DURECT CORP
Form 10-K/A
March 29, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K/A

(Amendment No. 1)

(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, 2016

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	(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 Section 15 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 than 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 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, 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 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

The aggregate market value of the voting stock held by non-affiliates of the registrant was approximately $135,648,965 as of June 30, 2016 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 141,892,834 shares of the registrant's Common Stock issued and outstanding as of March 9, 2017.

DOCUMENTS INCORPORATED BY REFERENCE

Part III incorporates information by reference from the definitive Proxy Statement for the 2017 annual meeting of stockholders, which is expected to be filed not later than 120 days after the Registrant's fiscal year ended December 31, 2016.

EXPLANATORY NOTE

This Form 10-K/A amends and restates in its entirety the Annual Report on Form 10-K of DURECT Corporation for the fiscal year ended December 31, 2016, as filed with the Securities and Exchange Commission on March 15, 2017 (the "Original Filing"), for the sole purpose of providing the stock performance graph in Part II, Item 5 of this Amendment No. 1, due to a filing error with the Original Filing. Except as expressly set forth herein, this Amendment No. 1 does not reflect events occurring after the date of the Original Filing or modify or update any of the other disclosures contained therein in any way other than as required to reflect the amendment discussed above. Accordingly, this Amendment No. 1 should be read in conjunction with our other filings with the Securities and Exchange Commission.

DURECT CORPORATION

ANNUAL REPORT ON FORM 10-K

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2016

TABLE OF CONTENTS

PART I

Item 1. Business.

Overview

We are a biopharmaceutical company with research and development programs broadly falling into two categories: (i) new chemical entities derived from our Epigenetic Regulator Program, in which we attempt to discover and develop molecules which have not previously been approved and marketed as therapeutics, and (ii) Drug Delivery Programs, in which we apply our formulation expertise and technologies largely to active pharmaceutical ingredients whose safety and efficacy have previously been established but which we aim to improve in some manner through a new formulation. We also manufacture and sell osmotic pumps used in laboratory research and design, develop and manufacture a wide range of standard and custom biodegradable polymers and excipients for pharmaceutical and medical device clients for use as raw materials in their products.

Our product pipeline currently consists of multiple investigational drug candidates in clinical development. DUR 928, a new chemical entity in Phase 1 development, is the lead candidate in DURECT's Epigenetic Regulator Program. An endogenous, orally bioavailable small molecule, DUR-928 has been shown in preclinical studies to play an important regulatory role in lipid homeostasis, inflammation, and cell survival. Human applications may include acute organ injury, chronic metabolic diseases such as nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH) and other liver diseases with both broad and orphan populations, and inflammatory skin conditions such as psoriasis. DURECT's advanced oral, injectable, and transdermal delivery technologies are designed to enable new indications and enhanced attributes for small-molecule and biologic drugs. One late-stage development program in this category is POSIMIR® (SABER®-Bupivacaine), an investigational analgesic product intended to deliver bupivacaine to provide up to 3 days of pain relief after surgery. Another late stage development program is REMOXY® ER (oxycodone), an investigational extended release pain relief drug based on DURECT's ORADUR® technology.

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 potential future collaborations and which over time may provide a pathway for us to develop our own commercial, sales and marketing organization.

New Chemical Entities from our Epigenetic Regulator Program

Our Epigenetic Regulator Program involves a multi-year collaborative effort with the Department of Internal Medicine at Virginia Commonwealth University (VCU), the VCU Medical Center and the McGuire VA Medical Center. The discoveries from this program are a result of more than 20 years of lipid research by Shunlin Ren, M.D., Ph.D., Professor of Internal Medicine at the VCU Medical Center and a recipient of multiple grants from the National Institutes of Health (NIH) for metabolic disease research. Epigenetics is the study of how reversible modifications of a cell's DNA or histones (proteins associated with DNA) affect gene expression without altering the DNA sequence. Epigenetics is the study of large scale effects on cellular function and interrelated collections of epigenetic modifications. Epigenetic modifications play an important role in regulation of key cellular processes. DUR-928 is the program's lead product candidate. We hold the exclusive worldwide right to develop and commercialize DUR-928 and related molecules discovered in the program.

NOTE: POSIMIR®, SABER®, CLOUD®, TRANSDUR®, ORADUR®, ALZET® and LACTEL® are trademarks of DURECT Corporation. Other trademarks referred to belong to their respective owners.

