DURECT CORP
Form 10-K
March 02, 2012
Table of Contents

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

x **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: 000-31615

DURECT CORPORATION

(Exact name of registrant as specified in its charter)

Delaware	**94-3297098**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

10260 Bubb Road

Cupertino, CA 95014

(Address of principal executive offices, including zip code)

Registrant s telephone number, including area code: (408) 777-1417

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

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock $0.0001 par value per share	**The NASDAQ Stock Market LLC**
Preferred Share Purchase Rights	**(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 x

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15 of the Act. YES ¨ NO x

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period than the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES x 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 x 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 registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. x

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

Large accelerated filer ¨ Accelerated filer x Non-accelerated filer ¨ Smaller reporting company ¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). YES ¨ NO x

The aggregate market value of the voting stock held by non-affiliates of the registrant was approximately $167,868,268 as of June 30, 2011 based upon the closing sale price on the NASDAQ Global Market reported for such date. Shares of Common Stock held by each officer and director and by each person who may be deemed to be an affiliate have been excluded. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

There were 87,547,149 shares of the registrant s Common Stock issued and outstanding as of February 29, 2012.

DOCUMENTS INCORPORATED BY REFERENCE

Part III incorporates information by reference from the definitive Proxy Statement for the 2012 annual meeting of stockholders, which is expected to be filed not later than 120 days after the Registrant s fiscal year ended December 31, 2011.

Table of Contents

DURECT CORPORATION

ANNUAL REPORT ON FORM 10-K

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2011

TABLE OF CONTENTS

Table of Contents

PART I

Item 1. Business.

Overview

We are a specialty pharmaceutical company focused on the development of pharmaceutical products based on our proprietary drug delivery technology platforms. Our product pipeline currently consists of seven investigational drug candidates in clinical development, with one program the subject of a New Drug Application (NDA) with the U.S. Food and Drug Administration (FDA) for which a Complete Response Letter was received in June 2011, one program in Phase III, two programs in Phase II and three programs in Phase I. The more advanced programs are in the field of pain management and we believe that each of these targets large market opportunities with product features that are differentiated from existing therapeutics. We have other programs underway in fields outside of pain management, including several efforts underway which seek to improve the administration of biotechnology agents such as proteins and peptides.

A central aspect of our business strategy involves advancing multiple product candidates at one time, which is enabled by leveraging our resources with those of corporate collaborators. Thus, certain of our programs are currently licensed to corporate collaborators on terms which typically call for our collaborator to fund all or a substantial portion of future development costs and then pay us milestone payments based on specific development or commercial achievements plus a royalty on product sales. At the same time, we have retained the rights to other programs, which are the basis of future collaborations and over time may provide a pathway for us to develop our own commercial, sales and marketing organization.

Product Research and Development Programs

Our development efforts are focused on the application of our pharmaceutical systems technologies to potential products in a variety of chronic and episodic disease areas including pain, central nervous system (CNS) disorders, cardiovascular disease and other chronic diseases. Our more advanced product research and development efforts in these areas are set forth in the following table:

Product Candidate	Disease/Indication	Collaborator	Technology Platform	Stage
Remoxy (Oral controlled release oxycodone)	Chronic Pain	Pfizer/Pain Therapeutics (worldwide)	ORADUR	NDA resubmitted in December 2010 but not approved/ Complete Response Letter received in June 2011
POSIDUR (Controlled release injection of bupivacaine)	Post-Operative Pain	Hospira (U.S. and Canada); DURECT retains rights in rest of world	SABER	Phase III
ELADUR (Transdermal bupivacaine)	Pain	DURECT retains worldwide rights	TRANSDUR	Phase II
TRANSDUR-Sufentanil (Transdermal sufentanil)	Chronic Pain	DURECT retains worldwide rights	TRANSDUR	Phase II

NOTE: POSIDUR , SABER , TRANSDUR , ORADUR®, ELADUR®, DURIN®, CHRONOGESIC®, MICRODUR , ALZET® and LACTEL® are trademarks of DURECT Corporation. Other trademarks referred to belong to their respective owners.

Table of Contents

Product Candidate	Disease/Indication	Collaborator	Technology Platform	Stage
ORADUR-based opioid (hydrocodone)	Pain	Pfizer/Pain Therapeutics (worldwide)	ORADUR	Phase I
ORADUR-based opioid (hydromorphone)	Pain	Pfizer/Pain Therapeutics (worldwide)	ORADUR	Phase I
ORADUR-ADHD	Attention Deficit Hyperactivity Disorder (ADHD)	Orient Pharma (defined Asian and South Pacific countries); DURECT retains development and commercialization rights in North America, Europe, Japan and all other countries	ORADUR	Phase I
ORADUR-based opioid (oxymorphone)	Pain	Pfizer/Pain Therapeutics (worldwide)	ORADUR	IND accepted by the FDA
Relday (risperidone)	Schizophrenia/biopolar disorder	Zogenix (worldwide)	SABER	Preclinical
Various	Biologics Programs/Research Programs in other Therapeutic Categories	DURECT retains worldwide rights, except for certain feasibility projects whereby our collaborator generally has an option on rights	SABER/ DURIN	Preclinical/ Research Stage

Remoxy (ORADUR-Oxycodone)

Market Opportunity. Chronic pain is usually the result of an ongoing condition or significant problem associated with chronic diseases, including cancer, various neurological and skeletal disorders and other ailments such as severe arthritis or a debilitating back injury. As the condition gets worse, the pain often gets worse. Also, long-lasting pain can affect the nervous system to the point where pain persists even if the condition that originally caused the pain is stabilized or improved. This is one reason patients often need stronger pain medication even if their underlying condition has been treated. Chronic pain affects as many as 50 million Americans annually. OxyContin®, a brand name extended-release oral oxycodone-based painkiller, accounted for over $3.0 billion in worldwide sales in 2010.

