ZOGENIX, INC.
Form S-1/A
September 07, 2011
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**As filed with the Securities and Exchange Commission on September 7, 2011**

**Registration No. 333-176443**

# UNITED STATES

# SECURITIES AND EXCHANGE COMMISSION

**Washington, D.C. 20549**

# AMENDMENT NO. 1

# TO

# FORM S-1

# REGISTRATION STATEMENT

***Under***

***The Securities Act of 1933***

# ZOGENIX, INC.

**(Exact name of registrant as specified in its charter)**

| Delaware | 2834 | 20-5300780 |
|---|---|---|
| (State or other jurisdiction of incorporation or organization) | (Primary Standard Industrial Classification Code Number) | (I.R.S. Employer Identification Number) |

**12671 High Bluff Drive, Suite 200**

**San Diego, CA 92130**

**(858) 259-1165**

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

**Roger L. Hawley**

**Chief Executive Officer**

**Zogenix, Inc.**

**12671 High Bluff Drive, Suite 200**

**San Diego, CA 92130**

**(858) 259-1165**

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

***Copies to:***

| | |
|---|---|
| **Scott N. Wolfe, Esq.**<br>**Cheston J. Larson, Esq.** | **Eric S. Haueter, Esq.**<br>**Bradley S. Fenner, Esq.** |
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| **Michelle M. Khoury, Esq.**<br>**Latham & Watkins LLP**<br>**12636 High Bluff Drive, Suite 400**<br>**San Diego, CA 92130**<br>**(858) 523-5400** | **Faie R. Dorin, Esq.**<br>**Sidley Austin LLP**<br>**555 California Street, 20th Floor**<br>**San Francisco, CA 94104**<br>**(415) 772-1200** |

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, please 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 statement 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 of the Exchange Act.

| | |
|---|---|
| Large accelerated filer ¨ | Accelerated filer ¨ |
| Non-accelerated filer x (Do not check if a smaller reporting company) | 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 which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.**

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**The information in this 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 prospectus is not an offer to sell these securities or the solicitation of an offer to buy these securities in any state or other jurisdiction in which such offer, solicitation or sale is not permitted.**

**SUBJECT TO COMPLETION DATED SEPTEMBER 7, 2011**

**PROSPECTUS**

## 12,000,000 Shares of Common Stock

We are selling 12,000,000 shares of our common stock.

Our common stock is listed on the Nasdaq Global Market under the symbol ZGNX. On September 2, 2011, the last reported sale price of our common stock on the Nasdaq Global Market was $3.39 per share.

**Investing in our common stock involves a high degree of risk. Before buying any shares you should read the discussion of material risks of investing in our common stock in Risk Factors beginning on page 10.**

| | Per Share | Total |
|---|---|---|
| Public Offering Price | $ | $ |
| Underwriting Discounts and Commissions | $ | $ |
| Proceeds to us, before expenses | $ | $ |

We have granted a 30-day option to the underwriters to purchase up to 1,800,000 additional shares of our common stock (15% of the shares sold).

Cowen Healthcare Royalty Partners II, L.P., a current stockholder, Roger L. Hawley, our Chief Executive Officer, and Ann D. Rhoads, our Executive Vice President and Chief Financial Officer, have indicated an interest in purchasing $1.5 million, $100,000 and $100,000 of shares of our common stock in this offering, respectively. However, because indications of interest are not binding agreements or commitments to purchase, the underwriters may determine to sell more, less or no shares in this offering to any of these parties, or any of these parties may determine to purchase more, less or no shares in this offering. The underwriters will not receive an underwriting discount or commission on any sales of shares to these parties.

**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.**

The underwriters expect to deliver the shares on or about , 2011 through the book-entry facilities of The Depository Trust Company.

**Leerink Swann** **Wells Fargo Securities**

**Stifel Nicolaus Weisel** **William Blair & Company** **Oppenheimer & Co.**

The date of this prospectus is , 2011.

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We launched our first product, Sumavel® DosePro®, using our proprietary DosePro technology in January 2010.

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## ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission. This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of our business and the securities we are offering, you should carefully read the registration statement, including its exhibits and this prospectus before making an investment decision.

You should rely only on the information contained in this prospectus and in any free writing prospectus that we may provide to you in connection with this offering. Neither we nor any of the underwriters has authorized anyone to provide you with information different from, or in addition to, that contained in this prospectus or any such free writing prospectus. If anyone provides you with different or inconsistent information, you should not rely on it. Neither we nor any of the underwriters is making an offer to sell or seeking offers to buy these securities in any jurisdiction where or to any person to whom the offer or sale is not permitted. The information in this prospectus is accurate only as of the date on the front cover of this prospectus and the information in any free writing prospectus that we may provide you in connection with this offering is accurate only as of the date of that free writing prospectus. Our business, financial condition, results of operations and prospects may have changed since those dates.

For investors outside the United States: Neither we nor any of the underwriters has done anything that would permit this offering or possession or distribution of this prospectus or any free writing prospectus we may provide to you in connection with this offering in any jurisdiction where action for that purpose is required, other than in the United States. You are required to inform yourselves about and to observe any restrictions relating to this offering and the distribution of this prospectus and any such free writing prospectus outside of the United States.

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## PROSPECTUS SUMMARY

*This summary does not contain all of the information you should consider before buying shares of our common stock. You should read the entire prospectus carefully, especially the Risk Factors section and our financial statements and the related notes appearing at the end of this prospectus, before deciding to invest in shares of our common stock. Unless the context requires otherwise, references in this prospectus to Zogenix, we, us and our refer to Zogenix, Inc., including its consolidated subsidiary, Zogenix Europe Limited.*

### Overview

We are a pharmaceutical company commercializing and developing products for the treatment of central nervous system disorders and pain. Our first commercial product, Sumavel® DosePro® (*sumatriptan* injection) Needle-free Delivery System, was launched in January 2010. Sumavel DosePro offers fast-acting, easy-to-use, needle-free subcutaneous administration of *sumatriptan* for the acute treatment of migraine and cluster headache in a pre-filled, single-use delivery system. Sumavel DosePro is the first drug product approved by the U.S. Food and Drug Administration, or FDA, that allows for the needle-free, subcutaneous delivery of medication. Our lead product candidate, Zohydro, is a novel, oral, single-entity extended-release formulation of *hydrocodone* currently in Phase 3 development for the treatment of moderate to severe chronic pain in patients requiring around-the-clock opioid therapy. We reported positive top-line results from our pivotal Phase 3 efficacy trial for Zohydro in August 2011 and expect to submit a New Drug Application, or NDA, with the FDA by early 2012. Sumavel DosePro and Zohydro each has the potential to address significant unmet medical needs and become important and widely-used additions to the treatment options available to patients and physicians in the United States multi-billion dollar migraine and chronic pain markets, respectively.

Sumavel DosePro may serve as a treatment alternative to oral and nasal triptans and may offer simple, convenient administration when compared to traditional, needle-based *sumatriptan* injection. According to its Prescribing Information, Sumavel DosePro can provide onset of migraine pain relief in as little as ten minutes for some patients. As a result, we believe that Sumavel DosePro has the potential to be prescribed by a broad physician audience, especially for difficult to treat migraine episodes.

Migraine is a syndrome that affects approximately 30 million people in the United States, according to a 2010 National Headache Foundation press release. Triptans are the class of drugs most often prescribed for treating migraines. In the United States in the 12 months ended December 2010, triptans generated sales of approximately $3.5 billion and *sumatriptan*, including branded and generic forms, represented the largest market share of the seven approved triptans, with sales of approximately $2.1 billion, according to Wolters Kluwer Pharma Solutions (Source® PHAST Institution/Retail).

We launched the commercial sale of Sumavel DosePro in the United States in January 2010 with our co-promotion partner, Astellas Pharma US, Inc., or Astellas. Our sales and marketing organization is comprised of approximately 100 professionals. Our field sales force of approximately 80 representatives promotes Sumavel DosePro primarily to neurologists and other prescribers of migraine medications, including headache clinics and headache specialists. To build upon our success in growing Sumavel DosePro prescriptions, we have initiated activities to expand our field sales force in the United States to approximately 95 sales representatives by the end of the third quarter of 2011. Our promotional efforts are complemented by our collaboration with Astellas and approximately 400 of its sales representatives, who are promoting Sumavel DosePro primarily to primary care physicians, OB/GYNs, emergency medicine physicians and urologists in the United States. We also have entered into a partnership for Sumavel DosePro with Desitin Arzneimittel GmbH to accelerate development and regulatory approvals in Europe and further enhance the global commercial potential of Sumavel DosePro.

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Sumavel DosePro has demonstrated significant quarterly growth in total prescriptions since its launch in January 2010. For the six months ended June 30, 2011, we recognized $16.2 million in net product revenue from sales of Sumavel DosePro, represented by more than 32,000 aggregate dispensed prescriptions (Source® PHAST Retail, January 2011 June 2011). Sumavel DosePro continues to add new and repeat prescribers in both the neurology and primary care settings. The product is also gaining use from a range of patient segments, including new triptan users, patients being converted to the product from other migraine drugs and patients who have been prescribed Sumavel DosePro and also have other triptan prescriptions. This experience is consistent with our belief that many patients will selectively use Sumavel DosePro for their more challenging migraine episodes, while continuing to use oral triptans to treat their less severe migraine episodes. Through our ongoing efforts with the largest commercial health plans, Sumavel DosePro is achieving broad coverage in the United States, with a reimbursement claims approval rate of approximately 80% since launch through June 2011 (Source® Dynamic Claims January 2010 June 2011).

Our lead product candidate, Zohydro, is a novel, oral, single-entity extended-release formulation of *hydrocodone* currently in Phase 3 development for the treatment of moderate to severe chronic pain in patients requiring around-the-clock opioid therapy. Zohydro utilizes Elan Pharma International Limited s, or Elan s, proprietary Spheroidal Oral Drug Absorption System, or SODAS® Technology, which serves to enhance the release profile of *hydrocodone* to provide consistent 12-hour pain relief relative to existing immediate-release combination formulations. Most marketed *hydrocodone* products contain the analgesic combination ingredient *acetaminophen,* which if taken in high quantities over time can cause liver toxicity. In June 2009, the FDA organized a joint advisory committee meeting that highlighted the public health problem of liver injury related to the use of *acetaminophen* in both over-the-counter and prescription products. Zohydro, if approved, may represent the first available extended-release version of *hydrocodone* and also the first *hydrocodone* product that is not combined with another analgesic. As a result, we believe Zohydro could generate sales from both patients who are using immediate-release opioid products on a chronic basis and patients already using extended-release opioids. We initiated the Phase 3 clinical development program for Zohydro in March 2010 and reported positive top-line results from our pivotal Phase 3 efficacy trial in August 2011. The trial successfully met its primary efficacy endpoint in demonstrating a significant difference (p=0.008) between the mean changes in daily pain intensity Numeric Rating Scale (NRS) scores between Zohydro and placebo groups. We expect to submit an NDA with the FDA by early 2012. We in-licensed exclusive U.S. rights to Zohydro from Elan in 2007.

The American Pain Society estimated in 1999 that 9% of the U.S. adult population suffers from moderate to severe non-cancer related chronic pain. Chronic pain can be treated with both immediate-release and extended-release opioids. We define our target market for Zohydro as prescription, non-injectable *codeine*-based and extended-release *morphine*-based pain products. This market generated U.S. sales of approximately $13.5 billion for the year ended December 2010, based on average wholesale price, on approximately 206 million prescriptions. During the same period, existing *hydrocodone* products, the most commonly prescribed pharmaceutical products in the United States, generated $3.2 billion in sales on approximately 128 million prescriptions. (Source® PHAST Retail). We believe Zohydro has the potential to be an important therapeutic alternative to existing *hydrocodone* products, including the branded product Vicodin and its generic equivalents.

We are also developing Relday, a proprietary, long-acting injectable formulation of *risperidone* using Durect Corporation s SABER controlled-release formulation technology in combination with our DosePro needle-free, subcutaneous drug delivery system through a July 2011 development and license agreement with Durect. *Risperidone* is used to treat the symptoms of schizophrenia and bipolar disorder in adults and teenagers 13 years of age and older. If successfully developed and approved, we believe Relday may be the first once-monthly, subcutaneous antipsychotic product available in a needle-free delivery system. The existing long-acting injectable *risperidone* product achieved global net sales of $1.5 billion in 2010, according to industry reports, and requires twice monthly, 2 mL intramuscular injections with a 21 gauge or larger needle. We believe the combination of our DosePro technology with Durect s SABER controlled-release technology will allow Relday

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to be delivered subcutaneously without a needle on a once-monthly basis with a simplified dosing regimen, improved pharmacokinetic profile and significant reduction in injection volume versus currently marketed long-acting injectable antipsychotics. Based upon these characteristics, Relday may provide an important alternative to currently marketed long-acting injectable antipsychotics as well as a new long-acting treatment option for patients that currently use daily oral antipsychotic products. We intend to initiate clinical studies for Relday in patients with schizophrenia in early 2012 following the filing of an investigational new drug application.

Our DosePro technology is a novel, patent-protected, needle-free drug delivery system designed for self-administration of a pre-filled, single dose of liquid drug. We believe the FDA s approval of Sumavel DosePro represents an important validation of the technology. Results from our pre-clinical and clinical studies demonstrate that DosePro can be used successfully with small molecules and biological products, including protein therapeutics and monoclonal antibodies. We are building our internal product pipeline by investigating proven drugs that can be paired with DosePro to enhance their benefits and commercial attractiveness, such as with Relday. In addition to Relday, we are also evaluating the market potential, formulation requirements and clinical development pathway of an additional central nervous system, or CNS, compound that could be paired with DosePro to enhance its commercial attractiveness. We are also seeking to capitalize on our DosePro technology by out-licensing it to potential partners enabling them to enhance, differentiate or extend the life cycle of their proprietary injectable products. We acquired the DosePro technology and related intellectual property from Aradigm Corporation in August 2006.

Our management team has a proven clinical, regulatory, business development and commercialization track record at Zogenix and prior organizations, as well as significant expertise in CNS disorders and pain. Since our inception in 2006, our management team has successfully acquired, developed, obtained regulatory approval for and launched the commercial sale of Sumavel DosePro and completed a significant primary care co-promotion agreement in the United States and secured a European partnership for the product. We also completed in-licensing transactions for Zohydro and Relday and initiated Phase 3 development for Zohydro.

**Investment Highlights**

We believe we are differentiated by the unique characteristics of our marketed product, Sumavel DosePro, and our lead product candidate, Zohydro, each of which addresses large market opportunities, as well as our established commercial infrastructure, our innovative technology and the depth of experience of our management team. The following represents the key attributes that help differentiate our company:

Fully-integrated pharmaceutical company with established commercial infrastructure.

Sumavel DosePro, a differentiated entrant in the migraine market that has demonstrated significant quarterly growth in total prescriptions since its launch.

Zohydro, a novel, extended-release chronic pain therapy with positive top-line pivotal Phase 3 efficacy trial results and anticipated NDA submission by early 2012.

Validated, proprietary DosePro technology with broad range of potential applications, including our newest product candidate, Relday, a proprietary, long-acting injectable formulation of *risperidone*.

Experienced management team with unique commercial and development expertise, including CNS sales and marketing experience.

