Bellerophon Therapeutics, Inc.
Form 10-K
March 31, 2015
Table of Contents

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2014

or

o 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 001-36845

Bellerophon Therapeutics, Inc.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**47-3116175**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
53 Frontage Road Suite 301	
Hampton, New Jersey	**08827**
(Address of Principal Executive Offices)	(Zip Code)

Registrant s telephone number, including area code: **(908) 574-4770**

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

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.01 par value per share	**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. o Yes x No

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

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

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

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

Large accelerated filer	Accelerated filer	Non-accelerated filer x (Do not check if a smaller reporting company)	Smaller reporting company
o	o		o

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

The registrant s common stock began trading on the NASDAQ Global Market on February 13, 2015. As of February 13, 2015, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $63.1 million, based upon the closing price on the NASDAQ Global Market reported for such date. The registrant has elected to use February 13, 2015, the initial trading date of the registrant s common stock on the NASDAQ Global Market, as the calculation date because on June 30, 2014 (the last business day of the registrant s most recently completed second fiscal quarter), the registrant s common stock was not publicly traded. Shares of common stock held by each officer and director and by each person who is known to own 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates of the registrant. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of shares outstanding of the registrant s common stock, as of March 25, 2015: 12,905,392

Table of Contents

TABLE OF CONTENTS

Table of Contents

REFERENCES TO BELLEROPHON

In this Annual Report on Form 10-K, unless otherwise stated or the context otherwise requires:

- references to the Company, Bellerophon, we, us and our following the date of the Corporate Conversion refer to Bellerophon Therapeutics, Inc. and its consolidated subsidiaries;

- references to the Company, Bellerophon, we, us and our prior to the date of the Corporate Conversion refer to Bellerophon Therapeutics LLC and its consolidated subsidiaries; and

- references to the Corporate Conversion or corporate conversion refer to all of the transactions related to the conversion of Bellerophon Therapeutics LLC into Bellerophon Therapeutics, Inc., including the conversion of all of the outstanding units of Bellerophon Therapeutics, Inc. into shares of common stock of Bellerophon Therapeutics, Inc.

Table of Contents

FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our future results of operations and financial position, business strategy and plans and objectives of management for future operations, are forward-looking statements, are forward-looking statements. The words may, will, should, expects, plans, anticipates, could, intends, target, projects, conten estimates, predicts, potential or continue or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- the timing of the ongoing and expected clinical trials of our INOpulse and BCM product candidates, including statements regarding the timing of completion of the trials and the respective periods during which the results of the trials will become available;

- the timing of and our ability to obtain marketing approval of our product candidates, and the ability of our INOpulse and BCM product candidates to meet existing or future regulatory standards;

- our ability to operate, and the implementation of our business strategy, as a stand-alone company;

- our ability to comply with government laws and regulations;

- our commercialization, marketing and manufacturing capabilities and strategy;

- our estimates regarding the potential market opportunity for our product candidates;

- the timing of or our ability to enter into partnerships to market and commercialize our product candidates;

- the rate and degree of market acceptance of any product candidate for which we receive marketing approval;

- our intellectual property position;

- our expectations related to the use of proceeds from our initial public offering in February 2015;

- our estimates regarding expenses, future revenues, capital requirements and needs for additional funding and our ability to obtain additional funding;

- the success of competing treatments;

- our competitive position; and

- our expectations regarding the time during which we will be an emerging growth company under the Jumpstart Our Business Startups Act of 2012.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the Risk Factors section, that could cause actual results or events to differ

Table of Contents

materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

This Annual Report on Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information.

Table of Contents

PART I

Item 1. Business

Overview

We are a clinical-stage therapeutics company focused on developing innovative products at the intersection of drugs and devices that address significant unmet medical needs in the treatment of cardiopulmonary and cardiac diseases. We have two programs in advanced clinical development. The first program, INOpulse, is based on our proprietary pulsatile nitric oxide delivery device. We are currently developing two product candidates under our INOpulse program: one for the treatment of pulmonary arterial hypertension, or PAH, for which we intend to commence Phase 3 clinical trials in the second half of 2015, and the other for the treatment of pulmonary hypertension associated with chronic obstructive pulmonary disease, or PH-COPD, which is in Phase 2 development. Our second program is bioabsorbable cardiac matrix, or BCM, which is currently in a placebo-controlled clinical trial designed to support CE mark registration in the European Union. We completed enrollment of this trial in December 2014, with 303 patients having completed the treatment procedure, and we expect to report top line results in mid-2015. Assuming positive results, we intend to conduct a pivotal pre-market approval trial of BCM beginning in the first half of 2016, which will be designed to support registration in the United States. We are developing BCM for the prevention of cardiac remodeling, which often leads to congestive heart failure following an ST-segment elevated myocardial infarction, or STEMI.

Our Product Candidates

The following table summarizes key information about our development programs and product candidates. We have worldwide commercialization rights to all of our product candidates.

* We are currently conducting a single clinical trial for BCM that, assuming positive results, we plan to use as a CE mark registration trial in the European Union and following which we would conduct a second, larger clinical trial to support registration in the United States.

From the inception of our business through December 31, 2014, $194.6 million was invested in our development programs. Prior to our recent initial public offering, our sole source of funding was investments in us by our former parent company, Ikaria, Inc., or Ikaria. As used in herein, unless context otherwise requires, references to Ikaria refer to Ikaria, Inc. and its subsidiaries and any successor entity.

Table of Contents

INOpulse

Our INOpulse program is an extension of the technology used in hospitals to deliver continuous-flow inhaled nitric oxide. Use of inhaled nitric oxide is approved by the U.S. Food and Drug Administration, or the FDA, and certain other regulatory authorities to treat persistent pulmonary hypertension of the newborn. Ikaria has marketed continuous-flow inhaled nitric oxide as INOmax for hospital use in this indication since approval in 1999. In October 2013, Ikaria transferred to us exclusive worldwide rights to develop and commercialize pulsed nitric oxide in PAH, PH-COPD and pulmonary hypertension associated with idiopathic pulmonary fibrosis, or PH-IPF, with no royalty obligations. Our INOpulse program is built on scientific and technical expertise developed for the therapeutic delivery of inhaled nitric oxide. In 2010, Ikaria filed an investigational new drug application, or IND, for INOpulse for the treatment of patients with PAH, which is a form of pulmonary hypertension that is closely related to persistent pulmonary hypertension of the newborn. In 2012, Ikaria filed a second IND for INOpulse for the treatment of patients with PH-COPD. These INDs were included in the assets that were transferred to us by Ikaria.

Nitric oxide is naturally produced and released by the lining of the blood vessel and results in vascular smooth muscle relaxation, an important factor in regulating blood pressure. As the muscles of the blood vessels relax, this allows the heart to increase blood flow to tissues and organs of the body, including the lung. When administered through inhalation, nitric oxide acts to selectively reduce pulmonary arterial pressure in the lung with minimal effects on blood pressure outside of the lungs, an important safety consideration.

Inhaled nitric oxide is widely used in the hospital setting for the treatment of a variety of conditions and, as reported by Ikaria, over 450,000 patients have been treated with inhaled nitric oxide worldwide since its first such use. However, chronic outpatient use of this therapy has previously been limited by a lack of a safe and compact delivery system for outpatient use. We have designed our INOpulse device, which is the means by which inhaled nitric oxide is delivered to the patient, to be portable, which enables use by ambulatory patients on a daily basis inside or outside their homes. Our INOpulse device has a proprietary mechanism that delivers brief, targeted pulses of nitric oxide timed to occur at the beginning of a breath for delivery to the well-ventilated alveoli of the lungs, which minimizes the amount of drug required for treatment. We estimate this, and the higher concentration of nitric oxide we use, reduces the volume of drug delivered to approximately 5% of the volume required for equivalent alveolar absorption using standard continuous flow delivery systems, and also reduces the amount of nitric oxide, as well as its by-product nitrogen dioxide, that is exhaled and released into the patient s environment. INOpulse is designed to automatically adjust nitric oxide delivery based on a patient s breathing pattern to deliver a constant and appropriate dose of the inhaled nitric oxide over time, independent of the patient s activity level, thus ensuring more consistent dosing of the nitric oxide to the alveoli of the lungs.

In our recently completed INOpulse clinical trials, we used the first generation INOpulse device, which we refer to as the INOpulse DS device. In future clinical trials, we intend to use our second generation device, which we refer to as the Mark2. The Mark2 has approximately the same dimensions as a paperback book and weighs approximately 2.5 pounds. The Mark2 has a simple and intuitive user interface and a battery life of approximately 24 hours when recharged, which takes approximately four hours and can be done while the patient sleeps. Based on the doses we have evaluated in our clinical trials, we expect that the cartridge will need to be replaced once a day. In addition, we have developed a triple-lumen nasal cannula, which forms part of the Mark2 and enables more accurate dosing of nitric oxide and minimizes infiltration of oxygen, which can react with nitric oxide to form nitrogen dioxide. Our triple-lumen nasal cannula consists of a thin, plastic tube that is divided into three channels from end-to-end, including at the prongs that are placed in the patient s nostrils, with one channel delivering inhaled nitric oxide, a second for breath detection and a third available for oxygen delivery. INOpulse is designed to be compatible with many long-term oxygen therapy, or LTOT, systems. In the usability research we conducted, all eight patients with experience with the INOpulse DS device responded positively to the Mark2, and several of these patients indicated that the ability to take the Mark2 outside the home would likely reduce concerns with maintaining compliance.

Table of Contents

Our technology is based on patents we have exclusively licensed from Ikaria for the treatment of PAH, PH-COPD and PH-IPF. These include patents with respect to the pulsed delivery of nitric oxide to ensure a consistent dose over time, which expire as late as 2027 in the United States and as late as 2026 in certain other countries, as well as with respect to the special triple-lumen cannula that allows for safer and more accurate dosing of pulsed nitric oxide, which expires in 2033. We have also licensed several other patent applications from Ikaria for certain of the innovations included in the Mark2 and certain of the resulting patents, if issued, would expire as late as 2033.

INOpulse for PAH

We are developing INOpulse for the treatment of PAH to address a significant and unmet medical need in an orphan disease, which is a disease that affects fewer than 200,000 individuals in the United States. This program represents a potential first-in-class therapy for this indication. In October 2014, we completed a randomized, placebo-controlled, double-blind Phase 2 clinical trial of INOpulse for PAH. The data from this trial showed trends toward lower pulmonary vascular resistance in both active arms compared to placebo and a slight trend toward increased six-minute walk distance in the higher dose group. While neither result reached the threshold for statistical significance, additional exploratory analyses of patients who were compliant with therapy, assessed as being on therapy for greater than 12 hours per day, as well as a similar analysis of patients on LTOT showed clinically meaningful and statistically significant improvements in both the primary endpoint of pulmonary vascular resistance and the key secondary endpoint of six-minute walk distance, relative to placebo, for patients on the higher dose. These two sub groups each comprised more than 50% of the total patients enrolled in the trial. Statistical significance for clinical trials means that, should the trial have a positive outcome, the results have a low probability of having occurred because of chance rather than from the efficacy of the product.

We believe the results of this trial provide sufficient indication of clinical benefit and safety to continue development of INOpulse for PAH in pivotal Phase 3 clinical trials. We had an End of Phase 2 meeting with the FDA on January 8, 2015. Based on feedback from the FDA at this meeting, we are moving forward with Phase 3 development and plan to conduct two adequate and well-controlled confirmatory Phase 3 clinical trials, either sequentially or in parallel. In March 2015, we requested feedback on the proposed trial design from the Scientific Advice Working Party of the European Medicines Agency, or the EMA. We intend to finalize the clinical trial design following additional discussions with the FDA as well as with other regulatory authorities, including with the EMA.

The FDA has granted orphan drug designation to our nitric oxide program for the treatment of PAH. If a product with an orphan drug designation is the first to receive FDA approval, the FDA will not approve another product for the same indication that uses the same active ingredient for seven years, unless the other product is shown to be clinically superior.

PAH is characterized by abnormal constriction of the arteries in the lung that increases the blood pressure in the lungs which, in turn, results in abnormal strain on the heart s right ventricle, eventually leading to heart failure. While prevalence data varies widely, we estimate there are a total of at least 35,000 patients currently diagnosed with and treated for PAH in the United States and European Union. Moreover, because PAH is rare and causes varied symptoms, we believe there is significant under-diagnosis of the condition at its early stages. There are several approved therapies for PAH, and we estimate, based on public product sales data, that 2012 combined global sales for these therapies were over $4.0 billion. Most PAH patients are treated with multiple medications and many are on supportive therapy. We believe that approximately 20,000 patients have severe to very severe PAH and are treated with multiple therapies, including LTOT. Despite the availability of multiple therapies for this condition, PAH continues to be a life-threatening, progressive disorder. A French registry initiated in 2002 and a U.S. registry initiated in 2006 estimate that the median survival of patients with PAH is three and five years from initial diagnosis, respectively.

Table of Contents

INOpulse for PH-COPD

We are also developing INOpulse for the treatment of PH-COPD. The data from an initial three-month, open-label chronic-use Phase 2 trial conducted by a third party, which we in-licensed, showed that pulsed inhaled nitric oxide significantly reduced pulmonary arterial pressures in PH-COPD patients on LTOT and did so without causing hypoxemia, or an abnormally low level of oxygen in the blood, which is a significant concern for these patients. In June 2012, Ikaria submitted the data from this trial to the FDA as part of the IND package for INOpulse for PH-COPD. Based on discussions with the FDA, we believe this trial is an adequate Phase 2 trial. The FDA asked us to confirm the dose range and the safety related to hypoxemia in PH-COPD patients using the INOpulse device, prior to proceeding to large scale trials. Following this guidance, we conducted a Phase 2 acute dose ranging randomized placebo-controlled trial in 159 patients with the INOpulse DS device, with doses ranging from 3 mcg to 75 mcg. This trial, which we completed in July 2014, identified a dose range that showed similar reduction in pulmonary arterial pressure versus baseline when compared to the initial acute effects of pulsed inhaled nitric oxide in the original chronic-use trial. In addition, in our confirmatory trial, none of the INOpulse doses tested had an adverse effect on hypoxemia relative to placebo. While the reduction in pulmonary arterial pressure did not reach statistical significance versus placebo in this acute setting, which was the primary endpoint of the trial, we believe that the results have confirmed a dose range for this therapy that delivers a significant reduction in pulmonary arterial pressure versus baseline and does not cause hypoxemia in patients with PH-COPD. We are currently evaluating our trial design for chronic use in this population in a three-month Phase 2b trial and plan to finalize the protocol following discussions with regulatory authorities in the United States and European Union.

COPD is a disease characterized by progressive and persistent airflow limitations. Patients with more severe COPD frequently have hypoxemia and may be treated with LTOT. Despite treatment with oxygen, hypoxemia can progress and contribute to pulmonary hypertension. In 2010, Datamonitor estimated that over 1.4 million COPD patients in the United States were being treated with LTOT. Based on academic studies, we estimate that 50% of COPD patients on LTOT have pulmonary hypertension. PH-COPD patients have a lower median life expectancy and a higher rate of hospitalization than COPD patients with similar respiratory disease but without pulmonary hypertension. Currently, there are no approved therapies for treating PH-COPD, and the only generally accepted treatments are LTOT, pulmonary rehabilitation and lung transplant.

BCM

Our second program, BCM, is a medical device intended to prevent congestive heart failure following a STEMI, which is a type of severe heart attack. Patients who suffer a STEMI are at an increased risk for congestive heart failure due to potential cardiac remodeling, which is a structural change in the size and shape of the heart that affects its ability to function normally.

BCM is delivered during a minimally invasive, commonly performed cardiac procedure called a percutaneous coronary intervention procedure. BCM is a formulated sterile solution of sodium alginate and calcium gluconate designed to be administered as a liquid through the coronary artery. When administered following a STEMI, BCM flows into damaged heart muscle where, in the presence of abnormally high extracellular calcium released by the damaged cells, it forms a protective hydrogel meshwork within the wall of the heart s left ventricle. Based on pre-clinical animal studies, we believe that BCM has the potential to act as a flexible scaffold to provide physical support to the ventricle wall in the early stages of recovery following a STEMI and prevent further structural damage while the heart muscle heals. In addition, in our pre-clinical animal studies, as calcium levels in the damaged area returned to normal, BCM dissolved and was excreted through normal kidney function.

In a 27-patient pilot clinical trial conducted in 2009, BCM was safely administered within seven days following a STEMI. Patients showed no deterioration from baseline of important measures of left ventricular function at one, three and six month measurements. Follow-up safety data for these patients, which was obtained four years after the completion of the pilot clinical trial, showed one death from T-cell lymphoma likely a

Table of Contents

preexisting condition and one hospitalization from congestive heart failure. One patient was lost to follow-up in year four, but this patient had no device related adverse events through the three-year evaluation. These results were below the incidence of adverse events of approximately 25% to 30% we expected for patients following an acute myocardial infarction, or AMI, commonly known as a heart attack. This expectation was based on our review of publicly reported data from two long-term third-party studies of AMI patients.

We initiated a clinical trial of BCM in December 2011 and enrolled the first patient in April 2012. We completed enrollment of this trial in December 2014, with 303 patients having completed the treatment procedure at almost 90 clinical sites in Europe, Australia, North America and Israel. We expect to report top line results in mid-2015, following a six-month follow-up period for all patients. This trial is a CE mark registration trial in the European Union. If the results of this trial are positive, we expect it would form the basis for our application for CE marking in the European Union and we would expect to conduct a second, larger clinical trial to support approval in the United States through the premarket approval, or PMA, pathway.

In the United States, we are developing BCM under an investigational device exemption, or IDE. We sponsored an IDE application for our ongoing feasibility clinical trial of BCM to prevent ventricular remodeling and heart failure in patients who are at high risk for ventricular remodeling after an AMI and a successful percutaneous coronary intervention. The FDA has designated BCM as a Class III device. Class III devices are those which the FDA deems to pose the greatest risk, such as those that are life sustaining or life supporting. As a result, the FDA regulates Class III devices under the most rigorous device approval pathway, the PMA process. Device approval under the PMA pathway must be supported by extensive data, including from pre-clinical studies and clinical trials, that demonstrate the safety and efficacy of the device for its intended use. In August 2013, the FDA confirmed that no additional pre-clinical studies were required to support a PMA application. Assuming positive results from this trial, we intend to conduct a pivotal pre-market approval trial of BCM beginning in the first half of 2016, which will be designed to support registration in the United States.

We have an exclusive worldwide license to BCM from BioLineRx Ltd. and its subsidiary, or BioLine, including with respect to issued composition of matter patents on BCM that expire as late as 2029 in the United States, with a possible patent term extension to 2032 to 2034 depending on the timing of marketing approval and other factors, and 2024 in certain other countries. We licensed this product candidate in 2009, following completion of the 27-patient pilot clinical trial conducted by BioLineRx Ltd.

Data from the American Heart Association and the European Association for Percutaneous Cardiovascular Interventions suggests that a total of over 1,900,000 patients suffer a heart attack in the United States and European Union each year, with at least 750,000 of these patients having a STEMI. Following a STEMI, patients are at increased risk of developing cardiac remodeling and subsequent congestive heart failure, and data from long-term third-party studies suggest that the five-year post-AMI rate of congestive heart failure or death is approximately 35% to 40%.

Our Strategy

Our goal is to become a leader in developing and commercializing innovative products at the intersection of drugs and devices that address significant unmet medical needs in the treatment of cardiopulmonary and cardiac diseases. The key elements of our strategy to achieve this goal include:

- *Advance the clinical development of INOpulse.* One of our lead product candidates is INOpulse for PAH. Based on the results from our recently completed Phase 2 clinical trial in PAH, we intend to initiate a Phase 3 clinical trial for this indication in the second half of 2015. In addition, we believe the results of the PH-COPD clinical trials support continued Phase 2 development and we plan to evaluate our options for further development, including potentially through partnerships.

- *Advance the clinical development of BCM in the prevention of cardiac remodeling following a STEMI.* One of our other lead product candidates is BCM. Assuming positive results from our

Table of Contents

ongoing clinical trial, we expect to file for CE marking in the European Union in the second half of 2015 and to initiate a pivotal trial in early 2016 to support a PMA submission seeking marketing approval in the United States.

- *Leverage our historical core competencies to expand our pipeline.* We have years of institutional experience in the use of inhaled nitric oxide in treating pulmonary hypertension and in the development of drug-device combination product candidates. If we successfully advance INOpulse for the two product candidates we are currently developing, we expect to develop INOpulse for treatment of PH-IPF and, subject to obtaining additional license rights from Ikaria, potentially other outpatient pulmonary hypertension indications. Our longer-term vision is to identify and opportunistically in-license innovative therapies that are at the intersection of drugs and devices and to develop and commercialize these product candidates.

- *Build commercial infrastructure in select markets.* As we near completion of the development of our product candidates, we expect to build a commercial infrastructure to enable us to market and sell certain of our product candidates with a specialized sales force and to retain co-promotion or similar rights, when feasible, in indications requiring a larger commercial infrastructure. While we may partner with third parties to commercialize our product candidates in certain countries, we may also choose to establish commercialization capabilities in select countries outside the United States.

INOpulse

INOpulse Scientific Background

Nitric oxide is a naturally occurring molecule produced by many cells of the body. Researchers found that nitric oxide is produced and released by the lining of the blood vessel and plays a role in controlling muscle tone in blood vessels. In particular, nitric oxide results in vascular smooth muscle relaxation in blood vessels and thus is an important factor in regulating blood pressure. As the muscles of the blood vessels relax, blood flow increases, helping the heart to deliver more blood to the body. When administered by inhalation to patients with pulmonary hypertension, we expect inhaled nitric oxide to act in a similar manner to naturally produced nitric oxide.

The scientific journal *Science* named nitric oxide Molecule of the Year in 1992. Additionally, the three researchers who discovered the role of nitric oxide as a signaling molecule in the cardiovascular system earned the Nobel Prize for Physiology or Medicine in 1998.

In 1991, Dr. Warren Zapol and his associates at the Massachusetts General Hospital discovered that inhaling nitric oxide in gas form could reduce high blood pressure in the lungs, a condition known as pulmonary hypertension. Nitric oxide is a rapid and potent vasodilator, which means it dilates, or widens, blood vessels. When inhaled, it quickly dilates blood vessels in the lungs, which reduces blood pressure in the lungs, strain on the right ventricle and shunting of de-oxygenated blood away from the lungs. Because more blood can flow through the lungs, blood levels of oxygen improve. In addition, inhaled nitric oxide improves the efficiency of oxygen delivery, and because it is a gas, it goes only to the portions of the lung that are ventilated, or receiving air flow, and increases blood flow only in these areas. Thus, inhaled nitric oxide improves ventilation-perfusion matching, an important element of lung function involving the air that reaches the lungs, or ventilation, and the blood that reaches the lungs, or perfusion. Inhaled nitric oxide is quickly inactivated after contact with blood, and is selective for the lungs, meaning that it has minimal effects on blood pressure outside of the lungs, which is an important safety consideration.

In 1999, the FDA approved the use of inhaled nitric oxide for the short-term treatment of persistent pulmonary hypertension of the newborn. Based on this approval, and similar approvals from foreign regulatory authorities, continuous-flow inhaled nitric oxide, which is administered to ventilated patients by a dedicated in-hospital device, is marketed by Ikaria and its commercialization partners worldwide as INOmax (INOflo in

Table of Contents

Japan). Inhaled nitric oxide is widely used in the hospital setting for a variety of conditions and, as reported by Ikaria, over 450,000 patients have been treated with inhaled nitric oxide worldwide since its commercial launch. However, chronic outpatient use of this therapy has previously been limited by the lack of a safe and compact delivery system for outpatient use.

INOpulse Drug-Device Combination

Our INOpulse device has a proprietary mechanism that delivers brief, targeted pulses of nitric oxide, timed to occur at the beginning of a breath and targeted for delivery to the well-ventilated alveoli of the lungs. INOpulse is portable and therefore allows for treatment of ambulatory patients on a daily basis inside or outside their homes. INOpulse is designed to automatically adapt based on a patient s breathing pattern to deliver a constant dose of the drug over time, independent of the patient s activity level, thus ensuring predictable dosing in the alveoli of the lungs. We estimate that, because of the pulsed delivery and higher concentration of nitric oxide we use, the volume of drug delivered is reduced to approximately 5% of the volume required for equivalent alveolar absorption using standard continuous-flow delivery systems.