Development Strategy. Remoxy is an oral, long-acting oxycodone gelatin capsule under development with Pain Therapeutics, Inc. (Pain Therapeutics) to which we have licensed exclusive, worldwide, development and commercialization rights under a development and license agreement entered into in December 2002. Subsequently, Pain Therapeutics has sublicensed the worldwide commercialization rights of Remoxy (except for Australia and New Zealand) to King Pharmaceuticals, Inc. (King) and, as of March 2009, we began working directly with King on further development of Remoxy. In February 2011, Pfizer Inc (Pfizer) acquired King and thereby assumed the rights and obligations of King with respect to Remoxy. Remoxy is formulated with our ORADUR technology and incorporates several abuse-deterrent properties with the convenience of twice-a-day dosing. Oxycodone is also the active drug ingredient in OxyContin, a brand name extended-release oral

Table of Contents

painkiller, which achieved annual worldwide sales of greater than $3.0 billion in 2010. Under the agreement with Pain Therapeutics, subject to and upon the achievement of predetermined development and regulatory milestones, we are entitled to receive milestone payments of up to $9.3 million in the aggregate for Remoxy and other licensed ORADUR-based opioids. As of December 31, 2011, we had received $1.7 million in cumulative milestone payments. We also receive reimbursement for our research and development efforts on Remoxy and a manufacturing profit on our supply of key product excipients for use in Remoxy. In addition, if commercialized, we will receive royalties for Remoxy and other licensed products which do not contain an opioid antagonist of between 6.0% to 11.5% of net sales depending on sales volumes.

Clinical Program. In December 2007, Pain Therapeutics and King announced that the pivotal Phase III trial for Remoxy successfully met its primary endpoint ($p<0.01$) that was prospectively defined by the FDA during the Special Protocol Assessment process. In addition, the study achieved statistically significant results in secondary endpoints such as Quality of Analgesia ($p<0.01$) and Global Assessment ($p<0.01$). Pain Therapeutics submitted an NDA for Remoxy to the FDA in June 2008, and in August 2008 the FDA accepted the NDA and granted priority review. In December 2008, Pain Therapeutics received a Complete Response Letter for its NDA for Remoxy in which the FDA determined that the NDA was not approved. According to Pain Therapeutics, the FDA indicated that additional non-clinical data would be required to support the approval of Remoxy, but the FDA has not requested or recommended additional clinical efficacy studies prior to approval. King assumed responsibility for further development of Remoxy from Pain Therapeutics in March 2009. In July 2009, King met with the FDA to discuss the Complete Response Letter. According to King and Pain Therapeutics, the outcome of that meeting provided King with a clearer path forward to resubmit the Remoxy NDA and to address all FDA comments in the Complete Response Letter. King took over the NDA from Pain Therapeutics and resubmitted the NDA in December of 2010. On June 23, 2011, a Complete Response Letter from the FDA was received by Pfizer on the resubmission to the NDA for REMOXY. The FDA s June 2011 Complete Response Letter raised concerns related to, among other matters, the Chemistry, Manufacturing, and Controls section of the NDA for REMOXY. Pfizer has efforts underway to resolve these issues. Sufficient information does not yet exist to accurately assess the time required to resolve the concerns raised in the FDA s Complete Response Letter. On January 31, 2012, Pfizer stated that it intended to conduct two bioavailability studies in the second quarter of 2012 and anticipated meeting with the FDA during the third quarter to discuss next steps.

Additional ORADUR-Opioid Products in Development

Since 2006, we also worked with Pain Therapeutics and King on the development of three additional ORADUR abuse-resistant opioid drug candidates which would address the chronic pain market. Phase I clinical trials have been conducted for two of these ORADUR-based products (hydrocodone and hydromorphone), and an IND has been accepted by the FDA for the third ORADUR-based opioid (oxymorphone).

POSIDUR

Market Opportunity. According to data published by the Center for Disease Control and Prevention, there are approximately 72 million ambulatory and inpatient surgical procedures performed annually in the U.S. Epidemiological studies indicate that up to 100% of surgical patients experience postoperative pain, with 50-75% reporting inadequate pain relief. The current standard of care for post-surgical pain includes oral opiate and non-opiate analgesics and muscle relaxants. While systemic opioids can effectively control post-surgical pain, they commonly cause side effects including drowsiness, constipation, nausea and vomiting and cognitive impairment. Effective pain management can be compromised if patients fail to adhere to recommended dosing regimens because they are suffering from these side effects. Post-surgical pain also can be treated effectively with local anesthetics; however, the usefulness of current conventional medications is limited by their short duration of action.

Table of Contents

Development Strategy. We are developing POSIDUR, a sustained-release formulation of bupivacaine, using our SABER delivery system for the treatment of post-surgical pain. Bupivacaine is a local anesthetic agent currently used in the hospital for anesthesia and analgesia and for which the patent covering the chemical entity has expired. The physician would administer POSIDUR at the time of surgery to the surgical site. This formulation is designed to provide sustained regional analgesia from a single dose. We believe that by delivering effective amounts of a potent analgesic to the location from which the pain originates, improved pain control can be achieved with minimal exposure to the remainder of the body and reduced need for systemic analgesics, thus minimizing side effects. POSIDUR is intended to provide local analgesia for up to 3 days, which we believe coincides with the time period of greatest need for post-surgical pain control in most patients.

POSIDUR is the subject of a collaboration agreement with Hospira, Inc. (Hospira) to develop and commercialize POSIDUR in the U.S. and Canada. POSIDUR was also the subject of a collaboration agreement with Nycomed Danmark ApS (Nycomed) to develop and commercialize POSIDUR in the European Union (E.U.) and certain other countries. In January 2012 Nycomed (now owned by Takeda) gave notice that its rights with respect to POSIDUR were being returned to us. Please see Third Party Collaborations for additional information.