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**Our Strategy**

Our core strategy is to commercialize and develop differentiated CNS and pain therapeutics that can address significant unmet medical needs and overcome limitations of existing products. Key elements of our strategy include:

- Increasing sales and continuing to drive patient and physician adoption of Sumavel DosePro in the United States.
- Developing and commercializing Zohydro for the treatment of moderate to severe chronic pain.
- Expanding our product pipeline in CNS disorders and/or pain, including through the development of our newest product candidate, Relday.
- Obtaining regulatory approvals for Sumavel DosePro outside of the United States.
- Out-licensing our proprietary DosePro technology.
- Securing rights to complementary products and product candidates that address CNS disorders and/or pain.

**Our Risks**

Our business and our ability to execute our business strategy are subject to a number of risks that you should be aware of before you decide to buy our common stock. In particular, you should consider the following risks, which are discussed more fully in Risk Factors :

- We will require 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 largely dependent on the commercial success of Sumavel DosePro. For the six months ended June 30, 2011, we recognized only $16.2 million in net product revenue from sales of Sumavel DosePro, and we may never significantly increase these sales or become profitable.
- We are at an early stage of commercialization and have incurred significant net losses since our inception and anticipate that we will incur continued net losses for at least the next several years. Our net loss attributable to common stockholders was $45.6 million in 2008, $45.9 million in 2009, $73.6 million in 2010 and $38.2 million for the six months ended June 30, 2011.
- We may not be successful in executing our sales and marketing strategy for the commercialization of Sumavel DosePro and, as part of this strategy, we are dependent on our collaboration with Astellas to promote Sumavel DosePro primarily to primary care physicians, OB/GYNs, emergency medicine physicians and urologists. If we are unable to successfully execute such strategy, or if our co-promotion agreement with Astellas is amended, terminated or otherwise restructured, we may not be able to generate significant revenue.

We face intense competition, including from generic products, and if our competitors market and/or develop treatments for migraine, pain or psychotic disorders that are marketed more effectively, approved more quickly than our product candidates or demonstrated to be safer or more effective than our product or product candidates, our commercial opportunities may be reduced or eliminated.

We are dependent on numerous third parties in our supply chain, all of which are currently single source suppliers, for the commercial supply of Sumavel DosePro and sole source suppliers for the clinical supply of Zohydro and Relday, and if we experience problems with any of these suppliers, the manufacturing of Sumavel DosePro, Zohydro or Relday could be delayed.

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Zohydro and Relday are subject to extensive regulation, and we cannot give any assurance that they or any of our other product candidates will receive regulatory approval or be successfully commercialized.

Our clinical trials may fail to demonstrate acceptable levels of safety and efficacy of Zohydro, Relday or any of our other product candidates, which could prevent or significantly delay their regulatory approval.

Delays in the commencement or completion of clinical testing for Zohydro or pre-clinical or clinical testing for any of our other product candidates could result in increased costs to us and delay or limit our ability to pursue regulatory approval for, or generate additional revenues from, such product candidates.

Our success depends in part on our ability to protect our intellectual property. It is difficult and costly to protect our proprietary rights and technology, and we may not be able to ensure their protection.

We may encounter unexpected safety, manufacturing, supply, regulatory or other issues relating to Sumavel DosePro, which may limit its commercial sales or regulatory acceptance.

**Company Information**

We were formed as a Delaware corporation on May 11, 2006 as SJ2 Therapeutics, Inc. We commenced our operations on August 25, 2006 and changed our name to Zogenix, Inc. on August 28, 2006. Our principal executive offices are located at 12671 High Bluff Drive, Suite 200, San Diego, CA 92130, and our telephone number is 1-866-ZOGENIX (1-866-964-3649). We formed a wholly-owned subsidiary, Zogenix Europe Limited, in June 2010, a company organized under the laws of England and Wales and which is located in the United Kingdom, and whose principal operations are to support the manufacture of the DosePro technology. Our website address is www.zogenix.com. The information on, or accessible through, our website is not part of this prospectus.

DosePro®, Intraject®, Relday, Sumavel®, Zogenix and Zohydro are our trademarks. This prospectus also contains trademarks of other companies including Abilify®, Amerge®, Axert®, BOTOX®, Cambia, Fanapt®, Frova®, Geodon®, Imigran®, Imitrex®, Imitrex STATdose System®, Invega®, Latuda®, Lortab®, Maxalt®, Neurontin®, Relpax®, Relprevv, Risperdal®, Risperdal Consta®, SABER, Saphris®, Seroquel®, SODAS®, Sustenna, Treximet®, Vicodin®, Vicoprofen®, Voltaren®, Zomig® and Zyprexa®. Unless otherwise specified, all prescription, prescriber and patient data in this prospectus is from Wolters Kluwer Pharma Solutions, Source® Pharmaceutical Audit Suite (PHAST), Institutional/Retail, Source® PHAST Retail, Source® Prescriber or Source® Dynamic Claims.

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**The Offering**

| | |
|---|---|
| **Common stock offered** | 12,000,000 shares of common stock (or 13,800,000 shares if the underwriters option to purchase additional shares is exercised in full). |
| **Common stock to be outstanding after this offering** | 46,473,278 shares of common stock (or 48,273,278 shares if the underwriters option to purchase additional shares is exercised in full). |
| **Use of proceeds** | We intend to use the net proceeds from this offering to fund the cost of submitting an NDA to the FDA for U.S. regulatory approval of Zohydro, to fund the initial clinical development of Relday and to fund the ongoing commercialization of Sumavel DosePro and for working capital and other general corporate purposes. |
| **Risk factors** | You should read the Risk Factors section of this prospectus for a discussion of the factors to consider carefully before deciding to purchase any shares of our common stock. |
| **Nasdaq Global Market symbol** | ZGNX |

The number of shares of common stock to be outstanding after this offering is based on 34,473,278 shares outstanding as of July 31, 2011, and excludes:

- 508,271 shares of common stock issuable upon the exercise of warrants outstanding as of July 31, 2011, at a weighted average exercise price of $9.70 per share;
- 3,327,795 shares of common stock issuable upon the exercise of options and restricted stock units outstanding as of July 31, 2011, at a weighted average exercise price of $4.07 per share; and
- 2,054,292 additional shares of common stock reserved for future issuance under our 2010 equity incentive award plan, or 2010 Plan, and our 2010 employee stock purchase plan, or Purchase Plan, as of July 31, 2011, plus any annual increases in the number of shares of common stock reserved for future issuance under the 2010 Plan and the Purchase Plan pursuant to evergreen provisions and any other shares that may become issuable under the 2010 Plan or the Purchase Plan pursuant to their terms, as more fully described in Compensation Discussion and Analysis Employee Equity Incentive Plans.

Except as otherwise indicated, all information in this prospectus assumes:

- no exercise by the underwriters of their option to purchase up to an additional 1,800,000 shares of common stock; and
- no exercise of outstanding options or warrants since July 31, 2011.

Cowen Healthcare Royalty Partners II, L.P., a current stockholder, Roger L. Hawley, our Chief Executive Officer, and Ann D. Rhoads, our Executive Vice President and Chief Financial Officer, have indicated an interest in purchasing $1.5 million, $100,000 and $100,000 of shares of our common stock in this offering, respectively. However, because indications of interest are not binding agreements or commitments to purchase, the underwriters may determine to sell more, less or no shares in this offering to any of these parties, or any of these parties may

determine to purchase more, less or no shares in this offering. The underwriters will not receive an underwriting discount or commission on any sales of shares to these parties.

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**Summary Financial Data**

The following table summarizes certain of our financial data. The summary statement of operations data for the years ended December 31, 2010, 2009 and 2008 are derived from our audited financial statements included elsewhere in this prospectus. The summary statement of operations data for the six months ended June 30, 2011 and 2010 and the historical balance sheet data as of June 30, 2011 have been derived from our unaudited interim financial statements, which are included elsewhere in this prospectus. The unaudited interim financial statements have been prepared on the same basis as the audited financial statements and, in the opinion of management, reflect all adjustments, consisting primarily of normal recurring adjustments, necessary to fairly present our financial position as of June 30, 2011 and results of operations for the six months ended June 30, 2011 and 2010. Our historical results of operations and financial condition are not necessarily indicative of the results or financial condition that may be expected in the future. The summary financial data set forth below should be read together with our financial statements and related notes, Selected Financial Data and Management s Discussion and Analysis of Financial Condition and Results of Operations included elsewhere in this prospectus.

| | June 30, | | Year Ended December 31, | | |
|---|---|---|---|---|---|
| | 2011 | 2010 | 2010 | 2009 | 2008 |
| | (In Thousands, Except Per Share Amounts) | | | | |
| **Statement of Operations Data** | | | | | |
| **Revenue:** | | | | | |
| Net product revenue | $ 16,151 | $ 6,118 | $ 19,069 | $ 0 | $ 0 |
| Contract revenue | 3,126 | 1,461 | 4,373 | 0 | 0 |
| Total revenue | 19,277 | 7,579 | 23,442 | 0 | 0 |
| **Operating expenses:** | | | | | |
| Cost of sales | 8,850 | 5,302 | 12,846 | 0 | 0 |
| Royalty expense | 630 | 382 | 843 | 0 | 0 |
| Research and development | 17,406 | 11,389 | 28,643 | 21,438 | 33,910 |
| Selling, general and administrative | 27,940 | 25,422 | 51,270 | 14,102 | 11,820 |
| Total operating expenses | 54,826 | 42,495 | 93,602 | 35,540 | 45,730 |
| **Loss from operations** | (35,549) | (34,916) | (70,160) | (35,540) | (45,730) |
| Other income (expense): | | | | | |
| Interest income | 19 | 3 | 5 | 10 | 696 |
| Interest expense | (2,515) | (1,511) | (10,013) | (9,188) | (1,718) |
| Change in fair value of warrant liability | 0 | (13,020) | 6,725 | (755) | 1,119 |
| Other income (expense) | (103) | 139 | (111) | (416) | 63 |
| Total other income (expense) | (2,599) | (14,389) | (3,394) | (10,349) | 160 |
| **Net loss before income taxes** | (38,148) | (49,305) | (73,554) | (45,889) | (45,570) |
| Provision for income taxes | (13) | 0 | (10) | 0 | 0 |
| **Net loss** | $ (38,161) | $ (49,305) | $ (73,564) | $ (45,889) | $ (45,570) |
| Net loss per share, basic and diluted | $ (1.12) | $ (37.44) | $ (17.63) | $ (40.97) | $ (52.68) |
| Weighted-average shares outstanding, basic and diluted | 34,015 | 1,317 | 4,173 | 1,120 | 865 |

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| | As of June 30, 2011 | | |
|---|---|---|---|
| | Actual | Pro Forma | Pro Forma As Adjusted |
| | | (In Thousands) | |
| **Balance Sheet Data:** | | | |
| Cash and cash equivalents | $ 7,672 | $ 37,172 | $ 74,872 |
| Working capital (deficit) | (61) | 29,439 | 67,139 |
| Total assets | 51,393 | 80,893 | 118,593 |
| Long-term debt, less current portion | 19,547 | 47,547 | 47,547 |
| Accumulated deficit | (236,263) | (236,263) | (236,263) |
| Total stockholders equity (deficit) | (7,142) | (5,642) | 32,058 |

The summary pro forma balance sheet data above gives effect to the borrowing of $30.0 million in July 2011 under our financing agreement with Cowen Healthcare Royalty Partners II, L.P., or Cowen Royalty, and receipt of $1.5 million from the sale and issuance of 388,601 shares of common stock to Cowen Royalty in connection with such financing, which in the aggregate resulted in net proceeds of $29.5 million, as if such transactions had occurred as of June 30, 2011. The summary pro forma as adjusted balance sheet data above additionally gives effect to our proposed sale of 12,000,000 shares of common stock in this offering and our receipt of the estimated net proceeds therefrom, based on the assumed public offering price of $3.39 per share, the last reported sale price of our common stock on the Nasdaq Global Market on September 2, 2011, after deducting the estimated underwriting discounts and commissions and estimated offering costs payable by us, and also assumes that Cowen Royalty, Roger L. Hawley and Ann D. Rhoads purchase all of the $1.5 million, $100,000 and $100,000 of shares of our common stock in this offering, respectively, that they have indicated an interest in purchasing as described above, as if such transactions had occurred as of June 30, 2011.

Each $1.00 increase or decrease in the assumed public offering price of $3.39 per share, the last reported sale price of our common stock on the Nasdaq Global Market on September 2, 2011, would increase or decrease, respectively, the pro forma as adjusted amount of cash and cash equivalents, working capital, total assets and total stockholders equity by approximately $11.3 million, assuming the number of shares offered by us, as set forth on the cover page of this prospectus, remains the same and after deducting the estimated underwriting discounts and commissions and estimated offering costs payable by us.

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## RISK FACTORS

*Investing in our common stock involves a high degree of risk. You should carefully consider the following risk factors, as well as the other information in this prospectus, before deciding whether to invest in shares of our common stock. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and prospects. In that case, the trading price of our common stock could decline, and you may lose all or part of your investment.*

### *Risks Related to Our Business and Industry*

**We will require 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.**

Our operations have consumed substantial amounts of cash since inception. To date, our operations have been primarily financed through the proceeds from the issuance of our common and preferred stock, including the proceeds from our initial public offering completed in November 2010, and borrowings under our loan and financing agreements with Cowen Healthcare Royalty Partners II, L.P, or Cowen Royalty, Oxford Finance LLC, as successor in interest to Oxford Finance Corporation, or Oxford, Silicon Valley Bank, or SVB, and, until June 30, 2011, General Electric Capital Corporation, or GE Capital. We believe, based on our current operating plan, that the net proceeds from this offering, together with our cash and cash equivalents as of June 30, 2011, future product revenues, borrowings available under our $10.0 million revolving credit facility and the net proceeds from our recently completed equity and royalty financing with Cowen Royalty, will be sufficient to fund our operations into the third quarter of 2012, although there can be no assurance in that regard. We will need to obtain additional funds to finance our operations beyond that point in order to:

- maintain and continue to increase our sales and marketing activities for Sumavel DosePro, particularly if our co-promotion agreement with Astellas Pharma US, Inc., or Astellas, is terminated, amended or otherwise restructured;
- qualify secondary sources for the manufacturing of Sumavel DosePro;
- fund our operations, continue to conduct clinical trials of Zohydro, initiate clinical trials for Relday and fund development of any other product candidate to support potential regulatory approval of marketing applications; and
- commercialize any of our product candidates or any products or product candidates that we may develop, in-license or otherwise acquire, if any of these product candidates receive regulatory approval.

In addition, our estimates of the amount of cash necessary to fund our business and development and commercialization activities may prove to be wrong, and we could spend our available financial resources much faster than we currently expect. Our future funding requirements will depend on many factors, including, but not limited to:

- the commercial success of Sumavel DosePro;
- the timing of regulatory approval, if granted, of Zohydro or any other product candidates;
- the rate of progress and cost of our clinical trials and other product development programs for Zohydro, Relday and our other product candidates and any other product candidates that we may develop, in-license or acquire;

the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights associated with Sumavel DosePro, Zohydro, Relday and any of our other product candidates;

the costs and timing of completion of outsourced commercial manufacturing supply arrangements for any product candidate;

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the costs of maintaining and expanding our sales and marketing infrastructure or establishing distribution capabilities;

the effect of competing technological and market developments; and

the terms and timing of any additional collaborative, licensing, co-promotion or other arrangements that we may establish.