Our major product research and development efforts for new chemical entities derived from our Epigenetic Regulator Program are set forth in the following table:

Product Candidate	Disease/Indication	Collaborator	Stage
• DUR-928, oral	• Metabolic disorders / chronic liver diseases	• DURECT holds worldwide development and commercialization rights under a license with Virginia Commonwealth University	• Phase 1
• DUR-928, injectable	• Acute organ injuries	• DURECT holds worldwide development and commercialization rights under a license with Virginia Commonwealth University	• Phase 1
• DUR-928, topical	• Inflammatory skin conditions such as psoriasis	• DURECT holds worldwide development and commercialization rights under a license with Virginia Commonwealth University	• Phase 1

During the course of this program, a number of compounds have been identified that may have therapeutic utility for various diseases and syndromes for orphan indications as well as for broader patient populations. The lead compound from this program (DUR-928) is an endogenous, orally available small molecule that modulates the activity of various nuclear receptors that play an important regulatory role in lipid homeostasis, inflammation and cell survival.

The biological activity of DUR-928 has been demonstrated in over 10 different animal disease models involving three animal species. Five of these disease models represent chronic disorders of hepatic lipid accumulation and dysfunction (e.g., nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) associated with diabetes) and five represent acute organ injuries (endotoxin shock, kidney, liver and brain).

We are pursuing the development of DUR-928 through three broad programs for: (i) chronic metabolic disorders or liver diseases using an oral formulation, (ii) acute organ injury using an injectable formulation, and (iii) inflammatory skin disorders such as psoriasis using a topical formulation. We are also evaluating additional indications beyond these programs.

In pharmacokinetic and toxicity studies conducted in mice, hamsters, rats, dogs and monkeys, DUR-928 has been found to be orally available and safe at all doses tested to date. These non-clinical results supported the initiation of DUR-928 into human safety trials with an oral formulation. Pharmacokinetic and toxicity studies with an injectable formulation were also conducted in rats and dogs; these non-clinical results supported the initiation of DUR-928 into human safety trials with an injectable formulation.

Chronic Metabolic Disease Program with DUR-928

Market Opportunity. Non-alcoholic fatty liver disease (NAFLD) affects approximately 30% of adults and 10% of children (about 81 million individuals) in the U.S. Non-alcoholic steatohepatitis (NASH), a more severe and progressive form of NAFLD, is one of the most common chronic liver diseases worldwide, with an estimated

prevalence of more than 10% of adults in the U.S., Europe, Japan and other developed countries. No drug is currently approved for NAFLD or NASH. In addition to these large populations of patients with liver disease, there are a number of orphan patient populations with various forms of liver disease for which we may seek to develop DUR-928, such as primary sclerosing cholangitis (PSC).

Clinical Program. The initial Phase 1 trial of DUR-928 was a single-site, randomized, double-blinded, placebo-controlled, single-ascending-dose study that evaluated the safety, tolerability and pharmacokinetics of DUR-928 when orally administered. The 30-subject study evaluated DUR-928 in five cohorts of healthy volunteers receiving DUR-928 (n=20 on drug, 10 on placebo) at escalating doses that resulted in peak plasma concentrations greater than 100-fold higher than endogenous levels. DUR-928 was well-tolerated at all dose levels, with no serious treatment-related adverse events reported. We subsequently conducted a Phase 1 multiple-ascending-dose, oral administration trial in 20 healthy subjects (n=16 on drug, 4 on placebo). Following multiple dosing, DUR-928 was well-tolerated at all doses, with no clinically significant changes in vital signs, laboratory values or ECG parameters, no serious drug-related adverse events reported and no subjects withdrawing from the study. Peak plasma concentrations achieved were greater than 100-fold higher than endogenous levels, no accumulation in plasma concentrations were observed with repeat dosing, and dose related increases in plasma concentrations were observed with peak plasma concentration at approximately 2-6 hours after dosing. We also conducted a food effect study with 8 healthy volunteers and observed no food effect on absorption.

Our first patient trial utilizing DUR-928 was an open-label, single-ascending-dose safety and pharmacokinetic (PK) Phase 1b trial in liver function impaired (NASH) patients and matched control subjects (matched by age, body mass index and gender with normal liver function). This study was conducted in Australia in successive cohorts evaluating single-dose levels (first a low dose and then a high dose) of orally administered DUR-928.

An abstract for this study has been accepted and data from the study will be presented at the International Liver Congress™ 2017 organized by the European Association for the Study of the Liver (EASL) in Amsterdam, April 19-23, 2017. In addition, an abstract describing our two STAM™ NASH mouse model studies has been accepted at the AASLD Emerging Trends Conference 2017: Emerging Trends in Non-alcoholic Fatty Liver Disease in Washington, DC. That data will be presented on March 17, 2017.

The low dose cohort consisted of 10 subjects with NASH (of which 4 were cirrhotic and 6 were not cirrhotic) and 6 matched control subjects. After a PK/safety review of this cohort, the study proceeded to the high dose cohort utilizing a dose four times larger than the low dose cohort. The high dose cohort consisted of 10 subjects with NASH (of which 2 were cirrhotic and 8 were not cirrhotic) and 6 matched control subjects. One patient (with a prior history of arrhythmia and an ongoing viral infection) in the high dose cohort experienced a serious adverse event (shortness of breath) which occurred without unusual biochemical changes and resolved without intervention but was considered possibly treatment related by the physician due to its temporal association with dosing. In both the low and high dose cohorts, the PK parameters were comparable between the NASH patients and the matched control subjects. In addition, the systemic exposure following the low and high doses of DUR-928 was dose dependent.

