

ZOGENIX, INC.
Form 10-K
March 12, 2012
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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

Form 10-K

(Mark One)

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2011

or

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission file number: 001-34962

Zogenix, Inc.

(Exact Name of Registrant as Specified in its Charter)

Delaware

20-5300780

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(State or Other Jurisdiction of

(I.R.S. Employer

Incorporation or Organization)

Identification No.)

12671 High Bluff Drive, Suite 200

San Diego, California
(Address of Principal Executive Offices)

92130
(Zip Code)

858-259-1165

(Registrant's Telephone Number, Including Area Code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock, par value \$0.001 per share	The NASDAQ Global Market

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer or a smaller reporting company. See definitions of "large accelerated filer", "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ☐ Accelerated filer ☐ Non-accelerated filer ☒ Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act of 1934). Yes ☐ No ☒

As of June 30, 2011, the aggregate market value of the registrant's common stock held by non-affiliates of the registrant was approximately \$54,202,873, based on the closing price of the registrant's common stock on the Nasdaq Global Market of \$4.01 per share.

The number of outstanding shares of the registrant's common stock, par value \$0.001 per share, as of March 1, 2012 was 65,368,792.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement to be filed with the Securities and Exchange Commission pursuant to Regulation 14A in connection with the registrant's 2012 Annual Meeting of Stockholders, which will be filed subsequent to the date hereof, are incorporated by reference into Part III of this Form 10-K. Such proxy statement will be filed with the Securities and Exchange Commission not later than 120 days following the end of the registrant's fiscal year ended December 31, 2011.

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ZOGENIX, INC.

FORM 10-K ANNUAL REPORT

For the Fiscal Year Ended December 31, 2011

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PART I

Forward-Looking Statements and Market Data

This Annual Report on Form 10-K and the information incorporated herein by reference contain forward-looking statements that involve substantial risks and uncertainties. These forward looking statement include, but are not limited to, statements about:

our ability to maintain and increase market demand for, and sales of, Sumavel DosePro;

our ability to successfully execute our sales and marketing strategy for the commercialization of Sumavel DosePro;

the progress and timing of clinical trials for our product candidates;

the timing of a New Drug Application submission to the U.S. Food and Drug Administration, or the FDA, for Zohydro;

the timing of submissions to, and decisions made by, the FDA and other regulatory agencies, including foreign regulatory agencies, and demonstrating the safety and efficacy of Zohydro or any other product candidates to the satisfaction of the FDA and such other agencies;

adverse side effects or inadequate therapeutic efficacy of Sumavel DosePro that could result in product recalls, market withdrawals or product liability claims;

the safety and efficacy of Zohydro and our other product candidate;

the market potential for migraine treatments, and our ability to compete within that market;

the goals of our development activities and estimates of the potential markets for our product candidates, and our ability to compete within those markets;

estimates of the capacity of manufacturing and other facilities to support our product and product candidates;

our ability to ensure adequate and continued supply of Sumavel DosePro to successfully meet anticipated market demand;

our expected third party research and development costs for Zohydro remaining through our NDA filing with and potential regulatory approval from the FDA;

our and our licensors ability to obtain, maintain and successfully enforce adequate patent and other intellectual property protection of our products and product candidates and the ability to operate our business without infringing the intellectual property rights of

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others;

our ability to obtain and maintain adequate levels of coverage and reimbursement from third-party payors for Sumavel DosePro or any of our other product candidates that may be approved for sale, the extent of such coverage and reimbursement and the willingness of third-party payors to pay for our products versus less expensive therapies;

the impact of healthcare reform legislation; and

projected cash needs and our expected future revenues, operations and expenditures.

The forward-looking statements are contained principally in the sections entitled Risk Factors, Management's Discussion and Analysis of Financial Condition and Results of Operations and Business. In some cases, you can identify forward-looking statements by the following words: may, will, could, would, should, expect, intend, plan, anticipate, believe, estimate, predict, project, potential, or variations of these terms or other comparable terminology, although not all forward-looking statements contain these words. These statements relate to future events or our future

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financial performance or condition and involve known and unknown risks, uncertainties and other factors that could cause our actual results, levels of activity, performance or achievement to differ materially from those expressed or implied by these forward-looking statements. We discuss many of these risks, uncertainties and other factors in this Annual Report on Form 10-K in greater detail under the heading Item 1A Risk Factors.

Given these risks, uncertainties and other factors, we urge you not to place undue reliance on these forward-looking statements, which speak only as of the date of this report. You should read this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. For all forward-looking statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995. We undertake no obligation to revise or update publicly any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

This Annual Report on Form 10-K also contains estimates, projections and other information concerning our industry, our business, and the markets for Sumavel DosePro, Zohydro, Relday and other drugs, including data regarding the estimated size of those markets, their projected growth rates, the incidence of certain medical conditions, statements that certain drugs, classes of drugs or dosages are the most widely prescribed in the United States or other markets, the perceptions and preferences of patients and physicians regarding certain therapies and other prescription, prescriber and patient data, as well as data regarding market research, estimates and forecasts prepared by our management. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources. In particular, unless otherwise specified, all prescription, prescriber and patient data in this Annual Report on Form 10-K is from Wolters Kluwer Pharma Solutions, Source® Pharmaceutical Audit Suite (PHAST) Institution/Prescription, Source® PHAST Prescription, Source® Prescriber or Source® Dynamic Claims. In some cases, we do not expressly refer to the sources from which this data is derived. In that regard, when we refer to one or more sources of this type of data in any paragraph, you should assume that other data of this type appearing in the same paragraph is derived from the same sources, unless otherwise expressly stated or the context otherwise requires.

DosePro®, Intraject®, Relday®, Sumavel®, Zogenix® and Zohydro® are our trademarks. All other trademarks, trade names and service marks appearing in this Annual Report on Form 10-K are the property of their respective owners. Use or display by us of other parties' trademarks, trade dress or products is not intended to and does not imply a relationship with, or endorsements or sponsorship of, us by the trademark or trade dress owner.

Unless the context requires otherwise, references in this Annual Report on Form 10-K to Zogenix, we, us and our refer to Zogenix, Inc., including, as of June 7, 2010, its consolidated subsidiary.

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Item 1. Business

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 (*hydrocodone* bitartrate, formerly ZX002) is a 12-hour extended-release formulation of *hydrocodone* without acetaminophen for the treatment of moderate to severe chronic pain requiring around-the-clock opioid therapy. We completed Phase 3 development of Zohydro in 2011, and we expect to submit the New Drug Application, or NDA, for Zohydro to the FDA early in the second quarter of 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, or NHF, press release. Triptans are the class of drugs most often prescribed for treating migraines. In the United States in the 12 months ended December 2011, triptans generated sales of approximately \$3.9 billion and *sumatriptan*, including branded and generic forms, represented the largest market share of the seven approved triptans, with sales of approximately \$2.3 billion, according to Wolters Kluwer Pharma Solutions (Source® PHAST Institution/Prescription).

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 116 professionals. Our field sales force of approximately 95 representatives has historically been complemented by our collaboration with Astellas and approximately 400 of its sales representatives. The target audience for Astellas sales effort was primarily comprised historically of prescribers classified as primary care physicians (including internal medicine, family practice and general practice), OB/GYNs, emergency medicine physicians and urologists, or collectively the Astellas Segment. The target audience for our sales effort was primarily comprised historically of neurologists and other prescribers of migraine medicines who fall outside the Astellas Segment. In addition, our representatives have historically had the right to call upon a specified number of key prescribers within the Astellas Segment and Astellas representatives historically had the right to call upon a specified number of neurologists.

Our collaboration with Astellas will terminate on March 31, 2012, at which time we will assume full responsibility for the commercialization of Sumavel DosePro. During the fourth quarter of 2011, the Zogenix sales force contributed approximately 73% of our Sumavel DosePro unit demand volume, including jointly called-on physicians, with the remaining unit demand volume derived by Astellas.

We increased our sales force from approximately 80 to approximately 95 professionals in 2011. Based on third-party data, approximately 86% of the prescription demand in the Astellas Segment was concentrated to a population of approximately 500 physicians, which we believe our sales force will be able to support after our transition plan, utilizing our Phase IV data, toolkits and other promotional activities. As such, we do not expect

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that all of the prescription demand contributed by the Astellas sales force will be foregone as a result of the early termination of the co-promotion agreement. However, in the event we are unsuccessful in transitioning the Astellas Segment to our sales force, our net product sales and financial results could be negatively impacted.

We have already begun to assume responsibility from Astellas for marketing Sumavel DosePro to selected high-prescribing primary care physicians and other Astellas-targeted physicians and professionals within the Astellas Segment pursuant to a promotion transition plan. We are currently evaluating potential co-promotion partners who could complement our sales force efforts for the commercial sale of Sumavel DosePro. We also have entered into a partnership for Sumavel DosePro with Desitin Arzneimittel GmbH, or Desitin, to accelerate development and regulatory approvals in Europe and further enhance the global commercial potential of Sumavel DosePro.

Sumavel DosePro has demonstrated significant quarterly growth in total prescriptions since its launch in January 2010. For the twelve months ended December 31, 2011, we recognized \$30.4 million in net product revenue from sales of Sumavel DosePro, represented by more than 71,779 aggregate dispensed prescriptions (Source[®] PHAST Prescription, January 2011 – December 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 81% since launch (Source[®] Dynamic Claims January 2011 – December 2011).

We believe our lead product candidate, Zohydro, has the potential to be an important therapeutic alternative to existing *hydrocodone* products, including the branded products Vicodin, Norco, Lorcet, Lortab and their generic equivalents, which contain the analgesic combination ingredient *acetaminophen* and, if taken in high quantities over time, can lead to serious side effects such as liver toxicity. Zohydro utilizes the SODAS Technology, Alkermes plc's proprietary multiparticulate drug delivery system that allows the development of customized extended-release profiles and serves to enhance the release profile of *hydrocodone* in Zohydro. We believe these release properties have the potential to provide longer lasting and more consistent pain relief with fewer daily doses than the commercially available formulations of *hydrocodone*. As a result of its unique single-entity extended-release profile, we believe Zohydro has the potential to generate sales from both patients who use immediate-release products on a chronic basis and patients already using extended-release products in the prescription opioid market. We in-licensed exclusive U.S. rights to Zohydro from Alkermes 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 \$14.2 billion for the year ended December 2011, based on average wholesale price, on approximately 217 million prescriptions. During the same period, existing *hydrocodone* products, the most commonly prescribed pharmaceutical products in the United States, generated \$3.5 billion in sales on approximately 134.6 million prescriptions. (Source[®] PHAST Prescription). 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'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 Corporation. *Risperidone* is used to treat the symptoms of schizophrenia and bipolar disorder in adults and

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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 \$1.58 billion in 2011 with 72% of net sales outside of the United States, 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 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 2012 following the filing of an investigational new drug, or IND, application. We completed a pre-IND meeting with the FDA in December 2009.

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 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. Total U.S. net product revenue from sales of Sumavel DosePro through December 31, 2011 was \$30.4 million. We continue to leverage our established commercial infrastructure and our investment in sales and marketing programs to help increase awareness and adoption of, and access to, Sumavel DosePro with prescribers, patients, third-party payors, pharmacists and employers. Our co-promotion collaboration with Astellas will terminate in March 2012, and beginning in the second quarter of 2012, we will assume full responsibility for the continued commercialization of Sumavel DosePro, with a focus on headache specialists, neurologists and primary care physicians in the United States. We are currently evaluating potential co-promotion partners who could complement our sales force efforts.