Until we can generate a sufficient amount of product revenue and cash flow from operations and achieve profitability, we expect to finance future cash needs through public or private equity offerings, debt financings, receivables financings or corporate collaboration and licensing arrangements. We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are unsuccessful in raising additional required funds, we may be required to significantly delay, reduce the scope of or eliminate one or more of our development programs or our commercialization efforts, or cease operating as a going concern. We also may be required to relinquish, license or otherwise dispose of rights to product candidates or products that we would otherwise seek to develop or commercialize ourselves on terms that are less favorable than might otherwise be available. If we raise additional funds by issuing equity securities, substantial dilution to existing stockholders would result. If we raise additional funds by incurring debt financing, the terms of the debt may involve significant cash payment obligations as well as covenants and specific financial ratios that may restrict our ability to operate our business. If we are unable to maintain sufficient financial resources, including by raising additional funds when needed, our business, financial condition and results of operations will be materially and adversely affected and we may be unable to continue as a going concern. If we are unable to continue as a going concern, we may have to liquidate our assets and may receive less than the value at which those assets are carried on our consolidated financial statements, and it is likely that investors will lose all or a part of their investment.

**We are largely dependent on the commercial success of Sumavel DosePro and although we have generated revenue from sales of Sumavel DosePro, we may never significantly increase these sales or become profitable.**

We anticipate that, for at least the next several years, our ability to generate revenues and become profitable will depend in large part on the commercial success of our only marketed product, Sumavel DosePro, which in turn, will depend on several factors, including our ability to:

successfully maintain and increase market demand for, and sales of, Sumavel DosePro through our sales and marketing efforts and those of Astellas, our co-promotion partner (or, in the event that our co-promotion agreement with Astellas is amended, terminated or otherwise restructured, as described under Business Collaboration, Commercial and License Agreements Astellas Co-Promotion Agreement, by expanding our sales force and/or through another co-promotion partner, if available);

obtain greater acceptance of Sumavel DosePro by physicians and patients;

maintain adequate levels of coverage and reimbursement for Sumavel DosePro from commercial health plans and government health programs, which we refer to collectively as third-party payors, particularly in light of the availability of other branded and generic competitive products;

maintain compliance with regulatory requirements;

establish and maintain agreements with wholesalers and distributors on commercially reasonable terms;

maintain commercial manufacturing arrangements with third-party manufacturers as necessary to meet commercial demand for Sumavel DosePro and continue to manufacture commercial quantities at acceptable cost levels; and

successfully maintain intellectual property protection for Sumavel DosePro.

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We cannot be certain that our continued marketing of Sumavel DosePro will result in increased demand for, and sales of, the product. For example, while we have generally experienced quarterly growth in total prescriptions from the launch of Sumavel DosePro in January 2010 through June 30, 2011, we have at certain times experienced a reduction in total and new prescriptions month over month. In addition, while we have initiated activities to expand our sales force in the United States by approximately 15 sales representatives by the end of the third quarter of 2011 to further promote Sumavel DosePro, there is no guarantee that this expansion will result in increased sales of Sumavel DosePro. If we fail to successfully increase sales of Sumavel DosePro, we may be unable to generate sufficient revenues to grow or sustain our business and we may never become profitable, and our business, financial condition and results of operations will be materially adversely affected.

**We are at an early stage of commercialization and have a history of significant net losses and negative cash flow from operations. We cannot predict if or when we will become profitable and anticipate that our net losses and negative cash flow from operations will continue for at least the next several years.**

We were organized in 2006, have a limited operating history and there is little historical basis upon which to assess how we will respond to competitive, economic or technological challenges. Our business and prospects must be considered in light of the risks and uncertainties frequently encountered by pharmaceutical companies in the early stages of commercialization.

We have generated significant net losses and negative cash flow from operations since our inception in 2006. For example, for 2008, 2009, 2010 and the six months ended June 30, 2011, we incurred net losses of $45.6 million, $45.9 million, $73.6 million and $38.2 million, respectively, our net cash used in operating activities was $41.3 million, $32.4 million, $72.0 million, and $40.5 million, respectively, and, at June 30, 2011, our accumulated deficit was $236.3 million. We expect our losses and negative cash flow to continue for at least the next several years as a result of the development expenses in connection with our ongoing clinical development for Zohydro, the initiation of clinical development for Relday and the cost of the sales and marketing expense associated with Sumavel DosePro. Our ability to generate revenues from Sumavel DosePro or any of our product candidates will depend on a number of factors, including, in the case of Sumavel DosePro, the factors described in the following two risk factors and, in the case of our product candidates, our ability to successfully complete clinical trials, obtain necessary regulatory approvals and negotiate arrangements with third parties to help finance the development of, and market and distribute, any product candidates that receive regulatory approval. In addition, we will be subject to the risk that the marketplace will not accept our products.

Because of the numerous risks and uncertainties associated with our product development and commercialization efforts, we are unable to predict the extent of our future losses or when or if we will become profitable and it is possible we will never become profitable. Our failure to increase sales of Sumavel DosePro or to successfully commercialize any of our product candidates that may receive regulatory approval would likely have a material adverse effect on our business, results of operations, financial condition and prospects and could result in our inability to continue operations.

**We may not be successful in executing our sales and marketing strategy for the commercialization of Sumavel DosePro and, as part of this strategy, we are dependent on our collaboration with Astellas to promote Sumavel DosePro primarily to primary care physicians, OB/GYNs, emergency medicine physicians and urologists. If we are unable to successfully execute such strategy or if our co-promotion agreement with Astellas is amended, terminated or otherwise restructured, we may not be able to generate significant revenue.**

Prior to the launch of Sumavel DosePro in January 2010, we built a commercial sales and marketing organization including sales, marketing, communications, managed markets, trade and distribution functions, which is now focused exclusively on marketing and selling Sumavel DosePro primarily to physicians, nurses and other healthcare professionals in the United States. Our field sales force includes approximately 80 sales representatives who are promoting Sumavel DosePro primarily to neurologists and other prescribers of migraine

medications, including headache clinics and headache specialists in the United States. We have initiated activities to expand our sales force in the United States to approximately 95 sales representatives by the end of the third quarter of 2011. Although we believe we have adequately sized our sales force in order to reach this audience, we may either increase or decrease the size of our sales force in the future based upon market conditions and actual sales performance. In that regard, if our co-promotion agreement with Astellas is amended, terminated or otherwise restructured, as described below, we would expect to either expand our sales force to promote Sumavel DosePro and/or seek another co-promotion partner, if available. In addition, we could lose sales personnel or the performance of our sales personnel as measured by actual sales may be disappointing. Many of our competitors have significantly larger sales and marketing organizations, and significantly greater experience than we do in selling, marketing and distributing pharmaceuticals, and we may not be able to compete successfully with them with the commercial infrastructure we have developed.

To complement our sales force, we entered into an exclusive co-promotion agreement with Astellas in July 2009 under which Sumavel DosePro is also being promoted primarily to primary care physicians, OB/GYNs, emergency medicine physicians and urologists, or collectively the Astellas Segment, in the United States by approximately 400 Astellas sales representatives. Although the agreement stipulates annual minimum levels of sales effort, we have limited control over the amount and timing of resources that Astellas dedicates to the promotion of Sumavel DosePro, and we do not hire, train or manage such resources. For example, Astellas could reduce the number of its sales representatives promoting Sumavel DosePro while still complying with these minimum requirements. The ability to generate revenue from our arrangement with Astellas depends on Astellas efforts in promoting Sumavel DosePro and its ability to achieve broad market acceptance and prescribing of Sumavel DosePro in the Astellas Segment.

We are subject to a number of additional risks associated with our dependence on our co-promotion arrangement with Astellas, including:

- Astellas could fail to devote sufficient resources to the promotion of Sumavel DosePro, including by failing to develop, deploy or expand its sales force as necessary;
- Astellas could terminate the co-promotion agreement for any or no cause upon 180-days written notice at any time, which may negatively impact our ability to generate, or prevent us from generating, sufficient revenue;
- Astellas could fail to comply with applicable regulatory guidelines with respect to the promotion of Sumavel DosePro, which could result in administrative or judicially imposed sanctions, including warning letters, civil and criminal penalties, and injunctions; and
- disputes regarding the co-promotion agreement that negatively impact or terminate the commercialization efforts of Astellas may negatively impact or prevent the generation of sufficient revenue or result in significant litigation or arbitration.

For the six months ended June 30, 2011, sales to the Astellas Segment represented approximately 40% of our net product revenue. Under the terms of the co-promotion agreement, Astellas may terminate the agreement for any reason or no reason upon 180-days written notice to us. The co-promotion agreement may also be terminated by Astellas or us for a number of other specified reasons, some of which are beyond our control. In the event Astellas terminates the agreement for specified reasons, including a material uncured breach by us of our minimum sales effort obligations and our failure to cure such breach within a specified period, we would be required to pay Astellas only the first of the two annual tail payments described below.

In addition, either party may terminate the agreement based upon, among other things, a failure of the Sumavel DosePro brand to achieve certain minimum sales levels in 2011, as defined in the co-promotion agreement. Based on our net product revenue through June 30, 2011, we do not expect to meet these 2011 minimum sales levels for Sumavel DosePro, and therefore expect that both we and Astellas will have the right to terminate the agreement on this basis. If either party were to exercise this termination right, it must provide

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90 days written notice to the other party, such notice to be provided within 30 days after the actual net sales of Sumavel DosePro through December 31, 2011 have been provided to Astellas pursuant to the terms of the co-promotion agreement. In the event of such a termination relating to sales levels of Sumavel DosePro, we would be required to make two annual tail payments to Astellas calculated as decreasing fixed percentages (ranging from a mid-twenties down to a mid-teen percentage) of net sales in the Astellas Segment in the last 12 months of its active promotion. In the event of a termination by us or Astellas, we would expect to either expand our sales force to promote Sumavel DosePro to certain physicians within the Astellas Segment and/or seek another co-promotion partner, if available. We may also seek to amend or restructure our co-promotion agreement with Astellas.

In addition, Astellas may terminate the co-promotion agreement in the event we undergo a change of control, as defined in the co-promotion agreement, if a governmental authority takes action that prevents or makes it unlawful for Astellas to perform its obligations under the agreement, in the event of our inability to supply commercial product, under certain circumstances where a third party asserts that the making or selling of Sumavel DosePro infringes the intellectual property rights of a third party, upon the occurrence of a large scale recall or market withdrawal of Sumavel DosePro, upon a material uncured breach by us or in the event of our insolvency or bankruptcy or other event which affects our ability to perform our obligations under the agreement.

We cannot assure you that Astellas will not terminate the agreement under the circumstances described above. As an alternative to termination, we and Astellas could agree to amend or otherwise restructure the current co-promotion agreement. Such amendment or restructuring could change the financial terms of our agreement, change our respective minimum sales force requirements, or otherwise materially alter our co-promotion relationship. Such an amendment or restructuring could require us to expand our sales force or otherwise invest significant additional financial resources in order to adequately support the successful sales and marketing of Sumavel DosePro.

In addition, our co-promotion agreement with Astellas expires on June 30, 2013, subject to a one-year extension at the option of Astellas. We cannot assure you that Astellas will enter into any extension of the agreement or, if it does so, that it will not condition any such extension upon changes in the agreement that could have a material adverse effect on us. If Astellas were to terminate the agreement or elect not to extend the agreement upon its expiration, we would lose the efforts of their sales force, and we would need to make arrangements with another third party to replace Astellas sales force, or significantly expand our sales and marketing organization. We may not be able to enter into such arrangements with third parties in a timely manner, on acceptable terms or at all. To the extent that we enter into another co-promotion or other licensing arrangement, our portion of retained product revenues is likely to be lower than if we directly marketed and sold Sumavel DosePro solely on our own, and a portion of those revenues generated will depend upon the efforts of such third parties similar to our dependence on Astellas, and these efforts may not be successful. If our co-promotion agreement with Astellas is terminated and we are unable to find another partner for the promotion of Sumavel DosePro in the primary care segment in the United States, we may not be able to expand our own sales and marketing capabilities to cover this segment and any such expansion could, in any event, substantially increase our expenses and capital requirements that we might not be able to fund.

If we are unable to successfully implement our commercialization plans and drive adoption by patients and physicians of Sumavel DosePro through our sales, marketing and commercialization efforts and the efforts of Astellas, then we will not be able to generate significant revenue which will have a material adverse effect on our business, results of operations, financial condition and prospects.

**If Sumavel DosePro and, if approved, Zohydro and Relday, or any other product candidate for which we receive regulatory approval does not achieve broad market acceptance or coverage by third-party payors, the revenues that we generate will be limited.**

The commercial success of Sumavel DosePro and, if approved, Zohydro and Relday, or any other product candidates for which we obtain marketing approval from the FDA or other regulatory authorities will depend

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upon the acceptance of these products by physicians, patients, healthcare payors and the medical community. Coverage and reimbursement of our approved product by third-party payors is also necessary for commercial success. The degree of market acceptance of Sumavel DosePro and any other product candidates for which we may receive regulatory approval will depend on a number of factors, including:

- our ability to provide acceptable evidence of safety and efficacy;
- acceptance by physicians and patients of the product as a safe and effective treatment;
- the relative convenience and ease of administration;
- the prevalence and severity of adverse side effects;
- limitations or warnings contained in a product s FDA-approved labeling;
- the clinical indications for which the product is approved;
- in the case of product candidates that are controlled substances, the U.S. Drug Enforcement Agency, or DEA, scheduling classification;
- availability and perceived advantages of alternative treatments;
- any negative publicity related to our or our competitors products;
- the effectiveness of our or any current or future collaborators sales, marketing and distribution strategies;
- pricing and cost effectiveness;
- our ability to obtain sufficient third-party payor coverage or reimbursement; and
- the willingness of patients to pay out of pocket in the absence of third-party payor coverage.

For example, while we believe the needle-free nature of our DosePro technology will appeal to patients, some patients may not react favorably to the subcutaneous delivery of drug products by DosePro. Our experience indicates that some patients will experience pain upon injection with the DosePro technology and/or reactions at the site of injection. Any undesirable side effects have the potential to limit market acceptance of our product candidates.

In addition, products used to treat and manage pain, especially in the case of opioids, are from time to time subject to negative publicity, including illegal use, overdoses, abuse, diversion, serious injury and death. These events have led to heightened regulatory scrutiny. Controlled substances are classified by the DEA as Schedule I through V substances, with Schedule I substances being prohibited for sale in the United

States, Schedule II substances considered to present the highest risk of abuse and Schedule V substances being considered to present the lowest relative risk of abuse. Zohydro contains *hydrocodone*, and we anticipate it will be regulated as a Schedule II controlled substance, and despite the strict regulations on the marketing, prescribing and dispensing of such substances, illicit use and abuse of *hydrocodone* is well-documented. Thus, the regulatory approval process and the marketing of Zohydro may generate public controversy that may adversely affect regulatory approval and market acceptance of Zohydro.

Our efforts to educate the medical community and third-party payors on the benefits of Sumavel DosePro and Zohydro and Relday, if approved, and any of our other product candidates for which we obtain marketing approval from the FDA or other regulatory authorities and gain broad market acceptance may require significant resources and may never be successful. If our products do not achieve an adequate level of acceptance by physicians, third-party payors and patients, we may not generate sufficient revenue from these products to become or remain profitable.