While this study was not designed to assess efficacy, we observed a dose dependent reduction of certain biomarkers after a single oral dose of DUR-928. In both cohorts, IL-18, an inflammatory mediator implicated in both liver and kidney diseases, decreased hours after DUR-928 dosing, with the effect greater in the NASH patients. Full length

CK-18 (a generalized cell death marker) and cleaved CK-18 (a cell apoptosis marker) were both greatly reduced after low and high doses of DUR-928, with the effect, again, more pronounced in NASH patients.

Collectively, the reduction of these biomarkers plus results from our animal and cell culture studies suggest potential therapeutic activity of DUR-928 for patients with liver disease. However, additional studies are required to evaluate the safety and efficacy of DUR-928, and there is no assurance that these biomarker effects will be observed in a statistically significant manner, or that DUR-928 will demonstrate safety or efficacy in treating NASH or other liver diseases in larger controlled trials.

Acute Organ Injury Program with DUR-928

Market Opportunity. Acute organ injury, including acute kidney injury (AKI) and other conditions, is another area of major unmet medical need for which effective pharmaceutical treatment is often lacking. AKI alone, for example, affects approximately 2.8 million patients per year in the U.S. and is associated with increased mortality, prolonged hospital stays, and worsening of chronic kidney disease. In addition to this large population of patients, there are a number of orphan and broad patient populations with various forms of acute organ injury for which we may seek to develop DUR-928.

Clinical Program. In addition to the oral administration clinical studies described above, we have conducted a Phase 1 single-site, randomized, double-blinded, placebo-controlled, single-ascending-dose study that evaluated the safety, tolerability and pharmacokinetics of four doses of DUR-928 when administered by injection. The 24-subject study evaluated DUR-928 in four cohorts of healthy volunteers (16 subjects on the drug, 8 on placebo) at escalating doses that resulted in dose proportionality of systemic exposure. DUR-928 was well-tolerated at all dose levels, with no serious treatment-related adverse events reported. We also conducted a multiple-dose study involving 10 healthy volunteers, in which participants received DUR-928 for 5 consecutive days (8 subjects on the drug, 2 on placebo) with the next to highest dose in the single dose study. No serious treatment related adverse events were reported, no subjects withdrew from the study, no accumulation in plasma concentrations were observed with repeat dosing, and the pain scores and injection site reactions were minimal. We also conducted a single-ascending-dose intravenous infusion (IV) study with 16 healthy volunteers and observed no treatment related serious adverse events and the systemic exposure related to IV infusion was dose proportional.

Our second Phase 1b study with DUR-928, also being conducted in Australia, is an open-label, single-ascending-dose safety and pharmacokinetic study in patients with impaired kidney function (stage 3 and 4 chronic kidney disease) and matched control subjects (matched by age, body mass and gender with normal kidney function). This study is being conducted in successive cohorts evaluating single-dose levels (first a low dose and then a high dose) of DUR-928 administered by intramuscular injection.

The low dose cohort consisting of 6 kidney function impaired patients and 3 matched control subjects has been completed. After a PK/safety review of this cohort, the study has proceeded to the high dose cohort utilizing a dose four times larger than the low dose cohort. Data from the low dose cohort showed the PK parameters between the kidney function impaired patients and the matched control subjects were comparable. The high dose cohort of this study is currently enrolling patients.

We have been working with our clinical advisors to design several Phase 2 studies and are planning to submit INDs which are required to enable these studies to take place in the United States in 2017. In 2016, we held a pre-IND meeting with the Cardiovascular and Renal Products Division of the FDA, and we are utilizing feedback from that meeting as well as from our clinical advisors to prepare an IND which is required to enable a future Phase 2 kidney disease clinical trial in the United States. In addition, we submitted an initial IND in late December 2016 for a proposed Phase 2 liver study. The FDA has requested certain drug-drug interaction data and has made suggestions as to modifications to our proposed protocol. We are working to address FDA’s request and are consulting with our clinical advisors to finalize the study protocol.

Psoriasis Program with DUR-928

Market opportunity. Psoriasis is an autoimmune / inflammatory skin condition that affects approximately 7.5 million Americans. It is generally considered to be undertreated and there is treatment dissatisfaction. Current treatments consist of topicals, typically as first line therapy that seek to slow down or normalize excessive cell reproduction and reduce inflammation associated with psoriasis. Steroids are the most commonly used topical treatments and they are referred to as anti-inflammatory agents because they reduce the swelling and redness of lesions. If topicals are insufficient, then systemic medications are used