TITAN PHARMACEUTICALS INC
Form 10-K/A
April 02, 2019

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K/A

(Amendment No. 1)

(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, 2018

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 001-13341

TITAN PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**94-3171940**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification Number)**
400 Oyster Point Blvd., Suite 505, South San Francisco, California	**94080**
(Address of principal executive offices)	**(Zip code)**

Registrant's telephone number, including area code: (650) 244-4990

Securities registered pursuant to Section 12(b) of the Act: Common Stock, $0.001 par value

Securities registered pursuant to Section 12(g) of the Act: Common Stock, $0.001 par value

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(d) of the Exchange 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 Exchange Act 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 the filing requirements for the past 90 days. Yes x No ¨

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted 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 such files). x Yes ¨ No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) 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, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of “large accelerated filer,” “accelerated filer,” “smaller reporting company,” and “emerging growth company” in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer	¨	Accelerated filer	¨
Non-accelerated filer	x	Smaller Reporting Company	x
		Emerging growth company	¨

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ¨

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant based on the closing price on June 29, 2018 was approximately $22.6 million.

As of March 25, 2019, 13,413,628 shares of common stock, $0.001 par value, of the registrant were issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE:

NONE

EXPLANATORY NOTE

We are filing this Annual Report on Form 10-K/A (this "Amendment") to correct the Form 10/K for the year ended December 31, 2018 filed on April 1, 2019 (the "Original Filing"). The Amendment is being filed to correct all of the references to basic and diluted net loss per common share and the number of common shares used in such calculation for the year ended December 31, 2018 in the Original Filing, as well as the reference to net loss per share for the quarter ended December 31, 2018 that appears in the Notes to Financial Statements, which amounts were inadvertently transposed.

Except as described above, no changes have been made to the Original Filing and this Amendment does not modify, amend or update in any way any of the financial or other information contained in the Original Filing nor does it reflect events that may have occurred subsequent to the Original Filing.

PART I

NOTE REGARDING FORWARD-LOOKING STATEMENTS

Statements in this Annual Report on Form 10-K or in the documents incorporated by reference herein may contain "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 (the "Securities Act") and Section 21E of the Securities Exchange Act of 1934 (the "Exchange Act"). Reference is made in particular to the description of our plans and objectives for future operations, assumptions underlying such plans and objectives and other forward-looking terminology such as "may," "expects," "believes," "anticipates," "intends," "projects," or similar terms, variations of such terms or the negative of such terms. Forward-looking statements are based on management's current expectations. Actual results could differ materially from those currently anticipated due to a number of factors, including but not limited to, uncertainties relating to the commercialization of Probuphine®, financing and strategic agreements and relationships; difficulties or delays in the regulatory approval process; uncertainties relating to manufacturing, sales, marketing and distribution of our drug candidates that may be successfully developed and approved for commercialization; adverse side effects or inadequate therapeutic efficacy of our drug candidates that could slow or prevent product development or commercialization; dependence on third party suppliers; the uncertainty of protection for our patents and other intellectual property or trade secrets; and competition.

We expressly disclaim any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in our expectations or any changes in events, conditions or circumstances on which any such statement is based.

References herein to "we," "us," "Titan," and "our company" refer to Titan Pharmaceuticals, Inc. unless the context otherwise requires.

Probuphine ® and ProNeura™ are trademarks of our company. This Annual Report on Form 10-K also includes trade names and trademarks of companies other than Titan.

Item 1. Business

Overview

We are a pharmaceutical company developing therapeutics utilizing our proprietary long-term drug delivery platform, ProNeura**,** for the treatment of select chronic diseases for which steady state delivery of a drug provides an efficacy

and/or safety benefit. We have been transitioning to a commercial stage enterprise since May 25, 2018 when we reacquired Probuphine (buprenorphine) implant, or Probuphine, from our former licensee. Probuphine is the first product based on our ProNeura technology approved in the U.S. and Canada for the maintenance treatment of opioid use disorder, or OUD, in eligible patients. Since the reacquisition, we have been implementing a strategic plan focused on building a new foundation in support of an effective U.S. product relaunch targeting select OUD market segments best suited for Probuphine. Importantly, this included the establishment of a small experienced commercial team and the engagement of new strategic partners to facilitate the product order and distribution process in order to expand patient access to treatment with Probuphine.

ProNeura consists of a small, solid rod made from a mixture of ethylene-vinyl acetate, or EVA, and a drug substance. The resulting product is a solid matrix that is placed subdermally in the inside part of the upper arm in a short physician office-based outpatient procedure, and is removed in a similar manner at the end of the treatment period. The drug substance is released continuously through the process of diffusion-controlled dissolution, resulting in a steady rate of release (generally similar to intravenous administration), thereby avoiding the fluctuating peak and trough levels of oral dosing that often pose problems in many disease settings. We believe that our ProNeura long term drug delivery platform has the potential to be used in the treatment of other chronic conditions where maintaining stable, around the clock blood levels of a medication may benefit the patient and improve medical outcomes. While our primary focus is on the commercialization of Probuphine, we are also engaged in research and development efforts on a product pipeline based on this platform technology.

Probuphine

Probuphine, our first marketed product based on our ProNeura drug delivery technology, is a six-month buprenorphine implant for the maintenance treatment of opioid addiction in patients who have achieved and sustained prolonged clinical stability on a dose of up to 8 mg per day of oral buprenorphine, a patient population that represents approximately 25% of oral buprenorphine prescriptions. Treatment with Probuphine requires a healthcare provider to be trained and certified under the Probuphine Risk Evaluation and Mitigation Strategy, or REMS, program to insert a set of four implants (each approximately the size of a one-inch matchstick), sub-dermally in the patient’s upper arm under local anesthetic during a short (about 15 minutes) in-office procedure. After insertion, Probuphine delivers buprenorphine continuously for six months. Thereafter, the implants are removed and can be replaced with a new set of implants in the opposite arm.