Developing and commercializing Zohydro for the treatment of moderate to severe chronic pain. We completed our Phase 3 clinical program for Zohydro which was focused on establishing safety and efficacy of extended-release single-entity *hydrocodone* to treat moderate to severe chronic pain in patients requiring around-the-clock opioid therapy. We reported top-line results from our pivotal Phase 3 efficacy trial in August 2011 and expect to submit an NDA with the FDA early in the second quarter of 2012. If we receive FDA approval, we intend to consider co-promotion and other partnering opportunities for Zohydro, and an expansion of our sales and marketing infrastructure, including expanding our field sales force to between 170 and 220 representatives, to both launch Zohydro and continue to support Sumavel DosePro.

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Expanding our product pipeline in CNS disorders and/or pain, including through the development of our newest product candidate, Relday. We are utilizing our proprietary DosePro technology to add to our internal product pipeline. We plan to initiate clinical development of Relday in 2012 and are also evaluating the market potential, formulation requirements and clinical development pathway of an additional CNS compound that could be paired with DosePro to enhance its commercial attractiveness.

Out-licensing our proprietary DosePro technology. We are evaluating opportunities to out-license the DosePro needle-free drug delivery technology to partners seeking to enhance, differentiate or extend the life-cycle of their injectable products. These opportunities include biologics and small molecules that are both currently marketed products and development stage product candidates.

Securing rights to complementary products and product candidates that address CNS disorders and/or pain. To strategically leverage our commercial resources and generate additional revenue, we are seeking third-party co-promotion opportunities. In the future, we will also consider in-licensing or acquisition opportunities with a focus on product candidates that utilize novel technologies to improve the profile of existing compounds for CNS disorders and/or pain.

Our Product and Product Candidates

Sumavel DosePro for the Acute Treatment of Migraine and Cluster Headache

We launched the commercial sale of Sumavel DosePro in the United States in January 2010 with our original co-promotion partner, Astellas. Our Sumavel DosePro (*sumatriptan* injection) Needle-free Delivery System offers fast-acting, easy-to-use subcutaneous administration of *sumatriptan* for the acute treatment of migraine and cluster headache. Sumavel DosePro utilizes our proprietary DosePro system which enables patients to self-administer subcutaneous *sumatriptan* in three easy steps. 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. 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 Market

Migraine is a chronic neurovascular disorder characterized by episodic attacks. According to the National Headache Foundation, more than 29.5 million people in the United States suffer from migraines, with women three times more likely to suffer migraines than men. Migraine attacks typically manifest themselves as moderate to severe headache pain, with symptoms that often include nausea and/or vomiting and abnormal sensitivity to light and sound. Migraines can severely limit the normal daily functioning of patients, who may seek dark, quiet surroundings until the episode has passed. According to the International Headache Society, the duration of untreated or unsuccessfully treated migraine episodes ranges from four to 72 hours. According to data published in the March 2002 issue of *Neurology*, 63% of patients suffer one or more attacks per month, 25% of patients have one or more attacks per week and the median duration of an untreated migraine is approximately 24 hours. Overall, the cost burden of migraine in the United States was estimated by Thomson Medstat in June 2006 to approach \$25 billion annually, including \$12.7 billion in direct medical costs and \$12 billion in indirect costs related to employee absenteeism, short-term disability and workers' compensation costs to employers.

Cluster headaches are characterized by groups or clusters of debilitating headaches lasting weeks or months, then disappearing for months or years. This type of headache affects an estimated one million sufferers in the United States, and approximately 90% of these sufferers are male, according to the NHF website. Due to the severe nature of cluster headache, patients are commonly treated with prescription medication.

Acute therapies dominate the prescription migraine and cluster headache market and are used during intermittent attacks. The goals of acute therapy are to stop the attack quickly and consistently, minimize the use of backup and rescue medications, enhance self-care and restore the patient's ability to function, use the least amount of medication and limit adverse side effects.

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A major advancement in the acute treatment of migraine began in 1993 with the launch of the first triptan, *sumatriptan* injection (Imitrex), in the United States. All triptans are selective agonists for the 5-HT_{1B} and 5-HT_{1D} receptors. Triptans presumably exert their antimigrainous effect through binding to vascular 5-HT₁ receptors, which have been shown to be present on both the human basilar artery, one of the major arteries that supplies blood to the brain, and the outermost membrane covering the brain. Triptans activate these receptors to cause vasoconstriction, an action in humans correlated with the relief of migraine and cluster headache. *Sumatriptan* was subsequently joined by other drugs in the triptan class. By the year 2003, there were seven approved triptans in the United States with a focus on oral delivery forms to offer convenience of dosing for migraine patients. *Sumatriptan* is the only triptan available in oral, nasal and subcutaneous forms, each of which has different pharmacokinetic properties.

Triptans remain the drugs of choice and the most often prescribed therapy for the acute treatment of migraine and cluster headache. The following table provides a breakdown of the U.S. triptan market, including sales and doses prescribed for oral (tablets and melts), nasal and injectable forms of triptan for the 12 months ended December 2011.

U.S. Triptan Market**(12 months ended December 2011)**

Triptan Form	Sales (millions)	\$ Share	Doses (millions)	Dose Share
Oral Tablet	\$ 3,032	77.80%	119.4	85.6%
Oral Melt	407	10.4	13.7	9.8
Nasal	118	3.0	2.9	2.1
Injectable	341	8.8	3.5	2.5
Total	\$ 3,898	100%	139.5	100%

Source [®] PHAST Institution/Prescription.

As indicated in the prior table, the triptan market is dominated by oral dosage forms (tablets and melts), with approximately 95% of U.S. triptan doses taken as oral formulations and the remaining 5% split between injectable and nasal formulations. Branded and generic *sumatriptan*, in all dosage forms, remains the most prescribed triptan molecule with sales of approximately \$2.3 billion (60% dollar share of the triptan market). Of that amount, the injectable forms of sumatriptan accounted for \$341 million. By comparison, ergotamine agents, another class of drugs used for the acute treatment of migraine, including injectable DHE and Migranal, accounted for \$74 million in sales in the United States during the same 12-month period. (Source [®] PHAST Institution/Prescription). Sumatriptan is the only triptan available to patients in the injectable form and, with the exception of Sumavel DosePro, all other forms of injectable sumatriptan make use of needle-based injections for their administration.

In five major European countries (France, Germany, Italy, Spain and the United Kingdom), triptans generated total sales of approximately \$550 million for the 12 months ended June 2007, according to average wholesale price data published by IMS Health MIDAS. Of that \$550 million, the European equivalent of Imitrex, Imigran, represented sales of approximately \$148 million, of which the injectable form accounted for approximately \$35 million.

Migraine Market Dynamics

The type of migraine treatment utilized by patients often depends on the frequency and severity of the headache, its speed of onset and previous response to medication. In published studies, migraine sufferers most often cite faster onset of pain relief as a key therapeutic attribute they would like from their migraine medication.

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Patients with more frequent or severe migraines or those who do not respond to simple analgesics may seek medical attention with a primary care physician initially and then with a headache clinic or neurology specialist if needed. Once a physician makes a diagnosis of migraine, oral triptans are generally prescribed as first-line therapy.

If a patient does not respond to one triptan product, the physician may switch to another triptan or dosage form or add another triptan or dosage form to a patient's treatment armamentarium. Market research conducted on our behalf by Boston Healthcare Associates, Inc. indicates that it is common for a migraine patient to be offered several different oral triptan options before being offered a nasal or injectable product. In addition, the same market research indicates that approximately 25% of migraine patients had two or more active prescriptions for different brands and/or forms of triptan therapy. We believe these patients maintain multiple prescriptions because they have found that certain medications or dosage forms work better for certain types of migraines and choose which medication to use based on the type of migraine episode they are experiencing.

Clinical research has substantiated that the nature of migraine episodes varies widely. In some episodes, patients can sense a migraine coming and take their medication accordingly. In other episodes, patients may wake up with a migraine already in progress or the migraine may come on suddenly. An estimated 48% of migraines occur between the hours of 4:00 a.m. and 9:00 a.m., according to an article published in the June 1998 issue of *Headache*. Migraines may also be associated with nausea and/or vomiting. Twenty-nine percent of patients reported vomiting as a symptom of migraine attacks, according to the American Migraine Study II, and epidemiological studies in migraine reveal that over 90% of patients have experienced nausea during a migraine attack and more than 50% have nausea with the majority of attacks, according to an article published in *Drugs* in 2003 (Volume 63, Issue 21). Depending on the type of migraine episode, a treatment may be more or less effective. For example, oral treatments may be of little value in a patient who is vomiting or who is experiencing migraine-associated gastric stasis. There is also clinical evidence that oral agents may be less effective when taken at a later stage of a migraine attack, rather than at an earlier stage. Consequently, rapid onset migraine and waking with a migraine attack may reduce the benefits to patients of oral triptans, because both represent fully-developed attacks.

The following table compares the time to maximum drug concentration in blood, or T_{max} , and pain relief of oral forms, including melts and tablets, and nasal forms of marketed triptans to *sumatriptan* injection. The data are derived from Prescribing Information for the different formulations of these marketed triptans:

Triptan Prescribing Information Data

Form/Product (API)	T_{max}	Relief at 1 hour (1)(2)	Relief at 2 hours (2)
Subcutaneous			
Sumavel DosePro (<i>sumatriptan</i> injection)	12 minutes	70%	81-82%
Nasal			
Imitrex (<i>sumatriptan</i>)	Not provided	38-46%	43-64%
Zomig (<i>zolmitriptan</i>)	3.0 hrs	60%	69-70%
Oral Melt			
Zomig-ZMT (<i>zolmitriptan</i>)	3.0 hrs	33-43%	63%
Maxalt-MLT (<i>rizatriptan</i>)	1.6-2.5 hrs	38-43%	59-74%
Oral Tablets			
Imitrex (<i>sumatriptan</i>)	2.0-2.5 hrs	28-36%	50-62%
Treximet (<i>sumatriptan/naproxen sodium</i>)	1.0 hrs	28%	57-65%
Zomig (<i>zolmitriptan</i>)	1.5 hrs	35-45%	59-67%
Maxalt (<i>rizatriptan</i>)	1.0-1.5 hrs	38-43%	60-77%
Amerge (<i>naratriptan</i>)	2.0-3.0 hrs	19-21%	50-66%(3)
Axert (<i>almotriptan</i>)	1.0-3.0 hrs	32-36%	55-65%
Frova (<i>frovatriptan</i>)	2.0-4.0 hrs	12%	37-46%
Relpax (<i>eletriptan</i>)	1.5 hrs	20-30%	47-77%

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- (1) Other than Sumavel DosePro (*sumatriptan* injection), we have estimated one-hour pain relief data for all forms/products based on Kaplan-Meier plots included in each product's Prescribing Information of the probability over time of obtaining headache response following treatment.
- (2) Range reflects headache relief data obtained in placebo controlled clinical studies, which include different doses of the same triptan.
- (3) Represents pain relief at four hours.

