sale of shares of common stock in this offering at an assumed initial public offering price of $ per share, which is the midpoint of the price range set forth on the cover page of this prospectus, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The pro forma as adjusted information presented in the summary balance sheet data is illustrative only and will change based on the actual initial public offering price and other terms of this offering determined at pricing. Each $1.00 increase or decrease in the assumed initial public offering price of $ per share, which is the midpoint of the price range set forth on the cover page of this prospectus, would increase or decrease each of cash, total assets and total stockholders equity on a pro forma as adjusted basis by approximately $, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same. Similarly, each increase or decrease of 1.0 million shares offered by us at the assumed initial public offering price would increase or decrease each of cash and cash equivalents, total assets and total stockholders equity on a pro forma as adjusted basis by approximately $.

	As of September 30, 2013		
	Actual	Pro forma	Pro forma as adjusted
	(unaudited, in thousands)		
Balance Sheet Data:			
Cash and cash equivalents	$ 17,733	$ 17,733	$
Total assets	22,068	22,068	
Deferred revenue	4,434	4,434	
Total liabilities	8,477	8,477	
Total convertible preferred stock	65,586		
Total stockholders (deficit) equity	(51,995)	13,591	

Table of Contents

RISK FACTORS

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 and $6.3 million for the years ended December 31, 2011 and December 31, 2012, respectively. As of September 30, 2013, we had an accumulated deficit of $60.4 million. Although we recognized $11.0 million of revenue during the nine months ended September 30, 2013 pursuant to our collaboration agreement with Maruishi Pharmaceutical Co., Ltd., or Maruishi, we nevertheless generated a net loss of $1.9 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 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 a New Drug Application, or 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.

Table of Contents

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.

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 current good manufacturing practices, or 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 September 30, 2013, along with the net proceeds from this 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.

Table of Contents

Future capital requirements will also depend on the extent to which we acquire or invest in additional complementary businesses, products and technologies. Until we can generate a sufficient amount of product revenue, if ever, we expect to finance future cash needs through public or private equity offerings, debt financings, 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;

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 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.

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.

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.

Table of Contents

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 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 Risk Evaluation and Mitigation Strategy, or REMS;
we could be sued and held liable for harm caused to patients; and
our reputation may suffer.

Table of Contents

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.

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

Table of Contents

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.

Table of Contents

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.

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;

Table of Contents

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

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

Risks Related to the Commercialization of Our Product Candidates

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

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

Specifically, there are a large number of companies developing or marketing therapies for the treatment and management of postoperative acute pain, moderate to severe chronic pain and neuropathic pain, including many major pharmaceutical and biotechnology companies. Among the companies that currently market or are developing therapies that, if approved, our product candidates would potentially compete with include: Pfizer, Cumberland Pharmaceuticals, 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

Table of Contents

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 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.

Table of Contents

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;
- 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

Table of Contents

patients may not immediately be receptive to such product candidate and may be slow to adopt it as an accepted treatment of pain. It is unlikely that any labeling approved by the FDA will contain claims that one of our product candidates is safer or more effective than competitive products or will permit us to promote such product candidate as being superior to competing products. Further, the availability of inexpensive generic forms of pain management products for acute pain and over-the-counter alternatives for chronic pain may also limit acceptance of our product candidates among physicians, patients and third-party 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.

Table of Contents

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 good laboratory practice, or 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.

Table of Contents

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 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. 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.

Table of Contents

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 prospectus. Any such termination or expiration would adversely affect us financially and could harm our business reputation. Our current collaborations and any future collaborations we might enter into may pose a number of risks, including the following:

- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could fail to make timely regulatory submissions for a product candidate;
- collaborators may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- collaborations, including our collaboration with Maruishi, may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If our current collaborations or any other collaborations we might enter into in the future do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product candidates could be delayed and we may need additional resources to develop our product candidates and our product platform. All of the

risks relating to our product development, regulatory approval and commercialization described in this prospectus also apply to the activities of our collaborators in their respective jurisdictions.

Table of Contents

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.

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.

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

29

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 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;

Table of Contents

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;

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 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

Table of Contents

these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state or federal authorities may curtail our use of these materials and interrupt our business operations. In addition, we could become subject to potentially material liabilities relating to the investigation and cleanup of any contamination, whether currently unknown or caused by future releases.

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

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

Risks Related to Intellectual Property

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

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

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

we may not have been the first to make the inventions covered by each of our pending patent applications and issued patents;
we may not have been the first to file patent applications for these inventions;
others may independently develop similar or alternative technologies or duplicate any of our product candidates or technologies;
it is possible that none of the pending patent applications will result in issued patents;
the issued patents covering our product candidates may not provide a basis for commercially viable active products, may not provide us with any competitive advantages, or may be challenged by third parties;

- we may not develop additional proprietary technologies that are patentable;
- patents of others may have an adverse effect on our business;
- noncompliance with governmental patent agencies requirements can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction, potentially allowing competitors to enter the market earlier than would otherwise have been the case;
- our competitors, many of whom have substantially greater resources than we do and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with, or eliminate our ability to make, use, and sell our potential product candidates; or
- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of available patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The United States Patent Office recently developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

Patent applications in the United States are maintained in confidence for at least 18 months after their earliest effective filing date. Consequently, we cannot be certain we were the first to invent or the first to file patent applications on CR845 or any other product candidates that we may develop, license or acquire. In the event that a third party has also filed a U.S. patent application relating to our product candidates or a similar invention, we may have to participate in interference proceedings declared by the U.S. Patent and Trademark Office to determine priority of invention in the United States. The costs of these proceedings could be substantial and it is possible that our efforts would be unsuccessful, resulting in a material adverse effect on our U.S. patent position. The results of these types of proceedings may reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. Such results could have a material adverse effect on our results of operations.

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

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

with any significant protection against competitive products, or otherwise be commercially valuable to us.

Table of Contents

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

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

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

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

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

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

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

- infringement and other intellectual property claims which, with or without merit, can be expensive and time consuming to litigate and can divert management s attention from our core business;

Table of Contents

- substantial damages for past infringement which we may have to pay if a court decides that our product infringes on a competitor s patent;
- a court prohibiting us from selling or licensing our product unless the patent holder licenses the patent to us, which it would not be required to do;
- if a license is available from a patent holder, we may have to pay substantial royalties or grant cross licenses to our patents; and
- redesigning our processes so they do not infringe, which may not be possible or could require substantial funds and time.

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

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

Competitors may infringe our issued patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent s claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

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

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

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

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

As is common in the biotechnology and pharmaceutical industry, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information

of their former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

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

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

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

The validity and enforceability of the patents and applications that cover our CR845 product 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, 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.

37

Table of Contents

Risks Related to Employee Matters, Managing Growth and Becoming 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 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

Table of Contents

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 currently estimate that we will incur incremental annual costs, including costs for additional personnel, of approximately $1 million associated with operating as a public company, although it is possible that our actual incremental annual costs will be higher than we currently estimate.

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.

After the completion of this offering, we will be 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. 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. 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.

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 this offering, we have never been 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 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.

Table of Contents

Risks Related to this Offering and Ownership of Our Common Stock

There is no established public market for our stock and a public market may not be obtained or be liquid and therefore you may not be able to sell your shares.

Prior to this offering, there has not been a public market for our common stock. If an active trading market for our common stock does not develop following this offering, you may not be able to sell your shares quickly or at the market price. The initial public offering price for the shares will be determined by negotiations between us and representatives of the underwriters and may not be indicative of prices that will prevail in the subsequent trading market.