INOpulse is configured to be highly portable and compatible with available modes of LTOT via nasal cannula delivery. Our recently completed clinical trials of INOpulse for PAH and INOpulse for PH-COPD utilized the first generation INOpulse DS device, which is derived from an older hospital-based system. While this device is portable and appropriate for use at home, to make INOpulse acceptable to a broader range of patients and to improve its usability, we are near completion of our second generation device, the Mark2, which we plan to use in future clinical trials.

The Mark2 is approximately the size of a paperback book and weighs approximately 2.5 pounds. It has a simple user interface and a battery life of approximately 24 hours when recharged, which takes approximately four hours and can be done while the patient sleeps. Based on the doses we evaluated in our clinical trials, we expect the cartridge will need to be replaced once a day. The Mark2 incorporates our proprietary triple-lumen nasal cannula, safety systems and proprietary software algorithms. The triple-lumen nasal cannula enables more accurate dosing of inhaled nitric oxide and minimizes infiltration of oxygen, which can react with nitric oxide to form nitrogen dioxide. Our triple-lumen nasal cannula consists of a thin, plastic tube that is divided into three channels from end-to-end including at the prongs that are placed in the patient s nostrils, with one channel delivering inhaled nitric oxide, a second for breath detection and a third available for oxygen delivery. Our device is designed to be compatible with many LTOT systems.

The Mark2 has been well received by patients in the usability research we have conducted. In addition to the baseline testing on the original INOpulse DS device, we have conducted two rounds of testing with COPD and PAH patients to evaluate the user interface, loading mechanism, size, carrying bag and other features. In the usability research we have conducted, all eight patients with experience with the INOpulse DS device responded positively to the Mark2, and several of these patients indicated that the ability to take the Mark2 outside the home would likely reduce concerns with maintaining compliance.

Based on discussions with the FDA, we are required to show that the amount and timing of inhaled nitric oxide delivery is similar across INOpulse device generations. We have developed a regulatory bridging strategy to meet these requirements. To facilitate the transition from our existing INOpulse DS device to the Mark2 in our INOpulse clinical program, we plan to conduct comparability testing of inhaled nitric oxide dosing with the Mark2 as compared to the INOpulse DS device. This testing will include a comparison of critical parameters, including pulse width and nitric oxide output. We will also assess whether the Mark2 will meet the performance specifications of the INOpulse DS device in addition to Mark2-specific requirements. In addition, we are developing a bridging test report that we expect to include in the regulatory package that we anticipate submitting to the FDA during the first half of 2015 to gain approval for the device transition. We discussed our bridging strategy with the FDA during a meeting in May 2013, and we believe that, assuming the Mark2 meets the specified comparability parameters,

this testing will be sufficient to gain FDA approval to use the Mark2 in future clinical trials, as planned.

Table of Contents

We have licensed from Ikaria several patents and patent applications for certain innovations in our INOpulse devices. These include patents with respect to the pulsed delivery of inhaled nitric oxide to ensure a consistent dose over time, which expire as late as 2027 in the United States and as late as 2026 in certain other countries, as well as a patent with respect to the triple-lumen cannula that allows for safer and more accurate dosing of pulsed inhaled nitric oxide, which expires in 2033. We have also licensed several other patent applications from Ikaria for certain of the innovations included in the Mark2 and certain of the resulting patents that, if issued, would expire as late as 2033.

In the European Union, where there is no formal drug-device designation, we expect INOpulse to be evaluated by the EMA as a drug with specific reference in the label to the device and cannula, which will require a separate CE mark from a Notified Body.

Introduction to Pulmonary Hypertension

Pulmonary hypertension is a disease characterized by constriction of the blood vessels in the lung, which causes blood pressure in the lung to rise and, in turn, increases the work required for the right ventricle of the heart to pump blood. The World Health Organization, or WHO, has endorsed a consensus classification for pulmonary hypertension that was updated most recently in 2013. The WHO classification has five broad pulmonary hypertension groups based on similarities in pathological and hemodynamic characteristics and therapeutic approaches. We are initially focusing development of INOpulse in indications included in WHO Groups 1 and 3 due to our view of the likelihood of success and the size and commercial viability of these markets. Group 1 pulmonary hypertension is comprised of patients with pulmonary arterial hypertension and is referred to as PAH. This Group combines conditions with a range of causes, all of which have a characteristic pattern of vascular remodeling. The constriction of the blood vessels and the resulting pressure on the heart is often the major reason for poor prognosis of PAH patients since they can be otherwise healthy. Most PAH-specific medications are vasodilators and work through one of the three key mechanistic pathways for vasoconstriction and vasodilation. We expect that, because inhaled nitric oxide is a vasodilator, patients in Group 1 will benefit from INOpulse. Group 3 pulmonary hypertension consists of pulmonary hypertension associated with lung disease or hypoxemia, which is an abnormally low level of oxygen in the blood. This Group includes patients with PH-COPD and PH-IPF, among others.

INOpulse for Pulmonary Arterial Hypertension

We are developing INOpulse for PAH to address a significant and unmet medical need in an orphan disease. This product candidate represents the development of a potential first-in-class therapy for this indication. Although current therapy for PAH provides some therapeutic benefit, there remains no cure, and approved therapies can have significant systemic side effects, such as hypotension and liver injury. INOpulse for PAH is designed to be a selective, short-acting pulmonary vasodilator and is being tested as an add-on therapy to existing PAH medications to evaluate its efficacy and side effect profile, in particular its ability to provide clinical benefit without adding to the systemic effects such as hypotension.

Disease Background and Market Opportunity

PAH is a life-threatening, progressive disorder characterized by abnormally high blood pressure, or hypertension, in the pulmonary artery, the blood vessel that carries blood from the heart to the lungs. PAH occurs when most of the very small arteries, or arterioles, throughout the lungs narrow in diameter, which increases the resistance to blood flow through the lungs. To overcome the increased resistance, pressure increases in the pulmonary artery and the right ventricle, which is the heart chamber that pumps blood into the pulmonary artery. In addition, PAH may

cause changes to the blood vessel lining that hinder the natural production of nitric oxide. Signs and symptoms of PAH occur when this increased pressure in the right ventricle cannot fully overcome the elevated resistance.

Table of Contents

There are a number of drugs approved for the treatment of PAH that work primarily by reducing pulmonary vascular resistance, which is the primary problem for these patients. However, despite the availability of multiple therapies for this condition, the mortality rate for PAH remains high, with estimates of median survival ranging from three to five years. Patients with PAH also report severe impairment of health-related quality of life, including poor general and emotional health and impaired physical functioning. The most common symptoms of PAH are shortness of breath during exertion and syncope, or fainting spells. People with PAH may experience additional symptoms, particularly as the condition worsens, including dizziness, swelling of the ankles or legs, chest pain and a racing pulse. These impairments to health-related quality of life are comparable and sometimes more severe than those reported in patients with severely debilitating conditions such as spinal cord injury.

Since PAH is an orphan condition with poor diagnosis rates, published prevalence estimates for PAH vary widely. Based on epidemiological studies and current treatment rates, we estimate that there are a total of at least 35,000 patients currently diagnosed and treated for PAH in the United States and European Union. The average age of PAH patients at diagnosis is approximately 50 years, and approximately 80% of PAH patients are female. PAH is often diagnosed late in the disease progression with approximately 73% of these patients already having progressed to WHO functional Class III or IV at the time of diagnosis.

PAH is characterized by abnormal constriction of the arteries in the lung. PAH patients are generally treated with one or more of the four major classes of approved medications, which are prostacyclin and prostacyclin analogs, phosphodiesterase type-5 inhibitors, endothelin receptor antagonists and a soluble guanylate cyclase stimulator, all of which potentially result in vasodilatory systemic effects and, therefore, hypotension. Current guidelines recommend treatment with multiple medications in Class III and IV patients with progressive disease but suggest treatment be carefully managed by experienced physicians. Approximately 45% of PAH patients are treated with more than one class of medication at a given time. In addition, since hypoxemia can be a problem in these patients, it is often treated with LTOT in accordance with broadly supported treatment guidelines in the United States and European Union.

We are testing INOpulse for PAH as an add-on therapy for use in patients whose disease is progressing and who use additional medications. If it is approved, we expect INOpulse will provide the greatest benefit to patients who require pulmonary arterial pressure reductions beyond the reductions achieved with the medication they are already using. Because of its localized effect and short-half life, we do not expect INOpulse will add to systemic blood pressure reductions of other PAH drugs. We believe that INOpulse is also likely to be preferentially prescribed for patients already on LTOT. Data from a U.S. and a French registry indicate that approximately 40% of patients are treated with oxygen at diagnosis for hypoxemia. Approximately 60% of the patients from our recently completed Phase 2 clinical trial were on LTOT. We believe that, as compared to patients who are not using a nasal cannula, patients who are accustomed to using a nasal cannula for delivery of oxygen are more likely to be prescribed and are more likely to be compliant with the use of INOpulse.

A 2013 report by CVS Caremark Specialty Analytics provided examples of PAH medications with annual prices ranging from approximately $100,000 to $150,000 per patient per year in the United States. We expect that, if approved, the price of INOpulse will be in the range of other established PAH medications.

Scientific Rationale for Use of INOpulse for PAH

Since the discovery of the significant role of nitric oxide in vasodilation, there has been an expectation in the scientific community that inhaled nitric oxide could be an effective therapy for PAH. According to the Cleveland Clinic Center for Continuing Education section on Pulmonary Hypertension, exogenous administration of nitric oxide by inhalation is probably the most effective and specific therapy for PAH, but cost and technical complexity of delivering inhaled nitric oxide have limited its use to the hospital. Although not approved for the treatment of PAH, data from an in-hospital survey conducted by Ikaria showed an estimated 1,000 to 2,000 INOmax uses in PAH patients in the United States each

year, indicating that physicians already use nitric oxide in some PAH patients. The difficulty in delivering inhaled nitric oxide outside of the hospital

Table of Contents

results from the size of the device and cylinder and the need for a specialized delivery system with built-in safety systems.

We are developing nitric oxide for treatment of PAH because nitric oxide is a proven vasodilator, and PAH is primarily a disease of high pulmonary vascular resistance. PAH is associated with impaired release of nitric oxide and thus we believe chronic administration of inhaled nitric oxide may be viewed as an adjunctive or replacement therapy in patients with PAH. The use of inhaled nitric oxide in PAH has been proposed since the role of nitric oxide in this disease was identified. This drug has been tested in limited investigational studies conducted at academic institutions.

One clinical trial conducted at an academic center in Spain in 11 patients, seven of whom had severe PAH and four of whom had severe chronic thromboembolic pulmonary hypertension, or CTEPH, evaluated the use of pulsed inhaled nitric oxide in an ambulatory setting. In this open-label, single-arm trial with no placebo control, patients were given ambulatory pulsed inhaled nitric oxide therapy via a nasal cannula for up to one year, after being withdrawn from PAH-specific therapy. The nitric oxide pulse was delivered to the patient at the beginning of each inspiration at a flow rate that was individualized for such patient. The goal of this trial was to evaluate the efficacy and safety of long-term treatment with inhaled nitric oxide outside the hospital setting.

At the start of this trial, patients were evaluated for various measures including the distance they were able to walk in six minutes and WHO functional class. At baseline, most of these patients had significant impairment of six-minute walk distance, with the ability to walk an average of 125 meters, and poor WHO functional class status, with nine patients in Class IV and two patients in Class III. After one month of therapy, overall, patients improved based on WHO functional class, with six patients in Class III and five in Class II, and had improvements in six-minute walk distance of 128 meters on average. After six months of treatment, patients did not worsen clinically, however, between months six and 12, seven patients were given a phosphodiesterase type-5 inhibitor due to clinical worsening. One patient who initially did well with the added phosphodiesterase type-5 inhibitor therapy developed severe right heart failure at month eight and died, and another patient received a lung transplant at month nine. The remaining nine patients all had clinical status at month 12 similar to their one month evaluation, and improvements in functional class and six-minute walk distance for the group persisted over time.

We do not expect INOpulse to have systemic effects beyond the pulmonary vasculature because of the short half-life of nitric oxide combined with its targeted delivery to the alveoli. When nitric oxide is delivered as a pulse at the beginning of inhalation, it travels to the alveoli where it diffuses rapidly across the alveolar capillary membrane into the adjacent vascular smooth muscle of pulmonary vessels. This transport is similar to the natural transport of endogenous nitric oxide from the endothelial cells, where it is produced, to the vascular smooth muscle cells where it relaxes the muscle and causes vasodilation of the pulmonary arteries. We believe this makes INOpulse unlikely to have intolerable side effects, such as systemic hypotension or drug-drug interactions. Given the need for PAH patients to be treated with multiple therapies and the potential for increased hypotension from each of the currently approved PAH therapies, we are developing INOpulse as an add-on or adjunctive therapy for PAH, where we believe it has the highest commercial potential.

Clinical Development Program

INOpulse for PAH is designated as a drug-device combination by the FDA and is being evaluated through the Division of Cardiovascular and Renal Products of the Center for Drug Evaluation and Research with consultation from the Center for Devices and Radiological Health. For our IND for PAH, we submitted data from animal studies in rats and sheep as well as the results of a Phase 1 trial of pulsed inhaled nitric oxide in healthy volunteers. In addition, we referenced additional data from Ikaria s new drug application, or NDA, in respect of INOmax. Based on this, the FDA has agreed that no further preclinical studies are required for clinical development of INOpulse for PAH.

Table of Contents

In the European Union, where there is no formal drug-device designation, we expect that INOpulse for PAH will be evaluated by the EMA as a drug with specific reference in the label to the device and cannula, which will require a separate CE mark from a Notified Body.

Phase 2 Clinical Trial

We recently completed Part A of our ongoing Phase 2 clinical trial of INOpulse for PAH in the United States and Canada. Our key inclusion criteria for patients in this trial were that they:

- be diagnosed with pulmonary hypertension WHO Group 1;
- be on at least one other PAH medication for at least 12 weeks prior to treatment with INOpulse; and
- demonstrate being able to walk between 100 and 450 meters within six minutes.

In addition, this trial excluded patients with evidence of significant left ventricular dysfunction.

The trial is being conducted in two parts, Part A and Part B. In October 2014, we completed Part A of this trial which was a randomized, placebo-controlled, double-blind clinical trial with patients randomized 1:1:1 to placebo or to one of two active doses, either 25 or 75 mcg/kg ideal body weight/hour, or mcg, for 16 weeks. Part B is an ongoing double-blind long-term extension of the initial trial with all patients on one of two doses of INOpulse for PAH to monitor the long-term safety and tolerability of the therapy. Eighty-one percent of the patients in Part A elected to enter the Part B long-term extension trial. The primary endpoint in this trial was a change in pulmonary vascular resistance from baseline at 16 weeks, which was the end of Part A. The target change in pulmonary vascular resistance was 190 dynes sec. cm-5, and the trial was powered for statistical significance at 130 dynes sec. cm-5. The main secondary endpoint was change in six-minute walk distance over the same period. A clinically meaningful change in six-minute walk distance is typically considered to be an increase of at least 30 to 35 meters. We expect to continue the ongoing Part B of this trial until the earliest of INOpulse for PAH being approved, clinical development of INOpulse for PAH being discontinued or our decision to discontinue Part B.

We typically use, and have used for this trial, a conventional method of assessing statistical significance known as a one-way analysis of variance, or ANOVA. In this method the threshold of statistical significance is reached when a measure known as the p-value is 0.05 or lower. Because we are using two doses, we are using a common adjustment to the significance threshold for the analysis in this trial, including the subgroup analysis, by requiring the p-value to be 0.025 or lower before it is considered significant. When the p-value is higher than this threshold it is considered that any directional benefit seen in the clinical trial could be due to chance rather than being a true measure of the efficacy of the product tested.

We randomized 80 patients for Part A of the Phase 2 clinical trial. The majority of the patients were female (79%), white (89%) and had idiopathic PAH (74%). The results from Part A of this trial, which are summarized in the table below, showed trends toward lower pulmonary vascular resistance in both the active arms compared to placebo and a slight trend toward increased six-minute walk distance in the higher dose group. However, neither result was statistically significant.

INOpulse for PAH Phase 2 Part A Trial Results for All Patients

			Inhaled nitric oxide dose (mcg/kg ideal body weight/hour)	
Parameter		**Placebo**	**25**	**75**
Total number of patients randomized		26	27	27
Pulmonary Vascular Resistance (dynes sec. cm-5)	Number analyzed	24	23	24
	Baseline (mean)	601.5	665.8	662.9
	Change from Baseline (mean)	47.2	-54.1	-15.0
	p-value (ANOVA)		0.091	0.178
6-Minute Walk Distance (m)	Number analyzed	24	24	23
	Baseline (mean)	367.5	326.8	300.7
	Change from Baseline (mean)	7.5	4.7	22.8
	p-value (ANOVA)		0.851	0.314

Table of Contents

In an analysis of baseline characteristics, patients randomized to placebo were younger and less sick than those on either of the active arms on many dimensions including baseline pulmonary vascular resistance, baseline six-minute walk distance, duration of disease and WHO severity class. In addition, fewer of the patients on placebo were on LTOT compared to either of the active arms with more patients on LTOT at the 75 mcg dose than on the 25 mcg dose.

INOpulse for PAH Phase 2 Trial Baseline Demographics

		Inhaled nitric oxide dose (mcg/kg ideal body weight/hour)	
	Placebo	**25**	**75**
Number of patients	26	27	27
Age (years) (mean)	52.0	56.3	57.9
WHO Severity (number in Classes III and IV)	19	21	23
Disease duration (years) (mean)	5.5	6.2	6.0
Pulmonary Vascular Resistance (dynes sec.cm-5) (mean)	601.5	665.8	662.9
6-Minute Walk Distance (m) (mean)	367.5	326.8	300.7
Use of LTOT	46.2%	59.3%	77.8%

During evaluation of the data, we observed that adherence to therapy was widely variable. LTOT was a pre-specified parameter recorded at baseline, and patients using LTOT at baseline were more adherent to using the device. Good adherence was retrospectively defined as an average use of greater than 12 hours per day. Specifically, patients using LTOT had a rate of 70% adherence as compared with 33% adherence in those patients not using LTOT. Based on this observation, we conducted non-scheduled, exploratory analyses by LTOT use and by compliance (defined as patients who had average daily use of 12 hours per day or more). Each of these subgroups comprised more than 50% of the total patients enrolled in the trial. The results of these analyses are summarized in the following table.

INOpulse for PAH Phase 2 Part A Trial Compliance to Therapy

		Percent of patients	
Average hours of use per day	**All patients**	**On LTOT**	**Not on LTOT**
< 4 Hours	6.3%	4.1%	9.7%
4-8 Hours	20.0%	8.2%	38.7%
8-12 Hours	17.5%	16.3%	19.4%
12-16 Hours	22.5%	30.6%	9.7%
16-20 Hours	16.3%	22.4%	6.5%
≥ 20 Hours	17.5%	18.4%	16.1%

Table of Contents

Among LTOT users, there was a clinically meaningful and statistically significant improvement versus placebo in both pulmonary vascular resistance and six-minute walk distance in patients at the 75 mcg dose and there was a statistically significant improvement in pulmonary vascular resistance and a positive trend in change in six-minute walk distance in patients on the 25 mcg dose.

In the subgroup of compliant patients who used INOpulse for an average of greater than 12 hours per day, the results were very similar to those of the LTOT subgroup. This was expected since there is a significant overlap between the compliant patient and the LTOT group, with approximately 80% of compliant patients also treated with LTOT at baseline. In the compliant group, when compared to placebo, there was a positive trend for change in pulmonary vascular resistance and a clinically meaningful and statistically significant improvement in six-minute walk distance in the 75 mcg dose arm and there was a statistically significant improvement in pulmonary vascular resistance and a non-significant change in six-minute walk distance in the 25 mcg dose arm.

INOpulse for PAH Phase 2 Part A Trial Results for Patient Subgroups

Pulmonary Vascular Resistance

			Inhaled nitric oxide dose (mcg/kg ideal body weight/hour)	
Parameter/Population		**Placebo**	**25**	**75**
Total number of patients randomized		26	27	27
On LTOT	Number analyzed	10	15	19
	Baseline (mean)	580.1	605.2	614.9
	Change from Baseline (mean)	125.5	-47.1	-17.5
	p-value (ANOVA)		0.018	0.024
≥ 12 hours per day (Compliant)	Number analyzed	10	12	18
	Baseline (mean)	527.6	747.2	670.6
	Change from Baseline (mean)	146.5	-66.9	-5.1
	p-value (ANOVA)		0.023	0.027

Six-Minute Walk Distance

			Inhaled nitric oxide dose (mcg/kg ideal body weight/hour)	
Parameter/Population		**Placebo**	**25**	**75**
Total number of patients randomized		26	27	27
LTOT	Number analyzed	10	15	18
	Baseline (mean)	333.5	301.5	292.2
	Change from Baseline (mean)	-10.7	9.1	34.9
	p-value (ANOVA)		0.320	0.021
≥ 12 hours per day (Compliant)	Number analyzed	10	12	16

	Baseline (mean)	330.0	316.3	294.5
	Change from Baseline (mean)	-10.1	8.5	37.0
	p-value (ANOVA)		0.374	0.021

Table of Contents

INOpulse was relatively well-tolerated in Part A of this trial. Our Independent Data Safety Monitoring Board evaluated the safety analysis from Part A of the trial in November 2014 and recommended proceeding with Part B of the trial. Drug-related serious adverse events, or SAEs, occurred in no patients in the placebo group and one subject in each of the 25 mcg and 75 mcg groups.

INOpulse Phase 2 Part A Trial Results for All Patients: Summary Safety Data

		Inhaled nitric oxide dose (mcg/kg ideal body weight/hour)	
Number of Patients	**Placebo**	**25**	**75**
Number of Patients	26	27	27
Total Adverse Events (AEs)	23	22	26
Drug related AEs	9	10	9
Total Serious Adverse Events (SAEs)	4	4	9
Drug related SAEs	0	1	1
Deaths	1	0	0
Discontinuation due to AEs	1	1	2

One patient in the placebo arm died during Part A of the trial due to worsening PAH. SAEs were reported for four patients in the placebo arm, including one each of: pneumonia/worsening PAH, catheter-related infection, ascites and left hip sciatica. Each of these were assessed by the investigator for the trial as unrelated. Four patients in the 25 mcg low-dose active treatment arm experienced SAEs, including bacteremia, myelodysplastic syndrome, increased shortness of breath and dyspnea, one of which was assessed as possibly related to trial therapy. The 75 mcg high-dose active treatment arm had nine patients with SAEs. The most common SAEs reported in the 75 mcg group were syncope and bronchitis/tracheobronchitis, one of which was assessed as possibly related to trial therapy. Discontinuation of trial therapy due to adverse events, or AEs, occurred for two patients in the 75 mcg arm and one subject in each of the 25 mcg and placebo arms.

Pivotal Phase 3 Clinical Trials

We believe the results from Part A of our Phase 2 clinical trial provide sufficient indication of clinical benefit and safety to continue development of INOpulse for PAH in pivotal Phase 3 clinical trials. We had an End of Phase 2 meeting with the FDA on January 8, 2015. Based on this discussion, we plan to conduct this Phase 3 program as two adequate and well-controlled confirmatory trials, and we will conduct these two trials either sequentially or in parallel. In March 2015, we requested feedback on the proposed trial design from the Scientific Advice Working Party of the EMA. We currently intend to begin the Phase 3 program in the second half of 2015 and we estimate that, once initiated, each trial will take approximately three years to complete.

We expect one of the trials to have two arms placebo and 75 mcg active dose and the other to have three arms placebo, 50 mcg active dose and 75 mcg active dose. Each arm is planned to have approximately 94 patients. Based on our discussions with the FDA, we expect that the primary endpoint of the trial will be change in six-minute walk distance evaluated at 18 weeks. In addition, we expect to have a secondary endpoint of time to clinical worsening, which we plan to analyze based on combined data from both trials to ensure adequate power for this assessment. We also plan to evaluate hemodynamic changes using right heart catheterization in a subset of patients.

We expect that enrollment for these trials will focus on patients with confirmed PAH who are treated with at least one approved PAH specific therapy and LTOT and who are willing to be compliant on therapy for at least 16 hours a day. We plan to conduct both trials with a two week run-in period, prior to the start of clinical dosing, to enrich enrollment for patients who show a high degree of adherence (i.e., an average of at least

Table of Contents

16 hours of use per day) during this run-in period. We plan to use the Mark2 in these Phase 3 clinical trials. Results from our usability testing suggest that compliance with the Mark2 may be better than was the case with the first generation INOpulse DS device. We expect that the Phase 3 clinical trials will be multi-center multi-country trials with a focus on sites in North America and Europe.

We intend to finalize the clinical trial design following additional discussions with the FDA as well as with other regulatory authorities, including with the EMA.