T_{max} closely correlates to speed of onset of pain relief, and has also been shown to be correlated with completeness of pain relief and pain freedom over time. Relief at two hours is the standard endpoint used in migraine studies and represents the percentage of patients reporting a reduction of migraine symptoms from a classification of severe or moderate to mild or none within two hours after taking the medication. As indicated in the prior table, *sumatriptan* injection has the earliest T_{max} , reaching maximum blood concentration in 12 minutes, as compared with one or more hours for the other marketed triptan products, and exhibits the highest percentage of patients reporting pain relief at two hours (81%-82%) as compared to all other marketed oral and nasal triptan products (37-77%). *Sumatriptan* injection is the only migraine product that explicitly reports pain relief at one hour in its Prescribing Information. The efficacy profile of *sumatriptan* injection has been suggested to be related to its faster rate (not extent) of drug absorption compared to oral and nasal forms of triptans. Nasal forms, while claimed by some to be fast-acting, have drug absorption profiles similar to oral forms because a large portion of the administered dose is usually swallowed prior to absorption.

Unmet Needs in Acute Migraine Therapy

Triptans have been widely used in clinical practice for more than 15 years and are generally considered to be safe and effective for many patients during their migraine episodes. However, more than half of all patients are unsatisfied with their current migraine therapy, as reported from a national survey of 500 migraine sufferers published by the NHF in June 2010 and supported by a grant from us and Astellas. Specifically, the NHF survey results indicate that three in four migraine sufferers said that their current medication did not work fast enough to get them back to their life when a migraine strikes suddenly or upon waking, and a majority of migraine sufferers said their prescription oral migraine medication was not useful for every migraine attack. Limitations of oral and nasal triptan formulations include:

Slower onset of pain relief. As shown in the prior table, compared to Sumavel DosePro, each oral and nasal triptan has a longer T_{max} , which is correlated with a slower onset of pain relief.

Lower degree of pain relief. As shown in the prior table, oral and nasal triptans may have a lower percentage of patients reporting pain relief at one and two hours following treatment as compared to Sumavel DosePro.

Significant numbers of non-responders. According to our market research with physicians and patients, approximately 30% of migraine patients fail to respond to an oral or nasal triptan.

Nasal route unpleasant. The nasal route is an alternative to oral delivery; however, nasal spray can be unpleasant in taste. Some of these limitations are more pronounced depending on the type of migraine episode the patient is suffering. For example, when waking with a migraine already in progress, speed to onset of pain relief is important. In migraines with nausea and/or vomiting, a patient may not be able to ingest an oral treatment.

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Despite its speed of onset and completeness of pain relief advantages over oral and nasal triptans, needle-based *sumatriptan* injection has been limited to less than 10% of the U.S. triptan market on a dollar basis and less than 3% on a total dose basis (Source[®] PHAST Institution/Prescription, January 2011 – December 2011). We believe this is largely due to limitations related to its delivery system which include:

Needle-based. Approximately 50% of patients refuse to use a needle-based injectable product for migraine because of needle anxiety or fear, or a lack of confidence in their ability to administer an injection correctly, according to physician market research conducted in 2006 by Palace Healthcare Group, Inc. on our behalf.

Cumbersome to use. The Imitrex STATdose System, or Imitrex STATdose, GSK's autoinjector for delivering *sumatriptan* with a needle, and its generic equivalents require more than 15 steps per their published instructions to prepare, administer and reload for its next use. This multi-step process, which patients have to complete during a migraine episode, is prone to error. Further, market research conducted by Palace Healthcare Group on our behalf finds that physicians report that the training required for Imitrex STATdose is a barrier to prescribing.

Needlestick risk. Needle-based systems may require special handling and needle disposal, or sharps, containers to avoid needlestick injuries.

Due to these limitations, there has historically been a limited prescriber base for injectable delivery forms of *sumatriptan*. Of an aggregate of over 360,000 prescribers of triptans in the United States, only an approximate 69,000 had written a prescription for *sumatriptan* injection (including Sumavel DosePro) in the 12 months ended December 31, 2011 (Wolters Kluwer Pharma Solutions, Source[®] Prescriber PHAST Prescription, January 2011 – December 2011). As a result, a limited number of patients are offered injectable delivery forms. Only 54% of migraine patients had ever been offered *sumatriptan* injection according to patient market research conducted by Boston Healthcare Associates, Inc. on our behalf.

Our Solution: Sumavel DosePro

Sumavel DosePro is a pre-filled, single-use disposable, needle-free drug delivery system that subcutaneously delivers 6 mg of *sumatriptan* in 0.5 mL of sterile liquid. Sumavel DosePro was designed to be portable, intuitive and easy-to-use. To use, the patient simply snaps off a plastic tip, flips back a lever and presses the end of the delivery system to the skin of the abdomen or thigh. Under the force of a small amount of compressed nitrogen gas, the liquid form of *sumatriptan* is expelled out of the device as a thin jet of medication, which pierces the skin and selectively deposits into the subcutaneous tissue. This process occurs in less than 1/10th of a second.

Due to its unique attributes, Sumavel DosePro has the potential to expand the dosage share for injectable *sumatriptan* beyond the traditional needle-based forms because it reduces the barriers inherent in needle-based delivery systems to being prescribed by physicians and accepted by patients. Sumavel DosePro may provide patients with the following benefits when compared to alternative triptan formulations:

Rapid, more complete, migraine pain relief. Sumavel DosePro can provide onset of migraine pain relief in as little as ten minutes for some patients, according to its Prescribing Information. The Prescribing Information for the product indicates that an average of 81% (vs. an average of 34% for placebo) of patients show pain relief at two hours following administration of Sumavel DosePro and that 49% of patients were pain free within 1 hour (vs. 9% for placebo) and 64% were pain free within two hours (vs. 15% for placebo) following administration.

Help for sufferers of morning migraines, fast onset migraine and migraines with vomiting. According to two studies published in the October 2006 issue of Clinical Therapeutics, 48% and 57% of patients with waking migraines were pain free at two hours (vs. 18% and 19% for placebo) following administration of *sumatriptan* injection. Subcutaneous *sumatriptan* is also as efficacious when

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administered early during a migraine attack as when the attack is full-blown. In addition, the pharmacokinetics of subcutaneously delivered *sumatriptan* is not affected by gastric stasis, nausea and/or vomiting.

Help for triptan tablet non-responders. Clinical research published in the January 2007 issue of Journal of Headache and Pain suggests injectable *sumatriptan* provides relief in up to 90% of migraine patients who have not responded to oral tablet triptans in at least two of their last three migraines. In this study, 43 patients who had failed to respond to oral triptans in at least two of their last three migraines were given *sumatriptan* injection for their next migraine. Of these patients, 91% reported pain relief at two hours, 56% reported being pain free at two hours and 32% reported sustained pain freedom through 24 hours following treatment of their first headache.

Simplicity, through a new, convenient and easy-to-use option. Sumavel DosePro is based on our unique delivery system which was designed to be portable, intuitive and easy-to-use, and can be disposed following use without the need of a sharps container. We believe healthcare providers appreciate the simplicity of DosePro because it is easy to train patients to use properly. Our usability study of Sumavel DosePro showed 98% of patients were able to self-administer Sumavel DosePro in the home during an acute migraine attack, without clinical supervision and with minimal prior training.

Needle-free, eliminating needle-based issues. Because it is needle-free, we believe Sumavel DosePro may eliminate the basis for patient needle phobia and fear. Additionally, it removes the risks of needlestick injury, the cost and inconvenience of needle disposal, issues resulting from poor injection technique and costs associated with professionally administered needle-based injections. Studies show when a choice between needle-based and needle-free injection is available, the majority of patients prefer needle-free injection. More specifically, in a head-to-head study conducted by GSK of Sumavel DosePro versus the European branded version of Imitrex STATdose, a needle-based delivery system, 61% of migraine patients preferred using Sumavel DosePro while only 18% preferred using the European branded version of Imitrex STATdose, with the remaining patients expressing no preference.

In addition, we believe that the unique attributes of Sumavel DosePro have the potential to reduce productivity loss in the workplace for patients suffering from migraine. According to a study published in the May 1998 issue of Archives of Internal Medicine, results from a placebo-controlled clinical study of 135 patients having migraine indicated that use of *sumatriptan* injection may reduce migraine-associated productivity loss. This decrease is a function of both a reduction in time lost due to reduced effectiveness while working and a reduction in time lost due to missing work altogether. Moreover, 52% of patients using *sumatriptan* injection (vs. 9% for placebo) returned to normal work performance within two hours after dosing.

Sumavel DosePro Commercialization Strategy

Working in collaboration with third-party advertising and market research organizations, we developed and are executing a sophisticated and comprehensive commercialization strategy for Sumavel DosePro supported by a range of marketing programs. This strategy and tactical plan was built taking into consideration the unmet needs in the migraine market in conjunction with the unique product attributes of Sumavel DosePro. Key objectives of our commercialization strategy are to:

validate the unmet needs of patients during challenging migraine episodes and position Sumavel DosePro as an effective treatment solution with prescribers;

build awareness of Sumavel DosePro with migraine sufferers in order to drive patient requests;

enhance speed of physician adoption by focusing promotional efforts on prescribers of migraine medications across specialties;

ensure a positive first-dose experience for patients; and

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achieve broad patient access to Sumavel DosePro by ensuring nationwide retail distribution and adequate third-party payor reimbursement status.

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In support of these strategic objectives, we are executing a variety of marketing programs to educate customers, which include direct-to-physician promotional materials, speaker programs, direct-to-patient programs, digital media, participation in selected medical conventions and reimbursement support programs. In addition, we provide product samples to physicians so that their patients may try Sumavel DosePro during an acute migraine attack before filling their first prescription.

Sumavel DosePro Regulatory Approval

We sought and received FDA marketing approval of Sumavel DosePro under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, or the FDCA, utilizing Imitrex *sumatriptan* injection as the reference listed product. Section 505(b)(2) of the FDCA 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. This expedited the development program for Sumavel DosePro by decreasing the overall scope of clinical and pre-clinical work required to be completed by us.

The clinical efficacy of subcutaneous injectable *sumatriptan* for migraine and cluster headache has been established by the reference listed product, Imitrex *sumatriptan* injection, which was approved in 1992. Based on our clinical bioequivalence studies, the FDA concluded that Sumavel DosePro is bioequivalent to injectable *sumatriptan* administered to the thigh or abdomen using Imitrex STATdose and is well tolerated when compared to this reference listed product. Our Sumavel DosePro NDA was approved by the FDA on July 15, 2009, and the Sumavel DosePro Prescribing Information includes the historical efficacy data of *sumatriptan* injection.

Sumavel DosePro Pivotal Clinical Program

Based on discussions with the FDA, and due to the existing body of data on injectable *sumatriptan*, our pivotal clinical program evaluated Sumavel DosePro in studies for pharmacokinetics, bioequivalence, safety, local injection site signs and reactions, and usability by patients with migraine. We conducted a single pivotal pharmacokinetics and bioequivalence clinical trial for the purpose of providing evidence of bioequivalence and safety of Sumavel DosePro as compared to Imitrex STATdose. This study, completed in April 2007, was a randomized, open-label, cross-over trial comparing safety, tolerability and pharmacokinetics in 54 subjects. The primary endpoint of bioequivalence was demonstrated in the commonly used abdomen and thigh injection sites. A separate 52-patient usability study was conducted in the second half of 2007 to evaluate the usability of Sumavel DosePro in patients during acute migraine attacks in an outpatient setting. In this study, 98% were able to use Sumavel DosePro correctly during a migraine attack on their first attempt, thus confirming the product candidate's ease of use. Further use of Sumavel DosePro by the same patients in their treatment of subsequent migraine attacks provided consistent evidence of usability in the outpatient setting. In addition, we concluded a successful safety trial with Sumavel DosePro in December 2007 to study the effect of repeat dosing and multiple injections. Adverse events seen in our clinical studies were consistent with previously reported adverse events for *sumatriptan* injection. The most common treatment-emergent adverse reactions (reported by at least 5% of patients) for *sumatriptan* injection as described in the Sumavel DosePro Prescribing Information summarizing two large placebo-controlled clinical trials were injection site reaction (59%), atypical sensations (42%), dizziness (12%), flushing (7%), chest discomfort (5%), weakness (5%), and neck pain/stiffness (5%).