The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above the initial public offering price.

The trading price of our common stock is likely 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;
- 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.

Table of Contents

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 will be influenced by the research and reports that equity research analysts publish about us and our business. We do not currently have and may never obtain research coverage by equity research analysts. Equity research analysts may elect not to provide research coverage of our common stock after the completion of this offering, and such lack of research coverage may adversely affect the market price of our common stock. In the event we do have equity research analyst coverage, we will 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;
- 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.

Table of Contents

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.

Upon completion of this offering, our executive officers, directors and 5% stockholders and their affiliates will beneficially own approximately of our outstanding voting stock, excluding any shares of common stock that our existing stockholders may purchase in this offering. As a result, these stockholders will 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 are being sold in this 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.

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.

Upon completion of this offering, we will have outstanding shares of common stock, assuming no exercise of outstanding options or warrants. Of these shares, the shares sold in this offering and additional shares will be freely tradable, additional shares of common stock will be eligible for sale in the public market beginning 90 days after the date of this prospectus, subject to volume, manner of sale and other limitations of Rule 144 and Rule 701, additional shares of common stock will be available for sale in the public market beginning 180 days after the date of this prospectus following the expiration of lock-up agreements between some of our stockholders and the underwriters, and shares issued or 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. 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, promptly following the completion of this offering, we intend to file one or more registration statements on Form S-8 registering the issuance of approximately 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 these registration statements 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 the restrictions of Rule 144 in the case of our affiliates. Holders of approximately shares of our common stock are entitled to rights with respect to the registration of their shares under the Securities Act of 1933, as

Table of Contents

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 could have a material adverse effect on the trading price of our common stock.

Our management will have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering and our stockholders will not have the opportunity as part of their investment decision to assess whether the net proceeds are being used appropriately. You may not agree with our decisions, and our use of the proceeds may not yield any return on your investment. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. Our failure to apply the net proceeds of this offering effectively could compromise our ability to pursue our growth strategy and we might not be able to yield a significant return, if any, on our investment of these net proceeds. You will not have the opportunity to influence our decisions on how to use our net proceeds from this offering. Pending their use, we may invest the net proceeds from this offering in short-term, investment-grade, interest-bearing instruments and U.S. government securities. These temporary investments are not likely to yield a significant return.

If you purchase our common stock in this offering, you will incur immediate and substantial dilution in the book value of your shares.

The initial public offering price is substantially higher than the net tangible book value per share of our common stock. Investors purchasing common stock in this offering will pay a price per share that substantially exceeds the book value of our tangible assets after subtracting our liabilities. Based on an assumed initial public offering price of $ per share, which is the midpoint of the price range set forth on the cover page of this prospectus, you will experience immediate dilution of $ per share, representing the difference between our pro forma net tangible book value per share, after giving effect to this offering, and the assumed initial public offering price. In addition, purchasers of common stock in this offering will have contributed approximately % of the aggregate price paid by all purchasers of our stock but will own only approximately % of our common stock outstanding after this offering. In addition, as of September 30, 2013, options and warrants to purchase an aggregate of 1,275,028 shares of our common stock at a weighted average exercise price of $0.67 per share were outstanding. The exercise of any of these options or warrants would result in additional dilution. As a result of the dilution to investors purchasing shares in this offering, investors may receive significantly less than the purchase price paid in this offering, if anything, in the event of a liquidation or sale of our company.

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 intend to take 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 this 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-

Table of Contents

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, 2012, we had federal and state net operating loss carryforwards of approximately $55.5 million and $50.8 million, respectively, and we also had federal and state research and development tax credit carryforwards of approximately $1.8 million and $0.6 million, respectively. Our net operating loss carryforwards will begin expiring in 2027 for federal purposes and 2028 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 this 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 they will be in effect following this 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 will have the authority to issue up to shares of preferred stock and to fix the price, rights, preferences, privileges, and restrictions of the preferred stock without any further vote or action by our stockholders. The issuance of shares of preferred stock may delay or prevent a change in control transaction. As a result, the market price of our common stock and the voting and other rights of our stockholders may be adversely affected. An issuance of shares of preferred

stock may result in the loss of voting control to other stockholders.

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

- our board of directors will be divided into three classes, with only one class of directors elected each year;
- our stockholders will be entitled to remove directors only for cause upon a 66 2/3% vote;

Table of Contents

- our stockholders will not be permitted to take actions by written consent;
- our stockholders will 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.

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains forward-looking statements that involve substantial risks and uncertainties. The forward-looking statements are contained principally in the sections of this prospectus titled Prospectus Summary, Risk Factors, Management s Discussion and Analysis of Financial Condition and Results of Operations and Business but are also contained elsewhere in this prospectus. In some cases, you can identify forward-looking statements by the words anticipate, believe, continue, could, estimate, expect, intend, may, might, objective, 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 prospectus, 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. Forward-looking statements include statements about:

The forward-looking statements in this prospectus 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 this offering, and the clinical milestones we expect to fund with such proceeds;
- the accuracy of our estimates regarding expenses, future revenues and capital requirements;
- our ability to obtain funding for our operations;
- our ability to obtain and maintain intellectual property protection for our product candidates and our ability to operate our business without infringing on the intellectual property rights of others;
- the success of competing drugs that are or become available; and
- the performance of third-party manufacturers and clinical research organizations.

You should refer to the Risk Factors section of this prospectus 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 prospectus 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.

Table of Contents

You should read this prospectus and the documents that we reference in this prospectus and have filed as exhibits to the registration statement, of which this prospectus is a part, 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.

We obtained the industry and market data in this prospectus 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 prospectus, including those discussed under the heading Risk Factors.

Table of Contents

USE OF PROCEEDS

We estimate that the net proceeds from our issuance and sale of shares of common stock in this offering will be approximately $ million, or approximately $ million if the underwriters exercise their option to purchase additional shares in full, based on an assumed initial public offering price of $ per share, which is the midpoint of the price range set forth on the cover page of this prospectus, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

A $1.00 increase (decrease) in the assumed initial public offering price of $ per share would increase (decrease) our expected net proceeds from this offering by approximately $ million, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same. We may also increase or decrease the number of shares we are offering. Each increase (decrease) of 1.0 million in the number of shares we are offering would increase (decrease) the net proceeds to us from this offering, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us, by approximately $ million, assuming the assumed initial public offering price stays the same.

We currently estimate that we will use the net proceeds from this offering as follows:

- approximately $44.0 million to conduct our planned Phase 3 clinical trials and other development activities for I.V. CR845;
- approximately $2.1 million to conduct our planned Phase 1 clinical trial for Oral CR845;
- approximately $4.6 million to conduct our planned Phase 2a clinical trials and other development activities for Oral CR845; and
- the remainder for working capital and other general corporate purposes.

These expected uses represent our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development, the status of and results from clinical trials, as well as any new collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs.

As a result, our management will have broad discretion in the application of the net proceeds from this offering, and investors will be relying on the judgment of our management regarding the application of the net proceeds from this offering. The timing and amount of our actual expenditures will be based on many factors, including cash flows from operations and the anticipated growth of our business. Pending these uses, we plan to invest these net proceeds in short-term, interest bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the United States. The goal with respect to the investment of these net proceeds is capital preservation and liquidity so that such funds are readily available to fund our operations.