Clinical Program. Our POSIDUR clinical development program has been devised to establish the safety and efficacy of POSIDUR for the treatment of post-surgical pain for up to 3 days. Toward that end, we have conducted 13 clinical studies in a variety of surgical models including hernia, appendectomy, shoulder surgery and various abdominal procedures. We have dosed over 1,000 humans with either POSIDUR or SABER-placebo, of which over 680 patients received POSIDUR. Leveraging on the well established history of use of bupivacaine, our strategy is to pursue a section 505(b)2 NDA application.

Phase IIb Inguinal Hernia Trial

Design

The POSIDUR Phase IIb clinical trial was designed to evaluate the tolerability, activity, dose response and pharmacokinetics of POSIDUR in patients undergoing open inguinal hernia repair. The trial was conducted in Australia and New Zealand as a multi-center, randomized, double blind, placebo-controlled study in 122 patients. Study patients were randomized into three treatment groups: patients that were treated with POSIDUR 2.5 mL (n=43), POSIDUR 5 mL (n=47) and placebo (n=32). The co-primary efficacy endpoints for the study were Mean Pain Intensity on Movement area under the curve (AUC), a measure of pain over a period of 1-72 hours post-surgery, and the proportion of patients requiring supplemental opioid analgesic medication during the study. Secondary efficacy endpoints included Mean Pain Intensity on Movement AUC over the period 1-48 hours post-surgery, mean total consumption of supplemental opioid analgesic medication, and time to first use of supplemental opioid analgesic medication. The threshold for statistical significance was considered to be at the $p<0.05$ level.

Results

Pain Control

In relation to the co-primary endpoint of pain reduction as measured by Mean Pain Intensity on Movement AUC 1-72 hours post-surgery, the patient group treated with POSIDUR 5 mL reported thirty-one percent (31%) less pain versus placebo ($p=0.0033$). A secondary endpoint measure reported a thirty-five percent (35%) reduction of pain as measured by Mean Pain Intensity on Movement AUC for the period 1-48 hours post-surgery between the POSIDUR 5 mL treatment group versus placebo ($p=0.0007$).

Consumption of Supplemental Opioid Analgesic Medication

Fifty-three percent (53%) of the study patients in the POSIDUR 5 mL group took supplemental opioid analgesic medications versus seventy-two percent (72%) of the placebo patients ($p=0.0909$). Although this

Table of Contents

positive trend for this co-primary endpoint in favor of the POSIDUR 5 mL group was not statistically significant, both secondary endpoints measuring opioid analgesic medication consumption were met at a statistically significant level. During the periods of 1-24 hours, 24-48 hours and 48-72 hours after surgery, placebo patients consumed approximately 3.5 (p=0.0009), 2.9 (p=0.0190) and 3.6 (p=0.0172) times more supplemental opioid analgesic medications (mean total daily consumption of opioid analgesic medication in morphine equivalents), respectively, than the POSIDUR 5 mL treatment group. In addition, the median time to first use of supplemental opioid analgesic medication after surgery for the placebo patients was 2.7 hours versus >72 hours for the POSIDUR 5 mL treatment group (p=0.0197).

Dose Finding

POSIDUR administered at the dose of 5 mL showed statistically significant activity relative to placebo whereas POSIDUR administered at 2.5 mL showed a positive trend relative to placebo on certain parameters but the results were not statistically significant.

Safety

The patient groups treated with POSIDUR 5 mL and POSIDUR 2.5 mL showed comparable safety profiles as the patient groups treated with placebo, and the drug administration appeared well tolerated. The side effects commonly observed with opioid medication use were less frequent in the POSIDUR 5 mL and 2.5 mL treatment groups compared to placebo.

Other Phase II Clinical Trials

In addition to the Phase IIb clinical trial described above, we have also conducted smaller exploratory Phase II studies in hernia, shoulder arthroscopy and appendectomy surgeries to evaluate different application techniques, clinical design and conduct as well as other investigational factors. These trials have been conducted in multiple cohorts, generally consisting of approximately 6 to 21 patients in each treatment group. In all the exploratory studies, patient groups treated with POSIDUR 5 mL and POSIDUR 2.5 mL showed comparable safety profiles as the patient groups treated with placebo, and the drug administration appeared well tolerated. Some treatment groups from these exploratory studies utilizing POSIDUR have shown positive activity as measured by reduction of pain or consumption of supplemental opioid analgesic medication versus placebo, while other treatment groups have not. We have evaluated these studies to understand the different results observed, and have applied our learnings in the design of our Phase III program.

In December 2009, we announced results from a 60 patient Phase IIb clinical trial of POSIDUR in patients undergoing arthroscopic shoulder surgery. Top line results showed a consistent reduction of pain scores (as measured by mean pain intensity on movement AUC, time normalized under the curve, during the period 0 to 72 hours post-surgery) in parallel with a reduction of opioid use (as measured by the amount of opioids taken in the three days post-surgery) in favor of POSIDUR versus placebo. These reductions were not statistically significant given the size of the study. In addition, there was a comparable safety profile between the two groups in this study and POSIDUR appeared well tolerated.