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, the United Kingdom, Norway and France.

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Sumavel DosePro Post-Approval Clinical Program

In addition to the clinical program completed in support of product approval, we have completed a Phase 4 open-label, multicenter study in the United States to evaluate treatment satisfaction, treatment confidence and subject preference for Sumavel DosePro in adult subjects diagnosed with migraine and currently treated with triptans. More than 200 subjects, who were predominantly taking oral triptan therapy, tried Sumavel DosePro to treat up to four migraines over a 60-day period. The study utilized the Patient Perception of Migraine Questionnaire-Revised, or PPMQ-R, to evaluate patient satisfaction with migraine treatment through analysis of efficacy, functionality, ease of use and tolerability/side effects. The primary endpoint PPMQ-R Overall Satisfaction score increased significantly from baseline to end of treatment ($p=0.0007$), an improvement that met the criterion for clinical significance. From baseline to the end of treatment, PPMQ-R scores also improved significantly for efficacy ($p<0.0001$), functionality ($p<0.0001$) and tolerability ($p=0.02$), but declined for ease of use ($p<0.0001$). In addition, the percentage of patients confident or very confident in treating repeated migraine attacks increased from 41.0% at baseline to 64.6% at the end of treatment with Sumavel DosePro. The magnitude of improvement in treatment satisfaction from baseline to the end of the treatment period was even greater in a prospectively defined subset of 90 patients who were identified as requiring a change in therapy through use of the Migraine-ACT (Migraine Assessment of Current Therapy) questionnaire. The four-item questionnaire is an assessment tool for use by primary care physicians to identify patients who require a change in their current acute migraine treatment. Using Sumavel DosePro, 33% of the 669 treated migraine episodes in the study had pain relieved in 15 minutes, with 70% achieving pain relief within 30 minutes. Pain freedom was achieved in 61% of the treated attacks within two hours. These incidences of pain relief and pain-free response for needle-free Sumavel DosePro are consistent with those demonstrated by previous double-blind, placebo-controlled clinical studies of injectable *sumatriptan*. Given that rapid pain reduction is the primary determinant of patient satisfaction with migraine, these results may explain the high rate of satisfaction with Sumavel DosePro reported by patients in the current study.

Sumavel DosePro 4mg Line Extension

Based upon physician feedback, we have initiated development of a 4 mg dosage strength of Sumavel DosePro. We have completed registration batch manufacture, and plan to submit an NDA supplement to the FDA to demonstrate the manufacturability and stability of the new dosage strength by the end of 2012. We anticipate commercializing the 4mg dosage strength in 2013, if approved.

DosePro and Sumavel DosePro Sound Enhancement

In order to further enhance the DosePro technology and Sumavel DosePro, we have completed additional engineering and design work aimed at softening the sound emitted by the DosePro device upon drug delivery. Rather than the current sound, which is similar to the opening of a can of soda, heard upon delivery with the current DosePro device, this enhanced version will sound like the click of a pen upon drug delivery. We expect to submit this minor manufacturing change to the FDA in 2012, and expect to introduce this change to the commercial product shortly thereafter, depending on the FDA's agreement.

DosePro and Sumavel DosePro Clinical Experience

The DosePro drug delivery system has been in development for more than fifteen years. During this time, more than 9,000 injections have been administered in multiple clinical studies to assure the proper functioning of the system and to establish the safety and tolerability of needle-free administration by DosePro. 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.

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Zohydro for the Treatment of Moderate to Severe Chronic Pain

Our lead product candidate, Zohydro (*hydrocodone* bitartrate), is a 12-hour extended-release formulation of *hydrocodone* without acetaminophen for the treatment of moderate to severe chronic pain requiring around-the-clock opioid therapy. We completed Phase 3 development of Zohydro in 2011, and we expect to submit an NDA for Zohydro to the FDA early in the second quarter of 2012. We believe Zohydro has the potential to be an important therapeutic alternative to existing extended-release opioids as well as immediate release *hydrocodone* products, including the branded products Vicodin, Norco, Lorcet, Lortab and their generic equivalents, which contain the analgesic combination ingredient *acetaminophen* and, if taken in high quantities over time, may lead to serious side effects such as liver toxicity. Zohydro utilizes the SODAS Technology, Alkermes' proprietary multiparticulate drug delivery system that allows the development of customized extended-release profiles and serves to enhance the release profile of *hydrocodone* in Zohydro. We believe these release properties have the potential to provide longer lasting and more consistent pain relief with fewer daily doses than the commercially available formulations of *hydrocodone*. As a result of its unique single-entity extended-release profile, we believe Zohydro will generate sales from both patients who use immediate-release products on a chronic basis and patients already using extended-release products in the prescription opioid market.

If Zohydro is approved by the FDA, it will be included in a Risk Evaluation and Mitigation Strategies, or REMS, program, compliant with FDA mandates and consistent with other extended release opioids. This program recognizes the abuse potential of opioids and lays out specific education materials to facilitate appropriate prescribing, dispensing and use of extended release opioids.

Zohydro also is expected be designated as a U.S. Drug Enforcement Agency, or DEA, Schedule II product, which will make it more tightly regulated than currently available *hydrocodone* products, all of which are currently designated as Schedule III products. This means that Zohydro will not qualify for automatic refills and prescribers will be required to comply with the REMS program outlined for Zohydro. We believe these restrictions will help facilitate more responsible prescribing of Zohydro in terms of the dose and capsule count should it receive FDA approval.

The Chronic Pain Market

Pain is a worldwide problem with serious health and economic consequences. 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 may be defined as pain that lasts beyond the healing of an injury or that persists beyond three months. Common types of chronic pain include lower back pain, arthritis, headache and face and jaw pain. While mild pain does not typically stop an individual from participating in his or her daily activities, moderate pain may prevent an individual from participating in his or her daily activities and severe pain typically stops an individual from participating in his or her daily activities and induces a patient to exhibit pain avoidance behaviors.

Chronic pain treatment depends on the individual patients, their diagnosis and their pain severity. Chronic pain patients typically first attempt to self-medicate with over-the-counter drugs such as *acetaminophen*, aspirin or another non-steroidal anti-inflammatory drug, or NSAID. Patients with more constant and/or moderate to severe pain typically seek medical attention and prescription pain medication from a primary care physician and, if necessary, are referred to a neurologist or a physical medicine or pain specialist. Physicians generally assess the patient and, if appropriate, start treatment with a trial of opioid therapy to determine the optimal opioid regimen. At this point, physicians commonly prescribe opioids, including products from the *codeine* and *morphine* classes. The general objective of the physician is to safely achieve adequate control of pain.

Physicians generally prefer to start patients on less potent opioids where possible. A trial of opioid therapy usually begins with short-acting doses taken on an as-needed basis. This allows the clinician and patient to assess the total opioid requirement. Patients taking substantial doses of short-acting opioids multiple times per day may

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find substitution of an extended-release agent, taken one to two times per day, extremely helpful to provide more constant pain relief. In theory, the more constant opioid blood levels of extended-release products may provide better pain relief and better sleep quality. Dosing intervals longer than every four to six hours may also provide improved patient adherence to the prescribed regimen and improved patient convenience. Finally, individual patients may do poorly on one opioid, but better after switching to another. This practice is called opioid rotation and is regularly employed in chronic pain management. Opioids, while generally effective for pain treatment, are associated with numerous potential adverse effects, including opioid induced bowel dysfunction, sedation, nausea, vomiting, decreased respiratory function, addiction and, in some instances, death.

Hydrocodone is often used as a starter opioid to initiate opioid therapy because it is viewed by many physicians as a less potent opioid and potentially more tolerable. Historically, *hydrocodone* preparations in the United States have been utilized primarily for treatment of acute pain following surgery or injury. For this purpose, they were combined with non-opioid analgesics, including *acetaminophen* or an NSAID, which treat the acute inflammatory component of the pain. These non-opioid analgesics are generally safe when used at lower doses or for short periods of time. However, at higher doses or over extended periods of time, they may significantly increase patient risk for gastrointestinal, liver and kidney damage.

As the practice of pain management has broadened to include chronic therapy for moderate to severe pain, physicians continue to broadly use *hydrocodone* combinations. In the United States, market research conducted by bioStrategies Group in 2011 on our behalf indicates that nearly 30% of the prescriptions of immediate-release combination products that include *hydrocodone* are for the treatment of chronic pain and that approximately half of those prescriptions, or 14%, would be replaced with an extended-release *hydrocodone* product if it were available. However, the non-opioid analgesic component in combination *hydrocodone* products can create a ceiling effect when physicians wish to escalate doses. For example, the most commonly prescribed dose of Vicodin (5 mg *hydrocodone*/500 mg *acetaminophen*) given at a maximum dose of eight tablets per day delivers 4 g of *acetaminophen*, which approaches or exceeds recommended *acetaminophen* dosing, while only delivering 40 mg of *hydrocodone*, based on the Vicodin Prescribing Information. If a further increase in opioid dose is warranted, a physician is compelled to transition to an opioid not in combination, such as *oxycodone*, or more potent opioids such as *fentanyl* or *oxymorphone*.

In the 12 months ended December 2011, our target market, which we define as prescription non-injectable *codeine*-based and extended-release *morphine*-based pain products, generated sales of approximately \$14.2 billion in the United States on approximately 217 million prescriptions. Of the \$14.2 billion, *hydrocodone* products, the most commonly prescribed opioid and the most commonly prescribed pharmaceutical products in the United States, generated \$3.5 billion in sales on approximately 134.6 million prescriptions. (Source[®] PHAST Prescription).

In June 2009, the FDA organized a joint meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Advisory Committee to discuss how to address the public health problem of liver injury related to the use of *acetaminophen* in both over-the-counter and prescription products. The expert panel specifically considered the elimination of combination prescription products containing *acetaminophen* (including Vicodin and its generics) from the U.S. market. Twenty of the 37 working group members (10 saying this was a high priority) voted in favor of removing such products from the market. The working group ultimately did not recommend withdrawal of these products stating that the benefits of access to Schedule III *acetaminophen*/*hydrocodone* combination products over Schedule II opioids outweighed the risk of removing the combinations from the market. The working group also noted that the logical choice to substitute for the combination products would be a single-entity formulation of *hydrocodone*. Subsequently, in January 2011, the FDA asked manufacturers of prescription combination products that contain *acetaminophen* to limit the amount of *acetaminophen* to no more than 325 mg in each tablet or capsule and will require manufacturers to update labels of all prescription combination *acetaminophen* products to warn of the potential risk for severe liver injury. There are currently no approved products formulated with *hydrocodone* alone, and we believe Zohydro has the potential to fill this treatment gap.

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Limitations of Current Hydrocodone Pain Therapies

While *hydrocodone* in combination products remains the most commonly prescribed opioid, currently available *hydrocodone* formulations have several major limitations, including:

Hydrocodone only available in short-acting/immediate-release form. There are currently no extended-release *hydrocodone* formulations on the market.