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.

48

Table of Contents

CAPITALIZATION

The following table sets forth our cash and cash equivalents and our capitalization as of September 30, 2013:

- on an actual basis;
- on a pro forma basis to reflect the automatic preferred stock conversion; and
- on a pro forma as adjusted basis to further reflect the filing of our amended and restated certificate of incorporation prior to the closing of this offering and our issuance and sale of shares of common stock in this offering at an assumed initial public offering price of $ per share, which is the midpoint of the price range set forth on the cover page of this prospectus, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this table together with our financial statements and the related notes appearing at the end of this prospectus and the Management s Discussion and Analysis of Financial Condition and Results of Operations section of this prospectus.

	As of September 30, 2013		
	Actual	Pro forma	Pro forma as adjusted
	(in thousands, except share and per share data)		
		(unaudited)	
Cash and cash equivalents	$ 17,733	$ 17,733	$
Convertible preferred stock:			
Convertible Series A preferred stock, $0.001 par value; 1,677,118 shares authorized, issued and outstanding, actual; no shares designated, issued or outstanding, pro forma and pro forma as adjusted	1,677		
Convertible Series B preferred stock, $0.001 par value; 2,254,417 shares authorized, issued and outstanding, actual; no shares designated, issued or outstanding, pro forma and pro forma as adjusted	4,509		
Convertible Series C preferred stock, $0.001 par value; 10,930,946 shares authorized, issued and outstanding, actual; no shares designated, issued or outstanding, pro forma and pro forma as adjusted	33,886		
Convertible Series D preferred stock, $0.001 par value; 12,260,845 shares authorized, 12,045,574 shares issued and outstanding, actual; no shares designated, issued or outstanding, pro forma and pro forma as adjusted	17,518		
Convertible Junior A preferred stock, $0.001 par value; 2,105,263 shares authorized, issued and outstanding, actual; no shares designated, issued or outstanding, pro forma and pro forma as adjusted	7,642		
Convertible Junior preferred stock, $0.001 par value; 173,611 shares authorized, issued and outstanding, actual; no shares designated, issued or	354		

outstanding, pro forma and pro forma as adjusted			
Total convertible preferred stock	65,586		
Stockholders (deficit) equity:			
Common stock, $0.001 par value; 50,000,000 shares authorized, 10,720,624 shares issued and outstanding, actual; 50,000,000 shares authorized, 42,106,178 shares issued and outstanding, pro forma; shares authorized, shares issued and outstanding, pro forma as adjusted	11	42	
Additional paid-in capital	8,357	73,912	
Accumulated deficit	(60,363)	(60,363)	
Total stockholder deficit	(51,995)	13,591	
Total capitalization	$ 13,591	$ 13,591	$

Table of Contents

(1) A $1.00 increase (decrease) in the assumed initial public offering price of $ per share, which is the midpoint of the price range set forth on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash and cash equivalents, additional paid-in capital, total stockholders deficit and total capitalization by approximately $ million, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same. Each increase (decrease) of 1.0 million in the number of shares we are offering would increase (decrease) the pro forma adjusted amount of each of cash and cash equivalents, additional paid-in capital, total stockholders deficit and total capitalization by approximately $ million, assuming that the assumed initial public offering price stays the same.

The number of shares of our common stock to be outstanding after this offering is based on 42,106,178 shares of our common stock (including preferred stock on an as-converted basis) outstanding as of September 30, 2013, and excludes:

49,628 shares of common stock issuable upon exercise of an outstanding warrant as of September 30, 2013 at an exercise price of $4.03 per share;

1,225,400 shares of common stock issuable upon exercise of stock options outstanding as of September 30, 2013 pursuant to our 2004 Plan at a weighted-average exercise price of $0.54 per share; and

shares of common stock reserved for issuance under our 2014 Plan, which will become effective upon the signing of the underwriting agreement for this offering.

Table of Contents

DILUTION

If you invest in our common stock, your interest will be diluted immediately to the extent of the difference between the initial public offering price per share you will pay in this offering and the pro forma as adjusted net tangible book value per share of our common stock after this offering. Net tangible book value per share represents our total tangible assets less total liabilities, divided by the number of shares of our common stock outstanding.

As of September 30, 2013, our net tangible book value was $13.6 million, or $1.27 per share of common stock. On a pro forma basis, after giving effect to the automatic preferred stock conversion, our tangible book value would have been $13.6 million, or $0.32 per share of common stock. After giving further effect to our issuance and sale of shares of common stock in this offering at an assumed initial public offering price of $ per share, which is the midpoint of the price range set forth on the cover page of this prospectus, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, the pro forma as adjusted net tangible book value as of September 30, 2013 would have been $ million, or $ per share. This represents an immediate increase in pro forma net tangible book value to existing stockholders of $ per share and an immediate dilution to new investors purchasing common stock in this offering of $ per share.

The following table illustrates this per share dilution to the new investors purchasing shares of common stock in this offering:

Assumed initial public offering price per share		$
Net tangible book value per share at September 30, 2013	$ 1.27	
Decrease in pro forma net tangible book value per share attributable to the automatic preferred stock conversion	(0.95)	
Pro forma net tangible book value per share as of September 30, 2013	0.32	
Increase in net tangible book value per share attributable to new investors purchasing shares in this offering		
Pro forma as adjusted net tangible book value per share after this offering		
Dilution per share to new investors in this offering		$

A $1.00 increase or decrease in the assumed initial public offering price of $ per share, which is the midpoint of the price range set forth on the cover page of this prospectus, would increase or decrease the pro forma as adjusted net tangible book value after this offering by $ per share and the dilution in net tangible book value per share to investors in this offering by $ per share, assuming that the number of shares offered by us, as set forth on the cover of this prospectus, remains the same. Each increase or decrease of 1.0 million shares in the number of shares offered by us would increase or decrease our pro forma as adjusted net tangible book value per share after this offering by approximately $ per share and decrease or increase the dilution to investors participating in this offering by approximately $ per share, assuming that the assumed initial public offering price remains the same.

If the underwriters exercise their option to purchase additional shares in full, the pro forma as adjusted net tangible book value will increase to $ per share, representing an immediate increase in pro forma net tangible book value to existing stockholders of $ per share and an immediate dilution in pro forma net tangible book value of $ per share to new investors.

51

Table of Contents

The following table summarizes, on the pro forma as adjusted basis described above as of September 30, 2013, the differences between the number of shares of common stock purchased from us, the total consideration paid to us, and the average price per share paid or to be paid by existing stockholders and by new investors purchasing shares of common stock in this offering. The calculation below is based on an assumed initial public offering price of $ per share, which is the midpoint of the price range set forth on the cover page of this prospectus, before the deduction of estimated underwriting discounts and commissions and estimated offering expenses payable by us:

	Shares Purchased		Total Consideration		Average Price per Share
	Number	Percent	Amount	Percent	
Existing stockholders		%		%	
New investors					
Total		%		%	

The foregoing table and calculations are based on 42,106,178 shares of our common stock (including preferred stock on an as-converted basis) outstanding as of September 30, 2013 and exclude:

- 49,628 shares of common stock issuable upon exercise of an outstanding warrant as of September 30, 2013 at an exercise price of $4.03 per share;
- 1,225,400 shares of common stock issuable upon exercise of stock options outstanding as of September 30, 2013 pursuant to our 2004 Plan at a weighted-average exercise price of $0.54 per share; and
- shares of common stock reserved for issuance under our 2014 Plan, which will become effective upon the signing of the underwriting agreement for this offering.