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

Despite the implementation of security measures, our internal computer systems and those of our current and any future partners, contractors and consultants are vulnerable to damage from cyber-attacks, computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. For example, we recently experienced failures in our information systems and computer servers, which may have been the result of a cyber-attack. These failures resulted in an interruption of our normal business operations and required substantial expenditure of financial and administrative resources to remedy. We cannot be sure that similar failures will not occur in the future. System failures, accidents or security breaches can cause interruptions in our operations, and can result in a material disruption of our commercialization activities, drug development programs and our business operations. The loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Similarly, we rely on a large number of third parties to supply components for and manufacture our product and product candidates, warehouse and distribute Sumavel DosePro and conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the commercialization of Sumavel DosePro and development of Zohydro, Relday or any of our other product candidates could be delayed.

**Our short operating history makes it difficult to evaluate our business and prospects.**

We commenced our operations on August 25, 2006. Our operations to date have been limited to organizing and staffing our company, scaling up manufacturing operations with our third-party contract manufacturers, building a sales and marketing organization, conducting product development activities for our product and product candidates, in-licensing rights to Zohydro and Relday, and commercializing Sumavel DosePro. Moreover, Sumavel DosePro is our only product that is approved for sale. 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 depend on wholesale pharmaceutical distributors for retail distribution of Sumavel DosePro, and if we lose any of our significant wholesale pharmaceutical distributors, our business could be harmed.**

The majority of our sales of Sumavel DosePro are to wholesale pharmaceutical distributors who, in turn, sell the products to pharmacies, hospitals and other customers. Three wholesale pharmaceutical distributors, Cardinal Health, Inc., McKesson Corporation and AmerisourceBergen Corporation, individually comprised 46.2%, 34.8% and 11.1%, respectively, of our total gross sales of Sumavel DosePro for the six months ended June 30, 2011, which may result in substantial fluctuations in our results of operations from period to period. The loss of any of these wholesale pharmaceutical distributors accounts or a material reduction in their purchases could have a material adverse effect on our business, results of operations, financial condition and prospects.

In addition, these wholesale customers comprise a significant part of the distribution network for pharmaceutical products in the United States. This distribution network has undergone, and may continue to undergo, significant consolidation marked by mergers and acquisitions. As a result, a small number of large wholesale distributors control a significant share of the market. Consolidation of drug wholesalers has increased, and may continue to increase, competitive and pricing pressures on pharmaceutical products. In addition, at times, wholesaler purchases may exceed customer demand, resulting in reduced wholesaler purchases in later quarters, which may result in substantial fluctuations in our results of operations from period to period. We cannot assure you that we can manage these pricing pressures or that wholesaler purchases will not decrease as a result of this potential excess buying.

Our sales can be greatly affected by the inventory levels our wholesalers carry. We monitor wholesaler inventory of Sumavel DosePro using a combination of methods. Pursuant to distribution service agreements with

our three largest wholesale customers, we receive inventory level reports. For most other wholesalers where we do not receive inventory level reports, however, our estimates of wholesaler inventories may differ significantly from actual inventory levels. Significant differences between actual and estimated inventory levels may result in excessive production (requiring us to hold substantial quantities of unsold inventory), inadequate supplies of products in distribution channels, insufficient product available at the retail level, and unexpected increases or decreases in orders from our wholesalers. These changes may cause our revenues to fluctuate significantly from quarter to quarter, and in some cases may cause our operating results for a particular quarter to be below our expectations or the expectations of securities analysts or investors. If our financial results are below expectations for a particular period, the market price of our common stock may drop significantly.

**We face intense competition, including from generic products, and if our competitors market and/or develop treatments for migraine, pain or psychotic disorders that are marketed more effectively, approved more quickly than our product candidates or demonstrated to be safer or more effective than our products, our commercial opportunities will be reduced or eliminated.**

The pharmaceutical industry is characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary therapeutics. We face competition from a number of sources, some of which may target the same indications as our product or product candidates, including large pharmaceutical companies, smaller pharmaceutical companies, biotechnology companies, academic institutions, government agencies and private and public research institutions, many of which have greater financial resources, sales and marketing capabilities, including larger, well-established sales forces, manufacturing capabilities, experience in obtaining regulatory approvals for product candidates and other resources than us. Many large, well-capitalized companies offer products in the United States that compete with Sumavel DosePro. Sumavel DosePro currently competes with branded products in the triptan class such as Imitrex and Treximet marketed by GlaxoSmithKline, or GSK, as well as six other branded triptan therapies being sold by AstraZeneca PLC, Endo Pharmaceuticals Holdings Inc., Johnson & Johnson, Merck & Co., Inc., and Pfizer Inc. In addition to those migraine therapeutics there are other marketed non-triptan migraine therapeutics such as Cambia sold by Nautilus Neurosciences, Inc. and Migranal sold by Valeant Pharmaceutical International. We also face competition from generic *sumatriptan* injection, now marketed in the United States as an authorized generic of the Imitrex STATdose System, or Imitrex STATdose, by Par Pharmaceutical Companies, Inc. and Sandoz Inc. (a Novartis AG company). In addition, in June 2010 the FDA approved Alsuma (*sumatriptan* injection), a needle-based autoinjector which was developed and is manufactured and marketed by Pfizer and its subsidiary, Meridian Medical Technologies. Finally, generic injectable *sumatriptan* in the form of vials and prefilled syringes is available from a number of pharmaceutical companies, and most recently, the FDA granted approval for a needle-based generic *sumatriptan* auto-injector from Sun Pharmaceutical Industries Limited in June 2011. Although these products may not be directly substituted for Sumavel DosePro, generic versions of *sumatriptan* injection and alternative autoinjector forms of *sumatriptan* injection may reduce the future adoption of Sumavel DosePro by third-party payors and consumers, as financial pressure to use generic products may encourage the use of a generic product over Sumavel DosePro. Sumavel DosePro is currently more expensive on a per dose basis than most of the competing branded and all of the generic triptan products for migraine, which may also limit the coverage and reimbursement by third-party payors, which could adversely affect adoption by physicians and patients.

If approved for the treatment of moderate to severe chronic pain, we anticipate that Zohydro would compete against other marketed branded and generic pain therapeutics. Opioid therapeutics generally fall into two classes: *codeines*, which include *oxycodones* and *hydrocodones,* and *morphines*. Zohydro is a *hydrocodone*, the most commonly prescribed opioid in the United States, and we expect Zohydro will compete with therapeutics within both the *codeine* and *morphine* classes. These therapeutics include both Schedule II and Schedule III products (meaning that they are considered controlled substances by the DEA) being marketed by companies such as Endo Pharmaceuticals Holdings Inc., Johnson & Johnson, Mallinckrodt Inc., Pfizer, Purdue Pharma L.P., Teva Pharmaceutical Industries Limited and Watson Pharmaceuticals, Inc.

In addition to already marketed therapeutics, we also face competition from product candidates that are or could be under development by many of the above-mentioned entities and others. For example, there are several

products for the treatment of migraine under development by large pharmaceutical companies such as GSK and Merck & Co., and other smaller companies such as NuPathe, Inc. and MAP Pharmaceuticals, Inc. If approved, Zohydro may also compete with at least 15 opioid product candidates under development, including abuse and diversion resistant formulations of currently available opioids, novel opioids and alternative delivery forms of various opioids under development at other pharmaceutical companies, including single-entity extended-release *hydrocodone* product candidates being developed by Cephalon, Inc., Egalet A/S, Pfizer and Purdue Pharma L.P. Zohydro may also face competition from non-opioid product candidates including new chemical entities, as well as alternative delivery forms of non-steroidal anti-inflammatory drugs. These new opioid and non-opioid product candidates are being developed by companies such as Acura Pharmaceuticals, Inc., Altea Therapeutics Corporation, Collegium Pharmaceutical, Inc., Eli Lilly and Company, Elite Pharmaceuticals, Inc., Hospira Inc., Inspirion Delivery Technologies, LLC, Intellipharmaceutics International Inc., Pfizer and QRxPharma Ltd.

If approved for the treatment of schizophrenia, we anticipate that Relday will compete against other marketed, branded and generic, typical and atypical antipsychotics, including both long-acting injectable and oral products. Currently marketed long-acting injectable atypical antipsychotic products include Risperdal Consta, and Invega Sustenna marketed by Johnson & Johnson, and Zyprexa Relprevv marketed by Eli Lilly & Company. Currently approved and marketed oral atypical antipsychotics include Risperdal (*risperidone*) and Invega (*paliperidone*) marketed by Johnson & Johnson, generic *risperidone*, Zyprexa (*olanzapine*) marketed by Eli Lilly and Company, Seroquel (*quetiapine*) marketed by AstraZeneca PLC, Abilify (*aripiprazole*) marketed by BMS/Otsuka Pharmaceutical Co., Ltd., Geodon (*ziprasidone*) marketed by Pfizer, Fanapt (*iloperidone*) marketed by Novartis AG, Saphris (*asenapine*) marketed by Merck & Co., Latuda (*lurasidone*) marketed by Dainippon Sumitomo Pharma and generic *clozapine*. Finally, in addition to these currently marketed products, we may also face competition from additional long-acting injectable product candidates that could be developed by the large companies listed above, as well and by other pharmaceutical companies such as Alkermes, Inc., NuPathe, Inc. and Novartis AG, each of which has announced they are developing long-acting antipsychotic product candidates.

We expect Sumavel DosePro and, if approved, Zohydro, Relday and any of our other product candidates, to compete on the basis of, among other things, product efficacy and safety, time to market, price, patient reimbursement by third-party payors, extent of adverse side effects and convenience of treatment procedures. One or more of our competitors may develop needle-free injectable products, products to address chronic pain or other products that compete with ours, obtain necessary approvals for such products from the FDA, or other agencies, if required, more rapidly than us or develop alternative products or therapies that are safer, more effective and/or more cost effective than any products developed by us. If any of our product candidates receive the requisite regulatory approval and classification and are marketed, the competition which we will encounter will have, and the competition we are currently encountering with our Sumavel DosePro product has had and will continue to have, an effect on our product prices, market share and results of operations. We may not be able to differentiate any products that we are able to market from those of our competitors, successfully develop or introduce new products that are less costly or offer better results than those of our competitors, or offer purchasers of our products payment and other commercial terms as favorable as those offered by our competitors.

In addition, competitors may seek to develop alternative formulations of our product candidates and/or alternative drug delivery technologies that address our targeted indications. The commercial opportunity for Sumavel DosePro and our product candidates could be significantly harmed if competitors are able to develop alternative formulations and/or drug delivery technologies outside the scope of our products. Compared to us, many of our potential competitors have substantially greater:

- capital resources;
- research and development resources and experience, including personnel and technology;
- drug development, clinical trial and regulatory resources and experience;
- sales and marketing resources and experience;

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manufacturing and distribution resources and experience;

name recognition; and

resources, experience and expertise in prosecution and enforcement of intellectual property rights.

As a result of these factors, our competitors may obtain regulatory approval of their products more rapidly than we are able to or may obtain patent protection or other intellectual property rights that limit or block us from developing or commercializing our product candidates. Our competitors may also develop drugs that are more effective, more useful, better tolerated, subject to fewer or less severe side effects, more widely prescribed or accepted or less costly than ours and may also be more successful than us in manufacturing and marketing their products. If we are unable to compete effectively with the marketed therapeutics of our competitors or if such competitors are successful in developing products that compete with Sumavel DosePro or any of our product candidates that are approved, our business, results of operations, financial condition and prospects may be materially adversely affected.

**We are dependent on numerous third parties in our supply chain, all of which are currently single source suppliers, for the commercial supply of Sumavel DosePro and for the clinical supply of Zohydro and Relday, and if we experience problems with any of these suppliers, the manufacturing of Sumavel DosePro, Zohydro and Relday could be delayed.**

While we own most of the specialized equipment used to manufacture critical components of Sumavel DosePro, we do not own or operate manufacturing facilities and currently lack the in-house capability to manufacture Sumavel DosePro, Zohydro, Relday or any other products or product candidates. Our DosePro device and Sumavel DosePro are manufactured by contract manufacturers, component fabricators and secondary service providers. Final aseptic fill, finish, assembly and packaging of Sumavel DosePro are performed at Patheon UK Limited, Swindon, United Kingdom, a specialist in the aseptic fill/finish of injectables and other sterile pharmaceutical products. In addition, Nypro Limited, located in Bray, Ireland, manufactures the actuator assemblies and injection molded components for our DosePro device and MGlas AG, located in Münnerstadt, Germany, manufactures the specialized glass capsule that houses the *sumatriptan* active pharmaceutical ingredient, or API, in our DosePro device. Each of these manufacturers and each other company that supplies, fabricates or manufactures any component used in our DosePro device is currently the only qualified source of their respective components. We currently rely on Dr. Reddy s Laboratories as the only supplier of *sumatriptan* API for use in Sumavel DosePro. We also outsource all manufacturing and packaging of the clinical trial materials for Zohydro and Relday to third parties. Although we plan to qualify additional manufacturers and suppliers of some of the components used in Sumavel DosePro, there can be no assurance that we will be able to do so and the current manufacturers and suppliers of these components will likely be single source suppliers to us for a significant period of time. Similarly, under our license agreements, Elan Pharma International Ltd., or Elan, is the exclusive manufacturer of Zohydro and Durect is the exclusive manufacturer of Relday for all clinical trials through Phase 2 clinical trials and has the option to supply Relday for Phase 3 clinical trials and, if approved, commercial distribution. We may never be able to establish additional sources of supply for Zohydro or Relday.

Manufacturers and suppliers are subject to regulatory requirements covering, among other things, manufacturing, testing, quality control and record keeping relating to our product and product candidates, and are subject to ongoing inspections by regulatory agencies. Failure by any of our manufacturers or suppliers to comply with applicable regulations may result in long delays and interruptions to our manufacturing supply, and increase our costs, while we seek to secure another supplier who meets all regulatory requirements. Accordingly, the loss of any of our current third-party manufacturers or suppliers could have a material adverse effect on our business, results of operations, financial condition and prospects.

Reliance on third-party manufacturers and suppliers entails risks to which we would not be subject if we manufactured Sumavel DosePro or our product candidates ourselves, including:

reliance on the third parties for regulatory compliance and quality assurance;

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- the possible breach of the manufacturing agreements by the third parties because of factors beyond our control or the insolvency of any of these third parties or other financial difficulties, labor unrest, natural disasters or other factors adversely affecting their ability to conduct their business; and

- the possibility of termination or non-renewal of the agreements by the third parties, at a time that is costly or inconvenient for us, because of our breach of the manufacturing agreement or based on their own business priorities.

If our contract manufacturers or suppliers fail to deliver the required commercial quantities of Sumavel DosePro and its various components, the quantities of Zohydro, Relday or any of our other product candidates required for our clinical trials and, if approved, for commercial sale, on a timely basis and at commercially reasonable prices, and we are unable to find one or more replacement manufacturers or suppliers capable of production at a substantially equivalent cost, in substantially equivalent volumes and quality, and on a timely basis, we would likely be unable to meet demand for our products and would have to delay or terminate our pre-clinical or clinical trials, and we would lose potential revenue. It may also take a significant period of time to establish an alternative source of supply for our product, product candidates and components and to have any such new source approved by the FDA or any applicable foreign regulatory authorities. Furthermore, any of the above factors could cause the delay or suspension of initiation or completion of clinical trials, regulatory submissions or required approvals of our product candidates, cause us to incur higher costs and could prevent us from commercializing our product candidates successfully.