INOpulse for PH-COPD

We are developing INOpulse for PH-COPD to address a significant unmet medical need that we believe is often overlooked in everyday clinical practice because of the lack of available therapy. Pulmonary hypertension is more prevalent among those COPD patients who have advanced loss of respiratory function and low peripheral blood oxygen levels requiring treatment with LTOT. The co-morbidity of pulmonary hypertension in these patients leads to cardiovascular complications from the added strain on the right ventricle of the heart. Current drug therapies for COPD are targeted to relieve the symptoms and complications of the respiratory component of the disease. Unlike these therapies, INOpulse is directed at treating the cardiovascular complications of PH-COPD. We believe PH-COPD patients on LTOT who are at risk for cardiovascular complications could benefit from use of INOpulse in addition to any respiratory benefits that result from their existing treatments.

Disease Background and Market Opportunity

COPD is a progressive disease caused by chronic inflammation and destruction of the airways and lung tissue. While COPD is primarily a respiratory disease, over time, as the disease progresses, the chronic pulmonary restrictions and resulting deprivation of adequate oxygen, or hypoxia, can contribute to vasoconstriction in the pulmonary arterial bed. In addition, COPD patients can have deficiency in endogenous nitric oxide production in their lungs, which can worsen vasoconstriction. This pulmonary vasoconstriction puts pressure on the right side of the heart, making it less able to cope with stressors and potentially leading to progressive cardiac dilation, heart failure and death. This cardiovascular component of COPD is, we believe, often overlooked despite pulmonologists general awareness of the problem, in part because there are no specific therapies for the condition in these patients. While it is widely believed that the cardiovascular complications of COPD occur only in the advanced stage of the disease as a consequence of chronic hypoxemia, recent findings demonstrate an earlier involvement of the cardiovascular system in this disease.

In 2010, Datamonitor estimated that approximately 12 million patients in the United States were being treated for COPD and that over 1.4 million of these patients were being treated with LTOT. Based on academic studies, we estimate that 50% of COPD patients on LTOT in the United States have pulmonary hypertension. Even though the degree of pulmonary hypertension in these patients is milder than in PAH patients, data published in literature suggests that even small elevations in mean pulmonary artery pressure in patients with advanced COPD can impact hospitalization, patient-assessed functional outcomes and mortality. Pulmonary hypertension is a well-known predictor of increased morbidity and mortality in COPD patients and is associated with poor quality of life, worse clinical outcomes and shorter survival time. Based on a long-term study completed in 1992 and published in 1995, PH-COPD patients had a four-year survival rate of approximately 50%. By contrast, in this same long-term study, COPD patients with similar pulmonary functions, but without pulmonary hypertension, had a four-year survival rate of 80%.

We expect INOpulse for PH-COPD, if approved, would be a treated as a specialty drug. Specialty drugs are typically high-cost medications, often ranging in price in the United States from approximately $15,000 to $50,000 per patient per year, used to treat rare or complex conditions, requiring close clinical management and special handling and distributed through specialty pharmacies.

Table of Contents

Scientific Rationale for Use of INOpulse for PH-COPD

The mechanism of action of inhaled nitric oxide in vasodilation at the alveolar smooth muscle in PH-COPD is similar to its action in PAH. Like endogenous pulmonary nitric oxide, inhaled nitric oxide works by selectively relaxing lung vascular smooth muscles, causing dilation of pulmonary blood vessels and consequently increased pulmonary blood flow. This reduces the elevated pulmonary artery pressure in patients with PH-COPD.

PH-COPD patients generally have hypoxemia as a result of deteriorating lung function, which can be treated with supplemental oxygen therapy. However, these patients are not treated with currently approved PAH-specific drugs because these drugs can worsen hypoxemia. This worsening can occur when these drugs, which are systemically bioavailable, cause indiscriminate pulmonary vasodilation, even in poorly ventilated alveoli, resulting in lower average blood oxygenation levels. We believe that inhaled nitric oxide, as a locally active selective pulmonary vasodilator with minimal systemic effects, can drop pulmonary arterial pressures, and when delivered with INOpulse as a targeted pulse to the well-ventilated alveoli, avoid this indiscriminate vasodilation and the consequent lowering of blood oxygen levels.

The targeted delivery of inhaled nitric oxide to specific alveoli is important because early trials with continuous-flow inhaled nitric oxide reduced pulmonary arterial pressure in PH-COPD patients but also resulted in lowering of blood oxygen levels. It was postulated that this unwanted effect might be avoided by administering nitric oxide as a brief pulse at the beginning of each breath because well-ventilated alveoli open faster, and a brief early pulse would only reach these alveoli. As early as 1997, this concept was demonstrated by testing inhaled nitric oxide in PH-COPD patients during exercise, which allowed the dose to mimic pulse dosing. Recently, data from a computational fluid-flow modeling study we conducted, using high resolution computed tomography scans and computer simulations, supported this hypothesis that early pulsed delivery of nitric oxide could be directed specifically to the well-ventilated alveoli.

Clinical Development Program

INOpulse for PH-COPD is designated as a drug-device combination by the FDA and is being evaluated through the Division of Cardiovascular and Renal Products of the Center for Drug Evaluation and Research with consultation from the Division of Pulmonary, Allergy, and Rheumatology Products and the Center for Devices and Radiological Health. In our IND for PH-COPD, we referenced all of the information in our IND for PAH and included data from a Phase 2 clinical trial that Ikaria commenced in 2005 but terminated due to lack of enrollment after one subject was treated. The one subject experienced a serious adverse event of hypoxia, which was deemed unrelated to treatment. The data referenced in our IND, as well as the years of use of the marketed product, demonstrate that nitric oxide is well tolerated. The FDA has agreed that the IND package is complete and adequate for supporting Phase 2 clinical development of INOpulse for PH-COPD. The FDA also agreed that no additional pre-clinical studies are needed to support product approval.

In the European Union, where there is no formal drug-device designation, we expect that INOpulse for PH-COPD will be evaluated by the EMA as a drug with specific reference in the label to the device and cannula, which will require a separate CE mark from a Notified Body.

In an initial three-month, open-label chronic-use Phase 2 trial, pulsed inhaled nitric oxide significantly reduced pulmonary arterial pressures in PH-COPD patients on LTOT and did so without causing hypoxemia, which is a significant concern for these patients. The inhaled nitric oxide was administered using a device that delivered pulsed nitric oxide as a fixed amount per breath along with the oxygen using a single lumen nasal

cannula. This trial, completed in 2000, was conducted in two parts, an initial acute dose titration part and a three-month chronic ambulatory use part. In the initial acute test, each patient was treated with doses of 10, 15, 20, 25 and 30 ppm nitric oxide in a step-wise escalation from the lowest to higher doses. Each patient was assessed for drops in mean pulmonary arterial pressures, or mPAP, as well as for changes in oxygenation levels. The mean acute change in mPAP in this trial was a reduction of approximately 4 mmHg from a baseline of 27

Table of Contents

mmHg across all doses. In another measure of the hemodynamic effects of the drug, the pulmonary arterial systolic pressure reduced by 2.7 to 3.6 mmHg across the nitric oxide doses tested. Based on the individual mPAP and oxygenation level changes in the acute test, each patient was assigned an individualized dose to be used in the second part of the trial which was a three-month evaluation. The patients were then randomized to either the control group for treatment with oxygen therapy or to the active group for treatment with both oxygen and the individually selected dose of nitric oxide over a period of three months. A total of 32 patients completed the three month portion per protocol, 15 of whom had been randomized to drug therapy and 17 of whom were randomized to the control group. At the end of the three month chronic use portion of the trial, patients in the nitric oxide arm had a statistically significant decrease from baseline in mPAP of 6.8 mmHg compared to an increase in mPAP of 0.9 mmHg in the oxygen alone control arm of the trial ($p < 0.001$) demonstrating a sustained and potentially strengthened effect of inhaled nitric oxide on mPAP over three months. In addition, at the three month evaluation, the patients treated with pulsed inhaled nitric oxide had no worsening of blood oxygen levels compared to the control group suggesting no worsening of oxygen exchange in the lungs.

In June 2012, this data was submitted to the FDA as part of the IND package for INOpulse for PH-COPD. Based on discussions with the FDA, we believe this trial is an adequate Phase 2 trial. The FDA has asked us to confirm the dose range and the safety related to hypoxemia in PH-COPD patients using the INOpulse device, prior to proceeding to large scale trials. Following this guidance, we conducted a Phase 2 acute dose ranging randomized placebo-controlled trial in 159 patients with the INOpulse DS device, with doses ranging from 3 mcg to 75 mcg. This Phase 2 trial, which we completed in July 2014, identified a dose range that showed similar efficacy versus baseline when compared to the initial acute effects of pulsed nitric oxide in the original chronic-use trial. The 10 mcg dose of INOpulse showed a decrease in pulmonary arterial systolic pressure from baseline of 5.4 mmHg ($p < 0.05$) and increasing the dose above 10 mcg did not result in a further decrease in pulmonary arterial systolic pressure from baseline indicating a plateau effect of the drug at 10 mcg and above. A post-hoc analysis of data combining all response data over the range of 10 mcg to 75 mcg showed a decrease in pulmonary arterial systolic pressure from baseline of 4.2 mmHg, which was significant and represented a mean decrease of approximately 9% from baseline. In addition, in our confirmatory trial, none of the INOpulse doses tested had an adverse effect on hypoxemia relative to placebo with a total of 48 patients with confirmed oxygenation level decrease greater than 5 mmHg from baseline (16/40 in placebo; 32/84 in inhaled nitric oxide). While the reduction in pulmonary arterial pressure did not reach statistical significance versus placebo in this acute setting, as the decrease in pulmonary arterial systolic pressure from baseline in the placebo group was 1.9 mmHg, we believe that the results have confirmed a dose range for this therapy that delivers a significant reduction in pulmonary arterial pressure versus baseline without causing hypoxemia in patients with PH-COPD.

We are currently designing a three-month Phase 2b trial to evaluate safety and efficacy for chronic use of INOpulse for PH-COPD. We plan to finalize the protocol following discussions with regulatory authorities in the United States and European Union. We currently intend to begin this Phase 2b trial in the second half of 2015 and, once initiated, we expect the trial will take approximately 18 months to complete.

INOpulse for Other Pulmonary Hypertension Conditions

Pulmonary hypertension disease is often classified according to the WHO classification system which groups patients with pulmonary hypertension according to the underlying etiologies, or causes, of the pulmonary hypertension. In this system, PAH is defined as Group 1 and PH-COPD is classified under Group 3, pulmonary hypertension due to lung disease and/or hypoxemia. We believe the mechanism of action of inhaled nitric oxide as a pulmonary vasodilator, and thus INOpulse, can be effective in treating pulmonary hypertension related to other conditions, including pulmonary hypertension associated with PH-IPF and other interstitial lung diseases, CTEPH and pulmonary hypertension associated with sarcoidosis.

While there are two recently approved treatments for IPF, there are currently no approved therapies for PH-IPF. In 2013, riociguat (Adempas) was the first drug therapy approved for treating CTEPH, although other PAH medications are sometimes used to treat this condition. Patients with sarcoidosis are often treated with

Table of Contents

steroids or other anti-inflammatory medications, however, there are no therapies approved to treat the PH associated with this disease.

Our current license from Ikaria covers only the development of INOpulse for PAH, PH-COPD and PH-IPF. We would need to obtain additional license rights from Ikaria before beginning development of INOpulse for any other indication.

BCM for Prevention of Cardiac Remodeling Following a STEMI

We are developing BCM through the medical device regulatory pathway to prevent congestive heart failure following a STEMI, which is a type of severe heart attack. Patients who suffer a STEMI are at increased risk for congestive heart failure due to potential cardiac remodeling, which is a structural change in the size and shape of the heart that affects its ability to function normally. This change includes thinning of the left ventricle wall at the infarction and the adjacent border zone, outward bulging of the infarcted region, hypertrophy of the non-infarcted portion of the left ventricle and dilation of the left ventricle chamber. Cardiac remodeling increases mechanical stresses on the left ventricular wall and reduces the efficiency of pumping blood often leading to congestive heart failure.

BCM is intended to prevent cardiac remodeling by reducing the abnormal increase in ventricular wall stress and structural changes in the heart after a STEMI. Once blood flow has been re-established to the affected heart muscle of a patient following a STEMI, a physician deploys BCM through the coronary artery related to the infarcted region of the left ventricle. BCM is designed to flow into the damaged heart muscle where it forms a flexible scaffold to enhance the mechanical strength of the heart muscle during recovery and repair, thereby preventing cardiac remodeling. We have an exclusive worldwide license to BCM under a license agreement we entered into with BioLine in August 2009.

Disease Background and Market Opportunity

An AMI is generally a sudden event resulting from a blockage of one or more of the arteries supplying blood to the heart. This can cause the heart muscle to die or temporarily stop working. In some patients, particularly those with large areas of the heart affected by the AMI, the dead or stunned muscle in the infarcted area can start to degrade even if blood flow is subsequently restored.

Given recent advances in treating AMIs, patients do not typically die of the acute event, especially in developed countries with good hospital systems. Instead, post-AMI patients are at an increased risk of congestive heart failure that results from the loss of structural support where the tissue has died, leading to a change in the shape of the heart, or remodeling, excess blood being left in the heart after it beats and increased strain on the left ventricular wall. This left ventricular dysfunction is characterized by increased ventricular volume and decreased ejection fraction, which is the fraction of blood in the heart that is pumped out each time it contracts. The early impact of the heart attack on ejection fraction and left ventricular end-systolic volume is predictive of left ventricular function one year after the initial event. This deterioration in left ventricular function, which indicates adverse ventricular remodeling, can eventually cause the heart not to pump enough blood to the body, leading to congestive heart failure. In a large controlled study, worsening of ventricular measures was predictive of both mortality and heart failure.

Data from long-term third-party studies suggests that the five-year post-AMI rate of congestive heart failure or death is approximately 35% to 40%. In addition, based on data presented from the study conducted in Olmstead County, Minnesota, we estimate that the three-year post-AMI

rate of congestive heart failure or mortality among patients who have had an AMI is approximately 30%. We are developing BCM to fill this unmet medical need by providing structural support of the heart muscle in the early days and months following an AMI, which is a critical period when the extracellular matrix is first degraded and then reconstituted as part of the heart s response to the injury and the time at which the heart is at high risk for remodeling. We expect that

Table of Contents

deploying BCM will help prevent cardiac remodeling and possibly the progression to advanced stages of congestive heart failure.

According to hospital claims data and American Heart Association estimates, in 2014, the estimated incidence of AMI hospital admissions in the United States will be over 900,000. There are two classifications of AMI, STEMI and non-STEMI. While both types of AMIs can cause significant damage to the heart, STEMIs tend to have more severe acute symptoms. We estimate that nearly one-third of AMI hospital admissions in the United States were for STEMI. Additionally, according to a report published in the European Heart Journal in 2010, over one million people suffer from AMI in Europe, over half of whom have a STEMI. The costs of treating the consequences of AMI can be substantial. The American Heart Association reported that the total cost of congestive heart failure in 2012 was approximately $30.0 billion in the United States, and we estimate that approximately 40% of these patients were treated for congestive heart failure following an AMI. The average hospitalization costs in the United States for congestive heart failure have been estimated to be in the range $17,000 to $21,000 per admission with total lifetime medical costs following congestive heart failure diagnosis estimated at more than $100,000 per patient. Therefore, we believe BCM could be a treatment that would help to prevent cardiac remodeling and thereby reduce the incidence of congestive heart failure, which could generate significant medical cost savings in addition to improving the quality of life of these patients.

Scientific Rationale for Use of BCM in the Prevention of Cardiac Remodeling Following a STEMI

BCM is a clear, low-viscosity solution containing sodium alginate and calcium gluconate. Alginates, which are complex sugars obtained from seaweed, have been used extensively in the food industry as well as by the pharmaceutical and medical device industries. In medical devices, alginates have been used as wound dressings, as bone-void fillers and to create dental impressions. BCM s specific, patent-protected composition has been optimized to be partially cross-linked by calcium ions and to maintain a free-flowing liquid state for injection into the blood stream. However, when injected into the heart following an AMI, we believe that BCM will flow into the damaged heart muscle where it will come into contact with the additional extracellular calcium that is released by the newly dead heart muscle cells, resulting in the formation of additional cross-links within the alginate. These cross-links turn BCM into a gel meshwork with mechanical properties similar to the normal extracellular cardiac matrix. Based on data from animal studies, we believe these properties allow BCM to provide temporary structural support to the wall of the heart while it heals after an AMI.

Once deposited, BCM remains in the infarct zone for a few months. As the heart heals and the extracellular calcium levels return to normal, the crosslinks in the gel slowly degrade, and the alginate returns to liquid form and is excreted via the kidneys. In our pre-clinical animal studies of BCM, tissue sample analysis has shown that most of the alginate dissipates within three months and is no longer detectable in the heart or elsewhere in the body within six months after BCM injection. In an academic study published in the Journal of the American College of Cardiology, pigs were injected with either BCM or saline following an AMI. In this study, the pigs that received saline had approximately 44% greater enlargement in left ventricular chamber volume after 60 days compared to the pigs that received two milliliters of BCM. In another academic study conducted in dogs with AMI, deploying BCM at any time within one week of an AMI reduced cardiac remodeling compared to placebo.

Clinical Development Program

BCM is a Class III medical device that we are developing to prevent cardiac remodeling and subsequent congestive heart failure after AMI following successful re-opening of the blood vessels. We are currently conducting a clinical trial of BCM, which is designed as a CE mark registration trial in the European Union. We refer to this trial as our PRESERVATION I trial, and it is designed as a double-blind, placebo-controlled trial, and the primary endpoint is change in anatomical measurements six months after device deployment.

The principal treatment for a STEMI is to re-establish blood flow in the blocked coronary artery at the earliest possible opportunity. This can be achieved by percutaneous coronary intervention, dissolving the

Table of Contents

blockage with medications or open heart surgery. BCM is designed to be deployed via a percutaneous coronary intervention into the previously blocked coronary artery after blood flow has been re-established.

We are developing BCM in the United States under an IDE and in consultation with a Notified Body in the European Union, which regulates the testing and use of devices. For our IDE application, we performed animal and *in vitro* studies and device effectiveness studies in pigs. Our pre-clinical studies demonstrated that BCM was well tolerated and showed activity in reducing cardiac remodeling after AMI in pigs when deployed in either a dedicated percutaneous coronary intervention procedure or during an initial percutaneous coronary intervention procedure. The FDA has agreed that the non-clinical package is complete and adequate for supporting clinical development, as specified in the IDE, and for registration of BCM.

The first human trial for BCM was a pilot clinical trial conducted by BioLine in Europe and completed in 2009, in which BCM was safely administered to 27 patients within seven days following a moderate to large STEMI and percutaneous coronary intervention. This open-label trial, in which all patients were treated with a two milliliter device, was conducted in multiple centers in Germany and Belgium and included patients who had experienced a first AMI of substantial size. The primary purpose of this trial was to evaluate the safety of BCM deployment. In addition, some efficacy parameters could be observed as all patients suffered a STEMI and had serial echocardiography studies performed at one, three and six months. A total of 27 patients (mean age 54±9 years) after a STEMI were treated during the course of this trial. Twenty-four patients were male, and 19 had experienced an anterior AMI with peak creatine kinase levels of 3183±1490 international units per liter. The time from symptom onset to primary percutaneous coronary intervention ranged from 0.6 to 84.7 hours (with a mean of 9.9±16.9 hours and a median of 3.8 hours). There were no serious adverse events observed with BCM at deployment. In this trial, eight patients experienced at least one treatment-emergent serious adverse event, and one event, a single episode of syncope that occurred 172 days after BCM deployment, was judged as possibly device related. In addition, 21 patients reported at least one adverse event in the initial six-month follow-up period. This data showed that BCM was well tolerated when deployed in patients following an AMI. In addition, standard echocardiogram measures of heart function were performed. In the six-month evaluation, patients in the trial, each of whom had large STEMIs, had measures of left ventricular function, including left ventricular end diastolic index, of left ventricular end systolic volume index and of left ventricular ejection fraction that indicated no change from baseline. Although interpretation of this data is limited by the lack of a control group, data from patients who were treated showed little change in these left ventricular measures, the worsening of which have been linked to mortality and heart failure.

In addition to the short-term testing during the first six months following the STEMI, the 27 patients had annual follow-up safety evaluations planned for up to five years. At the four-year follow-up evaluation, which is the most recent data set reported, 25 of the 27 patients were confirmed to still be alive. Of the two patients not confirmed alive, one died from T-cell lymphoma, which was likely a pre-existing condition, and one was lost to follow-up between the three- and four-year follow-up evaluations. However, the patient lost to follow-up had no device-related adverse events at the three-year follow-up evaluation. Of the 25 patients who were confirmed to be alive at year four, one had a hospitalization for congestive heart failure, which occurred within one year of device deployment. In addition, based on available data, during the four-year evaluation period, five patients experienced at least one cardiac ischemic event (nine cardiac ischemic events in total), none of which were considered to be related to BCM. This data from the four-year safety follow-up evaluations is better than we expected based on our review of publicly reported data from two long-term third-party studies of AMI patients, the Framingham Heart Study and the Olmstead County study. The data from these two studies suggest that the rate of congestive heart failure or death five years following an AMI is approximately 35% to 40%. In addition, based on data presented from the Olmstead County study, we estimate that the three-year post-AMI rate of congestive heart failure or mortality among patients who have had an AMI is approximately 30%.

Our ongoing PRESERVATION I trial is a CE mark registration trial for EU regulatory purposes and is comparable to a feasibility clinical trial in the United States. We completed enrollment of this trial in December 2014, with 303 patients having completed the treatment procedure at almost 90 clinical sites in Europe, Australia, North America and Israel. Our key inclusion criteria for this trial include that patients must have:

23

Table of Contents

- suffered from a large STEMI as measured by cardiac enzymes;
- clinical signs of significant cardiac damage;
- imaging evidence of impaired heart function; and
- had a primary percutaneous coronary intervention with a stent placed.

In this double-blind trial, patients are randomized in a two-to-one ratio to BCM or placebo. The trial device is injected in a second percutaneous coronary intervention two to five days after the initial myocardial infarction. The primary endpoint is change in the anatomical measurement of left ventricular end-diastolic volume index by echocardiography measured six months after device deployment. Secondary endpoints include the measurement of functional capacity of change in six-minute walk distance and the measurement of patient reported outcome as recorded on the quality of life tool of Kansas City Cardiomyopathy Questionnaire. Other endpoints include a measurement of BCM in the peripheral circulation as an assessment of the pharmacokinetics of BCM, electrocardiogram measures and other anatomic endpoints, including change in left ventricular end-systolic volume index and ejection fraction. In addition, as required by the trial protocol, we will follow all patients to monitor safety for a period of five years after device deployment. The Data Safety Monitoring Board for this trial has met six times to evaluate the safety data and on each occasion has approved the continuation of the trial as planned. We expect to report top line results from this trial in mid-2015. We also expect that if our PRESERVATION I trial is successful, we will rely on the results to seek CE marking for BCM in the European Union potentially in the first half of 2016.

Assuming positive results from our PRESERVATION I trial, we plan to conduct a second, larger clinical trial to support approval in the United States through the PMA pathway. We met with the FDA to discuss U.S. regulatory requirements for a pivotal clinical trial. Based on discussions with the FDA Center for Devices and Radiological Health in May 2010, we expect that our pivotal trial will include approximately 1,000 patients, having a composite endpoint of anatomic measurements of left ventricular end-diastolic volume index or ejection fraction, a patient outcomes measurement test and a functional measure such as six-minute walk distance or a cardiopulmonary stress test. We currently expect to begin this trial in the first half of 2016, and we estimate that, once initiated, the trial will take approximately two to three years to complete.

If the PRESERVATION I trial demonstrates that BCM is well tolerated and has a clinical benefit in severe STEMIs when deployed in a second percutaneous coronary intervention procedure, we intend to consider testing BCM in an expanded population, including patients with moderate STEMIs, and for deployment of BCM during the primary percutaneous coronary intervention procedure, eliminating the need for a second invasive procedure. We are currently designing a trial to evaluate the safety of deploying BCM in the primary percutaneous coronary intervention procedure after a large STEMI. The secondary objective of this trial will be to evaluate the efficacy of BCM six months after deployment using ventricular remodeling measures. We currently intend to begin this trial in the second half of 2015, assuming successful completion of PRESERVATION I, and we expect the trial will take approximately one year to complete.