The development and commercialization rights to Probuphine for the U.S. and Canada were originally licensed to Braeburn Pharmaceuticals, Inc., or Braeburn, in December 2012 and, following U.S. Food and Drug Administration, or FDA, approval in May 2016, Braeburn commenced a commercial launch during the first quarter of 2017. Progress was slow and we received royalty revenues of approximately $215,000 for the year ended December 31, 2017. In early 2018, Braeburn substantially reduced its field sales force and medical liaison personnel following its receipt of a complete response letter from the FDA for its weekly and monthly depot injection products. Anticipating a negative impact on Probuphine sales in the U.S., we began discussions for the return of the commercialization rights to Titan and on May 25, 2018, we entered into an agreement under which we received a $1 million payment from Braeburn, all of the Probuphine inventory and Braeburn's undertaking to provide certain transition services through the end of 2018.

During the latter half of 2018, we engaged the services of key consultants with expertise in launching and commercializing specialty pharmaceutical products, such as Probuphine, to fully understand Braeburn's product launch activities and its subsequent failure in the market. Based on feedback from key opinion leaders and these consultants, we believe that access to care for patients with Probuphine was negatively impacted by issues related to the complexity, timing and amount of reimbursement to patients and their doctors from insurance providers, as well as the restrictive requirements of the REMS program. Notwithstanding the enormity of the opioid addiction epidemic in our country, the hurdles to penetrating the market and growing sales of Probuphine have been considerable. We believe that a more focused commercialization strategy is necessary for success. This includes re-segmenting target customer markets and focusing on the following;

- high Probuphine-prescribing physicians with long-term recovery oriented treatment programs;
- residential treatment facilities, Veterans Administration hospitals and clinics that utilize medically assisted treatment, or MAT;
- academic institutions with addiction residency and fellowship programs; and
- the criminal justice system.

In addition, it is essential to improve access to reimbursement by third party payors which requires engaging the services of large specialty pharmacy organizations with pre-established relationships with the third-party payor plans. We also believe that Probuphine will benefit from the trend of opioid addiction treatment's move towards extended release formulations of buprenorphine, such as one month depot injections, the first of which was approved by the FDA at the end of 2017. The availability of one month depot injection formulations should enable clinicians and patients to become accustomed to longer duration procedure-oriented treatments, which in turn may lead to increased use of Probuphine during the maintenance treatment stage.

To implement the Probuphine relaunch, we undertook an equity financing in late September 2018 and engaged Dane Hallberg as our Chief Commercial Officer the following month. By the end of 2018, we had retained a small experienced sales and marketing team and began to address the product supply chain issues, notably the third-party payor pre-approval process and the logistics and distribution system, both of which have negatively impacted the product's acceptance and uptake. This has included identifying the need for a better centralized logistics service (referred to as a 'hub') that can service the combined process of product ordering and pre-approval by payors, as well as the expansion of the specialty pharmacy network to accelerate the pre-approval process and improve product distribution. In March 2019, we engaged the services of AllianceRx Walgreens Specialty Pharmacy, which we expect will help alleviate bottle necks in the third-party payor approval and product shipment process and are seeking to expand this network with a few additional large specialty pharmacies. We have also chosen AppianRx as our new hub which will be operational in early second quarter 2019. We believe that the engagement of AppianRx will lead to significant improvements in the automation and streamlining of the product supply chain process.

We are also committed to commencing two Phase 4 clinical studies with Probuphine during 2019 that were required by the FDA approval letter. One study will provide safety and pharmacokinetic information on both the implantation of Probuphine to a previously used anatomical site, as well as an alternate site, such as the abdomen. The second study is a registration study to evaluate the incidence of implant protrusion, migration and breakage during the treatment with Probuphine. We have been in discussions with the FDA regarding study design and protocol, and expect to commence the first study during the second quarter of 2019.

Probuphine received approval from the Canadian Health Authority in April 2018, and our licensee, Knight Therapeutics, Inc., or Knight, commenced its product launch in late October 2018. Knight is marketing Probuphine as a specialty product that, in addition to the typical benefits, can address some of the key needs in the Canadian market, particularly in providing buprenorphine maintenance treatment to OUD patients in rural communities where access to a clinic for frequent visits to fill prescriptions is not possible.

In March 2018, we entered into a purchase agreement with Molteni Farmaceuticci of Italy, or Molteni, pursuant to which Molteni acquired the European intellectual property related to Probuphine, including the Marketing Authorization Application, or MAA, that had been submitted to the European Medicines Agency, or EMA, in November 2017 and the exclusive right to commercialize the Titan supplied Probuphine product in Europe, as well as certain countries of the Commonwealth of Independent States, the Middle East and North Africa. We have been assisting Molteni in the MAA review process and during the second quarter of 2018 we had meetings with the rapporteur and co-rapporteur regulatory review teams to present our strategy and to address specific questions posed by these regulatory agencies. Together with Molteni, we have provided responses to all of the EMA's questions and expect that the final recommendation of the EMA on the Probuphine MAA and potential approval to occur during the second quarter of 2019.

ProNeura Continuous Drug Delivery Platform

Our ProNeura continuous drug delivery system consists of a small, solid rod made from a mixture of ethylene-vinyl acetate, or EVA and a drug substance. The resulting product is a solid matrix that is placed subdermally, normally in the inside part of the upper arm in a short physician office-based procedure and is removed in a similar manner at the end of the treatment period. The drug substance is released continuously through the process of diffusion-controlled dissolution. This results in a continuous, steady rate of release generally similar to intravenous administration. We believe that such long-term, almost linear release characteristics are desirable as they avoid the fluctuating peak and trough levels of oral dosing that often poses problems in a range of disease settings.