To the extent that options or warrants are exercised or new equity awards are issued under our 2014 Plan, there will be further dilution to investors participating in this offering. In addition, we may choose to raise additional capital in the future because of market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. If we raise additional capital through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

Table of Contents

SELECTED FINANCIAL DATA

The following selected financial data as of and for the years ended December 31, 2011 and December 31, 2012 have been derived from our audited financial statements included elsewhere in this prospectus. The following selected financial data for the nine months ended September 30, 2012 and 2013 and as of September 30, 2013 have been derived from our unaudited financial statements included elsewhere in this prospectus. Our unaudited financial statements have been prepared on the same basis as the audited financial statements and, in the opinion of our management, include all adjustments, consisting of normal recurring adjustments and accruals, necessary for a fair statement of the information for the interim periods. Our historical results for any prior periods are not necessarily indicative of results to be expected for a full year or for any future period.

You should read the following selected financial data in conjunction with our financial statements and the related notes appearing elsewhere in this prospectus and the Management s Discussion and Analysis of Financial Condition and Results of Operations section of this prospectus.

	Year Ended December 31,		Nine Months Ended September 30,	
	2011	2012	2012	2013
			(unaudited)	
	(in thousands, except share and per share data)			
Statement of Operations Data:				
Total revenue	$	$ 1,190	$ 1,190	$ 10,991
Operating expenses:				
Research and development	7,159	4,597	3,574	6,707
General and administrative	2,407	2,829	2,083	2,457
Total operating expenses	9,566	7,426	5,657	9,164
Operating income (loss)	(9,566)	(6,236)	(4,467)	1,827
Total other expense	(275)	(66)	(28)	(3,724)
Loss before benefit from income taxes	(9,841)	(6,302)	(4,495)	(1,897)
Benefit from income taxes	35	31	21	27
Net loss	$ (9,806)	$ (6,271)	$ (4,474)	$ (1,870)
Net loss available to common stockholders	$ (9,806)	$ (6,271)	$ (4,474)	$ (979)
Net loss per share:				
Basic	$ (1.21)	$ (0.76)	$ (0.54)	$ (0.10)
Diluted	$ (1.21)	$ (0.76)	$ (0.54)	$ (0.10)
Weighted average shares:				

Basic	8,089,370	8,249,996	8,225,901	10,202,188
Diluted	8,089,370	8,249,996	8,225,901	10,202,188
Pro forma loss per share available to common stockholders (unaudited):				
Basic		$ (0.17)		$ (0.03)
Diluted		$ (0.17)		$ (0.03)
Pro forma weighted average shares outstanding (unaudited):				
Basic		37,034,970		38,601,062
Diluted		37,034,970		38,601,062

Table of Contents

	As of December 31,		As of September 30,
	2011	2012	2013 (unaudited)
	(in thousands)		
Balance Sheet Data:			
Cash and cash equivalents	$ 4,097	$ 1,117	$ 17,733
Total assets	10,685	5,537	22,068
Deferred revenue			4,434
Total liabilities	4,581	3,098	8,477
Total convertible preferred stock	58,168	58,522	65,586
Total stockholders (deficit) equity	(52,064)	(58,133)	(51,995)

Table of Contents

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 prospectus. Some of the information contained in this discussion and analysis or set forth elsewhere in this prospectus, 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 the Risk Factors section of this prospectus 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

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 plan to 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.

Since our inception and through September 30, 2013, we have received net proceeds of $65.9 million from the sale of various series of convertible preferred stock, $3.9 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 $28.8 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 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 and $6.3 million for the years ended December 31, 2011 and December 2012, respectively. We generated a net loss of $1.9 million for the nine months ended September 30, 2013, although we recognized $11.0 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 September 30, 2013, we had an accumulated deficit of $60.4 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, beginning in the second half of 2014;

Table of Contents

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 this offering. As of September 30, 2013, we had cash and cash equivalents of approximately $17.7 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 this offering and our existing cash, cash equivalents and short-term investments, 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.

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.

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. During 2012, we received $0.6 million 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.

Table of Contents

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 of clinical development milestone payments under our license agreement with CKD. During the nine months ended September 30, 2013 (unaudited), we received revenue from the sale of clinical compound and earned a portion of the Maruishi deferred revenue. 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.

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;

Table of Contents

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 subsequent

closings. In accordance with 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

Table of Contents

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 Nine Months Ended September 30, 2012 and 2013

The following table sets forth our results of operations for the nine months ended September 30, 2012 and 2013 (in thousands).

	Nine months ended September 30,		Period-to-Period Change
	2012	2013	
	(unaudited)		(unaudited)
Revenue	$ 1,190	$ 10,991	$ 9,801
Cost and expenses:			
Research and development	3,574	6,707	3,133
General and administrative	2,083	2,457	374
	5,657	9,164	3,507
Operating income (loss)	(4,467)	1,827	6,294
Interest (expense), net	(28)	(3,724)	(3,696)
Loss before benefit from income taxes	(4,495)	(1,897)	2,598
Benefit from income taxes	21	27	6
Net loss	$ (4,474)	$ (1,870)	$ 2,604

Revenue

Revenue increased $9.8 million, to $11.0 million, for the nine months ended September 30, 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 $3.1 million to $6.7 million, for the nine months ended September 30, 2013, compared to the same period of 2012. The increase was primarily a result of a $0.2 million increase in payroll and recruiting costs, a $0.2 million increase in consultant services in support of preclinical studies and clinical trials, a $2.9 million increase in direct preclinical studies and clinical trial costs and a $0.1 million increase in travel costs, partially offset by an aggregate $0.2 million decrease in facility costs and depreciation and amortization expense. The increase in clinical trial costs resulted from the completion of the Phase 2 bunionectomy

trial.

The following table summarizes our research and development expenses by product candidate for the nine months ended September 30, 2012 and 2013 (in thousands):

	Nine Months Ended September 30,	
	2012	**2013**
External research and development expenses:		
I.V. CR845	$ 1,320	$ 3,352
Oral CR845	168	1,194
Internal research and development expenses	2,086	2,161
Total research and development expenses	$ 3,574	$ 6,707

Table of Contents

General and administrative expenses

General and administrative expenses increased by $0.4 million, to $2.5 million, for the nine months ended September 30, 2013, compared to the same period of 2012. The increase was primarily attributable to consulting services incurred in connection with the Maruishi license agreement of $0.4 million and a $0.1 million increase in payroll costs.

Interest expense, net

Interest expense, net, increased by $3.7 million, to $3.7 million, for the nine months ended September 30, 2013, compared to the same period of 2012. The increase in expense was 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

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.

Table of Contents

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 $29,000, to $66,000, 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 September 30, 2013, we have raised an aggregate of $102.8 million to fund our operations, of which $28.9 million consisted of upfront and milestone payments under our license agreements, primarily with Maruishi and CKD, $65.9 million consisted of proceeds from the sale of shares of our convertible preferred stock and $7.7 million consisted of net proceeds from debt financings. As of September 30, 2013, we had $17.7 million in cash and cash equivalents.

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

Table of Contents

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 notes in the aggregate amount of $3.9 million in principal plus accrued interest into 2,692,291 shares of Series D Preferred Stock. Subsequent to September 30, 2013, we repaid the remaining notes in the aggregate amount of $311,000 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 49,628 shares of common stock at an exercise price of $4.03. 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;

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.