Relationship with Ikaria after the Spin-Out

The development of our programs was initiated under the leadership of our scientific and development team while at Ikaria. Ikaria s lead product, INOmax, is an inhaled nitric oxide product used for treatment of persistent pulmonary hypertension of the newborn. Our understanding of the medical applications of nitric oxide and associated delivery devices, as well as our innovative approach to the pulsed delivery of nitric oxide, originated at Ikaria, and we in-licensed BCM while we were a part of Ikaria.

In October 2013, Ikaria completed an internal reorganization of certain assets and subsidiaries, in which it transferred to us exclusive worldwide rights, with no royalty obligations, to develop and commercialize pulsed nitric oxide in PAH, PH-COPD and PH-IPF. Following the internal reorganization, in February 2014, Ikaria

Table of Contents

distributed all of our then outstanding units to its stockholders through the payment of a special dividend on a pro rata basis based on each stockholder s ownership of Ikaria capital stock. We refer to Ikaria s distribution of our then outstanding units to its stockholders as the Spin-Out.

Shortly after the Spin-Out, Ikaria was acquired by entities affiliated with Madison Dearborn Partners. On March 5, 2015, Mallinckrodt plc, or Mallinckrodt, and Ikaria announced that they had entered into a definitive agreement under which a subsidiary of Mallinckrodt will acquire Ikaria. Mallinckrodt and Ikaria have announced that they expect this transaction to be completed in the second calendar quarter of 2015.

Ikaria retains the right to develop and commercialize inhaled nitric oxide products, including pulsed products, in all indications other than PAH, PH-COPD and PH-IPF.

In connection with the Spin-Out, we entered into several agreements with Ikaria providing for, among other things, the provision of transition services, the cross license of certain intellectual property, commitments not to compete, the manufacture and supply of the INOpulse drug and device and certain employee matters.

Transition Services Agreement

In February 2014, we entered into a transition services agreement with Ikaria, which we refer to as the TSA. Pursuant to the terms and conditions of the TSA, Ikaria has agreed to use commercially reasonable efforts to provide certain services to us, including human resources support, real estate support, information technology support, accounting and tax support, treasury support, financial planning and analysis support, purchasing support, management/executive services, legal services, quality services, regulatory services, drug and device safety services, business development support, biometrics support and manufacturing support. Ikaria is obligated, subject to the terms of the TSA (including the early termination provisions thereof and our obligation to use commercially reasonable efforts to provide the services for ourselves as soon as practicable), to provide such services until February 2016.

Ikaria has also agreed, on the terms and subject to the conditions of the TSA, to use commercially reasonable efforts to allow our employees to remain in Ikaria s Hampton, New Jersey facility for the continued operation of our business during the term of the TSA.

We are obligated to pay Ikaria a service fee in the amount of $772,000 per month and to reimburse Ikaria for any out-of-pocket expenses incurred in connection with its provisions of services under the TSA, any taxes imposed on Ikaria in connection with the performance or delivery of services under the TSA and any costs and expenses incurred by Ikaria in connection with the performance of any services that require resources outside of the existing resources of Ikaria or that otherwise interfere with the ordinary operations of Ikaria s business. This monthly service fee is be payable by us regardless of the frequency or quantity of services actually utilized by us under the TSA, and our obligation to pay such monthly service fee until February 2016 will survive any early termination of the TSA. At the time we entered into the TSA, we also entered into an escrow agreement, pursuant to which we deposited $18.5 million, representing the aggregate amount of the monthly service fees payable by us under the TSA, into escrow to guarantee our payment of such fees to Ikaria. We are also obligated to pay any fees, costs, expenses or other amounts incurred by Ikaria to obtain the right to allow our employees to remain in the Hampton, New Jersey facility during the term of the TSA.

Exclusive Cross-License, Technology Transfer and Regulatory Matters Agreement

In February 2014, we entered into an exclusive cross-license, technology transfer and regulatory matters agreement with Ikaria. Pursuant to the terms of the license agreement, Ikaria granted to us a fully paid-up, non-royalty bearing, exclusive license under specified intellectual property rights controlled by Ikaria to engage in the development, manufacture and commercialization of nitric oxide, devices to deliver nitric oxide and related services for or in connection with out-patient, chronic treatment of patients with PAH, PH-COPD or PH-IPF, which we refer to collectively as the Bellerophon indications.

Table of Contents

We have granted to Ikaria a fully paid-up, non-royalty-bearing, exclusive license under specified intellectual property rights that we control to engage in the development, manufacture and commercialization of products and services for or used in connection with the diagnosis, prevention or treatment, whether in- or out-patient, of certain conditions and diseases other than the Bellerophon indications and for the use of nitric oxide to treat or prevent conditions that are primarily managed in the hospital, which we refer to collectively as the Ikaria nitric oxide business.

We have agreed that, during the term of the license agreement, we will not, without the prior written consent of Ikaria, grant a sublicense under any of the intellectual property licensed to us under the license agreement to any of our affiliates or any third party, in either case that directly or indirectly competes with the Ikaria nitric oxide business. We have also agreed that we will include certain restrictions in our agreements with customers of our products to ensure that such products will only be used for the Bellerophon indications.

The license agreement will expire on a product-by-product basis for products for a specific Bellerophon indication at such time as we are no longer developing or commercializing any product for such indication. The license agreement may be terminated by either party in the event an act or order of a court or governmental authority prohibits either party from substantially performing under the license agreement. Either party may also terminate the license agreement in the event of an uncured material breach by the other party or in the event the other party is insolvent or in bankruptcy proceedings. Ikaria may also terminate the license agreement if we or any of our affiliates breach the agreements not to compete described below, or if we or any successor to our rights under the license agreement markets a generic nitric oxide product that is competitive with INOmax. Under certain circumstances, if the license agreement is terminated, the licenses granted to Ikaria by us will survive such termination.

Agreements Not to Compete

In September 2013, October 2013 and February 2014, we and each of our subsidiaries entered into an agreement not to compete with Ikaria. We refer to these agreements collectively as the agreements not to compete. Pursuant to the agreements not to compete, we and each of our subsidiaries agreed not to engage, anywhere in the world, in any manner, directly or indirectly, until the earlier of five years after the effective date of such agreement not to compete or the date on which Ikaria and all of its subsidiaries are no longer engaged in such business, in:

- the development, manufacture, commercialization, promotion, sale, import, export, servicing, repair, training, storage, distribution, transportation, licensing or other handling or disposition of any product or service (including, without limitation, any product or service that utilizes, contains or includes nitric oxide for inhalation, a device intended to deliver nitric oxide or a service that delivers or supports the delivery of nitric oxide), bundled or unbundled, for or used in connection with (a) the diagnosis, prevention or treatment, in both adult and/or pediatric populations, and whether in- or out-patient, of: (i) hypoxic respiratory failure associated with pulmonary hypertension, (ii) pulmonary hypertensive episodes and right heart failure associated with cardiovascular surgery, (iii) bronchopulmonary dysplasia, (iv) the management of ventilation-perfusion mismatch in acute lung injury, (v) the management of ventilation-perfusion mismatch in acute respiratory distress syndrome, (vi) the management of pulmonary hypertension episodes and right heart failure in congestive heart failure, (vii) pulmonary edema from high altitude sickness, (viii) the management of pulmonary hypertension episodes and right heart failure in pulmonary or cardiac surgery, (ix) the management of pulmonary hypertension episodes and right heart failure in organ transplant, (x) sickle cell vaso-occlusive crisis, (xi) hypoxia associated with pneumonia or (xii) ischemia-reperfusion injury or (b) the use of nitric oxide to treat or prevent conditions that are primarily managed in the hospital; or

- any and all development, manufacture, commercialization, promotion, sale, import, export, storage, distribution, transportation, licensing, or other handling or disposition of any terlipressin or any

Table of Contents

other product within the pressin family, (a) intended to treat (i) hepatorenal syndrome in any form, (ii) bleeding esophageal varices or (iii) septic shock or (b) for or in connection with the management of low blood pressure.

The agreements not to compete expressly exclude the Bellerophon indications.

In February 2014, we also entered into drug and device clinical supply agreements and an employee matters agreement with Ikaria See Manufacturing below for a description of the drug and device clinical supply agreements and Certain Relationships and Related Person Transactions Relationship with Ikaria for a description of the employee matters agreement.

BioLine License Agreement

In August 2009, we entered into a license agreement with BioLineRx Ltd. and BioLine Innovations Jerusalem L.P., under which we obtained an exclusive worldwide license to BCM. Under the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize at least one product containing BCM. We have established a joint development committee with BioLine to oversee the development of BCM.

We paid BioLine a $7.0 million upfront payment in 2009 and a $10.0 million milestone payment in 2010. Under the terms of the license agreement, if we achieve certain clinical and regulatory events specified in the license agreement, we will be obligated to pay milestone payments to BioLine that could total, in the aggregate, up to $115.5 million, and if we achieve certain commercialization targets specified in the license agreement, we will be obligated to pay additional milestone payments to BioLine that could total, in the aggregate, up to $150.0 million. In addition, we will be obligated to pay BioLine a specified percentage of any upfront consideration we receive for sublicensing BCM, as well as royalties on net sales, if any, at a percentage ranging from 11% to 15%, depending on net sales level, of any approved product containing BCM, subject to offsets for specified payments to third parties made in connection with BCM. Our obligation to pay BioLine royalties will expire on a product-by-product and country-by-country basis on the date on which BCM is no longer covered by a valid claim in the licensed patent rights in the given country.

BioLine has the option, exercisable under specified circumstances, to manufacture any product containing BCM for us pursuant to terms to be negotiated by the parties. If BioLine exercises this option, we would generally be obligated to purchase at least a specified percentage of our BCM requirements from BioLine at a price calculated using a pre-agreed methodology, and the parties would be required to establish a joint manufacturing committee to coordinate manufacturing efforts.

Except under specified circumstances, neither we, nor any other person that controls, is controlled by, or is under common control with us, may directly or indirectly acquire more than a specified percentage of the equity or debt securities of BioLine, or urge, induce, entice or solicit any other party to acquire such securities, without BioLine s consent.

We and BioLine have the right to terminate the license agreement for an uncured material breach by the other party. In addition, we have the right to terminate the license agreement if at any time we determine that further development of products containing BCM is not warranted.

Manufacturing

INOpulse Drug Product

In February 2014, we entered into a drug clinical supply agreement with Ikaria, or the drug supply agreement, pursuant to which Ikaria has agreed to use commercially reasonable efforts to manufacture and supply, and we have agreed to acquire from Ikaria, our requirements for nitric oxide for inhalation and

Table of Contents

corresponding placebo for use in our clinical programs for PAH, PH-COPD and PH-IPF. Pursuant to the drug supply agreement, we will pay to Ikaria an amount equal to Ikaria s internal and external manufacturing cost plus 20%. Under the terms of the drug supply agreement, we have also granted Ikaria a right of first negotiation in the event that we desire to obtain supply of nitric oxide for inhalation and corresponding placebo (or any variant thereof or any version with different specifications) for commercial use. The drug supply agreement will expire on a product-by-product basis on the date we discontinue clinical development of such product. In addition, either party may terminate the drug supply agreement in the event of an uncured material breach by the other party.

Ikaria manufactures pharmaceutical-grade nitric oxide at its facility in Port Allen, Louisiana. This facility, which we believe is operated in compliance with current Good Manufacturing Practices, or cGMP, is the only FDA-inspected site for manufacturing pharmaceutical-grade nitric oxide in the world. The primary manufacturing activity at the site is the commercial production of INOmax and production of INOpulse. This production includes the chemical synthesis of high-purity nitric oxide, which is the active pharmaceutical ingredient in INOmax and INOpulse, and the filling of the gas cylinders in which the products are packaged.

To support business outside of the United States, the Port Allen manufacturing facility has also successfully passed inspections by local agencies, the EMA, Health Canada; the Pharmaceutical and Medical Devices Agency, or PMDA, of Japan, and the Korean FDA, or KFDA. The EMA, the Health Protection Branch of Health Canada, PMDA and KFDA operate in a similar fashion to the FDA in that each requires submission of a dossier containing substantial evidence of safety and effectiveness prior to approval. These agencies monitoring of safety in a post-marketing setting also is similar to that of the FDA.

The operations that Ikaria currently performs for us consist of two steps. The first step is to manufacture the concentrated drug product, which Ikaria conducts using the same processes that it uses to manufacture its own drug product. The second step is the filling operation in which the pre-mix product is mixed to the appropriate concentration and filled into the final cartridges that we use with INOpulse. As we have reduced the size and weight of INOpulse, we have also developed a smaller, more-concentrated drug cartridge for INOpulse. The filling process has been developed by Ikaria as a high-throughput batch fill process that leverages several technologies that Ikaria has developed, and we have licensed, to fill smaller containers at a higher pressure and purity and at a significantly higher production rate than prior technology.

This manufacturing system is designed to be modular and can be expanded as needed. The current installed capacity within the Port Allen plant is sufficient to support our INOpulse clinical program as currently planned. In addition, the plant has the capacity to expand to meet additional demand. We have a license from Ikaria to use this fill process technology to work with additional companies, as needed, to produce the final cartridge. Commercial supply manufacturing can be supported with additional units installed at the Port Allen site or other regional locations, by Ikaria or other manufacturers, as determined by distribution requirements. For our clinical trials, Ikaria can supply and ship product from the Port Allen site and the current cartridges are expected to have a shelf life of at least one year. We are testing the finished product to potentially establish a shelf life of up to two years.

INOpulse Drug Delivery Systems

Ikaria has a drug delivery system manufacturing facility in Madison, Wisconsin, at which it designs, engineers, assembles, packages and distributes drug delivery systems, including INOpulse. We entered into a services agreement with Ikaria, effective as of January 1, 2015, which expires in February 2016, under which, among other things, Ikaria agreed to use commercially reasonable efforts to provide us with certain INOpulse device related services, including services related to device remediation, upgrades and refurbishment. In February 2015, we entered into an agreement with Flextronics Medical Sales and Marketing Ltd., a subsidiary of Flextronics International Ltd., or Flextronics, to manufacture and service the Mark2 devices that we expect to use in future clinical trials of INOpulse for PAH and INOpulse for PH-COPD.

28

Table of Contents

Each version of our INOpulse device currently under development will be pre-programmed at the time of manufacture to the dose setting specified for the applicable indication. Since PAH patients have the potential for rebound pulmonary hypertension, which is a sudden and serious increase in pulmonary arterial pressure that results from therapy withdrawal, patients with this condition are required to have a backup system. Accordingly, we will be required to provide PAH patients with either a separate backup device or a device with a built-in pneumatic, or non-electrical, backup system. Also, pursuant to the terms of our license agreement with Ikaria, we are required to lease and not to sell our INOpulse devices as well as to track and maintain control of the indications for which each are used. We intend to meet these requirements by maintaining close monitoring of the use of the devices, including through planned remote data downloads and a system diagnostic feature.

BCM Product

We currently outsource the manufacture of BCM for use in clinical trials. BCM is manufactured by a third-party under the terms of a manufacturing and supply agreement which expires in April 2017. We plan to enter into a manufacturing and supply agreement for BCM with a third-party prior to April 2017.

BCM is composed of ultra-pure sodium alginate and calcium-D-gluconate. We purchase sodium alginate from FMC BioPolymer AS (doing business as NovaMatrix) under the terms of a clinical supply agreement that expires in December 2018. We and FMC BioPolymer have agreed to negotiate a commercial supply agreement prior to the December 2018 expiration of the clinical supply agreement. Calcium-D-gluconate is a commodity item available from multiple suppliers. If BCM is approved for commercial sale, we will likely continue to outsource its manufacture to contract manufacturers.

BioLine has the option, exercisable under specified circumstances, to manufacture any product containing BCM for us pursuant to terms to be negotiated by the parties. If BioLine exercises this option, we would generally be obligated to purchase at least a specified percentage of our BCM requirements from BioLine at a price calculated using a pre-agreed methodology, and the parties would be required to establish a joint manufacturing committee to coordinate manufacturing efforts.

Competition

The biotechnology and pharmaceutical industries are highly competitive. There are many pharmaceutical companies, biotechnology companies, public and private universities and research organizations actively engaged in the research and development of products that may be similar to our products. In addition, other companies are increasingly looking at cardiac and cardiopulmonary indications as a potential opportunity. It is possible that the number of companies seeking to develop products and therapies for the treatment of unmet needs in our target markets will increase.

Our competitors, either alone or with their strategic partners, may have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in obtaining approval for therapies and achieving widespread market acceptance. We anticipate that we will face intense and increasing competition as new drugs and advanced technologies become available.

Currently, there are 12 drugs approved for the treatment of PAH, within the following categories: prostacyclin and prostacyclin analogs (including Flolan (epoprostenol), which is marketed by GlaxoSmithKline, Tyvaso (treprostinil), Orenitram (treprostinil) and Remodulin (treprostinil), which are marketed by United Therapeutics Corporation, and Ventavis (iloprost) and Veletri (epoprostenol), which are marketed by Actelion Pharmaceuticals US, Inc., or Actelion), phosphodiesterase type-5 inhibitors (including Adcirca (tadalafil), which is marketed by United Therapeutics Corporation, and Revatio (sildenafil), which is marketed by Pfizer Inc.), endothelin receptor antagonists (including Letairis (ambrisentan), which is marketed by Gilead Sciences, Inc., and Opsumit (macitentan) and Tracleer (bosentan), which are marketed by Actelion) and a soluble guanylate

Table of Contents

cyclase stimulator (Adempas (riociguat), which is marketed by Bayer HealthCare Pharmaceuticals Inc.). Actelion recently submitted an NDA to the FDA for selexipag, a selective prostacyclin receptor agonist.

There are also other treatments in Phase 1 and Phase 2 clinical development, including other nitric oxide generation and delivery systems, including GeNOsyl , which is being developed by GeNO LLC, and a nebulized formulation of nitrite, which is being developed by Mast Therapeutics.

Currently, there are no approved therapies for treating PH-COPD, and the only generally accepted treatments are LTOT, pulmonary rehabilitation and lung transplant, and we are not aware of any therapies for PH-COPD in advanced clinical development.

There are no generally accepted products approved for structural support to prevent cardiac remodeling following an AMI. Other product candidates that are currently in clinical development include stem cell therapies to restore heart muscle cells following an AMI, with large Phase 3 trials expected to be completed in 2018 or 2019. We do not expect BCM to compete with, or replace, current treatments for congestive heart failure following AMI, but instead believe it will become part of the treatment regimen used in conjunction with other therapies. In addition, because BCM can be delivered by a minimally invasive percutaneous coronary intervention procedure, we do not believe it will directly compete with devices that are used to treat congestive heart failure, which are designed for administration during open heart surgery or by intra-cardiac injection involving a thoracotomy procedure. These include: mesh restraining devices, for example HeartNet ; injectable biopolymers, for example Algisyl-LVR ; and implantable electro-stimulation devices, for example, CardioFit . In addition, volume reduction surgery or cardiac assist devices, or pumps, are sometimes used to treat patients with congestive heart failure.

Patents and Proprietary Rights

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to protect, for example, our product candidates, related technologies and/or other aspects of the inventions that are important to our business. Our owned and licensed patents and patent applications cover patentable subject matter from composition of matter, methods of use, manufacturing processes for BCM and method of administration, devices and device components, critical safety features and design components with respect to INOpulse. However, patent protection is not available for the composition of matter of the active pharmaceutical ingredients in INOpulse since nitric oxide is a naturally occurring molecule.

Actual protection afforded by a patent, which can vary from country to country, depends on the type of patent, the scope of its coverage and the availability of legal remedies in the country. We also rely on trade secrets and careful monitoring of our proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

We plan to continue to expand our intellectual property estate by filing patent applications directed to inventions which provide additional patent protection for our product offering, for instance, device enhancements, safety features and manufacturing processes. Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; maintain our licenses to use intellectual property owned by third parties; preserve the confidentiality of our trade secrets; and operate without infringing the valid and enforceable patents and other proprietary rights of third parties. We also consider know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and

maintain our proprietary positions.

A third party may hold intellectual property, including patent rights that are important or necessary to the development of our programs. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our product candidates, in which case we would be required to obtain a license

Table of Contents

from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially. For example, if we want to expand the indications for which we could develop and commercialize pulsed nitric oxide beyond PAH, PH-COPD and PH-IPF, we will need to obtain a license from Ikaria.

The patent positions of therapeutics companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and patent scope can be reinterpreted by the courts after issuance. Moreover, many jurisdictions permit third parties to challenge issued patents in administrative proceedings which may result in further narrowing or even cancellation of patent claims. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection from competitors. Any patents that we own or license may be challenged, narrowed, circumvented or invalidated by third parties.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months or potentially even longer, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. Moreover, we may have to participate in interference proceedings declared by the U.S. Patent and Trademark Office, or USPTO, to determine priority of inventions for any patent applications filed with the USPTO on or before March 15, 2013. Likewise, derivation proceedings may also be declared for any patent filings filed after March 15, 2013.

The patents and patent applications that relate to our programs are described below.

INOpulse

As of March 25, 2015, we hold exclusive licenses from Ikaria to at least 80 patents and pending patent applications in both the United States and foreign countries including Australia, Brazil, Canada, China, Europe, Hong Kong, India, Indonesia, Israel, Japan, Korea, Mexico, the Philippines, Russia and Singapore. Certain of these issued patents and patent applications, if issued, will expire as late as 2033. These patent rights have been exclusively licensed for the treatment of patients with PAH, PH-COPD and PH-IPF and cover methods of delivery and the drug delivery device, as well as important safety features and the ornamental design of the drug delivery device.

A primary basis for patent exclusivity is based on pending and issued in-licensed patents directed to proprietary methods of administering pulsed inhaled nitric oxide, as well as a device for delivering the same. This patent family expires as late as 2027 in the United States and as late as 2026 in Australia, Brazil, Canada, China, Europe, Hong Kong, Japan and Mexico.

Another important basis for patent exclusivity is based on an in-licensed portfolio of one issued U.S. patent, three pending U.S. patent applications, and two Patent Cooperation Treaty pending patent applications, in each case directed to novel nasal cannula features that we believe are necessary for the accurate, safe and efficacious administration of pulsed nitric oxide. Each of these patents and patent applications, if issued, will expire in 2033 in the United States and abroad.

Another in-licensed patent family relates to features of the drug delivery canister necessary for providing drug product for use with our proprietary pulsing drug delivery device. This patent family includes one issued U.S. patent, one issued Japanese patent, one issued Mexican patent, one issued Singaporean patent and three issued Australian patents, as well as 16 pending patent applications in the United States, Brazil, Canada, China, Europe, Hong Kong, India, Indonesia, Israel, Japan, Korea, Mexico, the Philippines, Russia and Singapore. These pending applications, if issued, will expire in 2029, as well will the issued Australian, Japanese, Mexican and Singaporean patents. The issued U.S. patent will expire in 2030.

Table of Contents

Several other patent families directed to device and safety features are pending. Furthermore, a design patent covering the ornamental design of the intended commercial device has been granted, and a design patent application is pending for the ornamental design of the clinical device.

In addition, the FDA has granted orphan drug designation to our nitric oxide program for the treatment of PAH, which could result in marketing exclusivity of seven years in the United States should this be the first NDA approved for inhaled nitric oxide in this indication. The active ingredient, nitric oxide, was previously approved by the FDA as a drug in a separate clinical application. Accordingly, any related patent rights will not be eligible for a patent term extension under relevant provisions of the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act.

BCM

Patent protection of BCM in the United States and in Australia, Canada, China, Europe, Hong Kong, India, Israel, Japan, Korea and Mexico is provided by issued composition of matter and method of treatment patents and patent pending applications, which we in-license from BioLine, that cover the intended commercial product. These issued patents are not limited to treatment of cardiac tissue, affording broad protection for the use of BCM in treating any damaged body tissue. We were notified by the European Patent Office in July 2014 and October 2014 that Notices of Opposition to two European patents that we licensed from BioLine, one of which covers the BCM intended commercial product described above, have been filed with the European Patent Office. A Notice of Opposition initiates a process during which the European Patent Office can decide to reconsider an issued patent and modify or revoke some or all of the patent claims. We have the right to respond to the Notices of Opposition before the European Patent Office makes a decision whether or not any or all of the patent claims are to be modified or revoked. We filed a response to the first patent opposition in December 2014, and we filed a response to the second patent opposition in March 2015, as we believe the two issued patents were properly examined and appropriately granted by the European Patent Office. Furthermore, we believe the arguments made in the Notices of Opposition misstate the facts and lack scientific merit.