The ProNeura platform was developed to address the need for a simple, practical method to achieve continuous long-term drug delivery, and, depending on the characteristics of the compound to be delivered, can potentially provide treatment on an outpatient basis over extended periods of up to 12 months. We believe that the benefits of this technology have been demonstrated by the clinical results seen to date with Probuphine, and, in addition, that the development and regulatory process have been affirmed by the FDA approval of this product. We have demonstrated the feasibility of the ProNeura platform with small molecules, hormones, and bio-active peptides. The delivery system works with both hydrophobic and hydrophilic molecules. We have also shown the flexibility of the platform by experimenting with the release characteristics of the EVA implants, layering the implants with varying concentrations of drug, and generating implants of different sizes and porosity to achieve a desired delivery profile. Formulation development is conducted at a dedicated pilot plant established by Titan at the South West Research Institute, or SWRI, in San Antonio, Texas that includes cGMP manufacturing and testing capabilities. We also receive support services from the vast array of SWRI groups with expertise in manufacturing and material sciences. The facilities are

compliant with both FDA and Drug Enforcement Agency, or DEA, requirements enabling us to work with controlled substances, and the manufacturing scale is ideal for product development during non-clinical and clinical testing stages.

Our Product Pipeline

Our goal is to expand our product pipeline using the ProNeura implant platform. We have been opportunistically evaluating other drugs for use with this technology, focusing on drugs where conventional treatment may be adversely impacted by fluctuating blood drug levels and/or poor patient compliance, and where existing therapeutic compounds have sufficient potency to be effective at low doses. With our resources focused on commercialization of Probuphine, further development of the ProNeura platform is currently being limited to non-clinical product development activity that is funded by external grants or other partners.

ProNeura-Ropinirole for Parkinson's Disease

Parkinson's disease, or PD, is a disease of the central nervous system characterized by the loss of dopaminergic neurons, which leads to increasing activity in the brain region that influences movement and motor function. According to the Parkinson's Disease Foundation, more than one million people in the U.S. suffer from PD, and this number is projected to double by 2030. Early stage PD patients are treated with daily doses of drugs designed to replace dopamine in the brain. However, these therapeutics typically lose their benefits after several years of chronic treatment and trigger serious side effects. About one-third of the treated patients develop motor response fluctuations and/or drug-induced dyskinesias within three to five years of treatment, and these symptoms are present in almost all patients after 10 to 12 years. Clinical and nonclinical research indicates that these motor side effects arise from the pulsatile dopaminergic stimulation resulting from current oral treatment. Continuous dopaminergic stimulation, or CDS, by subcutaneous infusion has been shown to palliate these motor complications, as well as to delay or prevent the onset of dyskinesias. We believe our ProNeura drug delivery technology provides a clinically-validated platform to safely and conveniently provide CDS for several months from a single treatment. Further, the subdermal placement of these implants eliminates many of the device-related complications associated with existing treatment modalities.

Based on these principles we designed an implant to deliver the drug ropinirole and conducted appropriate non-clinical studies, including a non-clinical study in an MPTP Parkinsonian primate model and demonstrated that a sustained non-fluctuating plasma level of ropinirole could be delivered safely for several months following implantation and could control PD symptoms without triggering dyskinesias in severely lesioned primates. Following further optimization of the implant and completion of the Investigational New Drug application, or IND, enabling non-clinical studies, we submitted the IND application to the FDA in early 2017 and it was cleared in August 2017 for commencement of the proposed Phase 1/2 clinical study. The trial is an open-label, sequential, dose escalation study that will enroll approximately 20 subjects with idiopathic Parkinson's disease. The primary objectives are to characterize the pharmacokinetic profile of the ropinirole implants, to evaluate their safety and tolerability, and to explore potential signals of efficacy using established disease-specific assessment scales. The first patient in the first cohort of the Phase 1/2 clinical study was treated in early October 2017 and in July 2018 the Data Safety Monitoring Board, or DSMB, completed a review of the data from the first cohort of patients and recommended that the trial continue with enrollment of the second cohort of patients. However, we chose to postpone further activity in this clinical study in order to focus our limited resources on commercialization of Probuphine. We do not anticipate further progress with this study until sufficient funds are available to support this program, either from a partner or future revenues from Probuphine.

Other ProNeura Product Feasibility Programs

Further development of the ProNeura platform has been limited to non-clinical product development activity that is funded by external grants and/or other partners.

We have conducted a feasibility assessment of a subcutaneous implant using our proprietary ProNeura sustained release technology to administer an opioid antagonist. We believe that a product able to deliver non-fluctuating, therapeutic levels of a mu-opioid receptor antagonist continuously for up to six months may be ideally suited for the prevention of opioid relapse and overdose in patients who have gone through a detoxification program. In September 2018, we were awarded a grant by the National Institute for Drug Addiction, or NIDA, in support of this program. The grant provides for approximately $2.67 million in funding during the first year and approximately $6.08 million during the second year subject to the terms and conditions specified in the grant, including our fund matching obligation in the amount of approximately $1.33 million during the first year. Funding during the second year is also subject to satisfactory progress of the project and the availability of funds to NIDA, although, as recently communicated by NIDA, it does not include any company fund matching obligations.

We are collaborating with the Walter Reed Army Institute of Research, or WRAIR, and SWRI in the early non-clinical evaluation of the ProNeura platform in malaria prophylaxis. The early data from this collaboration is encouraging and has been presented by the WRAIR staff at several conferences, and WRAIR has now received additional funding from the Department of Defense to continue the program with additional non-clinical testing of the atovaquone and proguanil implant formulations in large animal studies. WRAIR is also pursuing additional grant funding for testing other compounds that have shown promise as a prophylactic treatment for malaria and we will

collaborate with WRAIR and SWRI as needed for the preparation of these implant formulations that, if successful, could be available to us for potential commercialization.

During 2018, in collaboration with J.T. Pharmaceuticals, we conducted initial non-clinical testing for the development of a novel kappa opioid receptor agonist implant for the treatment of chronic pain. Based on this early work, we have collaborated on a National Institute of Health, or NIH, grant application and further development in 2019 will be possible only if the grant is approved. If successfully developed, this product would offer a potential non-addictive opioid analgesic for the treatment of chronic pain.