Table of Contents

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 the net proceeds from this offering, together with our existing cash and cash equivalents as of September 30, 2013, 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 and 2012 and the nine months ended September 30, 2012 and 2013 (in thousands).

	Year Ended December 31,		Nine Months Ended September 30,	
	2011	2012	2012	2013
			(unaudited)	
Net cash (used in) provided by operating activities	$ (6,845)	$ (6,031)	$ (4,536)	$ 7,893
Net cash (used in) provided by investing activities	45	511	511	(4)
Net cash provided by financing activities	9,136	2,540	49	8,727
Net (decrease) increase in cash and cash equivalents	$ 2,336	$ (2,980)	$ (3,976)	$ 16,616

Net cash (used in) provided by operating activities

Net cash provided by operating activities was $7.9 million for the nine months ended September 30, 2013. Net cash provided by operating activities for the period consisted primarily of net loss of $1.9 million, a $5.5 million cash inflow from net changes in operating assets and liabilities and $4.2 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 and depreciation and amortization expense of $0.6 million, partially offset by deferred rent costs of $0.2 million. The net change in operating assets and liabilities primarily consisted of $4.4 million of deferred revenue from the Maruishi license transaction and a $1.2 million increase in accounts payable and accrued expenses.

Table of Contents

Net cash used in operating activities was $4.5 million for the nine months ended September 30, 2012. Net cash used in operating activities for the period consisted primarily of net loss of $4.5 million and a $1.0 million cash outflow from net changes in operating assets and liabilities, partially offset by $1.0 million of net non-cash charges. Net non-cash charges primarily consisted of $0.8 million of depreciation and amortization expense, partially offset by deferred rent costs of $0.1 million. The net change in operating assets and liabilities primarily consisted of a $1.4 million decrease in accounts payable and accrued expenses, partially offset by a $0.3 million decrease in restricted cash and a $0.1 million decrease in prepaid expenses.

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 provided by investing activities was $0.5 million, $0.5 million and $45,000 for the nine months ended September 30, 2012, the year ended December 31, 2012 and the year ended December 31, 2011, respectively. For all periods, net cash provided by investing activities 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 used in investing activities was $4,000 for the nine months ended September 30, 2013, representing the purchase of office equipment.

Net cash provided by financing activities

Net cash provided by financing activities was $8.7 million for the nine months ended September 30, 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.

Net cash provided by financing activities was $0.1 million for the nine months ended September 30, 2012, which consisted primarily of $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.

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.

Table of Contents

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, 2012 (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	$ 4,234	$ 835	$ 2,659	$ 740	$
Long-term debt[1]	307	307			
Convertible promissory notes[2]	473	473			
Total	$ 5,014	$ 1,615	$ 2,659	$ 740	$

(1) Represents borrowings under our term loan from CII. All outstanding borrowings under this term loan were repaid in April 2013.
(2) The majority of these convertible notes were converted into Series D Preferred Stock in the third quarter of 2013, with the balance repaid in October 2013.

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 accounting principles generally accepted in the United States, or 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.

Table of Contents

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

We record revenue related to these agreements in accordance with 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 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 and the common stock values obtained with the assistance of an independent third party valuation firm.

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 remeasured 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 did not issue any stock options during the year ended December 31, 2012 or the nine months ended September 30, 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.

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 $311,000 in principal and accrued interest were

repaid in October 2013. For the nine months ended September 30, 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 2,398,867 shares of common stock. The company determined that this conversion represented an extinguishment of the preferred stock under U.S. GAAP and, accordingly, recorded a $0.9 million 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* and the assistance of an independent third party valuation firm 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 had an independent third party valuation performed to value of the Junior A Preferred Stock, and 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, no-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 $354,000, we recorded the remaining proceeds of $646,000 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. A description of these preferred stock valuations is set forth immediately below.

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. These estimates of fair value were determined with the assistance of an independent third party valuation firm. The valuation reports have been used as part of our analysis in reaching our conclusion on stock values. We reviewed the valuation methodologies, which took into consideration the guidance prescribed by the *American Institute of Certified Public Accountants Technical Practice Aid, Valuation of Privately-Held Company Equity Securities Issued as Compensation*,

or 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.

For each of the valuations described below, we utilized the income approach, consisting of a discounted cash flow, or DCF, analysis, to derive an estimated market value of the company s equity capital. The income

approach estimates the value of our company based on our expected future cash flows discounted to present value at a rate of return commensurate with the risks associated with the cash flows. Cash flows are estimated for future periods based on projected revenue and costs. These future cash flows are discounted to their present values using a risk adjusted discount rate. Because the cash flows are only projected over a limited number of years, it is also necessary under the income approach to compute a terminal value as of the last period for which discrete cash flows are projected. This terminal value capitalizes the future cash flows beyond the projection period and is determined by taking the projected revenue for the final year of the projection and applying a terminal exit multiple. This amount is then discounted to its present value using a discount rate to arrive at the present value of the terminal value. The discounted projected cash flows and terminal value are summed together to arrive at an indicated aggregate equity value under the income approach. In applying the income approach, we derived the discount rate from an analysis of the cost of capital of our comparable industry peer companies as of each valuation date and adjusted it to reflect the risks inherent in our business cash flows. We derived the terminal exit multiple from an analysis of the revenue multiples of our comparable industry peer companies as of each valuation date.

After deriving the indicated equity value, we then employed an option-pricing method, or OPM, as prescribed by the Practice Aid, to allocate the equity value across the various classes and series of our outstanding equity securities. The OPM treats common stock and preferred stock as call options on the enterprise s equity value, with exercise prices based on the liquidation preferences of the preferred stock.

May 15, 2012 Junior Preferred Stock

In connection with the issuance of shares of our newly designated Junior Preferred Stock to CKD on May 15, 2012, we estimated the fair value of our equity capital, using the DCF approach, to be $103.0 million. In deriving this value, we utilized management projections of future debt-free net cash flows, based on a number of assumptions we believed to be reasonable, and applied a discount rate of 23% to the projected cash flows. After deriving the estimated valuation of our equity capital, we used the OPM to derive a valuation of the Junior Preferred Stock on a controlling-interest, marketable basis of $2.52 per share. In applying the OPM, the time to liquidity was estimated as 1.5 years based on then-current plans and estimates of management regarding a liquidity event. The risk free rate of 0.25% was estimated using a continuously compounded interest rate on U.S Treasury STRIPS having a maturity similar to 1.5 years. The annual volatility was estimated to be 60% which was based on a group of publicly traded companies that are comparable to us. After applying a 5% discount for lack of control and a 15% discount for lack of marketability, we derived an estimated fair value of our Junior Preferred Stock of $2.04 per share as of May 15, 2012.

December 31, 2012 Series D Preferred Stock

In connection with the issuance of convertible promissory notes in December 2012, we estimated the fair value of our equity capital, using the DCF approach, to be $104.9 million. In deriving this value, we utilized management projections of future debt-free net cash flows, based on a number of assumptions we believed to be reasonable, and applied a discount rate of 23.5% to the projected cash flows. After deriving the estimated valuation of our equity capital, we used the OPM to derive a valuation of the Series D Preferred Stock on a controlling-interest, marketable basis of $3.05 per share. In applying the OPM, the time to liquidity was estimated as one year based on then-current plans and estimates of management regarding a liquidity event. The risk free interest rate was 0.22%. The annual volatility was estimated to be 60%. After applying a 5% discount for lack of control and a 10% discount for lack of marketability, we derived an estimated fair value of our Series D Preferred Stock of $2.61 per share as of December 31, 2012.