In June 2010, we announced results from a European Phase IIb hysterectomy clinical trial conducted by Nycomed of POSIDUR. In this study, 115 patients were randomly assigned to one of three treatment groups prior to undergoing open hysterectomy surgery: POSIDUR at a dose of 5 mL, an active comparator (commercially available bupivacaine HCI solution) or SABER-Placebo (SABER vehicle without drug). All patients were given a background pain treatment consisting of a daily dose of two or four grams (depending on the patient s weight) of paracetamol (acetaminophen). In addition, each patient was provided supplemental opioid rescue medication, if needed. With respect to efficacy, the primary endpoints of the study were to demonstrate: (1) non-inferiority of POSIDUR to SABER-Placebo (with all groups taking the background and supplemental pain treatment as

Table of Contents

described above) in terms of pain intensity on movement area under the curve (AUC) during the period 1-72 hours post-surgery, and (2) superiority of POSIDUR against SABER-Placebo in the total use of opioid rescue analgesia 0-72 hours post-surgery. Results from this study show that the first primary efficacy endpoint was met. With respect to the second primary efficacy endpoint, no statistically significant difference was shown in opioid use between the POSIDUR and SABER-Placebo groups. Secondary comparisons were performed towards the active comparator group with similar results. In this study, patients in all treatment groups only took a meaningful amount of opioids during a shorter period of time after surgery than was expected. In this study, there were no indications of systemic safety issues. The plasma concentration profiles were consistent with previous studies, confirming the sustained release profile of the product. Local observations (most commonly coded as post procedural haematomas) at the surgical site were observed with frequency in the POSIDUR and SABER-Placebo groups and not observed in the active comparator group. These events were temporary and resolved without treatment.

In February 2011, we announced results from a European Phase IIb shoulder clinical trial conducted by Nycomed of POSIDUR. In this study, 107 patients were randomly assigned to one of three treatment groups prior to undergoing elective arthroscopic shoulder surgery: POSIDUR at a dose of 5 mL, an active comparator (commercially available bupivacaine HCI solution) or SABER-Placebo (SABER vehicle without drug). All patients were given a background pain treatment consisting of a daily dose of two or four grams (depending on the patient s weight) of paracetamol (acetaminophen). In addition, each patient was provided supplemental opioid rescue medication, if needed. With respect to efficacy, the primary endpoints of the study were to demonstrate: (1) non-inferiority of POSIDUR to SABER-Placebo (with all groups taking the background and supplemental pain treatment as described above) in terms of pain intensity on movement area under the curve (AUC) during the period 1 72 hours post-surgery, and (2) superiority of POSIDUR against SABER-Placebo in the total use of opioid rescue analgesia 0 72 hours post-surgery. Results from this study demonstrate that the POSIDUR group experienced a statistically significant reduction in pain intensity of approximately 19% (p=0.0219) versus SABER-Placebo. The results of the pre-specified primary analysis indicated a clear clinically relevant trend in opioid sparing for POSIDUR compared to SABER-placebo and the pre-specified sensitivity analysis showed a statistically significant reduction of approximately 67% (p=0.013) in median opioid use in favor of POSIDUR. No statistical differences were found when POSIDUR was compared to the active comparator arm. Overall there was a comparable safety profile between the three groups in this study and POSIDUR appeared well tolerated.

U.S. Phase III Program

In January 2012, we announced top-line results for BESST (Bupivacaine Effectiveness and Safety in SABER Trial), a Phase III clinical trial in the U.S. BESST was an international, multi-center, randomized, double-blind, controlled trial evaluating the safety, efficacy, effectiveness, and pharmacokinetics of POSIDUR in 305 patients undergoing a variety of general abdominal surgical procedures. Eligible patients were randomly assigned to one of three cohorts:

Cohort 1: An active comparator cohort in which patients were randomized to receive either POSIDUR 5.0 mL or commercially available Bupivacaine HCl solution after laparotomy.

Cohort 2: An active comparator cohort in which patients were randomized to receive either POSIDUR 5.0 mL or commercially available Bupivacaine HCl solution after laparoscopic cholecystectomy.

Cohort 3: A double blind, placebo controlled cohort in which patients were randomized to receive either POSIDUR 5.0 mL or SABER-Placebo after laparoscopically-assisted colectomy.

Efficacy evaluation in the BESST trial encompassed a number of parameters. The two co-primary efficacy endpoints for Cohort 3 were mean pain intensity on movement (normalized) Area Under the Curve (AUC) during the period 0-72 hours post-dose and mean total morphine equivalent opioid dose for supplemental analgesia during the period 0-72 hours post-dose. The purpose of Cohorts 1 and 2 was to give us additional experience with the use of POSIDUR in a broader group of surgeries and patients.

Table of Contents

Results

Primary Endpoints Cohort 3 (POSIDUR versus SABER-Placebo, laparoscopically-assisted colectomy)

With respect to the co-primary efficacy endpoint of pain reduction as measured by mean pain intensity on movement (normalized) Area Under the Curve (AUC) during the period 0-72 hours post-dose, the patient group treated with POSIDUR 5.0 mL (660 mg) reported a mean pain reduction in pain scores of approximately 7% (p=0.1466). The statistical analysis plan included pain on movement as recorded at scheduled times through an electronic diary plus pain scores reported whenever supplemental opioids were administered with such scores attributed as if they were pain on movement. In the prespecified sensitivity analysis (which includes only scheduled pain assessment on movement scores as collected on the electronic diary), the patient group treated with POSIDUR 5.0 mL reported approximately 10% less pain versus placebo (p=0.0410). In relation to the co-primary efficacy endpoint of median total morphine-equivalent opioid dose for supplemental analgesia during the period 0-72 hours post-dose, the patient group treated with POSIDUR reported approximately 16% less opioids consumed versus the placebo group (p=0.5897). The prespecified level for statistical significance is $p<0.05$, unless one of the co-primary efficacy endpoints is not met in which case the standard for statistical significance for the remaining endpoint is $p<0.025$.