We have also conducted initial formulation studies and early *in vitro* testing for the potential development of an implant with a currently approved peptide for the treatment of adult type 2 diabetes mellitus. Additionally, in 2017 we completed early non-clinical development focused on formulation optimization of an implantable triiodothyronine (T3) product for the treatment of hypothyroidism. Any further development in these programs will depend on availability of additional funds through grants and/or interest from partners.

Agreements

Braeburn

In December 2012, we entered into a license agreement, or the Braeburn Agreement, with Braeburn pursuant to which we granted Braeburn an exclusive right and license to commercialize Probuphine in the United States of America and its territories, including Puerto Rico, and Canada. Under the Braeburn Agreement, as subsequently amended, Braeburn made a non-refundable up-front license fee payment of $15.75 million in 2012 and a milestone payment of $15 million upon FDA approval of the NDA in May 2016. The agreement also entitled us to royalties on net sales of Probuphine ranging in percentage from the mid-teens to the low twenties. In February 2016, Braeburn entered into a Distribution and Sublicense Agreement, or the Knight Agreement, with Knight pursuant to which it granted Knight exclusivity to commercialize and distribute Probuphine in Canada.

On May 25, 2018, we entered into a Termination and Transition Services Agreement, or the Transition Agreement, with Braeburn pursuant to which we regained all rights to the commercialization and clinical development of Probuphine granted under the Braeburn Agreement and, in addition to $1 million and all available inventory of Probuphine, Braeburn agreed to provide assistance to Titan through December 28, 2018 to help ensure that patients and their doctors continued to have support and access to this treatment. As part of the Transition Agreement, we assumed a significant number of Braeburn's commercial contracts relating to the commercialization of Probuphine in the U.S., including the Knight Agreement.

Knight

Under the Knight Agreement, as amended in August 2018, we granted Knight an exclusive license to commercialize Probuphine in Canada as well as a right of first negotiation in the event we intend to license our right to commercialize any of our other products in Canada. We are entitled to receive royalty payments from Knight on net sales of Probuphine in Canada ranging in percentage from the low-teens to the mid-thirties. In addition, we will be the exclusive supplier of Probuphine to Knight subject to a supply agreement between us and Knight. During the term of the Knight Agreement, we may not commercialize any product in Canada containing buprenorphine that is intended for a treatment duration of six months or more.

Unless earlier terminated, the initial term of the Knight Agreement will expire on the 15th anniversary of the date of the first commercial sale of Probuphine for opioid addiction in Canada, which occurred during the fourth quarter of 2018. If Probuphine is approved for another indication in Canada after the fifth anniversary of the first commercial sale of Probuphine for opioid addiction in Canada, we must negotiate in good faith whether to extend the initial term.

After the initial term, the Knight Agreement will automatically renew for two-year periods until either party provides the other party with written notice of its intent not to renew at least 180 days prior to the expiration of the initial term or then-current term. We or Knight may terminate the Knight Agreement in the event that (i) either party determines in good faith that it is not advisable for Knight to continue to commercialize Probuphine in Canada as a result of a bona fide safety issue, (ii) the other party has filed for bankruptcy, reorganization, liquidation or receivership proceedings, or (iii) the other party materially breached the agreement and has not cured such breach within a specified time period. In addition, subject to certain exceptions and requirements, we may terminate the Knight Agreement (i) if Knight discontinues the commercial sale of Probuphine for a period of at least three months and fails to resume sales within the specified cure period, or (ii) in the event that Knight commences any legal proceedings seeking to challenge the validity or ownership of any of our patents related to Probuphine.

In the event of termination, among other things, Knight shall (i) cease commercialization of Probuphine in Canada, (ii) transfer title to all current and pending regulatory submissions and regulatory approvals for Probuphine to us and (iii) pay any royalty payments generated by Knight’s sales of Probuphine in Canada due to us.

Molteni

On March 21, 2018, we entered into and on August 3, 2018 amended an Asset Purchase, Supply and Support Agreement, or the Purchase Agreement, with Molteni pursuant to which Molteni acquired the European intellectual property related to Probuphine, including the MAA under review by the EMA, and will have the exclusive right to commercialize the Titan supplied Probuphine product in Europe, as well as certain countries of the Commonwealth of Independent States, the Middle East and North Africa, or the Molteni Territory. We received an initial payment of €2.0 million ($2,448,000) for the purchased assets and an additional payment of €950,000 ($1,107,000) upon execution of the amendment. We will receive the following additional potential payments totaling up to €2.5 million (approximately $2,850,000) upon the achievement of certain regulatory and product label milestones, including: an aggregate of €1.0 million of milestone payments upon approval of the product reimbursement price in certain key countries, provided that the payments, which are subject to a 50% reduction if the EMA marketing authorization is not received on or prior to September 30, 2019, shall not be payable in the event such authorization is not received on or prior to March 31, 2020. Additionally, Titan is entitled to receive earn-out payments for up to 15 years on net sales of Probuphine in the Molteni Territory ranging in percentage from the low-teens to the mid-twenties.

The Purchase Agreement provides that Titan will supply Molteni with semi-finished product (i.e., the implant and the applicator) on an exclusive basis at a fixed price through December 31, 2019, with subsequent price increases not to exceed annual cost increases to Titan under its current manufacturing agreement and for the purchase of the active pharmaceutical ingredient.

Molteni will be prohibited from marketing a Competitor Product (as defined in the Purchase Agreement) in the Territory for the five year period following approval of the MAA. Thereafter, Molteni will be required to pay Titan a low single digit royalty on net sales by Molteni of any Competitor Product.

On March 21, 2018, we entered into an agreement, or the Loan Agreement, which amended and restated our prior loan agreement with Horizon Technology Finance Corp., or Horizon. Under the Loan Agreement, Horizon assigned $2,400,000 of the $4,000,000 outstanding principal balance of the loan to Molteni and Molteni was appointed collateral agent and assumed majority and administrative control of the debt. Molteni has the right to convert its portion of the debt into shares of our common stock at a conversion price of $7.20 per share and is required to effect this conversion of debt to equity if we complete an equity financing resulting in gross proceeds of at least $10,000,000 at a price per share of common stock in excess of $7.20 and repay the $1,600,000 principal balance of Horizon's loan amount.