**We may encounter delays in the manufacturing of Sumavel DosePro or fail to generate revenue if our supply of the components of our DosePro drug delivery system is interrupted.**

Our DosePro drug delivery system is sourced, manufactured and assembled by multiple third parties across different geographic locations in Europe, including the United Kingdom, Germany and Ireland. All contract manufacturers and component suppliers have been selected for their specific competencies in the manufacturing processes and materials that make up the DosePro system. The components of DosePro include the actuator subassembly, capsule subassembly, and the setting mechanism. The actuator subassembly is comprised of nine individual components which are collectively supplied by six different third-party manufacturers. The capsule subassembly that houses the sterile drug formulation *sumatriptan* is comprised of five different components also supplied by four third-party manufacturers. Each of these third-party manufacturers is currently the single source of their respective components. If any of these manufacturers is unable to supply its respective component for any reason, including due to violations of the FDA s Quality System Regulation, or QSR, requirements, our ability to manufacture the finished DosePro device will be adversely affected and our ability to meet the distribution requirements for any product sales of Sumavel DosePro and the resulting revenue therefrom will be negatively affected. Accordingly, there can be no assurance that any failure in any part of our supply chain will not have a material adverse effect on our ability to generate revenue from Sumavel DosePro, which in turn could have a material adverse effect on our business, results of operations, financial condition and prospects.

**We rely on third parties to perform many necessary services for our commercial products, including services related to the distribution, invoicing, storage and transportation of our products.**

We have retained third-party service providers to perform a variety of functions related to the sale and distribution of our products, key aspects of which are out of our direct control. For example, we rely on Cardinal Health 105, Inc. (a/k/a Specialty Pharmaceutical Services) to provide key services related to logistics, warehousing and inventory management, distribution, contract administration and chargeback processing, accounts receivable management and call center management, and, as a result, most of our inventory is stored at a single warehouse maintained by the service provider. We place substantial reliance on this provider 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 damage or natural disaster at their facilities, our ability to deliver product to meet commercial demand would be

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significantly impaired. In addition, we utilize third parties to perform various other services for us relating to sample accountability and regulatory monitoring, including adverse event reporting, safety database management and other product maintenance services. If the quality or accuracy of the data maintained by these service providers is insufficient, our ability to continue to market our products could be jeopardized or we could be subject to regulatory sanctions. We do not currently have the internal capacity to perform these important commercial functions, and we may not be able to maintain commercial arrangements for these services on reasonable terms.

**The perception that our DosePro needle-free drug delivery system should be pain free may limit patient adoption.**

We believe that there is a perception among some patients, physicians and other customers that a needle-free delivery system should be pain free. While our experience indicates that some patients will experience pain upon injection with the DosePro technology, this pain sensation is consistent with the pain sensation associated with injection with a fine gauge needle and can be generally characterized as transient mild discomfort. In addition, some patients will experience local injection site signs and reactions following injection with DosePro. The fact that the use of our DosePro system may be accompanied by a certain amount of pain upon injection and local injection site signs and reactions may limit its adoption by patients, physicians and other customers.

**Zohydro and Relday are subject to extensive regulation, and we cannot give any assurance that they or any of our other product candidates will receive regulatory approval or be successfully commercialized.**

We currently are developing Zohydro for the treatment of moderate to severe chronic pain and we plan to initiate clinical studies for Relday to treat the symptoms of schizophrenia. The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of opioid drug products, among other things, are subject to extensive regulation by the FDA, the DEA (in the case of Zohydro) and other regulatory authorities in the United States. We are not permitted to market Zohydro, Relday or any of our other product candidates in the United States unless and until we receive regulatory approval from the FDA. We cannot provide any assurance that we will obtain regulatory approval for Zohydro, Relday or any of our other product candidates, or that any such product candidates will be successfully commercialized.

We have not yet completed all necessary studies, nor submitted a new drug application, or NDA, or received marketing approval, for Zohydro and we have not yet commenced clinical studies for Relday. Obtaining approval of an NDA is a lengthy, expensive and uncertain process. The FDA also has substantial discretion in the drug approval process, including the ability to delay, limit or deny approval of a product candidate for many reasons. For example:

- the FDA may not deem a product candidate safe and effective;
- the FDA may not find the data from pre-clinical studies and clinical trials sufficient to support approval;
- the FDA may require additional pre-clinical studies or clinical trials;
- the FDA may not approve of our third-party manufacturers processes and facilities; or
- the FDA may change its approval policies or adopt new regulations.

Zohydro has undergone Phase 1 pharmacokinetics studies as well as Phase 2 clinical trials. However, these studies and trials were conducted by a third party and, accordingly, we did not directly participate in their design or execution. In addition, we will also need to successfully complete Phase 3 clinical trials to establish its safety and efficacy, additional Phase 1 studies, and additional pre-clinical studies prior to our submission of an NDA to the FDA for approval. We initiated the Phase 3 clinical development program for Zohydro in March 2010 and reported positive top-line results from our pivotal Phase 3 efficacy trial, Study 801, in August 2011 and completed enrollment in our open-label Phase 3 safety trial, Study 802, in November 2010. Zohydro and any of

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our other product candidates may fail to achieve their specified endpoints in clinical trials. Furthermore, product candidates such as Zohydro may not be approved even if they achieve their specified endpoints in clinical trials. The FDA may disagree with our trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials. The FDA may also approve a product candidate for fewer or more limited indications than we request, or may grant approval contingent on the performance of costly post-approval clinical trials. In addition, the FDA may not approve the labeling claims that we believe are necessary or desirable for the successful commercialization of our product candidates. Although we have not yet begun clinical studies for Relday, the development of Relday will be subject to most of the risks described in this paragraph.

If we are unable to obtain regulatory approval for Zohydro, Relday or any other product candidates on the timeline we anticipate, we will not be able to execute our business strategy effectively and our ability to generate additional revenues beyond Sumavel DosePro will be limited, which would have a material adverse impact on our business, results of operations, financial condition and prospects.

**Our clinical trials may fail to demonstrate acceptable levels of safety and efficacy for Zohydro, Relday or any of our other product candidates, which could prevent or significantly delay their regulatory approval.**

Our Zohydro and Relday product candidates and any other product candidates are prone to the risks of failure inherent in drug development. Before obtaining U.S. regulatory approval for the commercial sale of Zohydro, Relday or any other product candidate, we must gather substantial evidence from well-controlled clinical trials that demonstrate to the satisfaction of the FDA that the product candidate is safe and effective, and similar regulatory approvals would be necessary to commercialize the product candidate in other countries.

In light of widely publicized events concerning the safety risk of certain drug products, particularly opioid drug products, regulatory authorities, members of Congress, the Government Accountability Office, medical professionals and the general public have raised concerns about potential drug safety issues. These events have resulted in the withdrawal of drug products, revisions to drug labeling that further limit use of the drug products and establishment of risk management programs that may, for instance, restrict distribution of drug products after approval. In addition, the Federal Food, Drug, and Cosmetic Act, or FFDCA, as amended by the Food and Drug Administration Amendments Act of 2007, grants significant expanded authority to the FDA, much of which is aimed at improving the safety of drug products before and after approval. In particular, the FFDCA authorizes the FDA to, among other things, require post-approval studies and clinical trials, mandate changes to drug labeling to reflect new safety information and require a risk evaluation and mitigation strategy, or REMS, for certain drugs, including certain currently approved drugs. It also significantly expands the federal government s clinical trial registry and results databank, which we expect will result in significantly increased government oversight of clinical trials. Under the FFDCA, companies that violate these and other provisions of the law are subject to substantial civil monetary penalties, among other regulatory, civil and criminal penalties.

The increased attention to drug safety issues may result in a more cautious approach by the FDA in its review of our clinical trials. Data from clinical trials may receive greater scrutiny with respect to safety, which may make the FDA or other regulatory authorities more likely to terminate clinical trials before completion, or require longer or additional clinical trials that may result in a delay or failure in obtaining approval or approval for a more limited indication than originally sought.

With regard to Zohydro, top-line results from our pivotal Phase 3 efficacy clinical trial in patients with chronic lower back pain has shown what we believe is a clinically acceptable efficacy and safety profile which supports submission of an NDA for the treatment of moderate to severe pain in patients requiring around-the-clock opioid therapy. The trial successfully met the primary efficacy endpoint of the study in demonstrating a significant difference (p=0.008) between the mean changes in daily pain intensity Numeric Rating Scale (NRS) scores between Zohydro and placebo groups. The two key secondary endpoints were also met, specifically, the proportion of patients with at least 30% improvement in pain intensity and the improvement of overall satisfaction of medication. In the pivotal Phase 3 efficacy trial, the observed adverse events were

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similar to the side effects we observed in prior Phase 2 trials of Zohydro and consistent with the reported side effects of opioids currently prescribed for chronic pain. The incidence of adverse events was 33.7% and 28.8% in the open-label titration and double blind treatment periods, respectively. Overall, the most commonly reported adverse events (³2%) were constipation, nausea, somnolence, vomiting, diarrhea, insomnia, fatigue, headache, dizziness and dry mouth. These results may not be predictive of results obtained in our ongoing Phase 3 safety trial or any other required future trials, and we may be unable to demonstrate sufficient safety and efficacy to obtain the requisite regulatory approvals or approvals for commercially viable uses. In addition, the top-line data we have reported and may continue to report from our Zohydro clinical trials is based on preliminary analysis of key efficacy and safety data, and such data may change following a more comprehensive review of the data related to the applicable clinical trial, and may also change in connection with the continued review of such data as part our planned submission and the FDA s review of our NDA. A number of companies in the biotechnology and pharmaceutical industries have suffered significant setbacks in advanced clinical trials, even after promising results in earlier trials. If Zohydro is not shown to be safe and effective in clinical trials, this program could be delayed or terminated, which could have a material adverse effect on our business, results of operations, financial condition and prospects.

**Delays in the commencement or completion of clinical testing for Zohydro or pre-clinical or clinical testing for Relday or any of our other product candidates could result in increased costs to us and delay or limit our ability to pursue regulatory approval for, or generate revenues from, such product candidates.**

Clinical trials are very expensive, time consuming and difficult to design and implement. Delays in the commencement or completion of clinical testing for Zohydro or pre-clinical or clinical testing for Relday or any of our other product candidates could significantly affect our product development costs and business plan. In March 2010, we initiated a Phase 3 clinical development program for Zohydro, including a pivotal efficacy trial. We reported positive top-line results from our pivotal Phase 3 efficacy trial in August 2011 and are still conducting our fully-enrolled Phase 3 safety trial for Zohydro. Phase 3 clinical efficacy trials, in general, are significantly more complex and time-consuming and involve more patients than the Phase 1 and 2 clinical trials. We do not know whether our ongoing Phase 3 clinical trial of Zohydro will be completed on schedule, if at all. We expect to initiate clinical testing for Relday in patients with schizophrenia in early 2012. In addition, we do not know whether this or any other pre-clinical or clinical trials will begin on time or be completed on schedule, if at all. The commencement and completion of clinical trials can be delayed for a number of reasons, including delays related to:

- obtaining regulatory authorization to commence a clinical trial;
- reaching agreement on acceptable terms with prospective clinical research organizations, or CROs, clinical investigators and trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs, clinical investigators and trial sites;
- manufacturing or obtaining sufficient quantities of a product candidate for use in clinical trials;
- obtaining institutional review board, or IRB, approval to initiate and conduct a clinical trial at a prospective site;
- identifying, recruiting and training suitable clinical investigators;
- identifying, recruiting and enrolling subjects to participate in clinical trials for a variety of reasons, including competition from other clinical trial programs for the treatment of pain, migraine or similar indications;
- retaining patients who have initiated a clinical trial but may be prone to withdraw due to side effects from the therapy, lack of efficacy, personal issues, or for any other reason they choose, or who are lost to further follow-up;

uncertainty regarding proper dosing; and

scheduling conflicts with participating clinicians and clinical institutions.

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We believe that we have planned and designed an adequate Phase 3 clinical trial program for Zohydro, and we presented the trial design for our Phase 3 trials to the FDA at our End of Phase 2 meeting in June 2008. Although we believe the FDA has generally agreed with the design of our Phase 3 clinical trial program, the FDA could still determine that it is not satisfied with our plan, the details of our pivotal clinical trial protocols and designs or the results of our studies. While the FDA has provided us with a written record of our discussions and responses to our questions at our End of Phase 2 meeting, such records and responses do not guarantee that the FDA will deem our trial design to be sufficient for the purpose of obtaining marketing approval for Zohydro. We did not seek a Special Protocol Assessment from the FDA for our pivotal Phase 3 efficacy study for Zohydro (Study 801).

In addition, while we completed enrollment in our open-label Phase 3 trial, Study 802, in November 2010, chronic pain patients have historically been difficult to keep enrolled in clinical trials. If a significant number of patients fail to stay enrolled in any of our current or future clinical trials of Zohydro, Relday or any of our other product candidates and such failure is not adequately accounted for in our trial design and enrollment assumptions, our clinical development program could be delayed. Clinical trials may also be delayed or repeated as a result of ambiguous or negative interim results or unforeseen complications in testing. In addition, a clinical trial may be suspended or terminated by us, the FDA, the IRB overseeing the clinical trial at issue, any of our clinical trial sites with respect to that site, or other regulatory authorities due to a number of factors, including:

- failure to design appropriate clinical trial protocols;
- failure by us, our employees, our CROs or their employees to conduct the clinical trial in accordance with all applicable FDA, DEA or other regulatory requirements or our clinical protocols;
- inspection of the clinical trial operations or trial sites by the FDA or other regulatory authorities resulting in the imposition of a clinical hold;
- discovery of serious or unexpected toxicities or side effects experienced by study participants or other unforeseen safety issues;
- lack of adequate funding to continue the clinical trial, including the incurrence of unforeseen costs due to enrollment delays, requirements to conduct additional trials and studies and increased expenses associated with the services of our CROs and other third parties;
- lack of effectiveness of any product candidate during clinical trials;
- slower than expected rates of subject recruitment and enrollment rates in clinical trials;
- failure of our CROs or other third-party contractors to comply with all contractual requirements or to perform their services in a timely or acceptable manner;
- inability or unwillingness of medical investigators to follow our clinical protocols;
- in the case of Zohydro, regulatory concerns with opioid products generally and the potential for abuse and diversion of the drugs; and

unfavorable results from on-going clinical trials and pre-clinical studies.

Additionally, changes in applicable regulatory requirements and guidance may occur and we may need to amend clinical trial protocols to reflect these changes. Amendments may require us to resubmit our clinical trial protocols to IRBs for reexamination, which may impact the costs, timing or successful completion of a clinical trial. If we experience delays in completion of, or if we terminate, any of our clinical trials, the commercial prospects for Zohydro, Relday and our other product candidates may be harmed, which may have a material adverse effect on our business, results of operations, financial condition and prospects.