Cohorts 1 and 2 (POSIDUR versus commercially available Bupivacaine HCl solution after laparotomy and after laparoscopic cholecystectomy, respectively)

Cohorts 1 and 2 were prespecified to be pooled due to their small sample size. For Cohorts 1 and 2 (pooled), the mean reduction in pain on movement was approximately 20% (p=0.0111) for the POSIDUR group compared to the patient group treated with bupivacaine HCl. The median total morphine-equivalent opioid dose for supplemental analgesia during the period 0-72 hours post-dose for Cohorts 1 and 2 (pooled), the patient group treated with POSIDUR reported approximately 18% less opioids consumed compared to the bupivacaine HCl group (p=0.5455).

Safety

Overall, the POSIDUR patient groups showed a similar systemic safety profile as the patient groups treated with SABER-Placebo and active comparator. There were no signs of systemic safety issues. Local site reactions were observed more frequently in the POSIDUR and SABER-Placebo groups than in the active comparator groups; most of these observations were discolorations, the majority of which resolved without treatment during the trial. No negative safety signal has been seen in the initial cardiac and neurologic safety assessment in BESST; however further analysis is underway.

Next Steps

After a complete analysis of the BESST data and preparation of integrated safety and efficacy summeries combining our previous well controlled studies, we intend to hold a pre-NDA meeting with the FDA which we expect to occur in mid-2012, with a potential NDA submission under section 505(b)2 later this year.

ELADUR

Market Opportunity. Pain can arise from a variety of diseases and conditions, and in many instances, pain originates from a localized point in the body and can benefit from treatments which are administered and act locally as opposed to in a systemic fashion. One such example is post-herpetic neuralgia (PHN or post-shingles pain), a debilitating complication of herpes zoster, which is usually defined as the presence of pain at the site of eruption that lasts more than a month after the onset of a zoster eruption. The prevalence of PHN (including PHN lasting more than one year) is estimated to be approximately 144,000 people in the U.S. In addition to PHN, there are a number of other widely prevalent chronic and acute local pain conditions (e.g., neuropathic pain, sprains, strains, and contusions) that could benefit from a locally acting pain product.

Table of Contents

Development Strategy. Our transdermal bupivacaine patch (ELADUR) under development is intended to provide continuous delivery of bupivacaine for up to three days from a single application, as compared to a wearing time limited to 12 hours with currently available lidocaine patches. We anticipate that ELADUR will have several potential differentiating attributes compared with currently marketed lidocaine patches, including extended duration of action and better wearability. During 2008, we received Orphan Drug Designation for bupivacaine for relief of persistent pain associated with PHN, such that if ELADUR is the first bupivacaine product approved for PHN, ELADUR would be eligible to receive seven years of data exclusivity following its approval by the FDA. There can be no assurance that ELADUR will be the first bupivacaine product approved for PHN, and therefore ELADUR may not be entitled to the seven year data exclusivity period for orphan drugs. Effective October 2008, we licensed the worldwide development and commercialization rights for ELADUR to Alpharma Ireland Limited (Alpharma), which was acquired by King in December 2008. In February 2011, Pfizer acquired King and thereby assumed the rights and obligations of King with respect to ELADUR. In February 2012, Pfizer gave notice that its rights with respect to ELADUR were being returned to us. We intend to initiate discussions with other potential partners regarding licensing development and commercialization rights to this program. Please see Third Party Collaborations for additional information.

Clinical Program. In 2007, we reported positive results from a 60 patient Phase IIa clinical trial for ELADUR. In this study of patients suffering from PHN, ELADUR showed improved pain control versus placebo during the 3-day continuous treatment period. In addition, ELADUR appeared well tolerated overall, and patients treated with ELADUR and placebo exhibited similar safety profiles. In 2008, we conducted manufacturing scale-up and processing studies to secure additional supplies for Phase II and Phase III clinical trials, and developed our clinical and regulatory strategy for further development of this program. We reported top line data from a Phase II clinical trial conducted by King for ELADUR in April 2011. In this study of 263 patients suffering from chronic low back pain, the primary efficacy endpoint of demonstrating a positive treatment difference for the mean change in pain intensity scores from baseline to the mean of weeks 11 and 12 between ELADUR as compared to placebo was not met.

TRANSDUR-Sufentanil Patch

Market Opportunity. Chronic pain affects as many as 50 million Americans annually. One major class of drugs utilized to treat chronic pain is comprised of oral opioids, such as OxyContin, a branded extended-release oral oxycodone-based painkiller which accounted for over $3.0 billion in worldwide sales in 2010. Another major class of drugs utilized to treat chronic pain is transdermally delivered opioids such as Duragesic®, a leading transdermal fentanyl product which accounted for approximately $750 million in worldwide sales in 2010. It is our belief that a best-in-class sufentanil patch could compete effectively in both the transdermal fentanyl patch market and in the oral opioid market.

Development Strategy. Our transdermal sufentanil patch (TRANSDUR-Sufentanil) under development is based on our proprietary TRANSDUR transdermal technology and is intended to provide continuous delivery of sufentanil for up to seven days from a single application, as compared to the two to three days of relief provided by currently available fentanyl patches. Sufentanil is a highly potent opioid that is currently used in hospitals as an analgesic for which the patent covering the chemical entity has expired. We anticipate that the small size of our sufentanil patch (potentially as small as 1/5th the size of currently marketed transdermal fentanyl patches for a therapeutically equivalent dose) and longer duration of delivery may offer improved convenience and compliance for patients.

In March 2005, we entered into an agreement with Endo Pharmaceuticals, Inc. (Endo) granting Endo exclusive rights to develop, market and commercialize TRANSDUR-Sufentanil in the U.S. and Canada. In February 2009, Endo notified us that it was terminating the license agreement with us, and thereby returning Endo s rights to develop and commercialize TRANSDUR-Sufentanil in the U.S. and Canada to us effective August 26, 2009. We are in discussions with potential collaborators regarding licensing development and commercialization rights to this program to which we hold worldwide rights.