BCM will be regulated as a device and therefore data exclusivity will not be available. However, under the Hatch-Waxman Act, one issued U.S. patent covering the product will be eligible for patent term extension of up to five years to recover patent term lost during clinical trials. Accordingly, if the U.S. composition of matter patent that expires in 2029 is selected for this extension and a patent term extension is granted, certain rights under the patent may not expire until 2032 to 2034, depending on the timing of marketing approval and other factors. Corresponding issued patents in other countries will expire in 2024 and may also be eligible for patent term extensions. We do not expect to be granted a patent term extension for composition of matter patents in Europe, but patent term extensions may be available in other countries such as Japan and Israel.

Method of manufacturing patents that we have in-licensed have issued in the United States, Australia, China, Europe, India, Israel, Korea and Mexico and are pending in Canada. The U.S. issued patent expires in 2025 and the non-U.S. issued patents expire in 2024. The method of manufacturing patent applications we developed and own, if issued, will expire in the United States, Canada and Europe in 2032, not including any applicable patent term adjustment. Further, there is no abbreviated clinical trial pathway, such as an abbreviated new drug application, or ANDA, or a 505(b)(2) new drug application, for a device product approved via a PMA pathway.

Patent Term

The base term of a U.S. patent is 20 years from the filing date of the earliest-filed non-provisional patent application from which the patent claims priority. The term of a U.S. patent can be lengthened by patent term adjustment, which compensates the owner of the patent for administrative delays at the USPTO. In some cases, the term of a U.S. patent is shortened by terminal disclaimer that reduces its term to that of an earlier-expiring patent.

Table of Contents

The term of a U.S. patent may be eligible for patent term extension under the Hatch-Waxman Act to account for at least some of the time the drug or device is under development and regulatory review after the patent is granted. With regard to a drug or device for which FDA approval is the first permitted marketing of the active ingredient, the Hatch-Waxman Act allows for extension of the term of one U.S. patent. Thus, patent term extension is not available for INOpulse since the active moiety is nitric oxide, which is already subject to an approved NDA. The extended patent term cannot exceed the shorter of five years beyond the non-extended expiration of the patent or 14 years from the date of the FDA approval of the drug or device. Some foreign jurisdictions have analogous patent term extension provisions that allow for extension of the term of a patent that covers a device approved by the applicable foreign regulatory agency. In the future, if and when BCM receives FDA approval, we expect to apply for a patent term extension on the patent covering BCM that we believe will provide the best exclusivity position if extended.

Trade Secrets

In addition to patents, we rely on trade secrets and know-how to develop and maintain our competitive position. We typically rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. For example, elements of the manufacture of our products are based on trade secrets and know-how that are not publicly disclosed. We protect trade secrets and know-how by establishing confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and commercial partners. These agreements provide that all confidential information developed or made known during the course of an individual or entity s relationship with us must be kept confidential during and after the relationship. These agreements also provide that all inventions resulting from work performed for us or relating to our business and conceived or completed during the period of employment or assignment, as applicable, shall be our exclusive property. In addition, we take other appropriate precautions, such as physical and technological security measures, to guard against misappropriation of our proprietary technology by third parties.

Trademarks

We also seek trademark protection where available and when appropriate. The symbol indicates a common law trademark. Other service marks, trademarks and trade names appearing in this Annual Report on Form 10-K are the property of their respective owners.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, quality control, clearance, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products and medical devices. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drugs under the Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires 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 and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product

Table of Contents

recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

Our product candidates must be approved by the FDA through the NDA process before they may be legally marketed in the United States. An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of pre-clinical laboratory tests, animal studies and formulation studies in compliance with the FDA s good laboratory practice, or GLP, regulations;

- submission to the FDA of an IND, which must take effect before human clinical trials may begin;

- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;

- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;

- preparation and submission to the FDA of an NDA;

- review of the product by an FDA advisory committee, where appropriate or if applicable;

- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with cGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the product s identity, strength, quality and purity;

- payment of user fees and securing FDA approval of the NDA; and

- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by the FDA.

Pre-Clinical Studies

Pre-clinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as *in vitro* and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of pre-clinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the pre-clinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, are submitted to the FDA as part of an IND.

Companies usually must complete some long-term pre-clinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the drug 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 manufacturer 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.

Table of Contents

Human Clinical Studies in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence.

In addition, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their ClinicalTrials.gov website.

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 or IND so long as the clinical trial is conducted in compliance with GCP, and the FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- Phase 1: The drug is initially introduced into a small number of healthy human subjects or patients with the target disease (e.g., cancer) or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

- Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

- Phase 3: Phase 3 clinical trials are commonly referred to as pivotal studies, which typically denotes a study which presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a drug. In Phase 3 clinical trials, the drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, 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 are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical

Table of Contents

trial at its institution, or an institution it represents, 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. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the applicant to rely, in part, on the FDA s previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the applicant for approval of the application 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.

Thus, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) applicant can establish that reliance on the FDA s previous approval is scientifically appropriate, the applicant may eliminate the need to conduct certain pre-clinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Submission of an NDA to the FDA

NDAs for most new drug products are based on two full clinical studies that must contain substantial evidence of the safety and efficacy of the proposed new product. Assuming successful completion of required clinical testing and other requirements, the results of the pre-clinical and clinical studies, together with detailed information relating to the product s chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to an application user fee, currently exceeding $2.1 million, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding $104,000 per product and $554,000 per establishment. These fees are typically increased annually.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor by the 74th day after the FDA s receipt of the submission whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for priority review products are meant to be reviewed within six months of filing. The review process may be extended by the FDA for various reasons, including for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections cover all facilities associated with an NDA submission,

Table of Contents

including drug component manufacturing (such as Active Pharmaceutical Ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application 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. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

The FDA may refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides 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.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a drug for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a drug.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. The accelerated approval pathway is usually contingent on a sponsor s agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug s clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

The FDA s Decision on an NDA

On the basis of the FDA s evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA s satisfaction in a resubmission of the NDA, the FDA

Table of Contents

will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug s safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions which can materially affect the potential market and profitability of the product. In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

38

Table of Contents

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;

- fines, warning letters or holds on post-approval clinical trials;

- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;

- product seizure or detention, or refusal to permit the import or export of products; or

- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an ANDA to the agency. In support of such applications, a generic manufacturer may rely on the pre-clinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is bioequivalent to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug.

Upon approval of an ANDA, the FDA indicates whether the generic product is therapeutically equivalent to the RLD in its publication Approved Drug Products with Therapeutic Equivalence Evaluations, also referred to as the Orange Book. Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA s designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. In cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or

Table of Contents

bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant s product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product s listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicate that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA applicant or 505(b)(2) applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

Orphan Designation and Exclusivity

Under the Orphan Drug Act, FDA may designate a drug product as an orphan drug if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product). A company must request orphan product designation before submitting a NDA. If the request is granted, FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation, the product will be entitled to orphan product exclusivity. Orphan product exclusivity means that FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a

Table of Contents

different indication. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, a NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product 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. With enactment of the Food and Drug Administration Safety and Innovation Act, or FDASIA, in 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA s internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA s request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Patent Term Restoration and Extension

A patent claiming a new drug product or medical device may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted on a patent covering a new drug product or a Class III medical device is typically one-half the time between the date a clinical investigation on human beings is begun and the submission date of an application for premarket approval of the product or medical device, plus the time between the submission date of an application for approval of the product or medical device and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product s approval date. Only one patent applicable to an approved drug product or medical device is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs or medical devices for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Review and Approval of Medical Devices in the United States

Medical devices in the United States are strictly regulated by the FDA. Under the FDCA a medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or

Table of Contents

other similar or related article, including a component, part or accessory which is, among other things: intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes. This definition provides a clear distinction between a medical device and other FDA regulated products such as drugs. If the primary intended use of the product is achieved through chemical action or by being metabolized by the body, the product is usually a drug. If not, it is generally a medical device.

Unless an exemption applies, a new medical device may not be marketed in the United States unless and until it has been cleared through filing of a 510(k) premarket notification, or 510(k), or approved by the FDA pursuant to a PMA. The information that must be submitted to the FDA in order to obtain clearance or approval to market a new medical device varies depending on how the medical device is classified by the FDA. Medical devices are classified into one of three classes on the basis of the controls deemed by the FDA to be necessary to reasonably ensure their safety and effectiveness.

Class I devices are those low risk devices for which reasonable assurance of safety and effectiveness can be provided by adherence to the FDA s general controls for medical devices, which include applicable portions of the FDA s Quality System Regulation, or QSR, facility registration and product listing, reporting of adverse medical events and malfunctions and appropriate, truthful and non-misleading labeling, advertising and promotional materials. Many Class I devices are exempt from premarket regulation; however, some Class I devices require premarket clearance by the FDA through the 510(k) premarket notification process.

Class II devices are moderate risk devices and are subject to the FDA s general controls, and any other special controls, such as performance standards, post-market surveillance, and FDA guidelines, deemed necessary by the FDA to provide reasonable assurance of the devices safety and effectiveness. Premarket review and clearance by the FDA for Class II devices are accomplished through the 510(k) premarket notification procedure, although some Class II devices are exempt from the 510(k) requirements. Premarket notifications are subject to user fees, unless a specific exemption applies.

Class III devices are deemed by the FDA to pose the greatest risk, such as those for which reasonable assurance of the device s safety and effectiveness cannot be assured solely by the general controls and special controls described above and that are life-sustaining or life-supporting. A PMA application must provide valid scientific evidence, typically extensive pre-clinical and clinical trial data and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications (and supplemental PMA applications) are subject to significantly higher user fees than are 510(k) premarket notifications.

Clinical Studies in Support of Development of a Medical Device

The types of clinical studies required for the development and approval of a medical device differ from those required for drug products. Clinical trials involving a drug product typically involve a sequential process of Phase 1, 2 and 3 clinical trials to test for the safety and efficacy of the product. The clinical development of a medical device, on the other hand, is often conducted in three different sequential phases, which may overlap or be combined. Those phases are a pilot study, which may also be referred to as an early feasibility study; a feasibility study; and a pivotal study.

- Pilot Study: A pilot study is a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication. It may be used to evaluate the device design concept with respect to initial clinical safety and device functionality in a small number of subjects (generally fewer than ten initial subjects) when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. Information obtained from a pilot study may guide device modifications.

Table of Contents

- Feasibility Study: A feasibility study is a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study. Because the study of a near-final or final device design takes place later in development than a pilot study, the FDA has indicated that it expects to see more nonclinical (or prior clinical) data in a feasibility study IDE application. A feasibility study does not necessarily need to be preceded by a pilot study.

- Pivotal Study: A pivotal study is a clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects. Evidence from one or more pivotal clinical studies generally serves as the primary basis for the determination of reasonable assurance of safety and effectiveness of the medical device of a PMA and FDA s overall benefit-risk determination. A pivotal study may or may not be preceded by a pilot study or feasibility study.

These three stages in the development of a medical device may be dependent on each other and conducting a thorough evaluation in one stage can make the next stage more straightforward. To determine which type of clinical study is appropriate to pursue, a manufacturer will consider several factors, such as the novelty of the device, the device s intended clinical use, the stability of the device design and the amount of test data available to support the IDE application. A pilot study is appropriate when device changes are expected and when, due to the novelty of the device or its intended use, a clinical study is expected to provide information that cannot be practically obtained through additional nonclinical assessments. A pilot study may also be appropriate even if a device or a prototype of the device has previously been used clinically for the intended clinical use. A feasibility study or a pivotal study may be more appropriate if the device design is near-final or final, respectively, depending on the amount of data available to justify the study.

510(k) Premarket Notification

To obtain 510(k) clearance, a manufacturer must submit a premarket notification demonstrating that the proposed device is substantially equivalent to a predicate device, which is a previously cleared 510(k) device or a pre-amendment device that was in commercial distribution before May 28, 1976, for which the FDA has not yet called for the submission of a PMA application. The FDA s 510(k) clearance pathway usually takes from three to 12 months from the date the application is submitted and filed with the FDA, but it can take significantly longer and clearance is never assured. The FDA has issued guidance documents meant to expedite review of a 510(k) and facilitate interactions between applicants and the agency. To demonstrate substantial equivalence, a manufacturer must show that the device has the same intended use as a predicate device and the same technological characteristics, or the same intended use and different technological characteristics and does not raise new questions of safety and effectiveness than the predicate device. Most 510(k)s do not require clinical data for clearance, but the FDA may request such data.

The FDA seeks to review and act on a 510(k) within 90 days of submission, but it may take longer if the agency finds that it requires more information to review the 510(k). If the FDA determines that the device is substantially equivalent to a predicate device, the subject device may be marketed. However, if the FDA concludes that a new device is not substantially equivalent to a predicate device, the new device will be classified in Class III and the manufacturer will be required to submit a PMA to market the product. Devices of a new type that the FDA has not previously classified based on risk are automatically classified into Class III by operation of section 513(f)(1) of the FDCA, regardless of the level of risk they pose. To avoid requiring PMA review of low- to moderate-risk devices classified in Class III by operation of law, Congress enacted section 513(f)(2) of the FDCA. This provision allows the FDA to classify a low- to moderate-risk device not previously classified into Class I or II, a process known as the *de novo* process. A company may apply directly to the FDA for classification of its device as *de novo* or may submit a de novo petition within 30 days of receiving a not substantially equivalent determination.

43

Table of Contents

Modifications to a 510(k)-cleared medical device may require the submission of another 510(k). Modifications to a 510(k)-cleared device frequently require the submission of a traditional 510(k), but modifications meeting certain conditions may be candidates for FDA review under a special 510(k). If a device modification requires the submission of a 510(k), but the modification does not affect the intended use of the device or alter the fundamental technology of the device, then summary information that results from the design control process associated with the cleared device can serve as the basis for clearing the application. A special 510(k) allows a manufacturer to declare conformance to design controls without providing new data. When the modification involves a change in material, the nature of the new material will determine whether a traditional or special 510(k) is necessary.

Any modification to a 510(k)-cleared product that would constitute a major change in its intended use or any change that could significantly affect the safety or effectiveness of the device may, in some circumstances, requires the submission of a PMA, if the change raises complex or novel scientific issues or the product has a new intended use. A manufacturer may be required to submit extensive pre-clinical and clinical data depending on the nature of the changes.

The FDA requires every manufacturer to make the determination regarding the need for a new 510(k) submission in the first instance, but the FDA may review any manufacturer s decision. If the FDA disagrees with the manufacturer s determination and requires new 510(k) clearances or PMA approvals for modifications to previously cleared products for which the manufacturer concluded that new clearances or approvals are unnecessary, the manufacturer may be required to cease marketing or distribution of the products or to recall the modified product until it obtains clearance or approval, and the manufacturer may be subject to significant regulatory fines or penalties. In addition, the FDA is currently evaluating the 510(k) process and may make substantial changes to industry requirements.

Premarket Approval Application

The PMA process for approval to market a medical device is more complex, costly, and time consuming than the 510(k) clearance procedure. A PMA must be supported by extensive data, including technical information regarding device design and development, pre-clinical studies, clinical studies, manufacturing and controls information and labeling information, that demonstrates the safety and effectiveness of the device for its intended use. After a PMA is submitted, the FDA has 45 days to determine whether it is sufficiently complete to permit a substantive review. If the PMA is complete, the FDA will file the PMA. If the FDA accepts the application for filing, the agency will begin an in-depth substantive review of the application. By statute, the FDA has 180 days to review the application although, generally, review of the application often takes between one and three years, and may take significantly longer. If the FDA has questions, it will likely issue a first major deficiency letter within 150 days of filing. It may also refer the PMA to an FDA advisory panel for additional review, and will conduct a pre-approval inspection of the manufacturing facility to ensure compliance with the QSR, either of which could extend the 180-day response target. In addition, the FDA may request additional information or request the performance of additional clinical trials in which case the PMA approval may be delayed while the trials are conducted and the data acquired are submitted in an amendment to the PMA. Even with additional trials, the FDA may not approve the PMA application.

If the FDA s evaluations of both the PMA and the manufacturing facilities are favorable, the FDA will either issue an approval letter authorizing commercial marketing or an approvable letter that usually contains a number of conditions that must be met in order to secure final approval. If the FDA s evaluations are not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. The PMA process, including the gathering of clinical and nonclinical data and the submission to and review by the FDA, can take several years, and the process can be expensive and uncertain. Moreover, even if the FDA approves a PMA, the FDA may approve the device with an indication that is narrower or more limited than originally sought. The FDA can impose post-approval conditions that it believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. After approval of a PMA, a new PMA or PMA supplement may be required for a modification to the device, its labeling, or its

Table of Contents

manufacturing process. PMA supplements often require submission of the same type of information as an initial PMA application, except that the supplement is limited to information needed to support any changes from the device covered by the approved PMA application and may or may not require as extensive technical or clinical data or the convening of an advisory panel. The time for review of a PMA supplement may vary depending on the type of change, but it can be lengthy. In addition, in some cases the FDA might require additional clinical data.

Investigational Device Exemption

A clinical trial is typically required for a PMA and, in a small percentage of cases, the FDA may require a clinical study in support of a 510(k) submission. A manufacturer that wishes to conduct a clinical study involving the device is subject to the FDA s IDE regulation. The IDE regulation distinguishes between significant and nonsignificant risk device studies and the procedures for obtaining approval to begin the study differ accordingly. Also, some types of studies are exempt from the IDE regulations.

Significant risk devices are, among other things, devices that are substantially important in diagnosing, curing, mitigating, or treating disease or in preventing impairment to human health and present a potential for serious risk to the health, safety or welfare of a subject. Studies of devices that pose a significant risk require both FDA and an IRB approval prior to initiation of a clinical study. Nonsignificant risk devices are devices that do not pose a significant risk to the human subjects. A nonsignificant risk device study requires only IRB approval prior to initiation of a clinical study.

An IDE application must be supported by appropriate data, such as animal and laboratory testing results, showing that it is safe to test the device in humans and that the testing protocol is scientifically sound. An IDE application is considered approved 30 days after it has been received by the FDA, unless the FDA otherwise informs the sponsor prior to 30 calendar days from the date of receipt that the IDE is approved, approved with conditions, or disapproved. The FDA typically grants IDE approval for a specified number of subjects to be enrolled at specified study centers. The clinical trial must be conducted in accordance with applicable regulations, including but not limited to the FDA s IDE regulations and GCP. The investigators must obtain subject informed consent, rigorously follow the investigational plan and study protocol, control the disposition of investigational devices, and comply with all reporting and record keeping requirements. A clinical trial may be suspended or terminated by the FDA, the IRB or the sponsor at any time for various reasons, including a belief that the risks to the study participants outweigh the benefits of participation in the trial. Approval of an IDE does not bind the FDA to accept the results of the trial as sufficient to prove the product s safety and efficacy, even if the trial meets its intended success criteria.

Humanitarian Use Device

When a medical device is intended to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year, a manufacturer may seek approval through a humanitarian device exemption, or HDE, application to market its product as a humanitarian use device, or HUD. This pathway provides an incentive for the development of devices for the treatment or diagnosis of diseases affecting small populations and where a manufacturer s research and development costs could exceed market return. Thus, the purpose of the HDE is to encourage device manufacturers to develop devices for rare conditions or diseases.

Prior to submitting the HDE application the device manufacturer must request HUD designation from the FDA s Office of Orphan Products Development. The FDA seeks to respond to the request within 45 days of submission. If granted, a manufacturer may file an HDE application

for HUD approval.

An HDE application is similar to a PMA application but is exempt from the effectiveness requirements of a PMA. In submitting an HDE application a manufacturer is not required to include scientifically valid clinical investigation results demonstrating that the device is effective for its intended purpose. However, the

Table of Contents

application must contain sufficient information for the FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. The manufacturer must also demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that the manufacturer could not otherwise bring the device to market. The FDA seeks to act on an HDE application within 75 days after accepting the HDE for filing.

If the FDA approves the HDE, the manufacturer may market the HUD. However, an HUD may only be used in facilities that have established an IRB to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. HUDs are also subject to specific labeling requirements identifying the device as a HUD device and noting that although the device is authorized by the FDA, the effectiveness of the device for the specific indication has not been demonstrated. Moreover, a manufacturer cannot charge an amount for an HDE approved device that exceeds the costs of research and development, fabrication, and distribution.

Expedited Access PMA

The FDA has proposed a program to provide earlier access to high-risk medical devices that are intended to treat or diagnose patients with serious conditions whose medical needs are unmet by current technology. The Expedited Access Premarket Approval Application for Unmet Medical Needs for Life Threatening or Irreversibly Debilitating Diseases or Conditions program, or EAP, allows for earlier and more interactive engagement with FDA staff. It also involves senior FDA management and a collaboratively developed plan for collecting scientific and clinical data to support approval taken together, these features are meant to provide patients with earlier access to safe and effective medical devices by reducing the time associated with product development.

To be eligible for participation in the program, the medical device must be intended to treat or diagnose a life-threatening or irreversibly-debilitating disease or condition and represent one of the following:

- no approved alternative treatment exists;
- a breakthrough technology that provides a clinically meaningful advantage over existing technology;
- offers a significant, clinically meaningful advantage over existing approved alternatives; or
- availability of the device is in the patient s best interest.

The EAP must be accompanied by an acceptable data development plan that has been approved by the FDA. When utilizing the EAP program, the FDA will continue to apply the current approval standard of demonstrating a reasonable assurance of safety and efficacy.

Post-Marketing Restrictions and Enforcement

After a device is placed on the market, numerous regulatory requirements apply. These include, but are not limited to:

- submitting and updating establishment registration and device listings with the FDA;

- compliance with the QSR, which requires manufacturers to follow stringent design, testing, control, documentation, record maintenance, including maintenance of complaint and related investigation files, and other quality assurance controls during the manufacturing process;

Table of Contents

- unannounced routine or for-cause device inspections by the FDA, which may include our suppliers facilities; and

- labeling regulations, which prohibit the promotion of products for uncleared or unapproved or off-label uses and impose other restrictions on labeling; post-approval restrictions or conditions, including requirements to conduct post-market surveillance studies to establish continued safety data or tracking products through the chain of distribution to the patient level.

Under the FDA medical device reporting, or MDR, regulations, medical device manufacturers are required to report to the FDA information that a device has or may have caused or contributed to a death or serious injury or has malfunctioned in a way that would likely cause or contribute to death or serious injury if the malfunction of the device or a similar device of such manufacturer were to recur. The decision to file an MDR involves a judgment by the manufacturer. If the FDA disagrees with the manufacturer s determination, the FDA can take enforcement action.

Additionally, the FDA has the authority to require the recall of commercialized products in the event of material deficiencies or defects in design or manufacture. The authority to require a recall must be based on an FDA finding that there is reasonable probability that the device would cause serious adverse health consequences or death. Manufacturers may, under their own initiative, recall a product if any material deficiency in a device is found. The FDA requires that certain classifications of recalls be reported to the FDA within ten working days after the recall is initiated.

The failure to comply with applicable regulatory requirements can result in enforcement action by the FDA, which may include any of the following sanctions:

- untitled letters, warning letters, fines, injunctions or civil penalties;

- recalls, detentions or seizures of products;

- operating restrictions;

- delays in the introduction of products into the market;

- total or partial suspension of production;

- delay or refusal of the FDA or other regulators to grant 510(k) clearance or PMA approvals of new products;

- withdrawals of 510(k) clearance or PMA approvals; or

- in the most serious cases, criminal prosecution.

To ensure compliance with regulatory requirements, medical device manufacturers are subject to market surveillance and periodic, pre-scheduled and unannounced inspections by the FDA, and these inspections may include the manufacturing facilities of subcontractors.

Review and Approval of Combination Products in the United States

Certain products may be comprised of components that would normally be regulated under different types of regulatory authorities, and frequently by different Centers at the FDA. These products are known as combination products. Specifically, under regulations issued by the FDA, a combination product may be:

- a product comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

Table of Contents

- two or more separate products packaged together in a single package or as a unit and comprised of drug and device products;

- a drug or device packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug or device where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

- any investigational drug or device packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Under the FDCA, the FDA is charged with assigning a center with primary jurisdiction, or a lead center, for review of a combination product. That determination is based on the primary mode of action of the combination product. Thus, if the primary mode of action of a device-drug combination product is attributable to the drug product, the FDA Center responsible for premarket review of the drug product would have primary jurisdiction for the combination product. The FDA has also established an Office of Combination Products to address issues surrounding combination products and provide more certainty to the regulatory review process. That office serves as a focal point for combination product issues for agency reviewers and industry. It is also responsible for developing guidance and regulations to clarify the regulation of combination products, and for assignment of the FDA center that has primary jurisdiction for review of combination products where the jurisdiction is unclear or in dispute.