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**Our competitors could receive FDA approval for an extended-release hydrocodone product before we receive FDA approval for Zohydro, and thus could be granted regulatory exclusivity that could significantly delay our ability to receive approval for and commercialize Zohydro and therefore dramatically reduce its market potential. Our competitors could also pursue regulatory and other strategies to combat competition from 505(b)(2) products, which also may negatively affect the approval and commercialization of Zohydro and any of our other product candidates.**

The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Amendments, added Section 505(b)(2) to the FFDCA, or Section 505(b)(2). Section 505(b)(2) permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. For example, we obtained FDA marketing approval of Sumavel DosePro under Section 505(b)(2), and we intend to submit the NDA for Zohydro under Section 505(b)(2), and as such the NDA will rely, in part, on the FDA s previous findings of safety and effectiveness for *hydrocodone*.

Certain of our competitors may file a 505(b)(2) application for extended-release *hydrocodone* either before or shortly after we submit our own NDA for Zohydro. The first approved 505(b)(2) applicant for a particular condition of use, or change to a marketed product, such as a new extended-release formulation for a previously approved product, may be granted three-year Hatch-Waxman exclusivity if one or more clinical studies, other than bioavailability or bioequivalence studies, was essential to the approval of the application and was conducted/sponsored by the applicant. Three-year Hatch-Waxman exclusivity delays the FDA s approval of other 505(b)(2) applicants for the same condition of use or change to the drug product that was granted exclusivity, regardless of the date of submission of each NDA. We believe that several competitors are developing extended-release *hydrocodone* products, and if the FDA approves a competitor s 505(b)(2) application for its extended-release *hydrocodone* product before our application, and granted the competitor three-year exclusivity, the FDA would be precluded from making effective our NDA for Zohydro until after that three-year exclusivity period has run, and such delay would dramatically reduce our expected market potential for Zohydro. Additionally, even if our 505(b)(2) application for extended-release *hydrocodone* is approved first, we may still be subject to competition by other *hydrocodone* products, including approved products or other 505(b)(2) applications for different conditions of use that would not be restricted by the three-year exclusivity.

In addition, approval under Section 505(b)(2) generally requires the absence of any other patents covering the product candidate in question and competitors and others have the ability to take numerous steps to block or delay approval of product candidates under Section 505(b)(2), including:

- extending patent protection for existing products that would block Section 505(b)(2) approval of the product candidate by pursuing new patents for existing products that may be granted just before the expiration of one patent, which could extend patent protection for a number of years or otherwise delay the launch of generic, 505(b)(2) or other competing products;
- submitting Citizen Petitions to request the FDA to take adverse administrative action with respect to approval of a generic, 505(b)(2) or other competing product;
- filing patent infringement lawsuits, whether or not meritorious, to trigger up to a 30-month stay in the approval of a generic, 505(b)(2) or other competing product; and
- engaging in state-by-state initiatives to enact legislation or regulatory policies that restrict the substitution of some generic, 505(b)(2) or other competing drugs for brand-name drugs.

If any of these strategies are successful, our ability to obtain approval of and commercialize Zohydro and any of our other product candidates for which we rely on Section 505(b)(2) will be adversely affected.

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**We rely on third parties to conduct our pre-clinical and clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business could be substantially harmed.**

We have agreements with third-party CROs to conduct our Phase 3 trials for Zohydro, and anticipate that we may enter into other such agreements in the future regarding Relday or any of our other product candidates. We rely heavily on these parties for the execution of our clinical and pre-clinical studies, and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol. We and our CROs are required to comply with current good clinical practices, or GCPs. The FDA enforces these GCP regulations through periodic inspections of trial sponsors, principal investigators and trial sites. If we or our CROs fail to comply with applicable GCP regulations, the data generated in our clinical trials may be deemed unreliable and the FDA may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA and similar foreign regulators will determine that any of our clinical trials comply or complied with GCP regulations. In addition, our clinical trials must be conducted with product produced under current good manufacturing practices, or cGMPs, regulations, and require a large number of test subjects. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs on commercially reasonable terms, or at all. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, 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 or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or 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 additional revenues could be delayed.

Switching or adding additional CROs can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical 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, results of operations, financial condition and prospects.

**The development of a REMS for Zohydro could cause significant delays in the approval process for Zohydro and will add additional layers of regulatory requirements, including the requirement for a Medication Guide and educational requirements for prescribers and patients, which could significantly impact our ability to commercialize Zohydro and dramatically reduce its market potential.**

The Food and Drug Administration Amendments Act, or FDAAA, added Section 505-1 to the FFDCA. Section 505-1 permits FDA to require a REMS for a drug product to ensure the safe use of the drug. A REMS is a strategic safety program that the FDA requires to ensure that the benefits of a drug outweigh its risks. In determining whether a REMS is necessary, the FDA must consider the size of the population likely to use the drug, the seriousness of the disease or condition to be treated, the expected benefit of the drug, the duration of treatment, the seriousness of known or potential adverse events, and whether the drug is a new molecular entity. If the FDA determines a REMS is necessary, the drug sponsor must agree to the REMS plan at the time of approval. A REMS may be required to include various elements, such as a medication guide or patient package insert, a communication plan to educate health care providers of the drug s risks, limitations on who may prescribe or dispense the drug, requirements that patients enroll in a registry or undergo certain health evaluations or other measures that the FDA deems necessary to assure the safe use of the drug. In addition, the

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REMS must include a timetable to assess the strategy at 18 months, three years and seven years after the strategy s approval.

In February 2009, the FDA informed drug manufacturers that it will require a class-wide REMS for all long-acting and sustained-release opioid drug products. The FDA has since initiated efforts to develop a new standardized REMS for these opioid medications to ensure their safe use. In April 2011, FDA announced that it had finalized the elements of a class-wide REMS for these products. The central component of the opioid REMS program is an education program for prescribers and patients. Specifically, the REMS for these products must include a Medication Guide available for distribution to patients who are dispensed the drug, as well as a number of elements to assure safe use. These elements include training for prescribers who prescribe the drug; information provided to prescribers that prescribers can use to educate patients in the safe use, storage, and disposal of opioids; and information provided to prescribers of the existence of the REMS and the need to successfully complete the necessary training. Moreover, the REMS must include a timetable for submission of assessments that shall be no less frequent than 6 months, 12 months, and annually after the REMS is approved to assess the extent to which the elements to assure safe use are meeting the goals of the REMS and whether the goals or elements should be modified. The FDA expects that manufacturers of long-acting and extended-release opioids work together to provide educational materials as part of a class-wide single shared system to reduce the burden of the REMS on the healthcare system.

An extended-release formulation of *hydrocodone*, such as Zohydro, will be required to have a REMS that contains the elements of the recently-issued class-wide REMS for long-acting and sustained-release opioids. We intend to submit a REMS at the time of the NDA submission for Zohydro. The development of the REMS could cause significant delays in the approval process for Zohydro, and the educational requirements and requirements for a Medication Guide for patients could significantly impact our ability to commercialize Zohydro and dramatically reduce its market potential.

**Our commercialization partner for Sumavel DosePro in the European Union and three other countries, Desitin Arzneimittel GmbH, or Desitin, may not successfully develop, obtain approval for or commercialize Sumavel DosePro in those territories, which may adversely affect our ability to commercialize Sumavel DosePro both inside and outside the United States.**

In March 2008, we entered into a licensing and distribution agreement with Desitin pursuant to which we granted Desitin the exclusive right under our intellectual property rights related to Sumavel DosePro to develop, use, distribute, sell, offer for sale, and import Sumavel DosePro and any potential modified versions of Sumavel DosePro in the European Union, Norway, Switzerland and Turkey. In that regard, Desitin is not obligated under the agreement to pursue regulatory approval or commercialization of Sumavel DosePro in any of these countries except for Germany. Since we will depend on Desitin to develop, obtain regulatory approval for and, if regulatory approval is granted, commercialize Sumavel DosePro in these countries, we will have limited control over the success of Desitin s development, regulatory approval and commercialization efforts. Desitin submitted a Marketing Authorization Application for Sumavel DosePro to the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)) in Germany, the reference member state, through the Decentralized Procedure in October 2009, following completion of a European pivotal bioequivalence trial comparing needle-free Sumavel DosePro to a traditional needle-based autoinjector, Imigran-Inject, the European brand of Imitrex STATdose. In November 2010, Denmark became the first member of the European Union to approve marketing of Sumavel DosePro in that country. Subsequently, Sumavel DosePro has received marketing approval in Germany, Sweden, Norway and the United Kingdom.

Any additional clinical studies Desitin may be required to conduct as part of the regulatory approval process may not corroborate the results of the clinical studies we have conducted or may have adverse results or effects on our ability to maintain regulatory approvals in the United States or obtain them in other countries. In addition, although we believe that the U.S. market represents the largest commercial opportunity for Sumavel DosePro, Desitin may not develop Sumavel DosePro as fast or generate as large of a market as we would like or as the

market may expect and Desitin may not seek to develop, obtain approval for or commercialize Sumavel DosePro in countries for which it has exclusive rights, other than in Germany, where Desitin is required to develop, seek approval for and commercialize Sumavel DosePro. Any failure by Desitin to successfully commercialize Sumavel DosePro or to successfully obtain applicable foreign regulatory approval for Sumavel DosePro would limit our opportunity to receive revenue from the territories licensed to Desitin. Furthermore, negative developments occurring in those territories controlled by Desitin could have a negative impact on physician and patient impressions of our product in the United States and elsewhere.

**Our failure to successfully establish new partnerships with pharmaceutical companies or contract sales organizations to co-promote any additional product candidates that may receive regulatory approval may impair our ability to effectively market and sell such product candidates.**

Major pharmaceutical companies usually employ groups of sales representatives numbering in the thousands to call on the large number of primary care physicians. In connection with the launch of Sumavel DosePro in January 2010 we built a sales and marketing organization to promote Sumavel DosePro in the United States, including a focused sales force of approximately 80 representatives primarily targeting neurologists and other prescribers of migraine medications, including headache clinics and headache specialists. We have initiated activities to expand our sales force in the United States to approximately 95 sales representatives by the end of the third quarter of 2011. In addition, in July 2009, we entered into an exclusive agreement with Astellas under which Sumavel DosePro is also being marketed by Astellas in the United States and promoted primarily to primary care physicians, OB/GYNs, emergency medicine physicians and urologists by approximately 400 Astellas sales representatives. In order to expand the market opportunity for any additional product candidates that receive regulatory approval into the broader primary care physician audiences, we will need to continue to expand our sales and marketing personnel and commercial infrastructure and/or establish partnerships with pharmaceutical companies or contract sales organizations to co-promote such product candidates, particularly if our co-promotion agreement with Astellas is amended, terminated or otherwise restructured. We currently, and on an ongoing basis will have to, compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain sales and marketing personnel. We also face competition in our search for collaborators and potential co-promoters. To the extent we rely on additional third parties to commercialize any product candidates that may receive regulatory approval, we are likely to receive less revenues than if we commercialized these products ourselves. Further, by entering into strategic partnerships or similar arrangements, we may rely in part on such third parties for financial and commercialization resources. Even if we are able to identify suitable partners to assist in the commercialization of our product candidates, they may fail to devote the resources necessary to realize the full commercial potential of our products. In addition, we may lack the financial and managerial resources to increase the size of our sales and marketing organization to adequately commercialize any product candidates that may be approved, and any increase in our sales force would result in an increase in our expenses, which could be significant before we generate revenues from any newly approved product candidate. If we are unable to expand our sales and marketing infrastructure or enter into a third-party arrangement, we would not be able to successfully commercialize any approved products. Even if we are able to expand our sales and marketing personnel or successfully establish partnership arrangements, such sales force and marketing teams may not be successful in commercializing our products, which would adversely affect our ability to generate revenue for such products, which will have a material adverse effect on our business, results of operations, financial condition and prospects.

**Our failure to successfully acquire, develop and market additional product candidates or approved products would impair our ability to grow our business. In that regard, our DosePro delivery system cannot be used with drug formulation volumes greater than 0.5 mL, which will likely limit its use with drugs requiring larger formulation volumes.**

As part of our growth strategy we intend to seek to expand our product pipeline by exploring acquisition or in-licensing opportunities of proven drugs that can be paired with our DosePro needle-free drug delivery system. However, the current version of our DosePro drug delivery system cannot be used with drug formulation

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volumes greater than 0.5 mL. Many marketed and development-stage injectable products, including most biologics, have formulation volumes greater than 0.5 mL and would require reformulation, if possible, to accommodate the approved doses in smaller volumes that are compatible with DosePro. Any reformulation may increase the risk of failure during development, extend the development timelines, increase development costs and add complexity to the regulatory approval process and in some cases reformulation may not be possible. If we are not able to identify additional drug compounds that can be delivered via the current version of our DosePro technology, or if we are unable to successfully develop higher dose versions of this technology, our ability to develop additional product candidates and grow our business would be adversely affected. We will also seek opportunities to out-license the DosePro technology to partners seeking to enhance, differentiate, or extend the life-cycle of their injectable products. If we are unable to secure partnerships with companies that have compounds that can be delivered via the current version of our DosePro technology, or if we are unable to successfully develop higher dose versions of this technology, we will not be able to generate revenues from out-licensing our DosePro technology.

We have initiated early stage design and development of a larger volume, second generation version of our DosePro technology to accommodate drug formulation volumes greater than 0.5 mL, which if successfully developed, would allow for a broader range of potential applications for our technology. However, the full development of such technology will require substantial investment and we may consider entering into a third-party collaboration in order to obtain third-party financing to help fully develop such technology. There is no guarantee that we or any potential future third-party collaborator will be able to successfully develop such a device technology, whether for financial or technical reasons or otherwise.

Furthermore, we intend to in-license, acquire, develop and/or market additional products and product candidates in the areas of pain and central nervous system, or CNS, disorders. For example, in July 2011, we entered into a development and license agreement with Durect Corporation for a proprietary, long-acting, injectable formulation of *risperidone* using Durect s SABER controlled-release formulation technology in combination with our DosePro technology. Durect will be responsible for non-clinical, formulation and chemistry, manufacturing and controls development responsibilities. As a result, we will be dependent on Durect s successful completion of its responsibilities for Relday. In addition, because our internal research and development capabilities are limited, we may be dependent upon other pharmaceutical and biotechnology companies, academic scientists and other researchers to sell or license products or technology to us. The success of this strategy depends partly upon our ability to identify and select promising pharmaceutical product candidates and products, negotiate licensing or acquisition agreements with their current owners and finance these arrangements.

The process of proposing, negotiating and implementing a license or acquisition of a product candidate or approved product is lengthy and complex. Other companies, including some with substantially greater financial, marketing, sales and other resources, may compete with us for the license or acquisition of product candidates and approved products. We have limited resources to identify and execute the acquisition or in-licensing of third-party products, businesses and technologies and integrate them into our current infrastructure. Moreover, we may devote resources to potential acquisitions or licensing opportunities that are never completed, or we may fail to realize the anticipated benefits of such efforts. We may not be able to acquire the rights to additional product candidates, or license the rights to our DosePro technology, on terms that we find acceptable, or at all.

Further, any product candidate that we acquire may require additional development efforts prior to commercial sale, including pre-clinical or clinical testing and approval by the FDA and applicable foreign regulatory authorities. We expect to initiate clinical testing for Relday in patients in schizophrenia in early 2012. We may not be able to obtain necessary approvals to initiate such clinical testing in a timely manner or at all. In addition, all product candidates are prone to risks of failure typical of pharmaceutical product development, including the possibility that a product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities. In addition, we cannot provide assurance that any products that we develop or approved products that we acquire will be manufactured or sold profitably or achieve market acceptance.