Table of Contents

Clinical Program. In 2008, Endo successfully completed a Phase II clinical trial for TRANSDUR-Sufentanil in which they evaluated the conversion of patients on oral and transdermal opioids to TRANSDUR-Sufentanil. This Phase II trial met its primary and secondary objectives of establishing a successful dose-titration regimen and dose potency relationships, demonstrating safety and tolerability at the therapeutic dose, and achieving effective analgesic pain control. The Phase II data, extensive non-clinical data that had been generated by Endo and a potential regulatory pathway for the Phase III program were reviewed with the FDA at an end-of-Phase II meeting on February 19, 2009. It is our expectation that future development of this product candidate will follow a 505(b)2 pathway as discussed with FDA, which would allow us to reference third-party data, potentially reducing time and expense.

ORADUR-ADHD Program

Market Opportunity. Attention Deficit Hyperactivity Disorder (ADHD) is a neurobehavioral condition that is estimated to affect approximately 8% of U.S. children ages 4-17, according to the U.S. Centers for Disease Control and Prevention (the CDC). The principal characteristics of ADHD are inattention, hyperactivity, and impulsivity. The condition presents itself in childhood and can be life long as 65% of children with ADHD continue to present symptoms as adults. Over 50% of children with ADHD are currently treated with stimulants such as amphetamine or methylphenidate and sales of ADHD treatments were approximately $5.8 billion in 2010. The National Survey on Drug Use & Health estimates that 1.4 million Americans over the age of 12 abuse stimulants for euphoric highs and increased performance or wakefulness.

Development Strategy. We are developing a drug candidate (ORADUR-ADHD) based on DURECT s ORADUR Technology for the treatment of ADHD. This drug candidate is intended to provide once-a-day dosing with added tamper resistant characteristics to address common methods of abuse and misuse of these types of drugs. In August 2009, we entered into a development and license agreement with Orient Pharma Co., Ltd., a diversified multinational pharmaceutical, healthcare and consumer products company with headquarters in Taiwan, under which we granted to Orient Pharma development and commercialization rights in certain defined Asian and South Pacific countries to ORADUR-ADHD. DURECT retains rights to North America, Europe, Japan and all other countries not specifically licensed to Orient Pharma. Under our agreement with Orient Pharma, the parties will collaborate to perform a clinical development program through a Phase II study intended to produce a data package suitable for further development of the drug candidate by us as well as Orient Pharma in their respective territories. We will be responsible for formulation and study design of the Phase I and Phase II clinical program which Orient Pharma has agreed to fund and execute. Orient Pharma would be responsible for all remaining development and commercialization activities for ORADUR-ADHD in the licensed territory. If commercialized, we will be entitled to receive a royalty on sales of ORADUR-ADHD by Orient Pharma. Orient Pharma has committed to supply a portion of DURECT s commercial requirements in all territories other than the U.S. for ORADUR-ADHD. In 2010 and 2011, we conducted several Phase I clinical trials in this program with multiple formulations. Based on information from these trials, we are continuing to evaluate the lead formulations and are planning next steps in our ORADUR-ADHD program.

Relday

Market Opportunity. Risperidone is one of the most widely prescribed medications used to treat the symptoms of schizophrenia and bipolar I disorder in adults and teenagers 13 years of age and older. Relday is being developed to address unmet clinical needs in this large patient population. The existing long-acting injectable risperidone product, which achieved global net sales of $1.5 billion in 2010, requires twice monthly, 2 mL intramuscular injections with a 21 gauge or larger needle. We and Zogenix expect that, if approved, Relday will be the first once-monthly, subcutaneous antipsychotic product available in a needle-free delivery system to enter the long-acting injectable antipsychotic market. We and Zogenix also expect that, if approved, Relday will provide a new long-acting treatment option for patients that currently use daily oral antipsychotic products. The combined market for oral and injectable antipsychotic products is estimated at more than $16 billion in 2010. We and Zogenix believe the SABER controlled-release technology combined with Zogenix s DosePro technology

Table of Contents

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.

Development Strategy. Under the development and license agreement entered into in July 2011 after working together since October 2007 under a feasibility agreement, Zogenix will be responsible for the clinical development and commercialization of a proprietary, long-acting injectable formulation of risperidone using our SABER controlled-release formulation technology in combination with Zogenix s DosePro needle-free, subcutaneous drug delivery system. We will share non-clinical development responsibilities. Zogenix expects to initiate clinical studies for the new product candidate, Relday, in patients with schizophrenia in 2012 following filing of an Investigational New Drug (IND) application.

Biologics Programs

The proteins and genes identified by the biotechnology industry are large, complex, intricate molecules, and many are unsuitable as drugs. If these molecules are given orally, they are often digested before they can have an effect; if given by injection, they may be destroyed by the body s natural processes before they can reach their intended sites of action. The body s natural elimination processes require frequent, high dose injections that may result in unwanted side effects. As a result, the development of biotechnology molecules for the treatment of human diseases has been limited, and advanced drug delivery systems such as we possess are required to realize the full potential of many of these protein and peptide drugs. We have active programs underway to apply our drug delivery systems to various biotechnology drugs and drug candidates, and have entered into a number of feasibility studies with biotechnology and pharmaceutical companies to test their products in our systems.

Research Programs in other Therapeutic Categories

We have underway a number of research programs covering medical diseases and conditions other than pain. Such programs include various diseases and disorders including schizophrenia and cancer. In conducting our research programs and determining which particular efforts to prioritize for formal development, we employ a rigorous opportunity assessment process that takes into account the unmet medical need, commercial opportunity, technical feasibility, clinical viability, intellectual property considerations, and the development path including costs to achieve various critical milestones.