Review and Approval of Drug Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of drug products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Pursuant to the European Clinical Trials Directive, a system for the approval of clinical trials in the European Union has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of a European Union member state in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial after a competent ethics committee has issued a favorable opinion. Clinical trial application must be accompanied by an investigational medicinal product dossier with supporting information prescribed by the European Clinical Trials Directive and corresponding national laws of the member states and further detailed in applicable guidance documents.

To obtain marketing approval of a drug under European Union regulatory systems, an applicant must submit a marketing authorization application, or MAA, either under a centralized or decentralized procedure.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all European Union member states. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated

Table of Contents

as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the EMA, is responsible for conducting the initial assessment of a drug. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure is available to applicants who wish to market a product in various European Union member states where such product has not received marketing approval in any European Union member states before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state designated by the applicant, known as the reference member state. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment report and drafts of the related materials within 210 days after receipt of a valid application. Within 90 days of receiving the reference member state s assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials.

If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

Review and Approval of Medical Devices in the European Union

The European Union has adopted numerous directives and standards regulating, among other things, the design, manufacture, clinical trials, labeling, approval and adverse event reporting for medical devices. In the European Union, medical devices must comply with the Essential Requirements in Annex I to the EU Medical Devices Directive (Council Directive 93/42/EEC), or the Essential Requirements. Compliance with these requirements is a prerequisite to be able to affix the CE mark of conformity to medical devices, without which they cannot be marketed or sold in the European Economic Area, or EEA, comprised of the European Union member states plus Norway, Iceland, and Liechtenstein. Actual implementation of these directives, however, may vary on a country-by-country basis.

To demonstrate compliance with the Essential Requirements a manufacturer must undergo a conformity assessment procedure, which varies according to the type of medical device and its classification. Except for low risk medical devices, where the manufacturer can issue a CE Declaration of Conformity based on a self-assessment of the conformity of its products with the Essential Requirements, a conformity assessment procedure requires the intervention of a third-party organization designated by competent authorities of a European Union country to conduct conformity assessments, or a Notified Body. Notified Bodies are independent testing houses, laboratories, or product certifiers typically based within the European Union and authorized by the European member states to perform the required conformity assessment tasks, such as quality system audits and device compliance testing. The Notified Body would typically audit and examine the product s Technical File and the quality system for the manufacture, design and final inspection of the product before issuing a CE Certificate of Conformity demonstrating

compliance with the relevant Essential Requirements.

Table of Contents

Medical device manufacturers must carry out a clinical evaluation of their medical devices to demonstrate conformity with the relevant Essential Requirements. This clinical evaluation is part of the product s Technical File. A clinical evaluation includes an assessment of whether a medical device s performance is in accordance with its intended use, and that the known and foreseeable risks linked to the use of the device under normal conditions are minimized and acceptable when weighed against the benefits of its intended purpose. The clinical evaluation conducted by the manufacturer must also address any clinical claims, the adequacy of the device labeling and information (particularly claims, contraindications, precautions and warnings) and the suitability of related Instructions for Use. This assessment must be based on clinical data, which can be obtained from clinical studies conducted on the devices being assessed, scientific literature from similar devices whose equivalence with the assessed device can be demonstrated or both clinical studies and scientific literature.

With respect to implantable devices or devices classified as Class III in the European Union, the manufacturer must conduct clinical studies to obtain the required clinical data, unless relying on existing clinical data from similar devices can be justified. As part of the conformity assessment process, depending on the type of devices, the Notified Body will review the manufacturer s clinical evaluation process, assess the clinical evaluation data of a representative sample of the device s subcategory or generic group, or assess all the clinical evaluation data, verify the manufacturer s assessment of that data and assess the validity of the clinical evaluation report and the conclusions drawn by the manufacturer.

Even after a manufacturer receives a CE Certificate of Conformity enabling the CE mark on it products and the right to sell the products in the EEA countries, a Notified Body or a competent authority may require post-marketing studies of the products. Failure to comply with such requirements in a timely manner could result in the withdrawal of the CE Certificate of Conformity and the recall or withdrawal of the subject product from the European market.

A manufacturer must inform the Notified Body that carried out the conformity assessment of the medical devices of any planned substantial changes to the devices which could affect compliance with the Essential Requirements or the devices intended purpose. The Notified Body will then assess the changes and verify whether they affect the product s conformity with the Essential Requirements or the conditions for the use of the devices. If the assessment is favorable, the Notified Body will issue a new CE Certificate of Conformity or an addendum to the existing CE Certificate of Conformity attesting compliance with the Essential Requirements. If it is not, the manufacturer may not be able to continue to market and sell the product in the EEA.

In the European Union, medical devices may be promoted only for the intended purpose for which the devices have been CE marked. Failure to comply with this requirement could lead to the imposition of penalties by the competent authorities of the European Union Member States. The penalties could include warnings, orders to discontinue the promotion of the medical device, seizure of the promotional materials and fines. Promotional materials must also comply with various laws and codes of conduct developed by medical device industry bodies in the European Union governing promotional claims, comparative advertising, advertising of medical devices reimbursed by the national health insurance systems and advertising to the general public.

Additionally, all manufacturers placing medical devices in the market in the European Union are legally bound to report any serious or potentially serious incidents involving devices they produce or sell to the competent authority in whose jurisdiction the incident occurred. In the European Union, manufacturers must comply with the EU Medical Device Vigilance System. Under this system, incidents must be reported to the relevant authorities of the European Union countries, and manufacturers are required to take Field Safety Corrective Actions, or FSCAs, to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market. An incident is defined as any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient or user or of other persons or to a serious deterioration in their state of health. An FSCA may include the recall,

Table of Contents

modification, exchange, destruction or retrofitting of the device. FSCAs must be communicated by the manufacturer or its European Authorized Representative to its customers and to the end users of the device through Field Safety Notices. In September 2012, the European Commission adopted a proposal for a regulation which, if adopted, will change the way that most medical devices are regulated in the European Union, and may subject products to additional requirements.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which the costs of the products will be covered by third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication. Additionally, the containment of healthcare costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. A payor s decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

Healthcare Law and Regulation

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with third-party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations. Such restrictions under applicable federal and state healthcare laws and regulations, include the following:

Table of Contents

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;

- the federal False Claims Act imposes civil penalties, and provides for civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

- the federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA will require applicable manufacturers of covered drugs, devices, drugs and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Employees

As of December 31, 2014, we had 48 full-time employees, of which 41 employees were engaged in research and development and seven employees provided general and administrative support. Of our employees, 27 have earned advanced degrees. Our employees are not represented by a labor union or covered by a collective bargaining agreement.

Our Corporate Information

We were incorporated under the laws of the State of Delaware on October 17, 2013 under the name Ikaria Development LLC. We changed our name to Bellerophon Therapeutics LLC on January 27, 2014. On

Table of Contents

February 12, 2015, we converted from a Delaware limited liability company into a Delaware corporation and changed our name to Bellerophon Therapeutics, Inc. We currently have three wholly-owned subsidiaries: Bellerophon BCM LLC, a Delaware limited liability company; Bellerophon Pulse Technologies LLC, a Delaware limited liability company; and Bellerophon Services, Inc., a Delaware corporation. Our website address is www.bellerophon.com. The information contained on, or that can be accessed through, our website does not constitute part of this Annual Report on Form 10-K. We have included our website address in this Annual Report on Form 10-K solely as an inactive textual reference.

Our executive offices are located at 53 Frontage Road, Suite 301, Hampton, New Jersey 08827, and our telephone number is (908) 574-4770.

Available Information

We make available free of charge through our website our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. The information contained on, or that can be access through, our website is not a part of or incorporated by reference in this Annual Report on Form 10-K.

Table of Contents

Item 1A. Risk Factors

The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 2 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net loss was approximately $46.2 million for the year ended December 31, 2012, $62.0 million for the year ended December 31, 2013 and $59.7 million for the year ended December 31, 2014. We do not know whether or when we will become profitable. We have not generated any revenues to date from product sales. We have not completed development of any product candidate and have devoted substantially all of our financial resources and efforts to research and development, including pre-clinical studies and clinical trials. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our deficit and working capital. We anticipate that our expenses will increase substantially if and as we:

- continue our research and clinical development of our INOpulse program for the treatment of PAH and PH-COPD and of our BCM program for the prevention of left ventricular remodeling following a STEMI;
- identify, develop and/or in-license additional product candidates;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- in the future, establish a manufacturing, sales, marketing and distribution infrastructure;
- maintain, expand and protect our intellectual property portfolio;

- add equipment and physical infrastructure to support our research and development;

- hire additional clinical, regulatory, quality control and scientific personnel; and

- add operational, financial and management information systems and personnel, including personnel to support our product development and any future commercialization efforts and personnel and infrastructure necessary to help us comply with our obligations as a public company.

To become and remain profitable, we must succeed in developing and eventually commercializing products that generate significant revenue. We do not expect to generate significant revenue unless and until we are able to obtain marketing approval for, and successfully commercialize, one or more of our product candidates. This will require us to be successful in a range of challenging activities, including completing pre-clinical studies and clinical trials of our product candidates, discovering additional product candidates,

Table of Contents

obtaining regulatory approval for our product candidates, manufacturing, marketing and selling any products for which we may obtain regulatory approval, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payors. We are in the early stages of most of these activities and have not yet commenced other of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. If we are required by the FDA or the EMA to perform trials in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates, our expenses could increase.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could cause our stockholders to lose all or part of their investment in us.

In addition, our recurring losses from operations, accumulated deficit and our need to raise additional financing in order to continue to fund our operations, raise substantial doubt about our ability to continue as a going concern. Given our planned expenditures for the next several years, including, without limitation, expenditures in connection with our clinical trials, our independent registered public accounting firm may conclude that there is substantial doubt regarding our ability to continue as a going concern.

Our very limited operating history as a stand-alone company may make it difficult for our stockholders to evaluate the success of our business to date and to assess our future viability.

We were formed as a wholly-owned subsidiary of Ikaria in October 2013 and became a stand-alone company in February 2014 following the Spin-Out and, as such, have a very limited operating history as a stand-alone company. Prior to the Spin-Out, Ikaria assisted us by providing financing and certain corporate functions. Following the Spin-Out, Ikaria has no obligation to provide assistance to us other than on an interim basis as provided for in the agreements we entered into in connection with the Spin-Out. See Certain Relationships and Related Person Transactions Relationship with Ikaria.

Our operations to date have been limited to organizing and staffing our company, developing and securing our technology, and undertaking pre-clinical studies and clinical trials of our product candidates. We have not yet demonstrated the ability to successfully operate as a stand-alone company or to complete development of any product candidates, obtain marketing approvals, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions our stockholders make about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing products.

Assuming we obtain marketing approval for any of our product candidates, we will need to transition from a company with a research and development focus to a company capable of supporting commercial activities or we will need to enter into strategic partnerships. We may encounter unforeseen expenses, difficulties, complications and delays and may not be successful in such a transition.

Table of Contents

We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect our expenses to increase in connection with our ongoing activities, particularly as we initiate additional clinical trials of our INOpulse and BCM product candidates and continue research and development and seek regulatory approval for these and potentially other product candidates. In addition, if we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. In particular, the costs that may be required for the manufacture of any product candidate that receives marketing approval may be substantial. In addition, relative to previous years when we operated as a private company, we expect to incur additional costs in 2015 and future years associated with operating as a public company. As of December 31, 2014, we had cash and cash equivalents and restricted cash of $27.6 million. From the inception of our business through December 31, 2014, Ikaria made cumulative investments of $177.5 million in us and contributed an additional $80.0 million in cash to us in connection with the Spin-Out. Now that we are a stand-alone company, any additional funding will need to come from another source. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

We plan to use our current cash and cash equivalents and restricted cash, including the net proceeds of our initial public offering, primarily to fund our ongoing research and development efforts. We will be required to expend significant funds in order to advance development of our INOpulse and BCM product candidates and any other potential product candidates. Our existing cash and cash equivalents and restricted cash, including the net proceeds of our initial public offering, will not be sufficient to fund all of the efforts that we plan to undertake, such as the further development of INOpulse for PH-COPD or BCM, or to fund completion of clinical development or commercialization of any of our product candidates. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations or licensing arrangements or other sources. Adequate additional funding may not be available to us on acceptable terms or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

We believe that our existing cash and cash equivalents and restricted cash as of December 31, 2014, together with the net proceeds of our initial public offering, will enable us to fund our planned operating expenses and capital expenditure requirements at least into mid-2016. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Our future capital requirements will depend on many factors, including:

- the progress and results of our current and planned clinical trials of our INOpulse and BCM product candidates;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of operating as a stand-alone company;

- the cost and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;

- the revenue, if any, received from commercial sales of any product candidates for which we receive marketing approval;

- our ability to establish and maintain strategic partnerships, licensing or other arrangements and the financial terms of such agreements;

Table of Contents

- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;

- the scope, progress, results and costs of discovery, pre-clinical development and clinical trials for any other product candidates;

- the extent to which we acquire or in-license other product candidates and technologies;

- our headcount growth and associated costs; and

- the costs of operating as a public company.

Identifying potential product candidates and conducting pre-clinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for several years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of public or private equity offerings, debt financings and/or license and development agreements with collaboration partners. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of our stockholders may be materially diluted, and the terms of such securities could include liquidation or other preferences that adversely affect the rights of our stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include restrictive covenants that limit our ability to take specified actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. If we raise funds through collaborations, strategic partnerships or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us.

Risks Related to Our Business and Industry

We may be unable to make, on a timely or cost-effective basis, the changes necessary to operate as a stand-alone company, and we may experience increased or unexpected costs after the Spin-Out or as a result of the Spin-Out.

We have historically operated as part of Ikaria s broader corporate organization, and Ikaria has assisted us by providing certain corporate functions. However, following the Spin-Out, Ikaria is contractually obligated to provide to us only those services specified in a transition services agreement, or the TSA, a services agreement, or the 2015 Services Agreement, and the other agreements we entered into with Ikaria to govern our relationship following the Spin-Out. See Certain Relationships and Related Person Transactions Relationship with Ikaria for a summary of these agreements. The TSA and the 2015 Services Agreement provide for certain

Table of Contents

services to be provided until February 2016. We may be unable to replace in a timely manner or on comparable terms the services or other benefits that Ikaria previously provided to us that are not specified in the TSA, the 2015 Services Agreement or the other agreements. Also, upon the termination of the services provided under the TSA or other agreements, such services will be provided internally or by unaffiliated third parties, and we expect that in some instances, we will incur higher costs to obtain such services than we incurred under the terms of such agreements. Ultimately, we may be unable to replace in a timely manner or on comparable terms the services specified in such agreements. In addition, during the transitional services period, we will rely, in part, on the same executive team at Ikaria that also will continue to manage the business of Ikaria during such time, and there may be conflicting demands on their time, which could result in an inadequate level of attention to the demands of our business. If Ikaria and its employees do not continue to perform effectively the transition services and the other services that are called for under the TSA, the 2015 Services Agreement and other agreements, we may not be able to operate our business effectively and our business and financial condition could be adversely affected.

On March 5, 2015, Mallinckrodt and Ikaria announced that the two companies had entered into a definitive agreement under which a subsidiary of Mallinckrodt will acquire Ikaria and that they expect the acquisition will be completed in the second calendar quarter of 2015. While the TSA imposes binding obligations on Ikaria to perform in accordance with the TSA s terms, it is possible that following completion of the sale, as the new owner s influence on Ikaria s operations increases, Ikaria may not continue to provide the same level of performance under the TSA as Ikaria has provided to date. Moreover, to the extent that we desire to extend, renew or expand the scope of the TSA, it is also possible that Ikaria will not be willing to do so on reasonable terms, or at all. In any of these circumstances, our business, product development and financial statements could be materially adversely affected.

Prior to the Spin-Out, we utilized the executive management team and administrative resources of Ikaria. Many daily functions were performed by Ikaria, including those related to the preparation of our financial statements and the engagement of auditors to audit our financial statements, which have become our responsibility following the Spin-Out. We may need to acquire assets and resources in addition to those provided to us by Ikaria, and we may face difficulty in integrating newly acquired assets into our business. Additionally, as a stand-alone company, we no longer have access to Ikaria s financial resources. Instead, our ability to fund our capital needs will depend on our ongoing ability to generate cash from operations, enter into partnering arrangements, obtain debt financing and access capital markets, which are subject to general economic, financial, competitive, regulatory and other factors that are beyond our control. Our business, financial condition and results of operations could be harmed, possibly materially, if we have difficulty operating as a stand-alone company, fail to acquire necessary capital or assets that prove to be important to our operations, or are unable to enter into partnering or other business development arrangements.

We are also currently incurring and expect to continue to incur additional incremental expenses associated with being a stand-alone company. These incremental pretax expenses were approximately $5.0 million for the year ended December 31, 2014.

Our historical financial information is not necessarily representative of the results we would have achieved as a stand-alone company and may not be a reliable indicator of our future results.

The historical financial information we have included in this report may not reflect what our results of operations, financial position and cash flows would have been had we been a stand-alone company during the periods presented. This is primarily because:

- our historical financial information reflects allocations for services historically provided to us by Ikaria, which allocations may not reflect the costs we will incur for similar services in the future as a stand-alone company; and

58

Table of Contents

- our historical financial information does not reflect changes that we expect to incur in the future as a result of our separation from Ikaria and from reduced economies of scale, including changes in the cost structure, personnel needs, financing and operations of our business.

In addition, as a newly public company, we are also responsible for the additional costs associated with being a public company, including costs related to corporate governance and having listed and registered securities. Therefore, our historical financial information may not be indicative of our future performance as a stand-alone public company.

For additional information about our past financial performance and the basis of presentation of our financial statements, please see Management s Discussion and Analysis of Financial Condition and Results of Operations and our financial statements and the notes thereto included elsewhere in this Annual Report on Form 10-K.

The ownership by certain of our executive officers and directors of equity of Ikaria, as well as the continued roles of certain of our directors with Ikaria, may create, or may create the appearance of, conflicts of interest.

Because of their current or former positions with Ikaria, our chief business officer, Manesh Naidu, our chief clinical development officer, Reinilde Heyrman, our chief scientific officer, Martin Meglasson, our treasurer, David Abrams, and one of our directors, Daniel Tassé, own equity in Ikaria. In addition, two of our directors, Matthew Holt and Adam B. Weinstein, may be deemed to beneficially own equity in Ikaria. Such equity ownership may create, or may create the appearance of, conflicts of interest. The individual holdings of equity of Ikaria may be significant for some of these persons compared to such person s total assets. Ownership by certain of our executive officers and directors of equity of Ikaria creates, or may create the appearance of, conflicts of interest when these officers or directors are faced with decisions that could have different implications for Ikaria than the decisions have for us. In addition, Matthew Holt and Daniel Tassé are currently serving on our board of directors as well as Ikaria s board of directors, and Mr. Tassé is currently serving as the chief executive officer of Ikaria. The continued service at both companies creates, or may create the appearance of, conflicts of interest when these directors are faced with decisions that could have different implications for Ikaria than the decisions have for us, such as the allocation of time and resources to the provision of transitional services to us by Ikaria pursuant to the TSA, the 2015 Services Agreement and the other agreements.

We face substantial competition from other pharmaceutical, biotechnology and medical device companies and our operating results may suffer if we fail to compete effectively.

The pharmaceutical, biotechnology and medical device industries are highly competitive. There are many pharmaceutical, biotechnology and medical device companies, public and private universities and research organizations actively engaged in the research and development of products that may be similar to our product candidates. In addition, other companies are increasingly looking at the cardiopulmonary and cardiac disease market as a potential opportunity. Currently, there are 12 drugs approved for the treatment of PAH, within the following categories: prostacyclin and prostacyclin analogs (including Flolan® (epoprostenol), which is marketed by GlaxoSmithKline, Tyvaso® (treprostinil), Orenitram® (treprostinil) and Remodulin® (treprostinil), which are marketed by United Therapeutics Corporation, and Ventavis® (iloprost) and Veletri® (epoprostenol), which are marketed by Actelion Pharmaceuticals US, Inc., or Actelion), phosphodiesterase type-5 inhibitors (including Adcirca® (tadalafil), which is marketed by United Therapeutics Corporation, and Revatio® (sildenafil), which is marketed by Pfizer Inc.), endothelin receptor antagonists (including Letairis® (ambrisentan), which is marketed by Gilead Sciences, Inc., and Opsumit® (macitentan) and Tracleer® (bosentan), which are marketed by Actelion) and a soluble guanylate cyclase stimulator (Adempas® (riociguat), which is marketed by Bayer HealthCare Pharmaceuticals Inc.). Actelion recently submitted an NDA to the FDA for selexipag, a selective prostacyclin receptor agonist. There are also other treatments in Phase 1 and Phase 2 clinical development, including other nitric oxide generation and delivery systems, including GeNOsyl, which is being developed by GeNO LLC, and a nebulized formulation of nitrite, which is being developed by Mast

Therapeutics.

Table of Contents

Currently, there are no approved therapies for treating PH-COPD, and the only generally accepted treatments are LTOT, pulmonary rehabilitation and lung transplant, and we are not aware of any therapies for PH-COPD in advanced clinical development.

There are no generally accepted products approved for structural support to prevent cardiac remodeling following an AMI. Other product candidates that are currently in clinical development include stem cell therapies to restore heart muscle cells following an AMI, with large Phase 3 trials expected to be completed in 2018 or 2019. We do not expect BCM to compete with, or replace, current treatments for congestive heart failure following AMI, but instead believe it will become part of the treatment regimen used in conjunction with other therapies. In addition, because BCM can be delivered by a minimally invasive percutaneous coronary intervention procedure, we do not believe it will directly compete with devices that are used to treat congestive heart failure, which are designed for administration during open heart surgery or by intra-cardiac injection involving a thoracotomy procedure. These include: mesh restraining devices, for example HeartNet; injectable biopolymers, for example Algisyl-LVR; and implantable electro stimulation devices, for example, CardioFit. In addition, volume reduction surgery or cardiac assist devices, or pumps, are sometimes used to treat patients with congestive heart failure.

Many of our competitors, either alone or through their strategic partners, have substantially greater name recognition and financial, technical, manufacturing, marketing and human resources than we do and significantly greater experience and infrastructure in the research and clinical development of medical products, obtaining FDA and other regulatory approvals of those products, and commercializing those products around the world. Additional mergers and acquisitions in the pharmaceutical, biotechnology and medical device industries may result in even more resources being concentrated in our competitors. Large pharmaceutical and medical device companies in particular have extensive expertise in pre-clinical and clinical testing and in obtaining regulatory approvals for medical products. In addition, academic institutions, government agencies, and other public and private organizations conducting research may seek patent protection with respect to potentially competitive products or technologies. These organizations may also establish exclusive collaborative or licensing relationships with our competitors. Accordingly, our competitors may be more successful than we may be in obtaining approval for inhaled nitric oxide products and achieving widespread market acceptance. We anticipate that we will face intense and increasing competition as new products and technologies become available.

We will not be able to compete effectively unless we successfully:

- design, develop and commercialize products that are superior to other products in the market;
- attract qualified scientific, medical, sales and marketing, engineering and commercial personnel;
- obtain patent and/or other proprietary protection for our processes and product candidates; and
- obtain required regulatory approvals.

It is also possible that Ikaria will seek to develop and commercialize inhaled nitric oxide products or product candidates in PAH, PH-COPD and/or PH-IPF. While a subsidiary of Ikaria has granted to us an exclusive license to develop and commercialize pulsed nitric oxide in PAH, PH-COPD and PH-IPF and the scope of that license includes certain technology developed or acquired by that subsidiary after the date of the license agreement, the license does not include technology developed or acquired by other subsidiaries or affiliates of Ikaria. Because Ikaria and its subsidiaries and affiliates are not subject to any non-competition obligations in our favor, it is possible that these other subsidiaries or affiliates of Ikaria may seek to develop or commercialize inhaled nitric oxide or other products or product candidates, using technology not exclusively licensed to us, that are competitive with our products or product candidates.

Table of Contents

Risks Related to the Discovery, Development and Commercialization of Our Product Candidates

We are dependent on the success of our INOpulse and BCM product candidates and our ability to develop, obtain marketing approval for and successfully commercialize these product candidates. If we are unable to develop, obtain marketing approval for or successfully commercialize our product candidates, either alone or through a collaboration, or experience significant delays in doing so, our business could be materially harmed.