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If we are unable to license or acquire additional product candidates or approved products and successfully develop and commercialize them, or if we are otherwise unable to pair our DosePro delivery system with other drugs or out-license the DosePro technology to others, it would likely have a material adverse effect on our business, results of operations, financial condition and prospects.

**We may need to continue to increase the size of our organization, and we may experience difficulties in managing and financing growth.**

We increased our full-time employees from 48 as of October 31, 2009 to 150 as of July 31, 2011. In addition, we have initiated activities to expand our sales force in the United States from approximately 80 sales representatives to approximately 95 sales representatives by the end of the third quarter of 2011 and may need to further increase our sales force, perhaps substantially, if our co-promotion agreement with Astellas is amended, terminated or otherwise restructured. Any such increases in our sales force could substantially increase our expenses. We may need to continue to expand our managerial, operational and other resources in order to grow, manage and fund our existing business. Our management and personnel, systems and facilities currently in place may not be adequate to support this recent and any future growth, and we may be unable to fund the costs and expenses required to increase our necessary headcount and infrastructure. Our need to effectively manage our operations, any future growth and various projects requires that we:

- manage our internal and external commercialization efforts for Sumavel DosePro effectively while carrying out our contractual obligations to Astellas and other third parties and complying with all applicable laws, rules and regulations;
- manage our internal development efforts for Zohydro, Relday and our other product candidates effectively while carrying out our contractual obligations to licensors, collaborators and other third parties and complying with all applicable laws, rules and regulations;
- continue to improve our operational, financial and management controls, reporting systems and procedures; and
- attract and retain sufficient numbers of talented employees.

We may be unable to successfully implement or fund these tasks on a larger scale and, accordingly, may not achieve our commercialization and development goals. In addition, our management may have to divert a disproportionate amount of its attention away from day-to-day activities and towards managing these growth-related activities. Likewise, the anticipated increase in our sales force is expected to increase our expenses and any further increase of our sales force if the Astellas co-promotion agreement is amended, terminated or otherwise restructured may further increase our expenses, perhaps substantially. Our future financial performance and our ability to execute on our business plan will depend, in part, on our ability to effectively manage any future growth and our failure to effectively manage any growth could have a material adverse effect on our business, results of operations, financial condition and prospects.

**If we are unable to attract and retain key personnel, we may not be able to manage our business effectively or develop our product candidates or commercialize our product.**

Our success depends on our continued ability to attract, retain and motivate highly qualified management and key clinical development, regulatory, sales and marketing and other personnel. We are highly dependent on the development, regulatory, commercial and financial expertise of our senior management team. We may not be able to attract or retain qualified management and scientific and clinical personnel in the future due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses, particularly in the areas in Southern and Northern California, where we currently operate. Our industry has experienced a high rate of turnover of management personnel in recent years. If we are not able to attract, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development and commercialization objectives, our ability to raise additional capital and our ability to implement our business strategy. The loss of the services of any members of our senior

management team, especially our Chief Executive Officer, Roger L. Hawley, and President and Chief Operating Officer, Stephen J. Farr, Ph.D., could negatively impact the commercialization of Sumavel DosePro and could delay or prevent the development and commercialization of any other product candidates, including Zohydro or Relday. In addition, under the terms of our amended and restated loan and security agreement with Oxford and SVB, or the amended Oxford/SVB loan agreement, if our Chief Executive Officer, Chief Financial Officer or President resigns, is terminated or is no longer actively involved in his or her current position and is not replaced by a person acceptable to our board of directors within 120 days, an event of default would be triggered under the agreement, and the lenders would be able to demand immediate repayment of all borrowings outstanding under the agreement. Further, if we lose any members of our senior management team, we may not be able to find suitable replacements, and our business may be harmed as a result. In addition to the competition for personnel, our locations in California in particular are characterized by a high cost of living. As such, we could have difficulty attracting experienced personnel to our company and may be required to expend significant financial resources in our employee recruitment and retention efforts.

Although we have employment agreements with each of our executive officers, these agreements are terminable by them at will at any time with or without notice and, therefore, do not provide any assurance that we will be able to retain their services. We do not maintain key man insurance policies on the lives of our senior management team or the lives of any of our other employees. In addition, we have clinical advisors who assist us in formulating our clinical strategies. These advisors are not our employees and may have commitments to, or consulting or advisory contracts with, other entities that may limit their availability to us, or may have arrangements with other companies to assist in the development of products that may compete with ours. If we are unable to attract and retain key personnel, our business, results of operations, financial condition and prospects will be adversely affected.

**We may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.**

From time to time we may consider strategic transactions, such as acquisitions of companies, asset purchases and out-licensing or in-licensing of products, product candidates or technologies. Additional potential transactions that we may consider include a variety of different business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any such transaction may require us to incur non-recurring or other charges, may increase our near and long-term expenditures and may pose significant integration challenges or disrupt our management or business, which could adversely affect our operations and financial results. For example, these transactions may entail numerous operational and financial risks, including:

- exposure to unknown liabilities;
- disruption of our business and diversion of our management s time and attention in order to develop acquired products, product candidates or technologies;
- incurrence of substantial debt or dilutive issuances of equity securities to pay for acquisitions;
- higher than expected acquisition and integration costs;
- write-downs of assets or goodwill or impairment charges;
- increased amortization expenses;
- difficulty and cost in combining the operations and personnel of any acquired businesses with our operations and personnel;

impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and

inability to retain key employees of any acquired businesses.

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Accordingly, although there can be no assurance that we will undertake or successfully complete any transactions of the nature described above, any transactions that we do complete could have a material adverse effect on our business, results of operations, financial condition and prospects.

**If we are unable to achieve and maintain adequate levels of coverage and reimbursement for Sumavel DosePro, Zohydro, if approved, or any of our other product candidates for which we may receive regulatory approval on reasonable pricing terms, their commercial success may be severely hindered.**

Successful sales of our products depend on the availability of adequate coverage and reimbursement from third-party payors. Patients who are prescribed medicine for the treatment of their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their prescription drugs. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and commercial payors is critical to new product acceptance. 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 or may require co-payments that patients find unacceptably high. Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products.

In addition, the market for our products will depend significantly on access to third-party payors drug formularies, or lists of medications for which third-party payors provide coverage and reimbursement. The industry competition to be included in such formularies often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payors may refuse to include a particular branded drug in their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other alternative is available.

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 Sumavel DosePro or any of our other product candidates for which we may receive regulatory approval may not be available or adequate in either the United States or international markets, which could have a material adverse effect on our business, results of operations, financial condition and prospects.

**We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability if our insurance coverage for those claims is inadequate.**

The commercial use of our product and clinical use of our product and product candidates expose us to the risk of product liability claims. This risk exists even if a product is approved for commercial sale by the FDA and manufactured in facilities licensed and regulated by the FDA, such as the case with Sumavel DosePro, or an applicable foreign regulatory authority. Our product and product candidates are designed to affect important bodily functions and processes. Any side effects, manufacturing defects, misuse or abuse associated with Sumavel DosePro or our product candidates could result in injury to a patient or even death. For example, because our DosePro technology is designed to be self-administered by patients, it is possible that a patient could fail to follow instructions and as a result apply a dose in a manner that results in injury. In addition, Zohydro is an opioid pain reliever that contains *hydrocodone*, which is a regulated controlled substance under the Controlled Substances Act of 1970, or CSA, and could result in harm to patients relating to its potential for abuse. In addition, a liability claim may be brought against us even if our product or product candidates merely appear to have caused an injury. Product liability claims may be brought against us by consumers, health care providers,

pharmaceutical companies or others selling or otherwise coming into contact with our product or product candidates, among others. If we cannot successfully defend ourselves against product liability claims we will incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- the inability to commercialize our product or product candidates;
- decreased demand for our product or, if approved, product candidates;
- impairment of our business reputation;
- product recall or withdrawal from the market;
- withdrawal of clinical trial participants;
- costs of related litigation;
- distraction of management s attention from our primary business;
- substantial monetary awards to patients or other claimants; or
- loss of revenues.

We have obtained product liability insurance coverage for commercial product sales and clinical trials with a $10 million per occurrence and a $10 million annual aggregate coverage limit. Our insurance coverage may not be sufficient to cover all of our product liability related expenses or losses and may not cover 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, in sufficient amounts or upon adequate terms to protect us against losses due to product liability. If we determine that it is prudent to increase our product liability coverage based on sales of Sumavel DosePro, approval of Zohydro or otherwise, we may be unable to obtain this increased product liability insurance on commercially reasonable terms or at all. Large judgments have been awarded in class action or individual lawsuits based on drugs that had unanticipated side effects, including side effects that are less severe than those of Sumavel DosePro and our product candidates. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could decrease our cash and have a material adverse affect our business, results of operations, financial condition and prospects.

**We may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.**

Our corporate headquarters and other facilities are located in San Diego and the San Francisco Bay Area, which in the past have both experienced severe earthquakes. We do not carry earthquake insurance. As a result, earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects.

Our enterprise financial systems are located in our San Diego, California headquarters. Our manufacturing resource planning and enterprise quality systems are located in our Emeryville, California facility. If a disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters or our Emeryville facility, that damaged critical infrastructure, such as enterprise financial systems or manufacturing resource planning and enterprise quality systems, or that otherwise disrupted operations at either location, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business

continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business.

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**Our business involves the use of hazardous materials and we and our third-party manufacturers and suppliers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.**

Our research and development activities and our third-party manufacturers and suppliers activities involve the controlled storage, use and disposal of hazardous materials owned by us, including the components of our product and product candidates and other hazardous compounds. We and our manufacturers and suppliers are subject to laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. In some cases, these hazardous materials and various wastes resulting from their use are stored at our and our manufacturers facilities pending use and disposal. We cannot completely eliminate the risk of contamination, which could cause an interruption of our commercialization efforts, research and development efforts and business operations, injury to our employees and others, environmental damage resulting in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials generally comply with the standards prescribed by these laws and regulations, we cannot guarantee that this is the case or eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources. We do not currently carry biological or hazardous waste insurance coverage.

**In connection with the reporting of our financial condition and results of operations, we are required to make estimates and judgments which involve uncertainties, and any significant differences between our estimates and actual results could have an adverse impact on our financial position, results of operations and cash flows.**

Our discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States, or GAAP. The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses and related disclosure of contingent assets and liabilities. In particular, as part of our revenue recognition policy, our estimates of product returns, rebates and chargebacks require our most subjective and complex judgment due to the need to make estimates about matters that are inherently uncertain. Any significant differences between our actual results and our estimates and assumptions could negatively impact our financial position, results of operations and cash flows.

**Changes in accounting standards and their interpretations could adversely affect our operating results.**

GAAP are subject to interpretation by the Financial Accounting Standards Board, the American Institute of Certified Public Accountants, the Securities and Exchange Commission, or SEC, and various other bodies that promulgate and interpret appropriate accounting principles. These principles and related implementation guidelines and interpretations can be highly complex and involve subjective judgments. A change in these principles or interpretations could have a significant effect on our reported financial results, and could affect the reporting of transactions completed before the announcement of a change.

**Fluctuations in the value of the Euro or U.K. pound sterling could negatively impact our results of operations and increase our costs.**

Payments to our material suppliers and contract manufactures are denominated in the Euro and U.K. pound sterling. Our reporting currency is the U.S. dollar and to date all of the revenues generated by sales of Sumavel DosePro have been in U.S. dollars. For the six months ended June 30, 2011, $5.3 million (based on exchange rates as of June 30, 2011) of our materials, contract manufacturing costs and other manufacturing-related costs were denominated in foreign currencies. As a result, we are exposed to foreign exchange risk, and our results of

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operations may be negatively impacted by fluctuations in the exchange rate between the U.S. dollar and the Euro or U.K. pound sterling. A significant appreciation in the Euro or U.K. pound sterling relative to the U.S. dollar will result in higher expenses and cause increases in our net losses. Likewise, to the extent that we generate any revenues denominated in foreign currencies, or become required to make payments in other foreign currencies, fluctuations in the exchange rate between the U.S. dollar and those foreign currencies could also negatively impact our results of operations. We currently have not entered into any foreign currency hedging contracts to reduce the effect of changes in foreign currency exchange rates, and foreign currency hedging is inherently risky and may result in unanticipated losses.

**Our operating results are partially dependent on freight costs and our costs may increase significantly if we are unable to ship and transport finished products efficiently and economically across long distances and international borders.**

Our Sumavel DosePro product is manufactured in Europe and we transport significant volumes of that product across long distances and international borders. As a result, our operating results can be affected by changes in transportation costs. We generally ship our product by air freight, and freight rates can vary significantly due to a large number of factors beyond our control, including changes in fuel prices or general economic conditions. If demand for air freight should increase substantially, it could make it difficult for us to procure transportation space at prices we consider acceptable.

Because our products must cross international borders, we are subject to risk of delay due to customs inspection, if our documentation does not comply with customs rules and regulations or for similar reasons. In addition, any increases in customs duties or tariffs, as a result of changes to existing trade agreements between countries or otherwise, could increase our costs or the final cost of our products to our customers or increase our expenses. The laws governing customs and tariffs in many countries are complex, subject to many interpretations and often includes substantial penalties for noncompliance.

### *Risks Related to Our Financial Position and Capital Requirements*

**We have never generated net income or positive cash flow from operations and are dependent upon external sources of financing to fund our business and development.**

We launched our only approved product, Sumavel DosePro, in January 2010. Without a long history of sales, we may not accurately predict future sales, and we may never be able to significantly increase these sales, especially in light of our reliance on our partnership with Astellas to co-promote Sumavel DosePro. We have financed our operations almost exclusively through the proceeds from the issuance of our common and preferred stock, including the proceeds from our initial public offering completed in November 2010, and debt, and have incurred losses and negative cash flow from operations in each year since our inception. Our net loss applicable to common stockholders was $45.6 million in 2008, $45.9 million in 2009, $73.6 million in 2010 and $38.2 million for the six months ended June 30, 2011, and our cash used in operating activities was $41.3 million in 2008, $32.4 million in 2009, $72.0 million in 2010 and $40.5 million for the six months ended June 30, 2011. As of June 30, 2011, we had an accumulated deficit of $236.3 million. These losses and negative cash flow from operations have had a material adverse effect on our stockholders equity and working capital. Further, despite the revenues from Sumavel DosePro, we expect our losses to continue for at least the next several years as a result of the development expenses incurred in connection with our ongoing clinical development for Zohydro, the initiation of clinical development for Relday and the cost of the sales and marketing expense associated with Sumavel DosePro. In addition, if we obtain regulatory approval for Zohydro or any of our other product candidates, we expect to incur significant sales, marketing and manufacturing expenses as well as continued development expenses. As a result, we are and will remain dependent upon external sources of financing to finance our business and the development and commercialization of our approved product and product candidates. We cannot assure you that debt or equity financing will be available to us in amounts, at times or on terms that will be acceptable to us, or at all. Any shortfall

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in our cash resources could require that we delay or abandon certain development and commercialization activities and could otherwise have a material adverse effect on our business, results of operations, financial condition and prospects.