Industry Background

Chronic Diseases and Conditions

Although the pharmaceutical, biotechnology and medical device industries have played key roles in increasing life expectancy and improving health, many chronic, debilitating diseases continue to be inadequately addressed with current drugs or medical devices. Cardiovascular disease, cancer, neurodegenerative diseases, diabetes, arthritis, epilepsy and other chronic diseases claim the lives of millions of Americans each year. These illnesses are prolonged, are rarely cured completely, and pose a significant societal burden in mortality, morbidity and cost. The CDC estimates that the major chronic diseases are responsible for approximately 1.7 million deaths annually, or 70% of all deaths in the U.S. Chronic diseases cause major limitations in daily living for more than 25 million Americans. These diseases account for more than 70% of the cost of health care each year in the U.S. Demographic trends suggest that, as the U.S. population ages, the cost of treating chronic diseases will increase.

Current Approaches to Treatment

Drugs are available to treat many chronic diseases, but harmful side effects can limit prolonged treatment. In addition, patients with chronic diseases commonly take multiple medications, often several times a day, for the remainder of their lives. If patients fail to take drugs as prescribed, they often do not receive the intended benefits or may experience side effects, which are harmful or decrease quality of life. These problems become more

Table of Contents

common as the number of drugs being taken increases, the regimen of dosing becomes more complicated, or the patient ages or becomes cognitively impaired. It is estimated that only half of prescribed medicines are taken correctly.

The Pharmaceutical Industry. The pharmaceutical industry has traditionally focused on the chemical structure of small molecules to create drugs that can treat diseases and medical conditions. The ability to use these molecules as drugs is based on their potency, safety and efficacy. Therapeutic outcome and ultimately the suitability of a molecule as a drug depends to a large extent on how it gets into the body, distributes throughout the body, reacts with its intended site of action and is eliminated from the body. However, small molecules can act in diverse tissues throughout the body resulting in unwanted side effects.

Most drugs require a minimum level in blood and tissues to have significant therapeutic effects. Above a maximum level, however, the drug becomes toxic or has some unwanted side effects. These two levels define the therapeutic range of the drug. With conventional oral dosing and injections, typically a large quantity of drug is administered to the patient at one time, which results in high blood levels of drug immediately after dosing. Because of these high levels, the patient can be over-medicated during the period immediately following dosing, resulting in wasted drug and possible side effects. Due to distribution processes and drug clearance, the blood level of drug falls as time elapses from the last dose. For some duration, the patient is within the desired therapeutic range of blood levels. Eventually, the blood level of drug falls sufficiently such that the patient becomes under-medicated and experiences little or no drug effect until the next dose is administered.

The Biotechnology Industry. Over the past twenty-five years, the biotechnology revolution and the expanding field of genomics have led to the discovery of huge numbers of proteins and genes. Tremendous resources have been committed in the hope of developing drug therapies that would better mimic the body s own processes and allow for greater therapeutic specificity than is possible with small molecule drugs. Unfortunately, this huge effort has led to only a limited number of therapeutic products. The proteins and genes identified by the biotechnology industry are large, complex, intricate molecules, and many are unsuitable as drugs. If these molecules are given orally, they are often digested before they can have an effect; if given by injection, they may be destroyed by the body s natural processes before they can reach their intended sites of action. The body s natural elimination processes require frequent, high dose injections that may result in unwanted side effects. As a result, the development of biotechnology molecules for the treatment of human diseases has been limited.

The Drug Delivery Industry. In the last forty years, a multibillion dollar drug delivery industry has developed on the basis that medicine can be improved by delivering drugs to patients in a precise, controlled fashion. Several commercially successful oral controlled release products, transdermal controlled release patches, and injectable controlled release formulations have been developed. These products demonstrate that the delivery system can be as important to the ultimate therapeutic value of a pharmaceutical product as the active molecule or compound itself. However, drug delivery products on the market today can still be improved, for example, by providing reduced abuse potential, targeted delivery to minimize systemic effects and longer delivery durations where useful. Furthermore, traditional drug delivery products are generally not capable of administering biotechnology agents such as proteins and peptides.

The DURECT Solution: Pharmaceutical Systems

We are developing and commercializing pharmaceutical systems that will deliver the right drug to the right place, in the right amount and at the right time to treat chronic and episodic diseases and conditions. Our pharmaceutical systems enable optimized therapy for a given disease or patient population by controlling the rate and duration of drug administration. In addition, if advantageous for the therapy, our pharmaceutical systems can target the delivery of the drug to its intended site of action.

The Right Drug: By precisely controlling the dosage or targeting delivery to a specific site, we can expand the therapeutic use of compounds that would otherwise be too potent to be administered systemically, do not remain in the body long enough to be effective, or have significant side effects

Table of Contents

when administered systemically. This flexibility allows us to work with a variety of drug candidates including small molecules, proteins, peptides or genes.

The Right Place: In addition to enabling systemic delivery, if advantageous for the therapy, with precise placement of our proprietary catheters or biodegradable drug delivery formulations, we can design our pharmaceutical systems to deliver drugs directly to the intended site of action. This can ensure that the drug reaches the target tissue in effective concentrations, eliminate many side effects caused by delivery of the drug to unintended sites in the body, and reduce the total amount of drug administered to the body.

The Right Amount: Our pharmaceutical systems can automatically deliver drug dosages continuously within the desired therapeutic range for the duration of the treatment period, from days to up to months, without the fluctuations in drug levels typically associated with conventional pills or injections. This can reduce side effects, eliminate gaps in drug therapy, conveniently ensure accurate dosing and patient compliance, and may reduce the total amount of drug administered to the body.

The Right Time: Our pharmaceutical systems technologies are designed to minimize the need for intervention by the patient or care-giver and to enhance dosing compliance. In addition to reducing the cost of care, continuous drug therapy frees the patient from repeated treatment or hospitalization, improving convenience and quality of life. Our systems are well-suited to deliver drug for the right period of time for the intended indication, whether for hours or days for acute indications or months or years for treating chronic, debilitating diseases such as chronic pain, cancer, heart disease, and neurodegenerative diseases. We believe that it is more effective to treat chronic diseases with continuous, long-term therapy than with alternatives such as multiple conventional injections or oral dosage forms that create short-term effects.