Adherence dependent. Because *hydrocodone* is available only in immediate-release formulations that are dosed every four to six hours, its around-the-clock efficacy is dependent on diligent adherence by the patient. Published studies across therapeutic categories, including the treatment of diabetes, hypertension and infectious disease, demonstrate that patient adherence to drug regimens declines as the number of daily drug doses increases.

Inconsistent pain relief. Because of the dosing issues noted above, many patients experience suboptimal pain relief due to variable opioid blood levels, particularly towards the end of dosing intervals.

Opioid dose is limited by combination analgesics. The overwhelming majority of currently approved *hydrocodone* products include *acetaminophen* in their formulation. Because of the potential side effects of increasing *acetaminophen* doses, the *acetaminophen* component of these combination products can become a dose limiting factor. When this occurs, patients must limit their total *hydrocodone* dose to avoid potential liver and other side effects of *acetaminophen* and thus may receive a sub-optimal daily dose of *hydrocodone*, or they must switch to other single-entity opioids, such as *oxycodone*. *Hydrocodone* combinations with NSAIDs have similar dose limitations due to the gastrointestinal side effects associated with NSAIDs.

Widespread use of acetaminophen leading to increased toxicity risk. Even when combination products are carefully prescribed, patients are at risk of *acetaminophen* toxicity due to the prevalence of APAP in many over the counter products and individuals' lack of knowledge about the dangers and/or awareness of APAP in other products.

While extended-release, single-entity opioids exist, published study reports indicate that patients are regularly taking more daily doses of extended-release opioids than the recommended labeled dose, suggesting that not all of them provide true 12- or 24-hour dosing. For example, results from a study of 437 patients published in the May/June 2003 issue of the Journal of Managed Care Pharmacy indicated that despite the every 12-hours dosing regimen recommended in its Prescribing Information, patients taking extended-release *oxycodone* on average took 4.6 tablets per day, at an average dosing interval of only 7.8 hours. In the same study, among extended-release *oxycodone* patients, only 1.9% reported the duration of pain relief as 12 or more hours. A separate study published in the September/October 2004 issue of The Clinical Journal of Pain indicated that the prescribed frequency of dosing extended-release *oxycodone* determined through clinical practice was twice daily for 33% of patients, with 67% of patients requiring greater than twice daily dosing.

Our Solution: Zohydro

We believe that Zohydro, if approved, may provide patients and physicians with the following benefits when compared to existing opioid pain medications:

Single-entity hydrocodone. Zohydro, if successfully developed and approved by the FDA, is expected to be the first non-combination, extended-release *hydrocodone* product to be commercialized in the United States, giving physicians and patients a *hydrocodone* option unencumbered with *acetaminophen* or NSAIDs and their potential adverse effects.

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Twice daily dosing provides true around-the-clock relief. Zohydro, via its unique extended-release profile, is designed to provide consistent relief of moderate to severe chronic pain over a 12-hour period per dose. Clinical studies have shown a pharmacokinetic profile that supports the expected

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extended relief profile of Zohydro. In addition, there are five other marketed products using SODAS technology that dosed every 24 hours, which we believe helps validate the controlled release technology underlying the formulation of Zohydro.

Easier adherence/greater patient convenience. Because of its twice daily dosing regimen, Zohydro requires fewer daily doses than currently available *hydrocodone* formulations, thereby increasing the likelihood of patient adherence and convenience.

Another opioid option for chronic medication rotation. The unique profile of Zohydro provides another option for physicians investigating new alternatives to offer patients who require medication rotation due to tolerance, side effects or poor pain control.

Zohydro Phase 3 Clinical Development Program

We initiated a single pivotal Phase 3 efficacy trial (Study 801) in March 2010 and completed patient enrollment in February 2011. This trial is a randomized, 12-week, double-blind, placebo-controlled trial to evaluate the safety and efficacy of Zohydro for the treatment of moderate to severe chronic lower back pain in opioid-experienced adult subjects. Our trial utilizes a protocol design that has been used successfully to demonstrate the efficacy of other extended-release opioid therapies for chronic pain. Patients in this study were converted from their existing opioid treatment regimen to Zohydro and titrated to an effective dose of Zohydro during an initial up to 6-week open-label conversion and titration phase, and were then randomized to receive either placebo or active drug for a 12-week placebo-controlled treatment phase. During the entire study period, patients in both arms of the clinical trial had access to rescue medication. The primary efficacy endpoint in this trial is the mean change in average daily pain intensity scores between Zohydro and placebo. We confirmed the FDA's agreement on the trial design for Study 801 and the overall safety database requirements for an NDA submission at our End of Phase 2 meeting with the FDA conducted in June 2008. We did not seek a Special Protocol Assessment, or SPA, from the FDA for Study 801.

We reported positive top-line results for our pivotal Phase 3 efficacy trial in August 2011. The trial successfully met the primary efficacy endpoint in demonstrating a significant difference ($p=0.008$) between the mean changes from Baseline to Week 12 or Final Visit in average daily pain intensity Numeric Rating Scale (NRS) scores obtained from patient diaries between Zohydro and placebo groups. The two key secondary endpoints were also met. With respect to the responder analysis secondary endpoint, the proportion of patients with at least 30% improvement in pain intensity from screening to end of study was significantly higher for Zohydro compared to placebo (67.5% versus 31.1%; $p<0.001$). The proportion of patients with at least 50% improvement in pain intensity from screening to end of study was also significantly higher for Zohydro versus placebo (47.7% versus 23.3%; $p<0.001$). The other key secondary endpoint, using the Subject Global Assessment of Medication questionnaire, showed that patients on Zohydro were significantly more satisfied ($p<0.001$) with their pain treatment at the end of the study compared to their pre-study medication. The study further demonstrated that Zohydro was safe and generally well tolerated. 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 are typical adverse events associated with chronic opioid therapy.

To further assess the safety and tolerability of Zohydro as a chronic pain therapy, we also conducted an open-label Phase 3 trial in opioid-experienced adult subjects with any indication appropriate for continuous, around-the-clock opioid therapy for an extended period of time (Study 802). We completed the trial in December 2011. The goal of this trial was to evaluate the safety and tolerability of Zohydro for up to 12 months of treatment. The study further demonstrated that Zohydro was safe and generally well tolerated, and the incidence of adverse events was generally consistent with that seen in our pivotal Phase 3 efficacy trial. The safety and efficacy data from this trial is still being analyzed and will be submitted as part of our NDA to the FDA.

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Based upon feedback from the FDA at our End of Phase 2 meeting and our pre-NDA meetings in the fourth quarter of 2011, with the positive results of our pivotal Phase 3 efficacy trial and the completion of the Phase 3 safety trial, we do not believe that additional Phase 3 safety or efficacy trials will be required to support our NDA submission. We have initiated 2-year carcinogenicity studies in two animal species. We obtained FDA agreement on the protocols for both studies and have agreed with FDA that these studies are an ongoing commitment and are not required for submission or approval of an NDA for Zohydro. We expect to submit an NDA for Zohydro to the FDA early in the second quarter of 2012.

Prior Clinical Development of Zohydro

Our licensor for Zohydro, Alkermes, conducted pre-clinical and clinical studies of Zohydro under an IND initiated in 2002.

Phase 1 and Phase 2 Clinical Development. In single and multiple dose pharmacokinetic evaluations, Zohydro demonstrated detectable plasma concentrations of *hydrocodone* within 15 minutes of administration. Zohydro also demonstrated a sustained release effect significantly longer than currently available *hydrocodone* combination products such as Vicodin, as well as dose proportional pharmacokinetics. Consistent, steady-state plasma levels, which are believed to be desirable for chronic pain patients who require around-the-clock opioid therapy, were achieved within one week of the initiation of dosing. In addition, Zohydro has been tested under both fed and fasted conditions and the amount of drug exposure was not affected by food, which we believe provides the basis for a flexible administration regimen for chronic pain. We believe that these prior pharmacokinetic studies demonstrate that Zohydro displays a consistent, extended-release profile, dose-proportional pharmacokinetics and an acceptable safety profile.

Zohydro has also been evaluated in two separate Phase 2 pain studies. The first study was a randomized, single-dose, parallel group, placebo-controlled, active-comparator study to evaluate the safety, efficacy and pharmacokinetics of increasing doses of Zohydro in opioid-naïve adults immediately following bunion removal surgery. This study was designed to evaluate pain prevention rather than pain treatment. In this 241-patient study, patients were treated with either one of four doses of Zohydro (10, 20, 30 or 40 mg extended-release *hydrocodone bitartrate*), an active immediate-release comparator consisting of 10 mg *hydrocodone bitartrate* plus 325 mg *acetaminophen*, or placebo. The primary efficacy measurement was the visual analog scale of pain intensity from 0 to 12 hours after dosing. The 40 mg dose of Zohydro was significantly more effective ($p < 0.05$) versus placebo in controlling postoperative pain. In addition, efficacy of the 40 mg dose did not significantly differ from the *hydrocodone bitartrate/acetaminophen* active comparator in any of the efficacy outcome measures. None of the three lower doses of Zohydro were superior to placebo in the primary efficacy measurements. All four doses were found to be safe and well-tolerated. We believe this efficacy and safety information is useful in establishing proof-of-concept for Zohydro.

The second Phase 2 study was a four week, multiple-dose, safety, tolerability and pharmacokinetic dose-escalation study of Zohydro in opioid-experienced adults with chronic, moderate to severe osteoarthritis pain. The primary objective was to assess the safety, tolerability and pharmacokinetics of Zohydro at steady state over a range of escalating daily doses. Thirty-seven patients in two dosing cohorts received escalating doses of Zohydro over three weeks. This study demonstrated a clinically acceptable safety profile and a reduction in pain intensity for chronic moderate to severe osteoarthritis pain patients across multiple dosage strengths. We believe that the study also demonstrated a steady-state pharmacokinetic profile that is appropriate for the management of chronic pain. In both Phase 2 studies, patients experienced mild to moderate adverse events, such as nausea, vomiting, headache, dizziness, sweating, constipation and drowsiness, which are similar to the reported effects of opioids currently prescribed for chronic pain.

The data from these Phase 1 and Phase 2 studies were submitted to the FDA under our IND and were summarized in our End of Phase 2 meeting briefing package in support of progressing Zohydro into pivotal Phase 3 clinical studies.

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Relday for the Treatment of Schizophrenia

Relday is a proprietary, long-acting injectable formulation of *risperidone* using Durect's SABER controlled-release formulation technology in combination with our DosePro needle-free, subcutaneous drug delivery system. If successfully developed and approved, we believe Relday may be the first once-monthly, subcutaneous antipsychotic product available in a needle-free delivery system to enter the long-acting injectable antipsychotic market. We believe the combination of our DosePro technology with Durect's SABER controlled-release technology will allow Relday 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 2012 following the filing of an IND with the FDA. We completed a pre-IND meeting with the FDA in December 2009.

The Antipsychotic Market

Schizophrenia is a complex, chronic, severe and debilitating mental disorder that often develops between the ages of 16 and 30 years, and the NIMH estimates that the 12-month prevalence of schizophrenia is 1.1% of the U.S. adult population. The symptoms of schizophrenia are often categorized as positive, negative or cognitive in nature. Positive symptoms include hallucinations, delusions, disorganized thinking and movement disorders. Negative symptoms of schizophrenia can include flat affect, inability to feel pleasure and speaking little, and the cognitive symptoms of schizophrenia can include poor executive function, problems with working memory and attention deficits. This combination of symptoms often makes it challenging for many schizophrenic patients to care for themselves or hold jobs, resulting in significant societal costs. The direct and indirect costs of schizophrenia in the United States in 2002 were estimated at \$62.7 billion, including \$22.7 billion in direct medical costs for outpatient care, medications, inpatient care, and long-term care, according to an article published in 2005 in *The Journal of Clinical Psychiatry*.