We currently have no products approved for sale and have invested a significant portion of our efforts and financial resources in the development of our INOpulse for PAH, INOpulse for PH-COPD and BCM product candidates. Our prospects are substantially dependent on our ability to develop, obtain marketing approval for and successfully commercialize these product candidates. The success of our product candidates will depend on, among other things, our ability to successfully complete clinical trials of each product candidate. The clinical trial process is uncertain, and failure of one or more clinical trials can occur at any stage of testing. For example, although we believe our recently completed Phase 2 clinical trials of INOpulse for PAH and INOpulse for PH-COPD support advancement into a Phase 3 and a Phase 2b clinical trial, respectively, the primary endpoints for both INOpulse for PAH and INOpulse for PH-COPD were not statistically significant for any of the doses tested.

In addition to the successful completion of clinical trials, the success of our product candidates will also depend on several other factors, including the following:

- receipt of marketing approvals from the FDA or other applicable regulatory authorities;
- establishment of supply arrangements with third-party raw materials suppliers and manufacturers;
- establishment of arrangements with third-party manufacturers to obtain finished drug products that are appropriately packaged for sale;
- the performance of our future collaborators for one or more of our product candidates, if any;
- the extent of any required post-marketing approval commitments to applicable regulatory authorities;
- obtaining and maintaining patent, trade secret protection and regulatory exclusivity, both in the United States and internationally;

- protection of our rights in our intellectual property portfolio;
- launch of commercial sales if and when our product candidates are approved;
- a continued acceptable safety profile of our product candidates following any marketing approval;
- commercial acceptance, if and when approved, by patients, the medical community and third-party payors;
- establishing and maintaining pricing sufficient to realize a meaningful return on our investment; and
- competition with other products.

If we are unable to develop, receive marketing approval for, or successfully commercialize our product candidates, or experience delays as a result of any of these factors or otherwise, our business could be materially harmed.

Table of Contents

Clinical trials involve a lengthy and expensive process with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

We recently completed Phase 2 clinical trials of INOpulse for PAH and INOpulse for PH-COPD and are currently conducting a clinical trial of BCM. The risk of failure of all of our product candidates is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of development, including failure to demonstrate efficacy in a clinical trial or across a broad population of patients, the occurrence of severe or medically or commercially unacceptable adverse events, failure to comply with protocols or applicable regulatory requirements and determination by the FDA or any comparable non-U.S. regulatory authority that a drug product is not approvable. For example, although we believe our recently completed Phase 2 clinical trials of INOpulse for PAH and INOpulse for PH-COPD support advancement into a Phase 3 and a Phase 2b clinical trial, respectively, the primary endpoints for both INOpulse for PAH and INOpulse for PH-COPD were not statistically significant for any of the doses tested.

It is possible that even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of or intolerability caused by our product candidates, or mistakenly believe that our product candidates are toxic or not well tolerated when that is not in fact the case. Also, the exclusion criteria we define may not sufficiently rule out patients who are at a higher risk of being harmed by the treatment. For example, our exclusion criteria for pre-existing left heart dysfunction in our recently completed Phase 2 INOpulse clinical trials may not rule out patients who may experience an adverse event related to left ventricular function due to exposure to nitric oxide. In addition, patients who are not excluded for reactive pulmonary vasculature when exposed to nitric oxide may still experience pulmonary hypertension.

The outcome of pre-clinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results, particularly when earlier trials are small, open-label or non-placebo-controlled trials and in trials that have different endpoints than earlier trials. For example, we are relying on the results from a 32-patient Phase 2 PH-COPD trial, conducted in Austria, as part of our clinical development program of INOpulse for PH-COPD, and we may not be able to replicate the results of this trial in a larger trial or in a trial that uses a clinical endpoint rather than the anatomical endpoints used in the 32-patient trial. Similarly, for BCM, we are using the results of the 27-patient pilot trial conducted by BioLineRx Ltd. that used anatomical changes to measure efficacy and did not have a control group as support for our larger ongoing clinical trial, which may not achieve the same results as the BioLineRx Ltd. trial. Many companies in the biotechnology, pharmaceutical and medical device industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we cannot be certain that we will not face such setbacks.

The design of a clinical trial can determine whether its results will support approval of a product, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced or completed. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval. In addition, pre-clinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in pre-clinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we believe that the results of clinical trials for our product candidates warrant

Table of Contents

marketing approval, the FDA or comparable non-U.S. regulatory authorities may disagree and may not grant marketing approval of our product candidates.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the clinical trial protocols and the rate of dropout among clinical trial participants. Any Phase 3 or other clinical trials that we may conduct may not demonstrate the efficacy and safety necessary to obtain regulatory approval to market our product candidates.

INOpulse is a sophisticated electro-mechanical device comprised of components that may fail or deteriorate over time or with improper use. If we experience problems with, failure of, or delays in obtaining any INOpulse components, our business could be materially adversely harmed.

Because INOpulse is a sophisticated electro-mechanical device, the parts which comprise the device are subject to sudden failure or to wear and tear, which may result in decreased function or failure of those parts over time. Although we perform scheduled, preventive maintenance on our drug delivery system to limit device failures, and additional maintenance as needed whenever a user reports a device malfunction, components of our devices may fail. In addition, although we have designed INOpulse to be simple and easy to use and will provide user manuals and other training materials, users of INOpulse may use the devices improperly, which could cause the devices to fail or otherwise not work properly.

There are several components in INOpulse that are custom designed or assembled for us. We are dependent on a single company to supply us with some of these components. While we believe there are alternative suppliers from which we could purchase most of these components, there is a risk that a single-source supplier could fail to deliver adequate supply, or could suffer a business interruption that could affect our supply of these components.

We obtain some of the components for INOpulse through individual purchase orders executed on an as needed basis rather than pursuant to long-term supply agreements. Our business, financial condition or results of operations could be adversely affected if any of our principal third-party suppliers or manufacturers experience production problems, lack of capacity or transportation disruptions or otherwise cease producing such components.

We are transitioning our INOpulse delivery system to a next generation device that was not utilized in our recently completed INOpulse Phase 2 clinical trials. Failure by the FDA or other regulatory authority to support the transition and bridging strategy for our transition to the new device could increase our development costs and/or delay commencement of our future clinical trials of INOpulse.

Our recently completed INOpulse Phase 2 clinical trials utilized the first generation INOpulse DS device. We are near completion of a second generation INOpulse device, the Mark2, and we plan to transition our INOpulse delivery system from INOpulse DS to the Mark2 for any future INOpulse clinical trials. To facilitate the transition from our existing INOpulse DS device to the Mark2 in our clinical program, we plan to conduct comparability testing of nitric oxide dosing with the Mark2 as compared to the INOpulse DS device. This testing will include a comparison of critical parameters, including pulse width and nitric oxide output. We will also assess whether the Mark2 will meet the performance specifications of the INOpulse DS device in addition to Mark2-specific requirements. In addition, we are developing a bridging test

report that we expect to include in the regulatory package that we anticipate submitting to the FDA during the first half of 2015 to gain approval for the device transition. We discussed our strategy with the FDA during a meeting in May 2013, and we believe that, assuming the Mark2 meets the specified comparability parameters, this testing will be sufficient to gain FDA approval to use the Mark2 in future clinical trials, as planned. The FDA may not agree that our data support transition to this new device, in which case we may be required to provide additional data, perform a revised bridging assessment or repeat the Phase 2 clinical trial, any of which could increase our development

Table of Contents

costs and/or delay or prevent commencement of these future clinical trials. In addition, even if the FDA accepts our transition plan, use of the Mark2 in future clinical trials could produce results that are different than those we would expect based on the results from the Phase 2 clinical trial using the INOpulse DS device.

We intend to conduct, and may in the future conduct, clinical trials for certain of our product candidates at sites outside the United States, and the FDA may not accept data from trials conducted in such locations.

We have conducted, and may in the future choose to conduct, one or more of our clinical trials outside the United States. For example, our Phase 2 clinical trial of INOpulse for PAH included sites in Canada and our clinical trial of BCM includes sites in Europe, Canada, Australia and Israel.

Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of this data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with GCP in the case of drug trials, or the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords greater protection to the human subjects, in the case of device trials. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. Generally, the patient population for any clinical trials conducted outside of the United States must be representative of the population for whom we intend to seek approval in the United States. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will be dependent upon its determination that the trials also complied with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from trials conducted outside of the United States. If the FDA does not accept the data from our Phase 2 clinical trial of INOpulse for PAH in Canada or our clinical trial of BCM in Europe, Canada, Australia or Israel, or any future trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and delay or permanently halt our development of INOpulse for PAH and BCM or any future product candidates.

In addition, the conduct of clinical trials outside the United States could have a significant impact on us. Risks inherent in conducting international clinical trials include:

- foreign regulatory requirements that could restrict or limit our ability to conduct our clinical trials;
- administrative burdens of conducting clinical trials under multiple foreign regulatory schema;
- foreign exchange fluctuations; and
- diminished protection of intellectual property in some countries.

If clinical trials of our product candidates fail to demonstrate safety and efficacy of our product candidates to the satisfaction of the FDA and comparable non-U.S. regulators, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of these product candidates.

We are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Comparable non-U.S. regulatory authorities, such as the EMA, impose similar restrictions. We may never receive such approvals. We must complete extensive pre-clinical studies and clinical trials to demonstrate the safety and efficacy of our product candidates in humans before we will be able to obtain these approvals.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome. We have not previously submitted an NDA to the FDA or similar drug approval filings to comparable non-U.S. regulatory authorities for any of our product candidates.

Table of Contents

Any inability to successfully complete pre-clinical and clinical development could result in additional costs to us and impair our ability to generate revenues from product sales. In addition, if (1) we are required to conduct additional clinical trials or other testing of our product candidates beyond the trials and testing that we contemplate, (2) we are unable to successfully complete clinical trials of our product candidates or other testing, (3) the results of these trials or tests are unfavorable, uncertain or are only modestly favorable, such as in our Phase 2 clinical trials of INOpulse for PAH and INOpulse for PH-COPD, or (4) there are unacceptable safety concerns associated with our product candidates, we, in addition to incurring additional costs, may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as we intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or significant safety warnings, including boxed warnings;
- be subject to additional post-marketing testing or other requirements; or
- be required to remove the product from the market after obtaining marketing approval.

For example, the FDA has granted us an IDE for our ongoing clinical trial of BCM, which we refer to as our PRESERVATION I trial, which currently limits at 60 the number of patients we can enroll in the United States. This limitation is due to the novelty of BCM and the lack of prior data on administration to human patients of four milliliters of BCM that we are using in the trial because we did not conduct a pilot study of BCM with the four milliliter volume. Due to the lack of a pilot study or other data supporting the safety or efficacy of four milliliters of BCM in human patients, the FDA may require that, prior to approval, we conduct additional trials of BCM or that we provide additional data to support the safety and/or efficacy of four milliliters of BCM in human patients.

In addition, the FDA has asked us to conduct a study to test the environmental impact of using INOpulse at home. When inhaled nitric oxide is administered through INOpulse, a small portion of the nitric oxide will be exhaled or otherwise emitted and could react with oxygen in room air to form nitrogen dioxide, which is an environmental pollutant. The study will measure the nitrogen dioxide in the room air with use of INOpulse under actual or simulated patient use conditions. If the FDA or other regulatory authority requires us to conduct additional testing or determines that an unacceptable amount of nitrogen dioxide is formed through the use of INOpulse, we may be required to alter the design of INOpulse, which may not be possible, and the clinical development timeline for INOpulse may be delayed or prove to be more costly than we currently anticipate.

If we experience any of a number of possible unforeseen events in connection with clinical trials of our product candidates, potential marketing approval or commercialization of our product candidates could be delayed or prevented.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent marketing approval of our product candidates, including:

- clinical trials of our product candidates may produce unfavorable or inconclusive results;

- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;

Table of Contents

- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, patient enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;

- our third-party contractors, including those manufacturing our product candidates or components or ingredients thereof or conducting clinical trials on our behalf, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner or at all;

- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;

- we may experience delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;

- patients who enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with the clinical trial protocol, resulting in the need to withdraw such patients from the clinical trial, increase the needed enrollment size for the clinical trial or extend the clinical trial s duration;

- we may have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of a product candidate;

- regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or their respective standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar drug or drug candidate;

- the FDA or comparable non-U.S. regulatory authorities may disagree with our clinical trial design or our interpretation of data from pre-clinical studies and clinical trials;

- the FDA or comparable non-U.S. regulatory authorities may find regulatory non-compliance with the manufacturing processes or facilities of third-party manufacturers with which we enter into agreements for clinical and commercial supplies;

- the supply or quality of raw materials or manufactured product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply; and

- the approval policies or regulations of the FDA or comparable non-U.S. regulatory authorities may significantly change in a manner rendering our clinical data insufficient to obtain marketing approval.

Product development costs for us will increase if we experience delays in testing or pursuing marketing approvals and we may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of our product candidates. We do not know whether any pre-clinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. For example, although we recently completed a Phase 2 clinical trial for INOpulse for PH-COPD, we are currently evaluating our options for further Phase 2 development in this indication. Significant pre-clinical study or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to

Table of Contents

successfully commercialize our product candidates and may harm our business and results of operations. In addition, many of the factors that cause, or lead to, clinical trial delays may ultimately lead to the denial of marketing approval of any of our product candidates.

If we experience delays or difficulties in the enrollment of patients in clinical trials, we may not achieve our clinical development on our anticipated timeline, or at all, and our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our INOpulse or BCM product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in clinical trials. Patient enrollment is a significant factor in the timing of clinical trials, and is affected by many factors, including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the proximity of patients to clinical sites;
- the eligibility criteria for the trial;
- the design of the clinical trial;
- limitations placed on enrollment by regulatory authorities;
- efforts to facilitate timely enrollment;
- competing clinical trials; and
- clinicians and patients perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new product candidates that may be approved for the indications we are investigating.

For example, we may experience difficulty enrolling our clinical trials, including, but not limited to, any future clinical trials of INOpulse for PAH, which is an orphan disease due to the small number of patients who suffer from PAH, or any future clinical trials of INOpulse for PH-COPD because such trials may require that patients meet the restrictive enrollment criteria, such as having been diagnosed with both COPD and pulmonary hypertension, be undergoing treatment with LTOT and not having significant left ventricular dysfunction.

In addition, with respect to our PRESERVATION I trial, the FDA has limited us to enrolling a maximum of 60 patients in the United States. This limitation is due to the novelty of BCM and the lack of prior data on the administration to human patients of four milliliters of BCM that we are using in the trial because we did not conduct a pilot study of BCM with this dose. We will need to obtain the FDA s approval of any expansion of this U.S. enrollment cap, and such approval would likely be based on our submission of data to the FDA supporting the safety of four milliliters of BCM in human patients, if any. The Israeli Ministry of Health is also requiring that we submit to it additional safety data once 70 patients are enrolled in Israel.

Our inability to enroll a sufficient number of patients for our clinical trials could result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, delay or halt the development of and approval processes for our product candidates and jeopardize our ability to achieve our clinical development timeline and goals, including the dates by which we will commence, complete and receive results from clinical trials. Enrollment delays may also delay or jeopardize our ability to commence sales and generate revenues from our product candidates. Any of the foregoing could cause the value of our company to decline and limit our ability to obtain additional financing, if needed.

Table of Contents

We may not obtain orphan drug exclusivity, or we may not receive the full benefit of orphan drug exclusivity even if we obtain such exclusivity.

Regulatory authorities in some jurisdictions, including the United States and European Union, may designate drugs and biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States who have been diagnosed as having the disease or condition at the time of the submission of the request for orphan drug designation. The FDA has granted orphan drug designation to our nitric oxide program for the treatment of PAH. Accordingly, the first company to receive FDA approval for nitric oxide for the treatment of PAH will obtain seven years of marketing exclusivity, during which time the FDA may not approve another product containing nitric oxide as its active ingredient for the treatment of PAH, unless such product is shown to be clinically superior.

Even though we have obtained orphan drug designation for our nitric oxide program to treat PAH, and even if we obtain orphan drug designation for our product candidates in other indications or for our future product candidates, due to the uncertainties associated with developing pharmaceutical products, we may not be the first to obtain marketing approval for any particular orphan indication, or we may not obtain approval for an indication for which we have obtained orphan drug designation. Further, even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not protect the product effectively from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug, nor gives the drug any advantage in the regulatory review or approval process. Orphan drug exclusivity may be lost if the FDA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Serious adverse events or undesirable side effects or other unexpected properties of our product candidates may be identified during development that could delay or prevent the product candidate s marketing approval.

Serious adverse events or undesirable side effects caused by, or other unexpected properties of, our product candidates could cause us, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of one or more of our product candidates and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable non-U.S. regulatory authorities. If any of our product candidates is associated with serious adverse events or undesirable side effects or has properties that are unexpected, we may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many drugs or devices that initially showed promise in clinical or earlier stage testing have later been found to cause undesirable or unexpected side effects that prevented further development of the drug or device.

For example, in our recently completed Phase 2 clinical trial for INOpulse for PAH, serious adverse events were reported for four patients in the 25 mcg/kg ideal body weight/hour, or mcg, low-dose active treatment arm, including bacteremia, myelodysplastic syndrome, increased shortness of breath and dyspnea, one of which was assessed as possibly related to trial therapy. In the 75 mcg high-dose active treatment arm, nine patients had serious adverse events. The most common serious adverse events reported were syncope and bronchitis/tracheobronchitis, one of which was assessed as possibly related to trial therapy. Discontinuation of trial therapy due to adverse events occurred for two patients in the 75 mcg arm and one subject in the 25 mcg arm. Additional or more serious adverse events, undesirable side effects or other unexpected properties of INOpulse for PAH or our other product candidates could arise or become known either during further clinical development. If such an event occurs during development, clinical trials for our product candidates could be

Table of Contents

suspended or terminated and the FDA or comparable foreign regulatory authorities could order us or our collaborators to cease further development, require us to conduct additional clinical trials or other tests or studies or deny approval of the applicable product candidate. Further, pending discussions with regulatory authorities, we may be required to conduct a drug-drug interaction study of INOpulse for PH-COPD. We expect the FDA to require us primarily to study interactions with long-acting beta agonists, which is the only class of COPD drug that has been identified as having potential adverse cardiac side effects, to confirm that pulsed inhaled nitric oxide does not increase systemic bio-availability of inhaled beta agonists. If the results of such a study indicate increased bioavailability that we are not able to address to the satisfaction of the FDA, marketing approval of INOpulse for PH-COPD, if any, may be limited to patients who do not use long-acting beta agonists.

Additionally, INOpulse is an extension of the technology that is used in hospitals to deliver inhaled nitric oxide to neonates with a form of pulmonary hypertension called persistent pulmonary hypertension of the newborn. Persistent pulmonary hypertension is an FDA-approved use of inhaled nitric oxide, which is currently marketed by Ikaria as INOmax. Because INOpulse draws on the established efficacy and safety of INOmax, if any serious adverse events or undesirable side effects or other unexpected properties of INOmax or other inhaled nitric oxide delivery systems developed by Ikaria are identified, INOpulse may be adversely affected and we may be required to interrupt, delay or halt our INOpulse clinical trials.

We may not be successful in our efforts to identify or discover additional potential product candidates.

A significant portion of the research that we are conducting involves the development of innovative approaches to the pulsed delivery of nitric oxide. Our drug-device discovery efforts may not be successful in creating drugs or devices that have commercial value or therapeutic utility. Our research programs may initially show promise in creating potential product candidates, yet fail to yield viable product candidates for clinical development for a number of reasons, including that potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be product candidates that will receive marketing approval and achieve market acceptance. Currently, we are dependent on Ikaria for our business development functions pursuant to the TSA and lack the capability to bring such functions in-house. Accordingly, if Ikaria does not perform such business development functions effectively, our business and prospects may be materially and adversely affected.

Our research programs to identify new product candidates will require substantial technical, financial and human resources. We may be unsuccessful in our efforts to identify new potential product candidates. In addition, we may focus our efforts and resources on one or more potential product candidates that ultimately prove to be unsuccessful.

Pursuant to the terms of our license agreement with Ikaria, we only have the right to develop and commercialize pulsed nitric oxide in PAH, PH-COPD and PH-IPF; Ikaria retains the right to develop and commercialize inhaled nitric oxide products, including pulsed products, in all other indications. Additionally, we are limited in the scope of potential product candidates that we can identify or discover due to non-competition agreements that we entered into with Ikaria. Pursuant to these agreements, we and each of our subsidiaries agreed not to engage, anywhere in the world, in any manner, directly or indirectly, until the earlier of five years after the effective date of such non-competition agreement or the date on which Ikaria and all of its subsidiaries are no longer engaged in such business, in:

- the development, manufacture, commercialization, promotion, sale, import, export, servicing, repair, training, storage, distribution, transportation, licensing, or other handling or disposition of any product or service (including, without limitation, any product or service that utilizes, contains or includes nitric oxide for inhalation, a device intended to deliver nitric oxide or a service that delivers or supports the delivery of nitric oxide), bundled or unbundled, for or used in connection with (a) the diagnosis, prevention or treatment, in both adult and/or pediatric

populations, and whether in- or out-patient, of: (i) hypoxic respiratory failure associated with pulmonary hypertension,

Table of Contents

(ii) pulmonary hypertensive episodes and right heart failure associated with cardiovascular surgery, (iii) bronchopulmonary dysplasia, (iv) the management of ventilation-perfusion mismatch in acute lung injury, (v) the management of ventilation-perfusion mismatch in acute respiratory distress syndrome, (vi) the management of pulmonary hypertension episodes and right heart failure in congestive heart failure, (vii) pulmonary edema from high altitude sickness, (viii) the management of pulmonary hypertension episodes and right heart failure in pulmonary or cardiac surgery, (ix) the management of pulmonary hypertension episodes and right heart failure in organ transplant, (x) sickle cell vaso-occlusive crisis, (xi) hypoxia associated with pneumonia or (xii) ischemia-reperfusion injury or (b) the use of nitric oxide to treat or prevent conditions that are primarily managed in the hospital; or

- any and all development, manufacture, commercialization, promotion, sale, import, export, storage, distribution, transportation, licensing, or other handling or disposition of any terlipressin or any other product within the pressin family, (a) intended to treat (i) hepatorenal syndrome in any form, (ii) bleeding esophageal varices or (iii) septic shock or (b) for or in connection with the management of low blood pressure.

In the event that we or one of our subsidiaries materially breach the provisions of the non-competition agreements and do not cure such breach within 30 days after receiving written notice thereof from Ikaria, Ikaria will have the right to terminate the license agreement.

If we are unable to identify suitable additional compounds for pre-clinical and clinical development, or at all, our ability to develop product candidates and obtain product revenues in future periods could be compromised, which could result in significant harm to our financial position and adversely impact our stock price.

If any of our product candidates receives marketing approval and we, or others, later discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, our ability to market the product could be compromised.

Clinical trials of our product candidates are conducted in carefully defined subsets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the drug is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following undesirable events could occur:

- regulatory authorities may withdraw their approval of the product or seize the product;

- we may be required to recall the product or change the way the product is administered;

- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;

- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;

- regulatory authorities may require the addition of labeling statements, such as a black box warning or a contraindication;

- we may be required to create a handout, sometimes referred to as a Medication Guide, outlining the risks of the previously unidentified side effects for distribution to patients;

- we could be sued and held liable for harm caused to patients;

Table of Contents

- the product may become less competitive; and

- our reputation may suffer.

Any of these events could have a material and adverse effect on our operations and business and could adversely impact our stock price.

Even if one of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success, and the market opportunity for the product candidate may be smaller than we estimate.

We have never commercialized a product. Even if one of our product candidates is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. For example, physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Further, patients often acclimate to the therapy that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch therapies due to lack of reimbursement for existing therapies.

Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If any of our product candidates is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of, and potential market opportunity for, our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and safety of the product;

- the potential advantages of the product compared to alternative treatments;

- the prevalence and severity of any side effects;

- the clinical indications for which the product is approved;

- whether the product is designated under physician treatment guidelines as a first-line therapy or as a second- or third-line therapy;
- limitations or warnings, including distribution or use restrictions, contained in the product s approved labeling;
- our ability to offer the product for sale at competitive prices;
- our ability to establish and maintain pricing sufficient to realize a meaningful return on our investment;
- our ability to prevent use of our INOpulse for PH-COPD device by PAH patients due to expected pricing differences;
- the product s convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try, and of physicians to prescribe, the product;
- the strength of sales, marketing and distribution support;

Table of Contents

- the approval of other new products for the same indications;
- changes in the standard of care for the targeted indications for the product;
- the timing of market introduction of our approved products as well as competitive products and other therapies;
- availability and amount of reimbursement from government payors, managed care plans and other third-party payors;
- adverse publicity about the product or favorable publicity about competitive products; and
- potential product liability claims.