In consideration of Molteni's entry into the Purchase Agreement and the Loan Agreement, on March 21, 2018, we entered into an agreement with Molteni. or the Rights Agreement, pursuant to which, as amended, we agreed to (i) issue Molteni seven-year warrants to purchase 90,000 shares of our common stock at an exercise price of $7.20 per share, (ii) provide Molteni customary demand and piggy-back registration rights with respect to the shares of common stock issuable upon conversion of its loan and exercise of its warrants, (iii) appoint one member of Titan's board of directors if Mr. Seghi Recli is not then serving on the board and (iv) provide board observer rights to Molteni if it has not designated a board nominee, as well as certain information rights. The board designation, observer and information rights will terminate at such time as Molteni ceases to beneficially own at least one percent of our outstanding capital stock (inclusive of the shares issuable upon conversion of its note and exercise of its warrants).

In connection with the August 2018 amendment to the Purchase Agreement, Molteni made a convertible loan to us of €550,000 (approximately $642,000) upon submission of the response to the 120-day letter from EMA on September 14, 2018 in accordance with the amendment. The convertible loan will convert automatically into shares of our common stock upon the issuance by the EMA of marketing approval for Probuphine at a conversion price per share equal to the lower of (i) $3.42 (the closing price on the loan funding date) and (ii) the closing price on the conversion date. In the event the EMA has not granted marketing approval by December 31, 2019, the loan will become due and payable, together with accrued interest at the rate of 9.5% plus the amount by which the one-month LIBOR exceeds 1.1%.

Intellectual Property

Our goal is to obtain, maintain and enforce patent protection for our product candidates, formulations, processes, methods and any other proprietary technologies, preserve our trade secrets, and operate without infringing on the proprietary rights of other parties, both in the United States and in other countries. Our policy is to actively seek to obtain, where appropriate, the broadest intellectual property protection possible for our current product candidates and any future product candidates, proprietary information and proprietary technology through a combination of contractual arrangements and patents, both in the United States and abroad. However, patent protection may not afford us with complete protection against competitors who seek to circumvent our patents.

We also depend upon the skills, knowledge, experience and know-how of our management and research and development personnel, as well as that of our advisors, consultants and other contractors. To help protect our proprietary know-how, which may not be patentable, and for inventions for which patents may be difficult to enforce, we currently rely and will in the future rely on trade secret protection and confidentiality agreements to protect our interests. To this end, we require all of our employees, consultants, advisors and other contractors to enter into confidentiality agreements that prohibit the disclosure of confidential information and, where applicable, require disclosure and assignment to us of the ideas, developments, discoveries and inventions important to our business.

In June 2010, the United States Patent and Trademark Office (“USPTO”) issued a patent covering methods of using Probuphine for the treatment of opiate addiction. Titan is the owner of this patent which claims a method for treating opiate addiction with a subcutaneously implanted device comprising buprenorphine and EVA, a biocompatible copolymer that releases buprenorphine continuously for extended periods of time. This patent will expire in April 2024. A U.S. continuation application is currently pending which includes claims related to Probuphine for the treatment of pain. Related patents covering use of Probuphine with the continuous delivery technology for the treatment of opiate addiction have also been issued in Australia, Canada, Europe, India, Japan, Mexico, New Zealand, and Hong Kong. On March 21, 2018, we executed the Purchase Agreement with Molteni whereby the European intellectual property covering Probuphine, including the European patent, was acquired by Molteni. Patents covering certain dopamine agonist implants, including ropinirole implant, have already been issued or allowed in the United States, Europe, Japan, China, Australia, Canada, South Korea, Mexico, New Zealand, South Africa, Israel and Hong Kong.

We have filed additional patent applications for a heterogeneous implant designed with some unique properties that may provide benefits to the structural integrity of the implants and potentially enhance drug delivery. Corresponding patents have been granted in the US, Australia, Europe, Japan, South Korea, Mexico, Singapore, and South Africa, while applications remain pending in Canada, Hong Kong, and India.

Future court decisions or changes in patent law might materially affect the patents or patent applications, including, but not limited to, their expiration dates.

Competition

The pharmaceutical and biotechnology industries are characterized by rapidly evolving technology and intense competition. Many companies, including major pharmaceutical companies and smaller specialized biotechnology companies, are engaged in the development and commercialization of therapeutic agents designed for the treatment of the same diseases and disorders that we target. Many of our competitors have substantially greater financial and other resources, larger research and development staff and more experience in the regulatory approval process. Moreover, potential competitors have or may have patents or other rights that conflict with patents covering our technologies.

With respect to Probuphine, there are currently no other six-month implant formulations of buprenorphine on the market or in development. The primary competition it faces comes from Indivior, PLC (formerly the pharmaceutical business of Reckitt Benckiser Group, PLC), which markets globally a sublingual buprenorphine product (tablet and film formulations under the trade name Subutex and Suboxone) for the treatment of opioid dependence that currently holds the dominant market share of global sales. Indivior recently received FDA approval for a one month depot injection (tradename Sublocade) that became commercially available in the first quarter of 2018. Probuphine also faces competition from two additional proprietary daily dose formulations that have been approved by the FDA; the first is a sublingual tablet with the trade name of Zubsolv marketed by Orexo and the second is a buccal patch with the trade name of Bunavail marketed by Bio Delivery Sciences International. Several generic sublingual tablet formulations of buprenorphine similar to Suboxone and Subutex were approved by the FDA and have recently entered the opioid addiction treatment market. Other forms of buprenorphine are also in development by other companies, including intramuscular and intradermal one-week and one-month depot injections which, if approved, will also compete with our product. One additional depot formulation licensed to Braeburn has received tentative FDA approval that restricts marketing of the product in the U.S. until potentially November 2020. Alkermes, Inc. also markets Vivitrol®, a one-month depot injection of naltrexone as a maintenance treatment for opioid dependent patients who have successfully gone through a detoxification process and achieved abstinence.