Bipolar disorder, or manic depressive illness, is another chronic, recurring psychiatric illness that is characterized by extreme or unusual shifts in mood, energy and activity levels. In general, patients with bipolar disorder suffer over time from episodes of both mania and depression. The NIMH estimates that the average age of onset for bipolar disorder is 25 years, and the 12-month prevalence of bipolar disorder is 2.6% of the U.S. adult population. In many cases, the recurring episodes of mania and depression are so severe that the patient cannot maintain normal relationships or function normally at home, work or school, and suicide attempts occur in 25-50% of bipolar disorder patients.

First line therapy for most schizophrenia patients today are drugs generally known as atypical or second generation antipsychotics. These antipsychotics have been named atypical for their ability to treat a broader range of negative symptoms with improved side effect profiles versus the first-generation or typical antipsychotics, which were mostly introduced in the 1950s with drugs such as chlorpromazine and haloperidol. The first atypical antipsychotics to be approved by FDA in the United States were Clozaril (*clozapine*) in 1989, followed by Risperdal (*risperidone*) in 1993 and Zyprexa (*olanzapine*) in 1996. Similarly, over the last decade, atypical antipsychotics have become increasingly utilized in the treatment of bipolar disorder, either as monotherapy or as part of a polytherapy regimen, most often being prescribed in conjunction with a mood stabilizer such as lithium or valproic acid, and sometimes in conjunction with both a mood stabilizer and additional medications.

Patient compliance with medication has been a long-standing problem in the treatment of both schizophrenia and bipolar disorder. Results from the Clinical Antipsychotic Trials in Intervention Effectiveness conducted between 2001 and 2004, and published in *The New England Journal of Medicine* in 2005, indicated that over 70% of schizophrenia patients became non-compliant with their medication within 18 months of commencing therapy. Similarly a 2004 study of the VA National Psychosis Registry published in the journal

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Bipolar Disorder in October 2006 found that, of the 45% of bipolar patients who were being prescribed an antipsychotic, just over half of individuals appeared to be fully adherent with their antipsychotic medications, while the remaining individuals were either partially adherent or non-adherent with their antipsychotic medications.

In an attempt to improve patient compliance, physicians increasingly administer antipsychotic drugs through long-acting depot injections. Long-acting depot injections release medication slowly over weeks rather than over hours or days for conventional injections or oral medications, thereby dramatically reducing the number of times a patient needs to take their medication. Currently available long-acting injectable products include Risperdal Consta and Invega Sustenna, both marketed by Johnson & Johnson, and Zyprexa Relprevv, marketed by Eli Lilly & Co. These drugs provide two to four weeks of therapy per dose.

Overall, the global atypical antipsychotic market is estimated to be in excess of \$16.3 billion in 2010, based upon published sales reports of certain pharmaceutical companies. In 2010, atypical antipsychotics comprised approximately 90% of all antipsychotic prescriptions in the United States, according to data from Wolters Kluwer (Source[®] PHAST Prescription, January 2011 – December 2011). The existing long-acting injectable *risperidone* product, Risperdal Consta, achieved global net sales of \$1.5 billion in 2010, according to industry reports, and has a wholesale acquisition cost of approximately \$270 per bi-weekly dose, or more than \$500 per month, for the 25mg dosage strength (Source: Gold Standard). Finally, in the United States, prescribers of long-acting antipsychotics are highly concentrated with approximately 15,000 total prescribers of long-acting injectable products, including approximately 8,785 psychiatrists in 2011 (Source[®] PHAST Prescription, January 2011 – December 2011).

The Relday Opportunity

Market research conducted on our behalf by bioStrategies Group in 2007 indicates that psychiatrists see significant potential advantages for Relday over the currently marketed long-acting *risperidone* injectable, specifically identifying the subcutaneous, needle-free, and once-monthly features of Relday as important differentiators versus the currently marketed long-acting antipsychotics. We believe on the basis of our pre-clinical development work and market research that, if successfully developed and approved, Relday could potentially provide a significant improvements over existing treatment options for patients suffering from schizophrenia as a result of:

Subcutaneous delivery: All the currently available long-acting atypical antipsychotics are administered intramuscularly and, other than the lowest dosage strength of Invega Sustenna, have injection volumes greater than Relday. Intramuscular injections have been associated with inadvertent vascular injection, leading to rapid release of the drug and related adverse events, and in addition can also result in slow, painful and/or difficult injections. Utilizing the unique attributes of the Durect's SABER technology and the DosePro needle-free delivery system, Relday has been designed to be administered subcutaneously with an injection volume of 0.5mL or less.

Needle-free delivery: Relday is formulated to be administered using our proprietary DosePro needle-free delivery system. The currently available long-acting atypical antipsychotic products are delivered using a 23 gauge or larger needle, with Risperdal Consta requiring use of a 21 gauge or larger needle.

No reconstitution: Relday is formulated as a prefilled, single-dose product that does not require reconstitution, or the addition of a liquid diluent, prior to administration. Risperdal Consta and Zyprexa Relprevv both require reconstitution prior to injection, which is generally considered an inconvenience for busy healthcare practitioners.

Once a month dosing with no oral supplementation: Relday is formulated with a goal of providing a pharmacokinetic profile that will allow for once-monthly dosing without the need for supplementation with oral *risperidone*. Risperdal Consta provides therapy for only two weeks, resulting in more

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frequent physician visits and requires supplementation with oral *risperidone* for the first three weeks following initiation of therapy or following a missed dose of the injectable due to its pharmacokinetic profile.

Preferred active ingredient: Our market research indicated that in nearly all cases, long-acting injectable antipsychotics are prescribed to patients who have experience taking the same molecule orally and have demonstrated some level of acceptable efficacy and tolerability. Oral *risperidone* is now the second most commonly prescribed atypical antipsychotic compound in the United States, accounting for 24% of total prescriptions in the twelve months ended December 2011 (Source[®] PHAST Prescription, January 2011 – December 2011).

We intend to initiate clinical studies for Relday in patients with schizophrenia in 2012 following filing of an IND application. We completed a pre-IND meeting with the FDA in December 2009. Following initiation of clinical trials in the United States, we plan to seek a development and commercialization partner or partners for Relday in territories outside of the United States such as Europe and Japan. While our current development plans are focused on schizophrenia, in the future we may consider expanding the program to address additional indications, such as bi-polar disorder. If successfully developed and approved by the FDA, we plan to commercialize Relday in the United States further leveraging our commercial infrastructure and sales force.

Our DosePro Technology and Pre-clinical Pipeline

Our proprietary DosePro technology is a first-in-class, easy-to-use drug delivery system designed for self-administration of a pre-filled, single dose of liquid drug, subcutaneously, without a needle. The DosePro technology (formerly known as Intraject) has undergone more than ten years of design, process engineering, clinical evaluation and development work, including significant capital investment by the predecessor owners of the technology, Weston Medical Group, plc and Aradigm Corporation, or Aradigm. We believe the approval and launch of Sumavel DosePro in the United States validates the technology's commercial viability and readiness for other potential drug applications.

We believe that DosePro offers several benefits to patients compared to other subcutaneous delivery methods, and that it has the potential to become a preferred delivery option for patients and physicians for many injected medicines beyond *sumatriptan*, particularly those that are self-administered. These benefits include less anxiety or fear due to the lack of a needle, easier disposal without the need for a sharps container, no risk of needlestick injury or contamination, an easy-to-use three step process, no need to fill or manipulate the device, reliable performance, discreet use and portability. In several clinical trials and market research studies, DosePro has been shown to be preferred by patients over conventional needle-based systems. For example, in a head-to-head study conducted by GSK of Sumavel DosePro versus the European branded version of Imitrex STATdose, a needle-based delivery system, 61% of migraine patients preferred using Sumavel DosePro while only 18% preferred using the European branded version of Imitrex STATdose, with the remaining patients expressing no preference. In addition, in a market study conducted on our behalf by Boston Healthcare Associates, Inc., 76% of patients preferred Sumavel DosePro as a delivery method over Imitrex STATdose. In addition, DosePro requires less time from physicians and other caregivers to train patients to use the device.

Physician preference for DosePro as a needle-free alternative to conventional needle-based injections has also been demonstrated in market research studies. For example, in a study conducted by Palace Healthcare Group, Inc. on our behalf, 94% of primary care physicians and 98% of neurologists indicated they would be more willing to prescribe an injectable migraine product if it were needle-free.

In order to further enhance the DosePro technology and Sumavel DosePro, we have completed additional engineering and design work aimed at softening the sound emitted by the DosePro device upon drug delivery. Rather than the current sound, which is similar to the opening of a can of soda, heard upon delivery with the current DosePro device, this enhanced version will sound like the click of a pen upon drug delivery. We expect to submit this minor manufacturing change to the FDA in 2012, and expect to introduce this change to the commercial product shortly thereafter, depending on the FDA's agreement.

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Clinical studies suggest that DosePro will have significant versatility in its ability to deliver various types of therapeutic compounds, including both small molecules and biologic products where the dose volume is 0.5 mL or less. In addition to positive results using DosePro in clinical studies performed with saline and *sumatriptan*, there have been three positive single-dose human pilot studies conducted with a combination of a protein pharmaceutical and DosePro. These studies include pharmacokinetic bioequivalence studies comparing DosePro to a conventional needle injection for human growth hormone and erythropoietin, or EPO, and pharmacodynamic equivalence study using granulocyte colony-stimulating factor, or G-CSF. Pre-clinical work with monoclonal antibodies evaluating bioavailability, pharmacokinetics and a lack of immunogenicity has also been conducted. *In vitro* studies with DosePro technology have demonstrated the potential to allow the subcutaneous delivery of highly viscous formulations, which can be a limiting factor for use of traditional needle-based delivery systems. As a result of the versatility of DosePro to deliver various types of drug products, this technology may have significant market potential across a broad range of therapeutic areas, including those typically treated with small volume injectable products, such as hepatitis, infertility, multiple sclerosis and rheumatoid arthritis.

Since some drug formulations cannot be accommodated in a 0.5 mL dose volume, we have initiated early stage design and development of a larger volume, second generation version of our DosePro technology, 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 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.

Given its multiple benefits and therapeutic versatility, we believe the DosePro technology provides us with an opportunity to develop our own product candidates by pairing DosePro with proven drugs to enhance their commercial attractiveness such as with Relday. We are also evaluating the market potential, formulation requirements and clinical development pathway of an additional CNS compound that could be paired with DosePro to enhance its commercial attractiveness. We also believe DosePro provides an attractive licensing option for other pharmaceutical and biotech companies seeking to enhance, differentiate or extend the life-cycle of their own injectable products, and we are continuing to explore such arrangements with several established pharmaceutical companies. These opportunities include both currently marketed products as well as development stage product candidates.

Sales and Marketing

We have built a highly experienced sales and marketing organization in the United States focused on marketing and selling Sumavel DosePro to physicians, nurses and other healthcare professionals. Our sales and marketing organization is comprised of approximately 116 professionals. Our field sales force of approximately 95 representatives has historically promoted Sumavel DosePro primarily to neurologists and other prescribers of migraine medications, including headache clinics and headache specialists.