February 28, 2013 Series D Preferred Stock

In connection with the issuance of convertible promissory notes in February 2013, we estimated the fair value of our equity capital, using the DCF approach, to be $111.9 million. In deriving this value, we utilized management projections of future debt-free net cash flows, based on a number of assumptions we believed to be reasonable, and applied a discount rate of 23.5% to the projected cash flows. After deriving the estimated valuation of our equity capital, we used the OPM to derive a valuation of the Series D Preferred Stock on a controlling-interest, marketable basis of $3.29 per share. In applying the OPM, the time to liquidity was

Table of Contents

estimated as one year based on then-current plans and estimates of management regarding a liquidity event. The risk free interest rate was 0.18%. The annual volatility was estimated to be 60%. After applying a 5% discount for lack of control and a 10% discount for lack of marketability, we derived an estimated fair value of our Series D Preferred Stock of $2.81 per share as of February 28, 2013.

April 25, 2013 Junior A Preferred Stock

In connection with the issuance of shares of our newly designated Junior A Preferred Stock to Maruishi on April 25, 2013, we estimated the fair value of our equity capital, using the DCF approach, to be $163.4 million. In deriving this value, we utilized management projections of future debt-free net cash flows, based on a number of assumptions we believed to be reasonable, and applied a discount rate of 23% to the projected cash flows. After deriving the estimated valuation of our equity capital, we used the OPM to derive a valuation of the Junior A Preferred Stock on a controlling-interest, marketable basis of $4.25 per share. In applying the OPM, the time to liquidity was estimated as one year based on then-current plans and estimates of management regarding a liquidity event. The risk free interest rate was 0.12%. The annual volatility was estimated to be 60%. After applying a 5% discount for lack of control and a 10% discount for lack of marketability, we derived an estimated fair value of our Junior A Preferred Stock of $3.64 per share as of April 25, 2013.

Common Stock Valuation

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

We 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 with the assistance of an independent third party valuation firm, 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 the company s conditions had changed significantly since our most recent equity financing such that use of the market approach would be inappropriate.

December 31, 2011

In connection with our estimate of the fair value of our common stock as of December 31, 2011, the DCF analysis yielded an estimated fair value of our equity capital to be $79.1 million. In deriving this value, we utilized

management projections of future debt-free net cash flows, based on a number of assumptions we believed to be reasonable, and applied a discount rate of 25% to the projected cash flows. The market approach, based on the valuation of our July 2010 Series D Preferred Stock financing, implied an estimated fair value of our equity capital to be $49.6 million. Because of the time that had passed since the completion of the Series D Preferred Stock financing and the progress that we had made with respect to our clinical trial programs, we

determined that it was appropriate to apply a 75% weighting to the valuation implied by the DCF analysis and a 25% weighting to the value implied by the market approach. The resulting estimated fair value of our equity capital was $71.7 million. After deriving the estimated valuation of our equity capital, we used the OPM to derive a valuation of the common stock on a controlling-interest, marketable basis of $1.13 per share. In applying the OPM, the time to liquidity was estimated as 1.75 years based on then-current plans and estimates of management regarding a liquidity event. The risk free interest rate was 0.17%. The annual volatility was estimated to be 70%. After applying a 10% discount for lack of control and a 25% discount for lack of marketability, we derived an estimated fair value of our common stock of $0.77 per share as of December 31, 2011.

December 31, 2012

In connection with our estimate of the fair value of our common stock as of December 31, 2012, we estimated the fair value of our equity capital, using the DCF approach, to be $104.9 million. After deriving the estimated valuation of our equity capital, we used the OPM to derive a valuation of the common stock on a controlling-interest, marketable basis of $1.68 per share. In applying the OPM, the time to liquidity was estimated as one year based on then-current plans and estimates of management regarding a liquidity event. The risk free interest rate was 0.22%. The annual volatility was estimated to be 60%. After applying a 10% discount for lack of control and a 15% discount for lack of marketability, we derived an estimated fair value of our common stock of $1.29 per share as of December 31, 2012. Factors that contributed to an increase in the value of our common stock from the estimated value as of December 31, 2011 include our successful completion of our Phase 2b trial of I.V. CR845 in laparoscopic hysterectomy patients and our entry into the license agreement with CKD.

February 28, 2013

Concurrent with the February 28, 2013 closing of the convertible promissory notes, certain holders of our preferred stock that did not elect to participate in the note financing had their shares of preferred stock mandatorily converted to common stock at their respective conversion rates. We recorded the issuance of the common stock on February 28, 2013 at fair value. Similar to the preferred stock valuation discussion above, after deriving the estimated valuation of our equity capital, we used the OPM to derive a valuation of the common stock on a controlling-interest, marketable basis of $1.94 per share. In applying the OPM, the time to liquidity was estimated as one year based on then-current plans and estimates of management regarding a liquidity event. The risk free interest rate was 0.18%. The annual volatility was estimated to be 60%. After applying a 10% discount for lack of control and a 15% discount for lack of marketability, we derived an estimated fair value of our common stock of $1.49 per share as of February 28, 2013.

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.

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, 2011 and 2012 and September 30, 2013, we had cash and

cash equivalents of $4.1 million, $1.1 million and $17.7 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.

Table of Contents

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 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.

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.

Table of Contents

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 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 September 30, 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 Complete	Cara (worldwide, other than Japan and South Korea)
			Maruishi Pharmaceutical (Japan)

			Chong Kun Dang Pharmaceutical (South Korea)
Oral CR845	Acute & Chronic Pain	Phase 1	Cara (worldwide, other than Japan and South Korea) Maruishi Pharmaceutical (Japan only) for acute pain indication Chong Kun Dang Pharmaceutical (South Korea)
CR701	Neuropathic & Inflammatory Pain	Preclinical	Cara (worldwide)

Table of Contents

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 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.

Table of Contents

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

Chronic Pain Market

The most common causes of moderate-to-severe chronic pain are musculoskeletal problems and inflammatory conditions. Injuries from accidents resulting in fractures, dislocations or soft tissue injury, as well as lower back pain, are the most frequent causes of musculoskeletal pain. Although these injuries are mostly non-fatal, the cost in terms of long-term disability, medical expense and lost productivity is large. Moderate-to-severe chronic pain is typically treated with prescription products including immediate release and long-acting opioids, such as the branded products Oxycontin (oxycodone) 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 postmarket 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 postmarket 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.

Table of Contents

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 out patient setting.

We are currently planning the Phase 3 pivotal trials for I.V. CR845, 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 early 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 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

Table of Contents

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

Table of Contents

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 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

Table of Contents

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.

Table of Contents

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£0.001

**p£0.05

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 overal 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 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

Table of Contents

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.

Table of Contents

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.

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

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 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 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

Table of Contents

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.

85

Table of Contents

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 expect to commence these clinical 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.

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.

86

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.

Table of Contents

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 the first half of 2014 and, if the results of these trials are favorable, initiate a Phase 2a proof-of-concept trial in acute pain in the second half of 2014.

We are planning the following two Phase 1 clinical trials to determine the safety and pharmacokinetic profile of Oral CR845 when dosed in healthy subjects.