If successfully developed and approved for commercialization, our ProNeura ropinirole product for PD will face competition primarily from numerous daily dose dopamine agonist treatments currently in use that provide symptom relief from disease related immobility, as well as the complications associated with long-term levodopa therapy (e.g.

dyskinesias, tolerance). Approved products in the U.S. in addition to Requip XL®, which is marketed by GlaxoSmithKline, include Apokyn® (US WorldMeds LLC), Parlodel® (Novartis Pharmaceuticals Inc.), Mirapex ER® (Boehringer Ingelheim Pharmaceuticals Inc.) and Neupro® (UCB Inc.). There is a strong need for products providing continuous, stable, long term delivery of dopamine and dopamine agonists and the FDA recently approved a product called Duodopa®, the first and only treatment delivered via catheters directly into the duodenum that is capable of providing 16 continuous hours of carbidopa and levodopa for treatment of motor fluctuations in advanced PD. Duodopa is marketed globally by Abbvie. Also, we are aware of products in mid-stage clinical development that are capable of short to medium-term subcutaneous and subdermal delivery of levodopa/carbidopa using pumps.

Manufacturing

The manufacturing of Probuphine has primarily been conducted at DPT Laboratories, Inc., or DPT, and we have expanded the manufacturing facility at this contract manufacturer to establish commercial scale capability to support the market launch of Probuphine and ongoing demand. We have entered into a commercial manufacturing agreement with DPT that governs the terms of the production and supply of Probuphine. We are responsible for the manufacture and supply of Probuphine as needed by Knight for Canada and to Molteni for the Molteni Territory.

To date, we have obtained the supply of bupenorphine from Teva Pharmaceuticals, Inc., or Teva, under a commercial supply agreement similar to the one with DPT.

We are in the process of qualifying a new EVA manufacturer which will provide a second source of the material. The vendor that used to sterilize the Probuphine implants indicated that it will no longer sterilize Schedule III controlled substances, including Probuphine. While we have qualified another sterilization vendor and transitioned to a new sterilization process, we cannot guarantee that such services will be available indefinitely. Our use of these and other single-source suppliers of raw materials, components and finished goods exposes us to several risks, including disruptions in supply, price increases, late deliveries and an inability to meet customer demand. This could lead to customer dissatisfaction, damage to our reputation or customers switching to competitive products. Any interruption in supply could be particularly damaging to our ability to develop and commercialize Probuphine.

Finding alternative sources for these raw materials, components and finished goods would be difficult and in many cases entail a significant amount of time, disruption and cost. Any disruption in supply from any single-source supplier or manufacturing location could lead to supply delays or interruptions which would damage our business, financial condition, results of operations and prospects.

Sales and Marketing

Prior to Titan’s reacquisition of Probuphine commercialization rights in May 2018, Braeburn had sole responsibility for sales and marketing the product within the United States and, through Knight, in Canada. Commencing in June 2018, we began the process of transitioning to a commercial enterprise by engaging the services of key consultants with expertise in launching and commercializing specialty pharmaceutical products, such as Probuphine. Our goal was to fully understand the hurdles encountered by Braeburn in the prior product launch activities. Based on feedback from key opinion leaders and these consultants, we believe that access to care for patients with Probuphine was negatively impacted by issues related to the complexity, timing and amount of reimbursement to patients and their doctors from insurance providers, as well as the restrictive requirements of the REMS program. We also believe that the broad marketing strategy that was initially undertaken reflected an incomplete understanding of the market and did not provide the requisite systems to support the reimbursement process and patient and physician education.

In order to lay the groundwork for increased utilization of Probuphine, we believe it is necessary to streamline the product ordering, distribution and reimbursement processes, to support patients and providers seeking access to treatment, and to develop a more focused commercialization strategy. In October 2018 we engaged the services of Dane Hallberg, who has extensive experience in launching specialty products in the U.S. market, as Chief Commercial Officer. In November 2018, Titan established a promotional review committee (“PRC”) to ensure all Probuphine promotional materials are in compliance with FDA regulations and to support submissions to the FDA’s Office of the Prescription Drug Promotion (OPDP).

Over the last few months we have established pharmaceutical foundational best practices including, but not limited to, sales compliance training and certification; drafting and implementation of company-wide SOPs; Sunshine Act Reporting; federal and state licensing; and sales and promotional materials creation and review. We have also assembled a small sales and marketing team with responsibilities that include regional sales oversight, medical science liaison services, strategic product and brand recognition development, and REMS program management. We have also retained a medical access specialist to address third-party payor coverage and to improve the product distribution system.

Along with establishing the internal team, we have engaged key external services to support these functions, including public relations, product branding and advertising capabilities. We have also engaged AppianRx as our new hub and are working closely with them to establish more efficient systems for product ordering and third party payor pre-approval. We believe that the positive impact of an automated and streamlined product supply chain process will be realized in the second quarter of 2019

We have recently engaged the services of AllianceRx Walgreens Specialty Pharmacy, which we expect to help alleviate bottlenecks in the third-party payor approval and product shipment process, and we hope to add additional large specialty pharmacies to the network in the near future. We have made good progress in establishing a strong foundation for our commercial activities, as well as re-engaging the medical community to consider using Probuphine as an option for the long term maintenance treatment of OUD, all of which lays the ground work for further progress in the market place during the second half of 2019.

While our overall market strategy for the relaunch of Probuphine targets four market segments, we have focused initially on physicians who are already prescribing Probuphine, while in the longer term our plan is to expand our efforts to address three additional market segments.

High Probuphine-prescribing physicians with long-term recovery oriented treatment programs

While there are currently approximately 52,000 buprenorphine certified healthcare providers in the U.S., approximately 90% of prescriptions for treating the 600,000 – 700,000 patients treated with oral buprenorphine are written by approximately 6,000 providers. Moreover, while over 2,500 healthcare providers were previously trained and certified to administer Probuphine, to date less than 200 have prescribed the treatment.