We believe the key factors in the continued successful adoption of Sumavel DosePro will include expanding its use as an alternative to oral and nasal triptan therapy, converting current *sumatriptan* injectable users to Sumavel DosePro and building patient awareness and trial. We are specifically positioning Sumavel DosePro as a therapeutic alternative for oral triptan non-responders and dissatisfied patients, including those with morning migraines, fast progressing migraines and migraines accompanied by nausea and/or vomiting.

We believe our sales force is differentiated by its level of experience and background in the industry and accountability for sales results. Our field sales representatives have an average of 13 years of prior experience promoting pharmaceutical products and most have prior experience in the neurology and/or migraine space. In addition, our sales management team has on average 20 years of pharmaceutical industry experience, including an average of nine years of sales management experience. Each of our sales representatives and regional business

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directors undergoes a formal training program focused on disease background, our product, competitive products and territory management, as well as compliance with applicable laws. Our training program also includes significant ongoing and field-based learning to provide a comprehensive understanding and perspective as to our markets and disease states and the needs of both physicians and patients.

In addition to our field sales team, we also have an experienced team of field-based managed markets and trade directors. This team works closely with our regional business directors to engage with third-party payors to ensure and expand reimbursement coverage and patient access for our product and implement pharmacy based educational programs. To date, we have entered into a number of contracts with private health insurers, managed care organizations, government entities and other third-party payors that provide coverage for our products.

We are supporting this field based organization with an internal team which includes product management, communications, commercial analytics and sales operations staff. This team is focused on the implementation of a variety of marketing programs to educate customers, which include direct-to-physician promotional materials, speaker programs, direct-to-patient programs, digital media, participation in selected medical conventions and reimbursement support programs.

In addition, in July 2009, we entered into an exclusive co-promotion agreement with Astellas under which Sumavel DosePro was historically marketed by Astellas in the United States and promoted primarily to primary care physicians (including internal medicine, family practice and general practice), OB/GYNs, emergency medicine physicians and urologists, or collectively the Astellas Segment, by approximately 400 Astellas sales representatives. The target audience for our sales effort was primarily comprised historically of neurologists and other prescribers of migraine medicines who fall outside the Astellas Segment. In addition, our representatives have historically had the right to call upon a specified number of key prescribers within the Astellas Segment and Astellas representatives historically had the right to call upon a specified number of neurologists. This exclusive co-promotion agreement with Astellas will terminate on March 31, 2012, at which time we will assume full responsibility for the commercialization of Sumavel DosePro. We have already begun to assume responsibility from Astellas for marketing Sumavel DosePro to selected high-prescribing primary care physicians and other Astellas-targeted physicians and professionals within the Astellas Segment pursuant to a promotion transition plan. We are currently evaluating potential co-promotion partners who could complement our sales and marketing professionals for the continued marketing of Sumavel DosePro.

In March 2008, we entered into a licensing and distribution agreement with Desitin, a private German pharmaceutical company focused on the development, manufacturing and distribution of products for the treatment of CNS disorders. Under the terms of the agreement, we licensed to Desitin the exclusive development and commercialization rights to Sumavel DosePro for the European Union, Norway, Switzerland and Turkey. Desitin will oversee, and be responsible for the expenses related to, all clinical development, regulatory approval and commercialization efforts required to market Sumavel DosePro in the territories in which Desitin elects to develop and market Sumavel DosePro. Desitin received approval to market Sumavel DosePro in Denmark in November 2010 followed by approval in the United Kingdom, Sweden and Germany in December 2010 and Norway and France in February 2011. We have agreed to manufacture and supply the product to Desitin for commercial sale. Desitin has agreed to pay us a specified transfer price for commercial product and a low single-digit percentage royalty on net sales of the product. We retain full commercial rights to Sumavel DosePro in all other countries not licensed under the Desitin agreement, including the United States, Canada and the countries in Asia.

To build upon our continued success in growing Sumavel DosePro prescriptions, we expanded our sales force in the United States from approximately 80 sales representatives in 2010 to approximately 95 sales representatives at the end of the 2011. We are currently evaluating potential co-promotion partners who could complement our sales and marketing professionals for the continued marketing of Sumavel Dose Pro. For the launch of Zohydro, if approved, we intend to consider co-promotion and other partnering opportunities, and an expansion of our sales and marketing infrastructure, including expanding our field sales force to between 170 and

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220 representatives, to both launch Zohydro and continue to support Sumavel DosePro. We expect our primary target audiences may expand to include anesthesiologists, pain specialists, physical medicine specialists and additional primary care physicians. In addition, we expect that we will also consider opportunities to partner Zohydro to reach a broader physician audience. We will also evaluate third-party co-promotion opportunities that would allow us to strategically leverage our commercial resources and generate additional revenue in the United States.

Competition

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. We face competition not only in the commercialization of Sumavel DosePro or any product candidates for which we obtain marketing approval from the FDA or other regulatory authorities, but also for the in-licensing or acquisition of additional product candidates, and the out-licensing of our DosePro drug delivery technology.

Sumavel DosePro

Sumavel DosePro competes against other marketed migraine therapeutics. The largest class of marketed prescription products for treatment of migraine is the triptan class. The largest selling triptan is *sumatriptan*, with the branded products Imitrex and Treximet marketed by GSK and Sumavel DosePro marketed by us. There are six other branded triptan therapies being sold by pharmaceutical companies including AstraZeneca plc, Endo Pharmaceuticals Holdings Inc., Johnson & Johnson, Merck, and Pfizer, Inc. in the United States.

We also face competition from generic *sumatriptan* injectable, now marketed in the United States as an authorized generic of Imitrex STATdose by Par Pharmaceutical Companies and Sandoz Inc. (a Novartis AG company). In addition, we face competition from alternative autoinjector forms of *sumatriptan* injection including *sumatriptan* injection, a needle-based autoinjector which was developed and is manufactured and marketed by Pfizer, and a needle-based generic *sumatriptan* auto-injector from Sun Pharmaceutical Industries Limited. Finally, generic injectable *sumatriptan* in the form of vials and prefilled syringes is available from a number of pharmaceutical companies. Although these products and alternative autoinjector forms of *sumatriptan* injection may not be directly substituted for Sumavel DosePro, generic versions of injectable *sumatriptan* 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. In addition to these migraine therapeutics, there are other marketed non-triptan migraine therapeutics, such as Cambia sold by Nautilus Neurosciences, Inc. and Migranal sold by Valeant Pharmaceuticals International. Moreover, there are several product candidates under development that could potentially be used to treat migraines and compete with Sumavel DosePro, including products under development by large pharmaceutical companies such as GSK and Merck and smaller companies such as NuPathe, Inc. and MAP Pharmaceuticals, Inc. In addition, Allergan, Inc. is now marketing BOTOX botulinum toxin for the treatment of chronic migraine.

Zohydro

If approved for the treatment of moderate to severe chronic pain, Zohydro will compete against other marketed branded and generic pain therapeutics and may compete with additional product candidates currently under development or developed in the future. Current competitors in the opioid pain therapeutics space include,

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but are not limited to, Abbott Laboratories, Endo Pharmaceuticals Holdings Inc., Johnson & Johnson, Mallinckrodt Inc., Pfizer, Purdue Pharma L.P., Teva Pharmaceutical Industries Limited and Watson Pharmaceuticals, Inc. There are 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 Egalet A/S, Pfizer, Purdue Pharma L.P. and Teva Pharmaceutical Industries Limited. Zohydro may also face competition from non-opioid products, including new chemical entities, as well as alternative delivery forms of NSAIDs. In addition to the previously named companies, a number of pharmaceutical companies are developing new product candidates for pain including, but not limited to, Acura Pharmaceuticals, Inc., Altea Therapeutics Corporation, Collegium Pharmaceutical, Inc., Eli Lilly and Company, Elite Pharmaceuticals, Inc., Hospira, Inc., Inspirin Delivery Technologies, LLC, Intellipharma International Inc. and QRxPharma Ltd.

Relday

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 plc, NuPathe, Inc. and Novartis AG, each of which has announced they are developing long-acting antipsychotic product candidates.

DosePro Technology

Traditional needle and syringe remain the primary method for administering intramuscular and subcutaneous injections. The injectable drug market is increasingly adopting new injection systems including pre-filled syringes, pen injectors and autoinjector devices. The majority of these devices, however, still employ a needle. We will compete with companies operating in the needle-based drug delivery market. These companies include, but are not limited to, Becton, Dickinson and Company, Owen Mumford Ltd. and Ypsomed. Additional competition may come from companies focused on out-licensing needle-free technology including Antares Pharma Inc. and Bioject Inc., which have commercialized gas- or spring-driven, multiple-use, patient-filled, needle-free injectors, primarily for injecting human growth hormone or insulin for diabetes. Other companies may also be developing single-use, pre-filled, needle-free delivery systems. We also may experience future competition from alternative delivery systems which bypass the need for an injection, including inhaled, nasal, sublingual or transdermal technologies.

Distribution

We primarily sell Sumavel DosePro 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 46.0%, 34.9% and 10.9%, respectively, of our total gross sales of Sumavel DosePro for the year ended December 31, 2011.

We use a third-party logistics provider, Cardinal Health 105, Inc. (a/k/a Specialty Pharmaceutical Services), for key services related to logistics, warehousing and inventory management, distribution, contract administration and chargeback processing, accounts receivable management and call center management. In

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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.

Manufacturing

Sumavel DosePro and our DosePro technology are manufactured by contract manufacturers, component fabricators and secondary service providers. Suppliers of components, subassemblies and other materials are located in the United Kingdom, Germany, Ireland and the United States. 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. FDA regulations require that materials be produced under current Good Manufacturing Practices, or cGMPs, or Quality System Regulations, or QSR, as required for the respective unit operation within the manufacturing process. Manufacturing equipment specific to the production of critical DosePro components and assemblies was developed and purchased by us and the prior owners of the DosePro technology and is currently owned by us.

We manage the supply chain for Sumavel DosePro, consisting of the DosePro system and the active pharmaceutical ingredient, or API, internally with experienced operations professionals, including employees residing in the United Kingdom who oversee European contract manufacturing operations. We have entered into supply agreements relating to Sumavel DosePro with our critical contract manufacturers, most component fabricators and secondary service providers to secure commercial supply for Sumavel DosePro and expect manufacturing capacity to adequately support our projected Sumavel DosePro demand through 2012. Each of these manufacturers and each other company that supplies, fabricates or manufactures any component used in our DosePro device is currently the sole qualified source of their respective components. If demand exceeds our expectation in 2013 and beyond, we may be required to expand the capacity of some of our existing contract manufacturers and suppliers or qualify new manufacturers or suppliers.

DosePro systems intended for clinical trials of DosePro-based products other than Sumavel DosePro are provided by using the existing manufacturing infrastructure, supplemented with clinical scale aseptic fill/finish as appropriate for the stage and scale of the product under clinical development.

Clinical materials for our Zohydro clinical program are manufactured by Alkermes (formerly Elan Drug Delivery, Inc.) under the terms of our license agreement described under *Collaborations, Commercial and License Agreements* below.

The following are manufacturing and supply arrangements and agreements that we believe are material to the ongoing operation of our business.