CLIN1002-PO: This clinical trial will be a single ascending dose trial with 10 subjects per cohort, eight of whom will receive Oral CR845 and two of whom will receive placebo. It is anticipated that there will be up to 100 subjects in this trial with doses ranging from 0.1 mg up to 20 mg.

CLIN1003-PO: This clinical trial is expected to be a multiple ascending dose trial with subjects divided into three cohorts based on low, mid and high doses with 15 subjects per cohort, 10 of whom will receive Oral CR845 and five of whom will receive placebo.

Upon successful completion of the Phase 1 clinical trials, we are planning a Phase 2a proof-of-concept trial in patients with moderate-to-severe pain following bunionectomy surgery. We expect this trial will be a randomized, double-blind, placebo-controlled trial that will explore multiple doses of Oral CR845. The primary endpoint of the trial is anticipated to be the SPID at 48 hours.

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

Table of Contents

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.

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. 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. In addition to our two pivotal Phase 3 clinical trials using I.V. CR845 administered after surgery, we are also planning to run one optional supportive Phase 3 clinical trial with I.V. CR845 administered prior to and after surgery to patients undergoing hysterectomy or bunionectomy. We expect to commence these trials in the second half of 2014.

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.

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 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 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 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

Table of Contents

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 the first of these is 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 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.

91

Table of Contents

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 and national patents have been granted in 32 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 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

Table of Contents

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.

93

Table of Contents

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

Table of Contents

DPN. Topical prescription products currently marketed in the United States for neuropathic pain indications include Lidoderm, a lidocaine patch marketed by Endo Pharmaceuticals for PHN, and Qutenza, a capsaicin patch marketed by Acorda Therapeutics for PHN. 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;
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.

Table of Contents

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

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements.

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

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

The FDA may refer an application for a novel drug to an external advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured, referred to as a Pre-Approval Inspection. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with cGCP.

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

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific

conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA s satisfaction, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. For some products, an additional step of DEA review and scheduling is required.

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

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

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

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

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

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Although physicians, in the practice of medicine, may prescribe approved drugs for unapproved indications, pharmaceutical companies generally are required to promote their drug products only for the approved indications and

in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and

Table of Contents

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.

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 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 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

Table of Contents

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 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

Table of Contents

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 to 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 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.

Table of Contents

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 $4.8 million, $7.2 million and $4.6 million in 2010, 2011 and 2012, respectively, and $6.7 million for the nine months ended September 30, 2013. 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.

Facilities

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.

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.

Table of Contents

MANAGEMENT

Executive Officers and Directors

The following table sets forth information regarding our executive officers and directors as of December 31, 2013:

Name	Age	Position
Derek Chalmers, Ph.D., D.Sc.	49	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
Ed Hurwitz	50	Director
Charles Moller, Ph.D.	60	Director
Dean Slagel	43	Director
Martin Vogelbaum	50	Director

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

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. 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.

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

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

Table of Contents

Adolor Corporation (NASDAQ: ADLR) from 1994 to 1997. Prior to that, Dr. Lewis co-founded Cephalon, Inc. (NASDAQ: CEPH), serving as Director of Pharmacology from 1988 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.

Non-Employee Directors

Ed Hurwitz. Mr. Hurwitz has served as a member of our board of directors since November 2006. Mr. Hurwitz has served as a Director of Alta Partners, a venture capital firm, since June 2002. 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 several privately-held companies. 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.

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. 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 members. The members of our board of directors were elected in compliance with the provisions of our amended and restated certificate of incorporation and a voting agreement among certain of our stockholders, as amended. The voting agreement will terminate upon the closing of this offering and none of our stockholders will have any special rights regarding the election or designation of members of our board of directors.

Table of Contents

Our board of directors will consist of five members upon completion of this offering. In accordance with our amended and restated certificate of incorporation to be filed in connection with this offering, immediately after this offering, our board of directors will be 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 will be divided among the three classes as follows:

- The Class I directors will be Mr. Hurwitz and Dr. Moller, and their terms will expire at our first annual meeting of stockholders to be held following completion of this offering;
- The Class II directors will be Mr. Slagel, and his term will expire at our second annual meeting of stockholders to be held following completion of this offering; and
- The Class III directors will be Mr. Vogelbaum and Dr. Chalmers, and their terms will expire at our third annual meeting of stockholders to be held following completion of this 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.

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 this 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.

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 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;

Table of Contents

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.

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;

Table of Contents

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

Effective upon completion of this offering, we will adopt a Code of Business Conduct and Ethics, or the Code of Conduct, applicable to all of our employees, executive officers and directors. Following the completion of this offering, the Code of Conduct will be available on our website at *www.caratherapeutics.com*. The nominating and corporate governance committee of our board of directors will be 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.

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.

Non-Employee Director Compensation

We have not historically paid 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.

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.

We expect that our board of directors will adopt a director compensation plan for non-employee directors to be effective following the completion of this offering.

Table of Contents

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 following the completion of this offering may differ materially from the currently planned programs summarized in this discussion.

2013 Summary Compensation Table

The following table provides information regarding the compensation earned during the year ended December 31, 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
	2012	400,000				400,000
President and Chief Executive Officer						
James B. Jones, M.D., PharmD, FACEP[2]	2013	223,000	30,000			253,000
	2012	325,000				325,000
Former Chief Medical Officer						
Frédérique Menzaghi, Ph.D.	2013	275,000	30,000			305,000
	2012	275,000				275,000
Vice President Research and Development						
Josef Schoell	2013	190,000	15,000			205,000
	2012	190,000				190,000
Chief Financial Officer						

(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	100,000		0.99	11/7/2017
James B. Jones, M.D., PharmD, FACEP *Former Chief Medical Officer*	4/28/2011	234,500		0.34	9/6/2014[1]
Frédérique Menzaghi, Ph.D. *Vice President Research and Development*	7/11/2005	50,000		0.10	7/11/2015
	11/7/2007	50,000		0.99	11/7/2017
	8/14/2008	25,000		0.90	8/14/2018
	10/15/2010	79,166	20,834[2]	0.82	10/15/2020
Josef Schoell *Chief Financial Officer*	5/2/2005	100,000		0.10	7/11/2015
	8/29/2006	20,000		0.31	9/29/2016
	11/7/2007	30,000		0.99	11/7/2017
	8/14/2008	10,000		0.90	8/14/2018
	9/8/2011	14,062	10,938[2]	0.34	9/8/2021

Table of Contents

(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.

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

We have entered into offer letters with each of the executive officers in connection with his or her employment with us. These agreements provide for at will employment and set forth the terms and conditions of employment of each named executive officer, including base salary, target annual bonus opportunity, if any, standard employee benefit plan participation, the terms of the executive officer s initial stock option grant and vesting provisions with respect to the initial stock option grant, if any. These offer letters were each subject to the executive officers execution of our standard confidential information and invention assignment agreement.

None of our executive officers offer letters or stock option grants contain provisions for payments upon a termination or change in control, except that Dr. Jones option grant provided for accelerated vesting upon a change in control or the happening of certain events after a change in control. However, Dr. Jones employment with us terminated, and his vesting ceased, effective September 6, 2013.

Equity Incentive Plans

2014 Equity Incentive Plan

Our board of directors adopted, and our stockholders subsequently approved, our 2014 Equity Incentive Plan, or 2014 Plan, in . The 2014 Plan will become effective immediately upon the signing of the underwriting agreement for this offering. The 2014 Plan will terminate on 2023, unless sooner terminated by our board of directors. 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.