Our initial focus has been on the top tier of Probuphine prescribers to facilitate the growth of their businesses through increased utilization of the product. Utilizing some of the successful Probuphine practices, in the medium to longer term, we plan to establish centers that will provide sites for referrals from other health care providers. In addition, when our new hub, AppianRx, is operational in the second quarter, we expect to see improvement in the complexity of the supply chain and reimbursement process. In the longer term, some top tier Probuphine providers will also engage in investigator sponsored research which has the potential to generate new and clinically meaningful data, some of which will help us assess the potential for label expansion. We will also seek to partner with buprenorphine advocacy groups that can facilitate patient-healthcare provider location matching and broaden patient outreach.

Residential Treatment Facilities and Veterans Administration Hospitals

There are currently numerous residential addiction treatment facilities in the U.S. reflecting a large potential patient population who can benefit from Probuphine. These facilities have mostly relied on 12 step programs with the goal of complete and sustained abstinence while avoiding any MAT. However, the success of such programs has not withstood scrutiny, as it has been increasingly recognized that a very high percentage of patients with opiate addiction ultimately relapse. Consequently, the use of MAT as part of the management of OUD has been increasing, and is expected to rise substantially in the near term. Our plan is to establish alliances with a few large programs.

We believe that the Veterans Administration Hospitals present another opportunity for the use of Probuphine. Addiction to opiates is a problem among the veterans, however the ability to treat patients through the VA system is hampered by limited facilities and medical resources. We are exploring programs to train staff at the VA hospitals in the use of Probuphine for long term maintenance treatment which will help in reducing the frequency of visits to the clinic and better utilize available resources.

Academic institutions with addiction treatment and training programs

There are an increasing number of academic addiction medicine training programs that treat OUD patients. At the end of October 2018 we conducted a training seminar for 40+ Nurse Practitioner students at Drexel University who were interested in pursuing careers in addiction medicine and nearing completion of their degree program. This seminar was similar to the Probuphine certification training program and provided these nurses with an opportunity to get familiar with Probuphine. We plan to form alliances with institutions that already have the necessary trained personnel and equipment for doing small procedures, and facilitate the introduction and/or increased use of Probuphine for appropriate patients. This will also serve to introduce Probuphine to the next generation of addiction specialists. In the longer term, we expect that KOLs at some of these sites will initiate investigator sponsored studies which can generate clinically meaningful data while helping us assess the potential for label expansion.

Criminal Justice System

It is estimated that of the 2.3 million people currently confined in U.S. correctional facilities, approximately 25% suffer from OUD. Currently, less than 1% of U.S. prisons and jails allow access to medication for OUD due largely to the risk of misuse and diversion of sublingual formulations (pills, film), However, new research published by JAMA Psychiatry has demonstrated benefits of buprenorphine during incarceration and upon release. In Rhode Island, a recent study found that opioid overdose deaths dropped by nearly 2/3 when MAT was provided to all state inmates. A few criminal justice programs have begun to utilize medications in order to address jail overcrowding and recidivism related to OUD.

Our goal is to initially establish pilot projects with a few select criminal justice programs, with the goal of generating meaningful data that potentially supports the use of Probuphine in this setting. The first pilot program has been initiated within the Nevada criminal justice system which has commenced to establish procedures and processes for the introduction of MAT within its system. We will monitor progress and continue to work with the Nevada criminal justice system to introduce Probuphine for maintenance therapy when eligible stable patients are available later in the year.

REMS Program

As a condition to the FDA's approval of Probuphine, we are required to maintain the Probuphine REMS program, with the goal of mitigating the risk of complications of migration, protrusion, expulsion and nerve damage potentially associated with its improper insertion and removal, and also the risks of accidental overdose, misuse and abuse. The REMS program requires training for healthcare providers who prescribe, insert and remove Probuphine implants and provide patient counseling. The distribution of Probuphine is restricted to those healthcare providers who have completed the training and have received certification under the Probuphine REMS. Accordingly, we have established a REMS management team to monitor all aspects of the REMS program requirements along with the medical sales liason, or MSL, team to conduct the REMS training sessions for the certification of health care providers to prescribe and/or insert and remove Probuphine. The MSL team also provides on-going in-market technical support to assist heath care providers developing expertise with the Probuphine insertion and removal procedures.

Government Regulation

Government authorities in the United States at the federal, state and local level and in other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug products. Generally, before a new drug can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific to each regulatory authority, submitted for review and approved by the regulatory authority.

U.S. drug development

In the United States, the FDA regulates drugs and devices under the Food, Drug and Cosmetics Act, or FDCA. Drugs and devices are also subject to other federal, state and local statutes and regulations. Products composed of both a drug product and device product are deemed combination products. If marketed individually, each component would be subject to different regulatory pathways and reviewed by different centers within the FDA. A combination product, however, is assigned to a center that will have primary jurisdiction over its regulation based on a determination of the combination product's primary mode of action, which is the single mode of action that provides the most important therapeutic action. In the case of some of our product candidates, we expect the primary mode of action to be attributable to the drug component of the product, which means that the FDA's Center for Drug Evaluation and Research would have primary jurisdiction over the premarket development, review and approval. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other actions,

the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, untitled or warning letters, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement, or civil or criminal penalties. Additionally, a manufacturer may need to recall a product from the market. Any agency or judicial enforcement action could have a material adverse effect on us.