DURECT Pharmaceutical Systems Technology

Our pharmaceutical systems combine engineering with proprietary small molecule pharmaceutical and biotechnology drug formulations to yield proprietary delivery technologies and products. Through this combination, we are able to control the rate and duration of drug administration, as well as, when desired, target the delivery of the drug to its intended site of action, allowing our pharmaceutical systems to meet the special challenges associated with treating medical conditions over an extended period of time. Our pharmaceutical systems can enable new drug therapies or optimize existing therapies based on a broad range of compounds, including small molecule pharmaceuticals as well as biologics such as proteins, peptides and genes.

Our pharmaceutical systems are suitable for providing long-term drug therapy because they store highly concentrated, stabilized drugs in a small volume and can protect the drug from degradation by the body. This, in combination with our ability to continuously deliver precise and accurate doses of a drug, allows us to extend the therapeutic value of a wide variety of drugs, including those which would otherwise be ineffective, too unstable, too potent or cause adverse side effects. In some cases, delivering the drug directly to the intended site of action can improve efficacy while minimizing unwanted side effects elsewhere in the body, which often limit the long-term use of many drugs. Our pharmaceutical systems can thus provide better therapy for chronic diseases or conditions, or for certain acute conditions where longer drug dosing is required or advantageous, by replacing multiple injection therapy or oral dosing, improving drug efficacy, reducing side effects and ensuring dosing compliance. Our pharmaceutical systems can improve patients quality of life by eliminating more repetitive treatments, reducing dependence on caregivers and allowing patients to lead more independent lives.

We currently have five major technology platforms:

The SABER Delivery System

The SABER system is a patented controlled-release technology that can be formulated for systemic or local administration of active agents via the parenteral or oral route. We are researching and developing a variety of

Table of Contents

controlled-release products based on the SABER technology. These include injectable controlled release products for systemic and local delivery and oral products. We believe that our SABER system can provide the basis for the development of a state-of-the-art biodegradable, controlled-release injectable. The SABER system uses a high-viscosity base component, such as sucrose acetate isobutyrate (SAIB), to provide controlled release of a drug. When the high viscosity SAIB is formulated with drug, biocompatible excipients and other additives, the resulting formulation is liquid enough to inject easily with standard syringes and needles. After injection of a SABER formulation, the excipients diffuse away, leaving a viscous depot. Depending on how it is formulated, the SABER system can successfully deliver therapeutic levels of a wide spectrum of drugs from one day to three months from a single injection. Based on research and development work to date, our SABER technology has shown the following advantages:

Peptide/Protein Delivery The chemical nature of the SABER system tends to repel water and body enzymes from its interior and thereby stabilizes proteins and peptides. For this reason, we believe that the SABER system is well suited as a platform for biotechnology therapeutics based on proteins and peptides.

Less Burst Typically, controlled release injections are associated with an initial higher release of drug immediately after injection (also called burst). Animal and human studies have shown that injectables based on the SABER technology can be associated with less post-injection burst than is typically associated with other commercially available injectable controlled release technologies.

High Drug Concentration Drug concentration in a SABER formulation can be as high as 30%, considerably greater than is typical with other commercially available injectable controlled release technologies. As a result, smaller injection volumes are possible with this technology.

Ease of Administration Prior to injection, SABER formulations are fairly liquid and therefore can be injected through small needles. Additionally, because of the higher drug concentration of SABER formulations, less volume is required to be injected. Small injection volumes and more liquid solutions are expected to result in easier, less painful administration.

Strong Patent Protection The SABER system, SABER-like materials, and various applications of this technology to pharmaceuticals, medical devices and drug delivery are covered by United States and foreign patents. See Patents, Licenses and Proprietary Rights below.

Ease of Manufacture Compared to microspheres and other polymer-based controlled release injectable systems, SABER is readily manufacturable at low cost.

The SABER Technology is the basis of POSIDUR, which recently completed a Phase III clinical trial in the U.S. In our clinical studies thus far, SABER formulations have been observed to be safe and well-tolerated, and no significant side effects or adverse events were reported.

The SABER Technology is also the basis for SucroMate Equine, an injectable animal health drug utilizing our SABER technology to deliver the peptide deslorelin. This is the first FDA approved SABER injectable product and it was launched in 2011 by our collaborator, CreoSalus, Inc.

The TRANSDUR Transdermal Delivery System

Our TRANSDUR technology is a proprietary transdermal delivery system that enables delivery of drugs continuously for up to 7 days. The TRANSDUR technology is the basis for TRANSDUR-Sufentanil for which we have conducted Phase II clinical trials and for which we hold worldwide development and commercialization rights. The TRANSDUR technology is also the basis for ELADUR, for which we have conducted two Phase II clinical trials and for which we hold worldwide development and commercialization rights.

Table of Contents

The ORADUR Sustained Release Gel Cap Technology

We are developing ORADUR sustained release oral technology based on our SABER technology. We believe that ORADUR can transform short-acting oral capsule dosage forms into sustained release oral products. Products based on our ORADUR technology can take the form of an easy to swallow gelatin capsule that uses a high-viscosity base component such as sucrose acetate isobutyrate (SAIB) to provide controlled release of active ingredients for a period of 12 to 24 hours of drug delivery. Oral dosage forms based on the ORADUR gel-cap may also have the added benefit of being less prone to abuse (e.g., by crushing or alcohol or water extraction) than other controlled release dosage forms on the market today. These properties have the potential to make ORADUR-based products an attractive option for pharmaceutical companies that seek to