Types of Awards. The 2014 Plan provides for the grant of incentive stock options, nonstatutory 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 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, (assuming the 2014 Plan becomes effective before such date) and continuing through and including January 1, , by % 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 shares.

Section 162(m) Limits. No person may be granted awards covering more than million 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. Additionally, no person may be granted in a calendar year a performance stock award covering more than million shares or a performance cash award having a maximum value in excess of 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.

Table of Contents

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. No awards have been granted and no shares of our common stock have been issued under the 2014 Plan.

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 occurrence of the event giving rise to the termination for cause 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.

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.

Table of Contents

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 $100,000. 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 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 occurrence of the event giving rise to the termination for cause 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) total stockholder return; (5) return on equity or average stockholder s equity; (6) return on assets, investment or capital employed; (7) stock price; (8) margin (including gross margin); (9) income (before or after taxes); (10) operating income; (11) operating income after taxes; (12) pre-tax profit; (13) operating cash flow; (14) sales or revenue targets; (15) increases in revenue or product revenue; (16) expenses and cost reduction goals; (17) improvement in or attainment of working capital levels; (18) economic value added (or an equivalent metric); (19) market share; (20) cash flow; (21) cash flow per share; (22) share price performance; (23) debt reduction; (24) implementation or completion of projects or processes; (25) customer satisfaction; (26) stockholders equity; (27) capital expenditures; (28) debt levels; (29) operating profit or net operating profit; (30) workforce diversity; (31) growth of net income or operating income; and (32) to the extent that an award is not intended to comply with Section 162(m) of the Code, other measures of performance selected by our 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 goals are established, the compensation committee will appropriately make adjustments in the method of calculating the attainment of the performance goals as follows: (1) to exclude restructuring and/or other nonrecurring charges; (2) to exclude exchange rate effects, as applicable, for non-U.S. dollar denominated goals; (3) to exclude the effects of changes to U.S. GAAP; (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 U.S. GAAP; (6) to exclude the dilutive effects of acquisitions or joint ventures; (7) to assume that any business divested by our company achieved 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 our common stock 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 shareholders other than regular cash dividends; (9) to exclude the effects of stock based compensation and/or the award of bonuses under our bonus plans; and (10) to exclude the effect of any other unusual, non-recurring gain or loss or other extraordinary item. The performance goals may differ from participant to participant and from award to award.

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

Table of Contents

(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. As of September 30, 2013, options to purchase 1,225,400 shares of common stock were outstanding under the 2004 Plan, with a weighted average exercise price per share of $0.54. As of September 30, 2013, 1,894,498 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, 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) options granted under the 2004 Plan will terminate immediately upon an optionee s termination of employment for cause; (2) 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 (but will not continue to vest during such one-year period); and (3) 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.

Table of Contents

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 of 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.

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 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. 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, which will become effective upon the closing of this offering, 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, which will become effective upon the

closing of this offering, 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.

Table of Contents

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.

Table of Contents

CERTAIN RELATIONSHIPS AND RELATED PARTY TRANSACTIONS

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 $120,000; 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 elsewhere in Executive Compensation section of this prospectus.

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.

Table of Contents

2013 Bridge Financing

In December 2012 and February 2013, we issued an aggregate of $4.0 million aggregate 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 $300,000 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	$ 250,217	180,997
Devon Park Bioventures L.P.[5]	$ 502,113	365,576
Rho Ventures VI, L.P.[6]	$ 777,896	566,368
Derek Chalmers[7]	$ 181,833	132,607
Frédérique Menzaghi[8]	$ 28,688	
Michael E. Lewis[9]	$ 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) 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. 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.

Table of Contents

(6) 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.
(7) 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.
(8) Principal under this note and accrued interest was repaid in September 2013.
(9) 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.

Series D Preferred Stock Financing

In July 2010, we entered into a Series D Preferred Stock Purchase Agreement, or the Series D Purchase Agreement, pursuant to which we initially issued and sold to investors an aggregate of 3,312,853 shares of Series D Preferred Stock at a purchase price of approximately $1.44 per share, for aggregate consideration of $4.8 million. At additional closings held between August 2010 and August 2011, we issued and sold an aggregate of 7,073,204 additional shares of Series D Preferred Stock at a purchase price of approximately $1.44 per share, for aggregate additional consideration of $15 million.

The participants in this convertible preferred stock financing included the following holders of more than 5% of our capital stock or entities affiliated with them. The participants in the Series D Preferred Stock 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	Shares of Series D Preferred Stock
Ascent Biomedical Ventures and its affiliates[1]	977,984
Alta BioPharma Partners and its affiliates[2]	1,032,774
MVM International Life Sciences No. 1 L.P. and its affiliates[3]	1,032,774
Healthcare Private Equity Limited Partnership	516,388
Devon Park Bioventures LP.[4]	903,678
Rho Ventures VI, L.P.[5]	5,539,230

(1) These shares of Series D Preferred Stock were purchased by Ascent Biomedical Ventures I, LP and Ascent Biomedical Ventures I NY, LP.
(2) These shares of Series D Preferred Stock 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) These shares of Series D Preferred Stock were purchased by MVM International Life Sciences No. 1 LP and MVM Executive Limited.

(4) 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.

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

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 $99,000 per year, plus

Table of Contents

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 $126,000, $117,000 and $150,000 for the years ended December 31, 2011, 2012 and 2013, respectively.

Investor Rights Agreement

We are party to an investor rights agreement that provides certain holders of our convertible preferred stock, including certain holders of 5% of our capital stock and entities affiliated with certain of our directors, with certain registration rights, including the right to demand that we file a registration statement or request that their shares be covered by a registration statement that we are otherwise filing. For a more detailed description of these registration rights, please see Description of Capital Stock Registration Rights.

Voting Agreement

We are party to a voting agreement under which certain holders of our capital stock, including certain holders of 5% of our capital stock and entities affiliated with certain of our directors, have agreed to vote in a certain way on certain matters, including with respect to the election of directors. Upon the closing of this offering, the voting agreement will terminate and none of our stockholders will have any special rights regarding the election or designation of members of our board of directors.

Right of First Refusal and Co-sale Agreement

We are party to a right of first refusal and co-sale agreement with certain holders of our convertible preferred stock and our founders, including certain holders of 5% of our capital stock and entities affiliated with certain of our directors, pursuant to which the holders of convertible preferred stock have a right of first refusal and co-sale in respect of certain sales of securities by our founders. Upon the closing of this offering, the right of first refusal and co-sale agreement will terminate.

Indemnification Agreements

In connection with this offering, we will enter into indemnification agreements with each of our directors and executive officers. These agreements will provide that we will indemnify each of our directors and executive officers against any and all expenses incurred by that director or executive officer because of his or her status as one of our directors or executive officers to the fullest extent permitted by Delaware law, our amended and restated certificate of incorporation and our amended and restated bylaws, except in a proceeding initiated by such director or executive officer without board of director approval. In addition, the agreement will generally provide that, to the fullest extent permitted by Delaware law, we will advance all expenses incurred by our directors and executive officers in connection with a legal proceeding.

Policies and Procedures for Related Party Transactions

Our board of directors intends to adopt 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 will cover 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 $120,000 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.

121

Table of Contents

PRINCIPAL STOCKHOLDERS

The following table sets forth information as of September 30, 2013 about the number of shares of common stock and the perce