Patheon UK Limited

In November 2008, we entered into a manufacturing services agreement with Patheon UK Limited, or Patheon, located in Swindon, United Kingdom, a specialist in the aseptic fill/finish of injectables and other sterile pharmaceutical products. Under the terms of the agreement, Patheon serves as our exclusive manufacturer for the aseptic capsule assembly, filling and inspection, final device assembly and packaging of Sumavel DosePro, as well as other manufacturing and support services. Although we are not required to have any minimum quantity of Sumavel DosePro manufactured under the agreement, we have agreed to provide Patheon with forecasts of the required volumes of Sumavel DosePro we need, and we are required to pay Patheon a monthly manufacturing fee of £303,200, or approximately \$468,538 (based on the exchange rate as of December 31, 2011), over the remaining term of the agreement, aggregating to £6,670,400, or approximately £10,307,836, over the remaining initial term of the agreement. Under the agreement, we are also required to pay support and service fees, with the level of service fees increasing if annual production exceeds a specified volume. The agreement has an initial five-year term, which expires October 31, 2013. The parties may mutually agree in writing to renew the term for additional terms prior to the expiration of the then-current term. Either party may terminate the agreement

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(1) upon specified written notice to the other party, (2) upon written notice if the other party has failed to remedy a material breach of any of its representations, warranties or other obligations under the agreement within a specified period following receipt of written notice of such breach, and (3) immediately upon written notice to the other party in the event that the other party is declared insolvent or bankrupt by a court of competent jurisdiction, a voluntary petition of bankruptcy is filed in any court of competent jurisdiction by such other party or the agreement is assigned by such other party for the benefit of creditors. Patheon may also terminate the agreement upon specified written notice if we assign the agreement to certain specified parties.

Nypro Limited

Nypro Limited, located in Bray, Ireland, manufactures the actuator assemblies and injection molded components for our DosePro device pursuant to purchase orders. We do not currently have a long-term commercial supply agreement with Nypro.

MGlas AG

In May 2009, we entered into a commercial manufacturing and supply agreement with MGlas AG, located in Munnerstadt, Germany. Under the terms of the agreement, MGlas is our exclusive supplier of the glass capsule that houses the *sumatriptan* API in Sumavel DosePro (and will be the exclusive supplier of glass capsules for any future 0.5 mL DosePro product candidates or products). The agreement has an initial three-year term, which expires in May 2012. Prior to expiration of the agreement, we intend to extend the commercial manufacturing and supply agreement with MGlas to continue the exclusive supply of the glass capsule. Either party may terminate the agreement by providing the other party with specified written notice. In addition, either party may terminate the agreement immediately by written notice if the other party commits a material breach of its obligations which is either incapable of remedy or is not remedied within a specified period following receipt of written notice of such breach, or in the event the other party becomes insolvent or is subject to insolvency-related proceedings.

Dr. Reddy's Laboratories, Inc.

We are party to a supply agreement with Dr. Reddy's Laboratories, Inc., or Dr. Reddy's, which was originally entered into between Aradigm and Dr. Reddy's in September 2004. Under the terms of the agreement, Dr. Reddy's, a global pharmaceutical company and supplier of bulk API located in India, agreed to supply us with the *sumatriptan* API for Sumavel DosePro at a specified price. Dr. Reddy's has agreed to sell to us, and we agreed to purchase on a non-exclusive basis from Dr. Reddy's, not less than 50% of our quarterly requirements for *sumatriptan* in the United States, Canada and the European Union. The initial term of the agreement expires in 2020. The term of the agreement may be extended by us for successive one-year periods by written notice to Dr. Reddy's, unless Dr. Reddy's gives written notice to us that it does not wish to extend the term. We may terminate the agreement upon written notice if Dr. Reddy's is unable to deliver sufficient amounts of *sumatriptan* over a specified period of time. We may also terminate the agreement if we are negotiating an agreement with a third party to commercialize such third party's formulation of *sumatriptan* and such agreement would preclude us from sourcing *sumatriptan* from any party other than such third party. Either party may terminate the agreement upon written notice if the other party commits a material breach of its obligations and fails to remedy the breach within a specified time period, if the other party becomes insolvent or subject to bankruptcy proceedings, or where a force majeure event continues for a specified period of time.

Collaborations, Commercial and License Agreements

Durect Corporation Development and License Agreement

In July 2011, we entered into a development and license agreement with Durect. Under the terms of the agreement, we will be responsible for the clinical development and commercialization of Relday. Durect will be responsible for non-clinical, formulation and chemistry, manufacturing and controls, or CMC, development responsibilities. Durect will be reimbursed by us for its research and development efforts on the product.

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We paid a non-refundable upfront fee to Durect of \$2.25 million in July 2011. We are obligated to pay Durect up to \$103.0 million in total future milestone payments with respect to the product subject to and upon the achievement of various development, regulatory and sales milestones. We are also required to pay a mid single-digit to low double-digit percentage patent royalty on annual net sales of the product determined on a jurisdiction-by-jurisdiction basis. Further, until an NDA for Relday has been filed in the United States, we are obligated to spend no less than \$1.0 million in external expenses on the development of Relday in any trailing twelve month period beginning in July 2012. The patent royalty term is equal to the later of the expiration of all Durect technology patents or joint patent rights in a particular jurisdiction, the expiration of marketing exclusivity rights in such jurisdiction, or 15 years from first commercial sale in such jurisdiction. After the patent royalty term, we will continue to pay royalties on annual net sales of the product at a reduced rate for so long as we continue to sell the product in the jurisdiction. We are also required to pay to Durect a tiered percentage of fees received in connection with any sublicense of the licensed rights.

Durect granted to us an exclusive worldwide license, with sub-license rights, to Durect intellectual property rights related to Durect's proprietary polymeric and non-polymeric controlled-release formulation technology to make and have made, use, offer for sale, sell and import *risperidone* products, where *risperidone* is the sole active agent, for administration by injection in the treatment of schizophrenia, bipolar disorder or other psychiatric related disorders in humans. Durect retains the right to supply our Phase 3 clinical trial and commercial product requirements on the terms set forth in the agreement.

Durect may terminate the agreement with respect to specific countries if we fail to advance the development of the product in such country within a specified time period, either directly or through a sublicensee. In addition, either party may terminate the agreement upon insolvency or bankruptcy of the other party, upon written notice of a material uncured breach or if the other party takes any act that attempts to impair such other party's relevant intellectual property rights. We may terminate the agreement upon written notice if during the development or commercialization of the product, the product becomes subject to one or more serious adverse drug experiences or if either party receives notice from a regulatory authority, independent review committee, data safety monitoring board or other similar body alleging significant concern regarding a patient safety issue and, as a result, we believe the long-term viability of the product would be seriously impacted. We may also terminate the agreement with or without cause, at any time upon prior written notice.

Astellas Co-Promotion Agreement

In July 2009, we entered into a co-promotion agreement with Astellas. Under the terms of the agreement, we granted Astellas the co-exclusive right (with us) to market and sell Sumavel DosePro in the United States (excluding Puerto Rico and the other territories and possessions of the United States). Under the agreement, both Astellas and we were obligated to collaborate and fund the marketing of Sumavel DosePro and to provide annual minimum levels of sales effort directed at Sumavel DosePro. In December 2011, we entered into an amendment to the co-promotion agreement with Astellas, or the amended co-promotion agreement, whereby the agreement will terminate on March 31, 2012. We are responsible for the manufacture, supply, and distribution of commercial product for sale in the United States. In addition, we supply product samples to Astellas, and Astellas pays us for such samples, at an agreed upon transfer price.

The target audience for Astellas's sales efforts was primarily comprised historically of prescribers classified as primary care physicians (including internal medicine, family practice and general practice), OB/GYNs, emergency medicine physicians and urologists, or collectively the Astellas Segment. The target audience for our sales effort was primarily comprised historically of neurologists and other prescribers of migraine medicines who fall outside the Astellas Segment. In addition, our representatives have historically had the right to call upon a specified number of key prescribers within the Astellas Segment; conversely Astellas's representatives historically had the right to call upon a specified number of neurologists. Under the terms of the amended co-promotion agreement, beginning in the first quarter of 2012, we began to assume responsibility from Astellas for marketing Sumavel DosePro to selected high prescribing primary care physicians and other Astellas-targeted physicians and

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professionals within the Astellas Segment pursuant to a promotion transition plan. We will assume full responsibility for the commercialization of Sumavel DosePro following termination of the agreement in March 2012.

Under the agreement, Astellas has paid us upfront and milestone payments in an aggregate amount of \$20.0 million through December 31, 2011. Astellas is not obligated to pay us any additional milestone payments. In consideration for Astellas' performance of its commercial efforts, we are required to pay Astellas a service fee on a quarterly basis that represents a fixed percentage of between 45% and 55% of Sumavel DosePro net sales to the Astellas Segment. Astellas is not compensated for Sumavel DosePro sales to neurologists, any other prescribers not included in the Astellas Segment or for non-retail sales. In addition, upon completion of the co-promotion term in March 2012, we will be required to pay Astellas two additional annual tail payments in July 2013 and July 2014 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 12 months ending March 31, 2012.

Desitin License and Distribution Agreement

In March 2008, we entered into a licensing and distribution agreement with Desitin. Under the terms of the agreement, 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. Under the agreement, Desitin has the right, but with the exception of Germany not the obligation, at its own expense, to develop, obtain marketing approval and commercialize Sumavel DosePro in these territories. In addition, Desitin has a right of first refusal on the commercialization of any potential line extensions of Sumavel DosePro. We will manufacture and supply the product to Desitin for commercial sale in the licensed territories. Desitin will pay us a specified transfer price for commercial product and a low single-digit percentage royalty on net sales of the product for an initial term, on a country to country basis until the greater of ten years after the first commercial sale in that country or the expiration, in such country, of the last patent right to expire under the licensed technology. After the initial term, in countries where the product has had commercial sales, the agreement will be automatically renewed on a country-by-country basis by additional successive specified periods unless it is terminated by either party giving a specified prior written notice.

Either party may terminate the agreement upon a material uncured breach, insolvency or bankruptcy, adverse event which affects the other party's ability to perform its obligations under the agreement or upon the enactment of any law, decree or regulation which would impair or restrict either our right, title or interest in the intellectual property, or Desitin's right to market or distribute the product in accordance with the agreement, either party's right to terminate or elect not to renew the agreement as provided therein, or our right to collect the purchase price or royalties under the agreement. Either party may also terminate the agreement by giving 90 days prior written notice if continued marketing in the relevant territories is no longer possible due to advice from a relevant regulatory authority or clinical review board in such countries or due to serious adverse events caused by Sumavel DosePro anywhere in the world. Desitin may terminate the agreement upon a competent regulatory authority in the territories either imposing therapeutic indications not acceptable to Desitin or requiring the product to be marketed as a generic drug. Desitin also may terminate the agreement if more than one study regarding bioequivalence is required to obtain marketing authorization. We may terminate the agreement upon a specified prior written notice if in each of a specified number of consecutive calendar years Desitin fails to meet a specified percentage of sales forecasts to be mutually agreed upon under the agreement, if Desitin takes any act impairing our intellectual property rights or if Desitin ceases to carry on business in the marketing of pharmaceutical products in the territories. Desitin may also terminate the agreement, upon written notice, if the price at which we supply our product to Desitin exceeds a specified threshold.

Alkermes License Agreement (formerly Elan Pharma International Limited)

In November 2007, we entered into a license agreement with Alkermes, which was amended in September 2009. Under the terms of this license agreement, Alkermes granted to us an exclusive license in the United States

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and its possessions and territories, with defined sub-license rights to third parties other than certain technological competitors of Alkermes, to certain Alkermes intellectual property rights related to our Zohydro product candidate. The agreement grants us the exclusive right under certain Alkermes patents and patent applications to import, use,