Our product candidates must be approved by the FDA through the NDA process before they may be legally marketed in the United States. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- Completion of extensive nonclinical laboratory tests, animal studies and formulation studies in accordance with applicable regulations, including the FDA's Good Laboratory Practice, or GLP, regulations;

- Submission to the FDA of an IND application, which must become effective before human clinical trials may begin;

- Approval by an independent institutional review board, or IRB, or ethics committee at each clinical trial site before each trial may be initiated;

- Performance of adequate and well-controlled human clinical trials in accordance with applicable IND and other clinical trial-related regulations, referred to as good clinical practices, or GCPs, to establish the safety and efficacy of the proposed drug for each proposed indication;

- Submission to the FDA of an NDA for a new drug;

- A determination by the FDA within 60 days of its receipt of an NDA to file the NDA for review;

- Satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities where the drug is produced to assess compliance with cGMP requirements to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;

- Potential FDA audit of the nonclinical study and/or clinical trial sites that generated the data in support of the NDA; and

- FDA review and approval of the NDA, including consideration of the views of any FDA advisory committee, prior to any commercial marketing or sale of the drug in the United States.

The nonclinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

The data required to support an NDA is generated in two distinct development stages: nonclinical and clinical. For new chemical entities, the nonclinical development stage generally involves synthesizing the active component, developing the formulation and determining the manufacturing process, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies in the laboratory, which support subsequent clinical testing. These nonclinical tests include laboratory evaluation of product chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product. The conduct of the nonclinical tests must comply with federal regulations, including GLPs. The sponsor must submit the results of the nonclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. Some nonclinical testing may continue even after the IND is submitted, but an IND must become effective before human clinical trials may begin. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human trials. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials, including concerns that human research subjects will be exposed to unreasonable health risks, and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a drug candidate at any time before or during clinical trials due to safety concerns or non-compliance. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that could cause the trial to be suspended or terminated.

The clinical stage of development involves the administration of the drug candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other

things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completion. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of an NDA so long as the clinical trial is conducted in compliance with GCP and FDA is able to validate the data through an onsite inspection if the agency deems it necessary.

Clinical trials

Clinical trials are generally conducted in three sequential phases that may overlap, known as Phase 1, Phase 2 and Phase 3 clinical trials.

- Phase 1 clinical trials generally involve a small number of healthy volunteers who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the drug.

- Phase 2 clinical trials typically involve studies in disease-affected patients to determine the dose required to produce the desired benefits and provide a preliminary evaluation of efficacy. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected, as well as identification of possible adverse effects and safety risks.

- Phase 3 clinical trials generally involve large numbers of patients at multiple sites (from several hundred to several thousand subjects) and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use and to establish the overall benefit/risk relationship of the product and provide an adequate basis for physician labeling. Phase 3 clinical trials may include comparisons with placebo and/or comparator treatments.

Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA. Written IND safety reports must be submitted to the FDA and the investigators within 15 calendar days for serious and unexpected suspected adverse events, finding from other studies or animal or in vitro testing that suggests a significant risk for human subjects, and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Additionally, a sponsor must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within 7 calendar days. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the trial.

Pursuant to the Cures Act, the manufacturer of an investigational drug for a serious disease or condition is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for individual patient access to such investigational drug. This requirement applies on the later of 60 calendar days after the date of enactment of the Cures Act or the first initiation of a Phase 2 or Phase 3 trial of the investigational drug.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing

process must be capable of consistently producing quality batches of the drug candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

NDA and FDA review process

The results of the nonclinical studies and clinical trials, together with other detailed information, including extensive manufacturing information and information on the composition of the drug and proposed labeling, are submitted to the FDA in the form of an NDA requesting approval to market the drug for one or more specified indications. The FDA reviews an NDA to determine, among other things, whether a drug is safe and effective for its intended use and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. FDA approval of an NDA must be obtained before a drug may be offered for sale in the United States.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of pediatric data or full or partial waivers.

The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. The FDA must make a decision on accepting an NDA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the goals and policies agreed to by the FDA under Prescription Drug User Fee Act, or PDUFA, for drugs that do not contain a new chemical entity the FDA has 10 months from the receipt date in which to complete its initial review of a standard NDA and respond to the applicant, and six months from the receipt date for a priority NDA. For drugs containing a new chemical entity, these 10 and six month review timeframes are from the filing date of an NDA. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with cGMPs. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. In addition, before approving an NDA, the FDA may also audit data from clinical trials to ensure compliance with GCP requirements. Additionally, the FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. The review and evaluation of an NDA by the FDA is extensive and time consuming and may take longer than originally planned to complete, and we may not receive a timely approval, if at all.

After the FDA evaluates an NDA, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s), and/or other significant and time-consuming requirements related to clinical trials, nonclinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may resubmit the NDA addressing all of the deficiencies identified in the letter, withdraw the application, or request an opportunity for a hearing. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

There is no assurance that the FDA will ultimately approve a drug product for marketing in the United States and we may encounter significant difficulties or costs during the review process. If a product receives marketing approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain

contraindications, warnings or precautions be included in the product labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-marketing testing or clinical trials and surveillance to monitor the effects of approved products. For example, the FDA may require Phase 4 testing which involves clinical trials designed to further assess a drug's safety and efficacy and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. The FDA also may place other conditions on approvals including the requirement for a risk evaluation and mitigation strategy, or REMS, to assure the safe use of the drug. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory requirements or if problems occur following initial marketing. As a condition to the FDA's approval of Probuphine, Braeburn was required to put the Probuphine REMS in place.

505(b)(2) approval process

Section 505(b)(2) of the FDCA provides an alternate regulatory pathway to FDA approval for new or improved formulations or new uses of previously approved drug products. Specifically, Section 505(b)(2) was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments, and permits the filing of an NDA where at least one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. The applicant may rely upon the FDA's prior findings of safety and effectiveness for a previously approved product or on published scientific literature, in support of its application. The FDA may also require 505(b)(2) applicants to perform additional trials to support the changes from the previously approved drug and to further demonstrate the new drug's safety and effectiveness. The FDA may then approve the new product candidate for all or some of the labeled indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Expedited development and review programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs that meet certain criteria. Specifically, new drugs are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. Any product submitted to the FDA for marketing, including under the Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review. A product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or offers a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. Additionally, a drug may be eligible for designation as a breakthrough therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinical development. Fast Track designation, priority review, and breakthrough designation do not change the standards for approval but may expedite the development or approval process.

Pediatric trials