**Our independent registered public accounting firm has expressed substantial doubt as to our ability to continue as a going concern.**

In its report accompanying our audited consolidated financial statements for the year ended December 31, 2010, our independent registered public accounting firm included an explanatory paragraph stating that our recurring losses from operations and lack of sufficient working capital raise substantial doubt as to our ability to continue as a going concern. A going concern opinion could impair our ability to finance our operations through the sale of debt or equity securities or commercial bank loans. Our ability to continue as a going concern will depend, in large part, on our ability to generate positive cash flow from operations and obtain additional financing, neither of which is certain. If we are unable to achieve these goals, our business would be jeopardized and we may not be able to continue operations and may have to liquidate our assets and may receive less than the value at which those assets are carried on our consolidated financial statements, and it is likely that investors will lose all or a part of their investment. In addition, our amended Oxford/SVB loan agreement includes a covenant that the audit reports accompanying our annual consolidated financial statements for fiscal year 2010 and thereafter not include a going concern qualification and any breach of that covenant would permit the lenders to demand immediate repayment of all loans outstanding under the agreement and to seize and sell the collateral pledged to secure these loans. In March 2011, we obtained a waiver from Oxford and SVB for the breach caused by the receipt of the 2010 audit report from our independent registered public accounting firm which included a going concern qualification.

**Our level of indebtedness could adversely affect our ability to raise additional capital to fund our operations, limit our ability to react to changes in the economy or our industry and prevent us from meeting our obligations.**

As of June 30, 2011, the principal amount of our total indebtedness was approximately $28.7 million. In July 2011, we completed the royalty financing transaction with Cowen Royalty, which increased our total indebtedness by an additional $30.0 million. We have and expect to continue to make borrowings under our $10.0 million revolving credit facility to fund working capital and other cash needs and we may incur substantial additional indebtedness in the future, both under our $10.0 million revolving credit facility and any other debt facilities we may enter into in the future. Our outstanding debt and related debt service obligations could have important adverse consequences to us, including:

- heightening our vulnerability to downturns in our business or our industry or the general economy and restricting us from making improvements or acquisitions, or exploring business opportunities;
- requiring a significant portion of our available cash to be dedicated to the payment of principal and interest on our indebtedness, therefore reducing our ability to use our available cash to fund our operations, capital expenditures and future business opportunities;
- limiting our ability to obtain additional financing for working capital, capital expenditures, debt service requirements, acquisitions and general corporate or other purposes;
- limiting our ability to adjust to changing market conditions and placing us at a competitive disadvantage compared to our competitors who have greater capital resources; and
- subjecting us to financial and other restrictive covenants in our debt instruments, the failure with which to comply could result in an event of default under the applicable debt instrument that allows the lender to demand immediate repayment of the related debt.

If our cash flows and capital resources are insufficient to fund our debt service obligations, we may be forced to reduce or delay product development, sales and marketing, capital and other expenditures, sell assets,

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seek additional capital or restructure or refinance our indebtedness. These alternative measures may not be successful and may not permit us to meet our scheduled debt service obligations. This risk is increased by the fact that borrowings under our credit facility with Oxford and SVB bear interest at a variable rates, exposing us to the risk that the amount of cash required to pay interest will increase to the extent that market interest rates increase.

**Our debt instruments contain a number of financial covenants and other provisions, including a requirement that we attain specified future levels of revenues, which, if violated, could result in the immediate acceleration of our outstanding indebtedness.**

Our amended Oxford/SVB loan agreement includes covenants requiring, among other things, that (1) we achieve, as of the last day of each month, measured on a trailing three-month basis, actual revenues of at least a specified percentage of our projected revenue as provided to Oxford and SVB in the event we fail to maintain a liquidity ratio (defined, in general, as the ratio of (a) cash and cash equivalents deposited with SVB plus unused borrowing capacity under that agreement to (b) all debt, capital lease obligations and contingent obligations owed to the lenders) of 1.25 to 1.00, and (2) the audit report accompanying our year-end consolidated financial statements for fiscal year 2010 and thereafter not include a going concern qualification. As discussed above, the audit report from our independent registered public accounting firm accompanying our 2010 consolidated financial statements includes a going concern qualification and, as a result, our results of operations and financial condition will have to improve to a point where our auditors can deliver their audit report without this qualification in order to avoid a future breach of this covenant. In addition to certain other customary restrictive covenants, the amended Oxford/SVB loan agreement prohibits us, subject to certain customary exceptions, from (1) incurring any debt other than, among other things, debt under the amended loan agreement and other debt permitted thereunder, (2) entering into sale and leaseback transactions, (3) having a change in our management such that our Chief Executive Officer, Chief Financial Officer or President resigns, is terminated or is no longer actively involved in our management in his or her current position and is not replaced with a person acceptable to our board of directors within 120 days, (4) entering into mergers with, or acquisitions of all or substantially all the assets of, another entity with a value in excess of $100,000 or a change in control of our company (as defined in the amended Oxford/SVB loan agreement), (5) permitting liens to exist on our properties and (6) making distributions and investments. The amended Oxford/SVB loan agreement provides that an event of default will occur if, among other customary events of default, (1) there is a material adverse change in our business, operations or condition (financial or otherwise) or material impairment in the prospects of us repaying any portion of our obligations under the agreement, (2) there is a material impairment in the value of the collateral pledged to secure our obligations under the agreement or in the perfection or priority of such collateral, (3) we default in the payment of any amount payable under the agreement when due, or (4) we breach any covenant in the agreement (subject to a grace period in some cases). In 2009, 2010 and 2011, we were required to obtain amendments or waivers under our credit facilities, and we may in the future need to obtain waivers or amendments under our credit facilities or other debt instruments, in order to avoid a breach or default, particularly if our business deteriorates or does not perform in accordance with our expectations. Our amended Oxford/SVB loan agreement is secured by substantially all of our personal property (including, among other things, accounts receivable, equipment, inventory, contract rights or rights to payment of money, license agreements, general intangibles, including all intellectual property, and cash).

In connection with the Cowen Royalty transaction, we paid off all outstanding amounts under our prior loan and security agreement with GE Capital and terminated that agreement.

Pursuant to the terms of our $30.0 million royalty financing agreement with Cowen Royalty, or the Cowen Royalty financing agreement, we are required to make payments to Cowen Royalty of $10.0 million on each of January 31, 2015, 2016 and 2017, as well as fixed percentages of amounts received or recorded from our products sales.

Our obligations under the Cowen Royalty financing agreement are secured under a security agreement by a second priority security interest (junior to the security interest of Oxford and SVB under the amended

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Oxford/SVB loan agreement) in substantially all of our personal property (including, among other things, accounts receivable, equipment, inventory, contract rights or rights to payment of money, license agreements, general intangibles, including all intellectual property, and cash), to the extent necessary or used to commercialize our products. The security interest will be extinguished once the aggregate payments made by us to Cowen Royalty equals $75.0 million. If we are unable to repay the indebtedness or other amounts when due, whether at maturity, upon termination or if declared due and payable by the lender following a default, the lenders under the amended Oxford/SVB loan agreement and Cowen Royalty under the terms of the Cowen Royalty financing agreement generally have the right to seize and sell the collateral securing the indebtedness, and other amounts owing to it thereunder.

We have the option to terminate the Cowen Royalty financing agreement at our election prior to the termination date in connection with a change of control of our company, as defined in the Cowen Royalty financing agreement, upon the payment of a base amount of $52.5 million, or, if higher, an amount that generates a 19% internal rate of return on the borrowed amount as of the date of prepayment, in each case reduced by the revenue interest and fixed payments received by Cowen Royalty up to the date of such prepayment.

In addition, Cowen Royalty has the option to terminate the Cowen Royalty financing agreement at its election in connection with a change of control of our company, as defined in the Cowen Royalty financing agreement, the sale of all or substantially all of our assets (which includes the sale, transfer, assignment or licensing of our rights in the United States to either Sumavel DosePro or Zohydro), a bankruptcy event with respect to us or an event of default, as defined in the Cowen Royalty financing agreement, occurring thereunder. Upon such a termination by Cowen Royalty prior to the maturity date specified in the Cowen Royalty financing agreement, we are obligated to make a payment of a base amount of $45.0 million, or, if higher, an amount that generates a 17% internal rate of return on the borrowed amount as of the date of prepayment, in each case reduced by the revenue interests and fixed payments received by Cowen Royalty up to the date of prepayment. If we were required to accelerate the payment of these amounts upon a default, we would be required to find an alternate source of capital from which to draw funds and there can be no assurances that we would be able to do so on terms acceptable to us, or at all.

There can be no assurance that we will not breach the covenants or other terms of, or that an event of default or termination event will not occur under, our credit facilities or any other debt instruments and, if a breach or event of default or termination event occurs, there can be no assurance that we will be able to obtain necessary waivers or amendments from the lenders or refinance the related indebtedness or other amounts due and payable on terms we find acceptable, or at all.

As a result, any failure to pay our debt service obligations when due, any breach or default of our covenants or other obligations under debt instruments, or any other event that allows any lender to demand immediate repayment of borrowings or termination payments, could have a material adverse effect on our business, results of operations, financial condition and prospects. Furthermore, the arrangement under the Cowen Royalty financing agreement may make us significantly less attractive to potential acquirors, and in the event that we exercised our change of control pay-off option in order to carry out a change of control, the payment of such funds out of our available cash or acquisition proceeds would reduce acquisition proceeds for our stockholders.

**Our results of operations and liquidity needs could be materially negatively affected by market fluctuations and economic downturn.**

Our results of operations and liquidity could be materially negatively affected by economic conditions generally, both in the United States and elsewhere around the world. Domestic and international equity and debt markets have experienced and may continue to experience heightened volatility and turmoil based on domestic and international economic conditions and concerns. In the event these economic conditions and concerns continue or worsen and the markets continue to remain volatile, our results of operations and liquidity could be adversely affected by those factors in many ways, including making it more difficult for us to raise funds if necessary, and our stock price may decline. In addition, we maintain significant amounts of cash and cash

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equivalents at one or more financial institutions that are not federally insured. If economic instability continues, we cannot provide assurance that we will not experience losses on these investments.

**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.**

We may raise additional funds through public or private equity offerings, debt financings, receivables or royalty financings or corporate collaboration and licensing arrangements. To the extent that we raise additional capital by issuing equity securities or convertible debt, your ownership interest in us will be diluted. Debt financing typically contains covenants that restrict operating activities. Our obligations under the amended Oxford/SVB loan agreement are secured by substantially all of our personal property (including, among other things, accounts receivable, equipment, inventory, contract rights or rights to payment of money, license agreements, general intangibles, including all intellectual property, and cash). Our obligations under the Cowen Royalty financing agreement are secured under a security agreement by a second priority security interest (junior to the security interest of Oxford and SVB under the amended Oxford/SVB loan agreement) in substantially all of our personal property (including, among other things, accounts receivable, equipment, inventory, contract rights or rights to payment of money, license agreements, general intangibles, including all intellectual property, and cash). The security interest will be extinguished once the aggregate payments made by us to Cowen Royalty equals $75.0 million.

Each of the amended Oxford/SVB loan agreement and the Cowen Royalty financing agreement contains provisions which allow such lenders to accelerate the debt and seize and sell the collateral if, among other things, we fail to pay principal or interest when due or breach our obligations under the agreements or if a material adverse change in our business or any other event of default occurs. Any future debt financing we enter into may involve more onerous covenants that restrict our operations, may be secured by some or all of our assets, and will likely allow the lenders to accelerate the debt and seize and sell any collateral following a default. Our obligations under our outstanding debt agreements or any future debt financing will need to be repaid, which creates additional financial risk for our company, particularly if our business or prevailing financial market conditions are not conducive to paying-off or refinancing our outstanding debt obligations.

If we raise additional funds through collaboration, licensing or other similar arrangements, it may be necessary to relinquish potentially valuable rights to our current product or product candidates or proprietary technologies, or grant licenses on terms that are not favorable to us. If adequate funds are not available, our ability to achieve profitability or to respond to competitive pressures would be significantly limited and we may be required to delay, significantly curtail or eliminate the commercialization and development of our product or product candidates.

**Our ability to utilize our net operating loss and research and development income tax credit carryforwards may be limited.**

Under Section 382 of the Internal Revenue Code of 1986, as amended, or the IRC, substantial changes in our ownership may limit the amount of net operating loss and research and development income tax credit carryforwards (collectively, tax attributes) that could be utilized annually in the future to offset taxable income, if any. Specifically, this limitation may arise in the event of a cumulative change in ownership of our company of more than 50% within a three-year period as determined under the IRC, which we refer to as an ownership change. Any such annual limitation may significantly reduce the utilization of these tax attributes before they expire. Prior to our initial public offering in November 2010, we performed an IRC Section 382 and 383 analysis and determined that we had one ownership change, which occurred in August 2006 upon the issuance of convertible preferred stock. As a result of this ownership change, our ability to use our then existing tax attributes was limited. We expect the issuance of common stock in this offering, together with the issuance of common stock in our initial public offering and certain other transactions involving our common stock, will result in an

additional ownership change, which will further limit the amount of the tax attributes we may use to offset future taxable income, if any. In addition, any future equity financing transactions, private placements and other transactions that occur within the specified three-year period may trigger additional ownership changes, which could further limit our use of such tax attributes. Any such limitations, whether as the result of this offering, prior or future offerings of our common stock or sales of common stock by our existing stockholders, could have an adverse effect on our consolidated results of operations in future years.

***Risks Related to Regulation of our Product and Product Candidates***

**Our currently marketed product, Sumavel DosePro, is and any of our other product candidates that receive regulatory approval will be subject to ongoing and continued regulatory review, which may result in significant expense and limit our ability to commercialize such products.**

Even after we achieve U.S. regulatory approval for a product, the FDA may still impose significant restrictions on the approved indicated uses for which the product may be marketed or on the conditions of approval. For example, a product s approval may contain requirements for potentially costly post-approval studies and surveillance, including Phase 4 clinical trials, to monitor the safety and efficacy of the product. We will also be subject to ongoing FDA obligations and continued regulatory review with respect to the manufacturing, processing, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs and with GCPs and good laboratory practices, which are regulations and guidelines enforced by the FDA for all of our products in clinical and pre-clinical development, and for any clinical trials that we conduct post-approval. To the extent that a product is approved for sale in other countries, we may be subject to similar restrictions and requirements imposed by laws and government regulators in those countries.

In the case of Zohydro and any other product candidates or products containing controlled substances, we and our contract manufacturers will also be subject to ongoing DEA regulatory obligations, including, among other things, annual registration renewal, security, recordkeeping, theft and loss reporting, periodic inspection and annual quota allotments for the raw material for commercial production of our products. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP regulations, QSR requirements for medical device components or similar requirements, if applicable. If we or a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where, or processes by which, the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturer or us, including requiring product recall, notice to physicians, withdrawal of the product from the market or suspension of manufacturing. In that regard, because all of our contract manufacturers for Sumavel DosePro are located outside the United States, they may be subject to foreign laws and regulations governing the manufacture of drugs and devices, and any failure by them to comply with those laws and regulations may delay or interrupt supplies of our product.

If we, our product or product candidates or the manufacturing facilities for our product or product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- impose restrictions on the marketing or manufacturing of the product, suspend or withdraw product approvals or revoke necessary licenses;

- issue warning letters, show cause notices or untitled letters describing alleged violations, which may be publicly available;