The potential market opportunities for our product candidates are difficult to estimate precisely. Our estimates of the potential market opportunities, including our estimates with respect to pricing and reimbursement, are predicated on many assumptions, including industry knowledge and publications, third-party research reports and other surveys. While we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management, are inherently uncertain and the reasonableness of these assumptions has not been assessed by an independent source. If any of the assumptions proves to be inaccurate, the actual markets for our product candidates could be smaller than our estimates of the potential market opportunities.

If we are unable to establish sales, marketing and distribution capabilities or enter into acceptable sales, marketing and distribution arrangements with third parties, we may not be successful in commercializing any product candidates that we develop, if and when those product candidates are approved.

We do not have a sales, marketing or distribution infrastructure and have limited experience in the sale, marketing and distribution of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. We expect to build a commercial infrastructure to allow us to market and sell certain of our product candidates when approved, if any, using a specialty sales force in the United States, and we may choose to establish commercialization capabilities in select countries outside the United States. The development of sales, marketing and distribution capabilities will require substantial resources, will be time-consuming and could delay any product launch. We expect that we will commence the development of these capabilities prior to receiving approval of any of our product candidates. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing and distribution capabilities is delayed or does not occur for any reason, we could have prematurely or unnecessarily incurred these commercialization costs. Such a delay may be costly, and our investment could be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire or retain a sales force in the United States that is sufficient in size or has adequate expertise in the medical markets that we plan to target. If we are unable to establish or retain a sales force and marketing and distribution capabilities, our operating results may be adversely affected. If a potential partner has development or commercialization expertise that we believe is particularly relevant to one of our product candidates, then we may seek to collaborate with that potential partner

even if we believe we could otherwise develop and commercialize the product independently.

We may partner with third parties to commercialize our product candidates in certain countries outside the United States. As a result of entering into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues may be lower, perhaps substantially lower, than if we were to directly market and sell products in those markets. Furthermore, we may be unsuccessful in entering into the necessary arrangements with third parties or may be unable to do so on terms that are favorable to us. In addition, we may have little or no control over such third parties, and any of

Table of Contents

them may fail to devote the necessary resources and attention to sell and market our product candidates effectively.

If we do not establish sales and marketing capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing any of our product candidates that receive marketing approval.

Even if we are able to commercialize any product candidate that we develop, the product may become subject to unfavorable pricing regulations, third-party payor reimbursement practices or healthcare reform initiatives that could harm our business.

The commercial success of our product candidates will depend substantially, both in the United States and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish and maintain pricing sufficient to realize a meaningful return on our investment.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs and devices. Marketing approvals, pricing and reimbursement for new drug and device products vary widely from country to country. Some countries require approval of the sale price of a drug or device before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some non-U.S. markets, pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

Table of Contents

Our ability to commercialize our product candidates will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability to sell our product candidates profitably. These payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us to decrease the price we might establish for products, which could result in lower than anticipated product revenues. If the prices for our products, if any, decrease or if governmental and other third-party payors do not provide adequate coverage or reimbursement, our prospects for revenue and profitability will suffer. Approval of a product does not guarantee sufficient reimbursement to commercialize. For example, assuming positive results, approval of CE marking for BCM in the European Union may be achieved with our ongoing clinical trial but, based on current reimbursement practices in the European Union, this data may not be sufficient to gain sufficient reimbursement for us to invest in commercialization activities.

There may also be delays in obtaining coverage and reimbursement for newly approved products, and coverage may be more limited than the indications for which the product is approved by the FDA or comparable non-U.S. regulatory authorities. Moreover, eligibility for reimbursement does not imply that any product will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, by way of example, according to the use of the product and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost products or may be incorporated into existing payments for other services.

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. We cannot be sure that coverage will be available for any product candidate that we commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any our product candidates for which we obtain marketing approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

We anticipate that reimbursement of BCM will be based on the patient s diagnosis related group, or DRG, for patients who are covered by Medicare or Medicaid, or through similar reimbursement programs for patients to who are covered by private third-party payors. Within the DRG system, patients are classified by similar diagnoses, which are mapped from the International Statistical Classification of Diseases and Related Health Problems, or ICD, a medical classification list provided by the World Health Organization. The version of ICD that is currently in use with respect to DRG classifications is ICD-9. However, an updated version, ICD-10, has been adopted. We expect that DRG classifications will be required to be mapped against ICD-10 by October 2015 and, as a result, we believe that the DRG classifications will be mapped from ICD-10 rather than ICD-9 at the time we commercialize BCM, if ever, which would result in favorable reimbursement. However, if ICD-9 continues to be used for DRG classification mapping by hospitals or Medicare or Medicaid or other payors, or our expectations with respect to the applicable DRG classification prove incorrect, reimbursement for BCM may prove less favorable or inadequate. In addition, even if ICD-10 is adopted for reimbursement assessments, the mapping to the DRGs, or the amount reimbursed for the DRGs, may change, all of which could adversely affect the ability of our customers to gain sufficient reimbursement, and therefore, the adoption of, or price we could charge for, BCM.

Table of Contents

If the FDA or comparable non-U.S. regulatory authorities approve generic versions of any of our products that receive marketing approval, or such authorities do not grant our products appropriate periods of data exclusivity before approving generic versions of our products, the sales of our products could be adversely affected.

Once an NDA is approved, the product covered thereby becomes a reference listed drug in the FDA s publication, Approved Drug Products with Therapeutic Equivalence Evaluations. Manufacturers may seek approval of generic versions of reference listed drugs through submission of ANDAs in the United States, or through a similar process in foreign jurisdictions. In support of an ANDA, a generic manufacturer need not conduct clinical studies. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labeling as the reference listed drug and that the generic version is bioequivalent to the reference listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference listed drug may be typically lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference listed drug has expired. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product.

Competition that our products may face from generic versions of our products could materially and adversely impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on the investments we have made in those product candidates.

Product liability lawsuits against us could divert our resources, cause us to incur substantial liabilities and limit commercialization of any products that we may develop.

We face an inherent risk of product liability claims as a result of the clinical testing of our product candidates despite obtaining appropriate informed consents from our clinical trial participants. We will face an even greater risk if we commercially sell any product that we may develop. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. For example:

- improper use or failure of INOpulse may result in rebound pulmonary hypertension, which can be fatal in some patients;

- rebound pulmonary hypertension may also occur if both the primary and back-up devices fail before we can replace them, if the built-in back-up with a device does not work properly or if the patient does not carry or have access to his or her back-up device; and

- rebound pulmonary hypertension can also occur in patients who were not previously considered at risk for this reaction and who may not have been provided an adequate back-up device.

Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for products that we may develop;

Table of Contents

- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend resulting litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

Although we maintain general liability insurance of $1.0 million in the aggregate, umbrella insurance in the amount of $10.0 million in the aggregate and clinical trial liability insurance of $20.0 million in the aggregate, this insurance may not fully cover potential liabilities that we may incur. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if and when we begin the commercial sale of any product candidate that receives marketing approval. In addition, insurance coverage is becoming increasingly expensive. If we are unable to obtain or maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could adversely affect our business, financial condition, results of operations and prospects.

Our INOpulse devices use lithium-ion battery cells, which have been observed to catch fire or vent smoke and flame, and these events may raise concerns about the batteries we use.

The battery pack used in our INOpulse devices makes use of lithium-ion cells. On rare occasions, lithium-ion cells can rapidly release the energy they contain by venting smoke and flames in a manner that can ignite nearby materials. Highly publicized incidents of laptop computers and cell phones bursting into flames have focused consumer attention on the safety of these cells. There can be no assurance that the battery packs we use would not fail, which could lead to property damage, personal injury or death, and may subject us to lawsuits. We may also have to recall our products, if any, which would be time consuming and expensive. Also, negative perceptions in the healthcare and patient communities regarding the suitability of lithium-ion cells for medical applications or any future incident involving lithium-ion cells could seriously harm our business, even in the absence of an incident involving us.

Risks Related to Our Dependence on Third Parties

The intellectual property underlying INOpulse is exclusively licensed from Ikaria. If Ikaria terminates the license agreement, or fails to prosecute, maintain or enforce the underlying patents, our business will be materially harmed.

We have licensed the intellectual property underlying INOpulse from Ikaria. Despite our best efforts, Ikaria may conclude that we have breached a material term of the license agreement and, as a result, seek to terminate the agreement. In the event the license agreement is terminated, we will lose our ability to market INOpulse, and, upon Ikaria s written request, we will be required to transfer any regulatory approvals that we have obtained for INOpulse to Ikaria.

The license agreement prohibits us from sublicensing to any competitor of Ikaria any intellectual property licensed to us by Ikaria. In addition, we are required to ensure that all of our products, if any, are used solely for the chronic treatment of PAH, PH-COPD and PH-IPF and to enter into written agreements with any

Table of Contents

customers that contain restrictions on the use of our products and termination rights in the event such restrictions are violated.

Ikaria has the initial right, but not the obligation, to prosecute and maintain all patents that are licensed to us pursuant to the license agreement. While we have certain step-in rights to assume control if Ikaria declines to file, prosecute or maintain certain licensed patents that are core to our business, in the event Ikaria reasonably determines that our actions could materially impair its business operations or intellectual property rights, Ikaria may prohibit us from taking such actions. In addition, Ikaria has the initial right, but not the obligation, to initiate a legal action against a third party with respect to any actual or suspected infringement of patent rights licensed to us pursuant to the license agreement. We have the right to initiate legal action against a third-party infringer of licensed patents that are core to our business in the event Ikaria declines to take action with respect to such infringement, however, if Ikaria determines that our pursuit of any such action could materially impair its business operations or intellectual property rights, Ikaria may prohibit us from taking any such action.

The license agreement terminates, on an INOpulse product-by-INOpulse product basis, at such time as we are no longer actively and continuously engaged in the development or commercialization of such product. In addition, Ikaria may terminate the license agreement if, among other things, (1) we breach or fail to comply with any material term or condition required to be performed or complied with by us and do not cure such breach or failure within 30 days after receiving written notice of such breach from Ikaria, (2) we or any of our affiliates breaches any of our agreements not to compete with Ikaria, (3) we or any of our affiliates challenges the validity or enforceability of the licensed patents or (4) we or any person that is a successor to our license rights markets a generic nitric oxide product that is competitive with Ikaria s INOmax product. Upon termination of the license agreement with respect to any INOpulse product candidate, we will lose our ability to market such INOpulse product candidate, and upon, Ikaria s written request, be required to transfer any and all regulatory approvals relating to such INOpulse product candidate to Ikaria.

On March 5, 2015, Mallinckrodt and Ikaria announced that the two companies had entered into a definitive agreement under which a subsidiary of Mallinckrodt will acquire Ikaria and that they expect the acquisition will be completed in the second calendar quarter of 2015. While the license agreement imposes binding obligations on Ikaria to perform in accordance with the license agreement s terms, it is possible that following completion of the sale, as the new owner s influence on Ikaria s operations increases, Ikaria may perform differently under the license agreement than it has to date. Moreover, to the extent that we desire to expand the scope of the license agreement, it is possible that Ikaria will not be willing to do so on reasonable terms, or at all. In any of these circumstances, our business, product development and financial statements could be materially adversely affected.

We rely, and expect to continue to rely, on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We currently rely on third-party clinical research organizations, or CROs, to conduct our clinical trials. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. Our agreements with these third parties generally allow the third party to terminate the agreement at any time. If we are required to enter into alternative arrangements because of any such termination, the introduction of our product candidates to market could be delayed.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we design our clinical trials and will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with GCPs for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Our reliance on third parties that we do not control does not relieve us of

these responsibilities and requirements. We

Table of Contents

also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

We also expect to rely on other third parties to store and distribute drug and device supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We rely on Ikaria for our supply of nitric oxide for the clinical trials of INOpulse. Ikaria is the sole supplier of nitric oxide. Ikaria s inability to continue manufacturing adequate supplies of nitric oxide, or its refusal to supply us with commercial quantities of nitric oxide on commercially reasonable terms, or at all, could result in a disruption in the supply of, or impair our ability to market, INOpulse.

We have entered into a drug clinical supply agreement with Ikaria, pursuant to which Ikaria will manufacture and supply our requirements for nitric oxide for inhalation and corresponding placebo for use in clinical trials of INOpulse. Ikaria manufactures pharmaceutical-grade nitric oxide at its facility in Port Allen, Louisiana, which is the only FDA-inspected site for manufacturing pharmaceutical-grade nitric oxide in the world. Ikaria s Port Allen facility is subject to the risks of a natural disaster or other business disruption. We maintain under controlled storage conditions a two- to three-month supply of clinical trial drug product, but there can be no assurance that we would be able to meet our requirements for INOpulse if there were a catastrophic event or failure of Ikaria s manufacturing system. Because Ikaria s Port Allen facility is the only FDA-inspected site that can manufacture INOpulse and because the manufacture of a pharmaceutical gas requires specialized equipment and expertise, there are few, if any, third-party manufacturers to which we could contract this work in a short period of time. Therefore, any disruption in Ikaria s Port Allen facility, or the failure by Ikaria for any other reason to provide us with nitric oxide, could materially and adversely affect supplies of INOpulse and our ongoing and planned clinical trials. In addition, we do not currently have any arrangements with Ikaria to provide us with commercial quantities of nitric oxide. If we are unable to arrange for Ikaria to provide such quantities on commercially reasonable terms, or at all, we may not be able to successfully produce and market INOpulse or may be delayed in doing so.

On March 5, 2015, Mallinckrodt and Ikaria announced that the two companies had entered into a definitive agreement under which a subsidiary of Mallinckrodt will acquire Ikaria and that they expect the acquisition will be completed in the second calendar quarter of 2015. While the drug clinical supply agreement imposes binding obligations on Ikaria to perform in accordance with the agreement s terms, it is possible that following completion of the sale, as the new owner s influence on Ikaria s operations increases, Ikaria may not continue to provide the same level of performance under the drug clinical supply agreement as Ikaria has provided to date. Moreover, to the extent that we desire to expand the scope of the drug clinical supply agreement (to cover commercial quantities of nitric oxide or otherwise), it is also possible that Ikaria will not be willing to do so on reasonable terms, or at all. In any of these circumstances, our business, product development and financial statements could be materially adversely affected.

Table of Contents

We rely on third-party suppliers and manufacturers to produce and deliver clinical devices and supplies as well as for the servicing of these devices for our INOpulse product candidate, and may also do so for other product candidates. Any failure by a third-party supplier or manufacturer to produce or deliver supplies for us or to provide necessary servicing may delay or impair our ability to complete our clinical trials.

We currently rely, and expect to continue to rely, on third parties for supply of the device, cannula and certain other supplies for our INOpulse product candidate. These suppliers are, and any future third-party suppliers with whom we enter into agreements may be, our sole suppliers of these devices or any of our other current or future devices used in the INOpulse program. These suppliers are commonly referred to as single-source suppliers. In addition, in February 2015, we entered into an agreement with Flextronics to manufacture and service the Mark2 devices needed for our clinical trials planned in the second half of 2015. If our suppliers fail to deliver materials and provide services needed for the production of the INOpulse device and related supplies or for our other product candidates in a timely and sufficient manner, if they fail to comply with applicable regulations, or if we do not qualify alternate suppliers, clinical development or regulatory approval of our product candidates or commercialization of our products could be delayed, increasing our costs to complete clinical development and to obtain regulatory approval, which could deprive us of potential additional product revenue.

We rely on third-party suppliers and manufacturers to produce and deliver clinical drug supplies for our BCM product candidate and may also do so for other product candidates. Any failure by a third-party supplier or manufacturer to produce or deliver supplies for us may delay or impair our ability to complete our clinical trials.

We currently rely, and expect to continue to rely, on third parties for supply of the ingredients for our BCM product candidate. These suppliers are, and any future third-party suppliers with whom we enter into agreements may be, our sole suppliers of BCM or any of our other current or future product candidates. These suppliers are commonly referred to as single-source suppliers. If our suppliers fail to deliver materials and provide services needed for the production of BCM or our other product candidates in a timely and sufficient manner, if they fail to comply with applicable regulations, or if we do not qualify alternate suppliers, clinical development or regulatory approval of our product candidates or commercialization of our products could be delayed, increasing our costs to complete clinical development and to obtain regulatory approval, which could deprive us of potential additional product revenue.

In addition, we currently outsource the manufacture of BCM for use in clinical trials pursuant to the terms of a manufacturing and supply agreement with a third-party which expires in April 2017. We plan to enter into a manufacturing and supply agreement for BCM with a new third-party manufacturer prior to April 2017. If we fail to enter into a new manufacturing and supply agreement for BCM with a third-party prior to the expiration of our existing manufacturing and supply agreement or if such new agreement is on less favorable terms, our ability to complete our clinical trials for BCM may be impaired.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured product candidates ourselves, including reliance on the third party for regulatory compliance and quality assurance, the possibility of breach of the manufacturing agreement by the third party because of factors beyond our control (including a failure to synthesize and manufacture our product candidates in accordance with our product specifications) and the possibility of termination or nonrenewal of the agreement by the third party, based on its own business priorities, at a time that is costly or damaging to us. In addition, the FDA and other regulatory authorities require that our product candidates be manufactured according to cGMP and similar foreign standards. Any failure by our third-party manufacturers to comply with cGMP or failure to scale up manufacturing processes, including any failure to deliver sufficient quantities of product candidates in a timely manner, could lead to a delay in, or failure to obtain, regulatory approval of any of our product candidates. In addition, such failure could be the basis for action by the FDA or other regulatory authorities to withdraw approvals for product candidates previously granted to us and for other regulatory action, including recall or seizure, fines, imposition of operating restrictions, total or partial suspension of production or injunctions.

Table of Contents

We rely on our manufacturers to purchase the materials necessary to produce our product candidates for our clinical trials from third-party suppliers. There are a small number of suppliers for certain capital equipment and raw materials that are used to manufacture our product candidates. Such suppliers may not sell these raw materials to our manufacturers at the times we need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of these raw materials by our manufacturers. Any significant delay in the supply of a product candidate or the raw material components thereof for an ongoing clinical trial due to the need to replace a third-party manufacturer could considerably delay completion or increase the costs of our clinical trials, product testing and potential regulatory approval of our product candidates. If our manufacturers or we are unable to purchase these raw materials after regulatory approval has been obtained for our product candidates, the commercial launch of our product candidates would be delayed or there would be a shortage in supply, which would impair our ability to generate revenues from the sale of our product candidates.

We intend to rely on third parties to produce commercial supplies of any approved product candidates. Any failure by a third-party supplier or manufacturer to produce or deliver supplies for us may delay or impair our ability to commercialize our product candidates.

To date, our product candidates have been manufactured in small quantities for pre-clinical studies and clinical trials. If one or more of our product candidates are approved by the FDA or comparable regulatory authorities in other countries for commercial sale, we will need to manufacture such product candidate in larger quantities. We do not currently have any arrangements with Ikaria or another third-party manufacturer to provide commercial quantities of our product candidates. If we are unable to arrange for such a third-party manufacturing source, or fail to do so on commercially reasonable terms, we may not be able to successfully produce and market our product candidates or may be delayed in doing so.

If we successfully commercialize any of our product candidates, we may be required to establish or access large-scale commercial manufacturing capabilities. We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates, and we currently have no plans to build our own clinical or commercial scale manufacturing capabilities.

Our BCM product candidate currently in development is exclusively licensed from BioLineRx Ltd., and we may enter into additional agreements to in-license technology from third parties. If BioLineRx Ltd. or other future licensors terminate the applicable license, or fail to maintain or enforce the underlying patents, our competitive position and market share will be harmed.

We have an exclusive worldwide license for our BCM product candidate, subject to certain retained rights of the licensor, from BioLine. Under the terms of the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize at least one product containing BCM. BioLine has the right to terminate its license agreement with us for an uncured material breach by us, upon which our exclusive license for BCM will terminate.

We have also exclusively licensed INOpulse, for certain indications and settings, and subject to certain retained rights of the licensor, from Ikaria. See Certain Relationships and Related Person Transactions Relationship with Ikaria for a summary of our exclusive cross-license, technology transfer and regulatory matters agreement with Ikaria.

We may enter into additional license agreements as part of the development of our business in the future. Such licensors, if any, may be responsible for prosecution of certain patent applications and maintenance of certain patents. Such licensors may not successfully prosecute such

patent applications or maintain such patents, which we have licensed and on which our business depends. Our licensors may fail to pursue litigation against third-party infringers, may fail to prove infringement, or may fail to defend against counterclaims of patent invalidity or unenforceability. If these in-licenses are terminated, or if the underlying patents fail to provide the intended market exclusivity, competitors would have the freedom to seek regulatory approval of,

Table of Contents

and to market, products identical to ours. This could have a material adverse effect on our competitive business position and our business prospects.

We may have received better terms from unaffiliated third parties than the terms we received in our agreements with Ikaria.

The agreements related to the Spin-Out, including the separation and distribution agreement, TSA, license agreement, drug clinical supply agreement, device clinical supply agreement, agreements not to compete and the other agreements, were negotiated in the context of our separation from Ikaria while we were still part of Ikaria and, accordingly, may not reflect terms that would have resulted from arm s-length negotiations among unaffiliated third parties. The terms of the agreements we negotiated in the context of our separation related to, among other things, allocation of assets, liabilities, rights, indemnifications and other obligations among Ikaria and us. We may have received better terms from third parties because third parties may have competed with each other to win our business. Some of our board members are also members of the Ikaria board. See Certain Relationships and Related Person Transactions Relationship with Ikaria.

Third parties may seek to hold us responsible for liabilities of Ikaria that we did not assume in our agreements.

In connection with our separation from Ikaria, Ikaria has generally agreed to retain all liabilities that did not historically arise from our business. Third parties may seek to hold us responsible for Ikaria s retained liabilities. Under our agreements with Ikaria, Ikaria has agreed to indemnify us for claims and losses relating to these retained liabilities. However, if those liabilities are significant and we are ultimately liable for them, we cannot assure our stockholders that we will be able to recover the full amount of our losses from Ikaria.

Any disputes that arise between us and Ikaria with respect to our past and ongoing relationships could harm our business operations.

Disputes may arise between Ikaria and us in a number of areas relating to our past and ongoing relationships, including:

- intellectual property, technology and business matters, including failure to make required technology transfers and failure to comply with non-compete provisions applicable to Ikaria and us;
- labor, tax, employee benefit, indemnification and other matters arising from our separation from Ikaria;
- distribution and supply obligations;

- employee retention and recruiting;

- business combinations involving us;

- the nature, quality and pricing of transitional services Ikaria has agreed to provide us; and

- business opportunities that may be attractive to both Ikaria and us.

We may not be able to resolve any potential conflicts, and even if we do, the resolution may be less favorable than if we were dealing with an unaffiliated party.

Table of Contents

We may seek to enter into collaborations with third parties for the development and commercialization of our product candidates. If we fail to enter into such collaborations, or such collaborations are not successful, we may not be able to capitalize on the market potential of our product candidates.

We may seek third-party collaborators for development and commercialization of our product candidates. Our likely collaborators for any marketing, distribution, development, licensing or broader collaboration arrangements include large and mid-size pharmaceutical and medical device companies, regional and national biotechnology companies and pharmaceutical companies. We are not currently party to any such arrangement. However, if we do enter into any such arrangements with any third parties in the future, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our collaborators abilities to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our product candidates would pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;

- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;

- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;

- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;

- collaborators with marketing and distribution rights to one or more of our products may not commit sufficient resources to the marketing and distribution of such product or products;

- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;

- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our products or product candidates or that result in costly litigation or arbitration that diverts management attention and resources; and

- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

Table of Contents

If we are not able to establish collaborations, we may have to alter our development and commercialization plans.

Our drug and device development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. For some of our product candidates, we may decide to collaborate with biotechnology and pharmaceutical companies for the development and potential commercialization of those product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator s resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator s evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. The terms of our current or future license agreements may restrict our ability to enter into agreements on certain terms with future collaborators. For example, our license agreement with Ikaria prohibits us from granting a sublicense under any of the intellectual property licensed to us under such license agreement to any of our affiliates or any third party, in each case, that directly or indirectly competes with the Ikaria nitric oxide business, and any future license agreements may contain similar restrictions. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for our technology and products or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and product candidates. The patents we have licensed from Ikaria relating to INOpulse s feature of providing delivery of nitric oxide to ensure a consistent dose over time expire as late as 2027 in the United States and as late as 2026 in certain other countries, as well as a patent with respect to the triple-lumen cannula that allows for safer and more accurate dosing of pulsed inhaled nitric oxide, which expires in 2033. The patents we have licensed from BioLine relating to our BCM product candidate expire as late as 2029 in the United States, with a possible patent term extension to 2032 to 2034, and 2024 in certain other countries.

Table of Contents

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, pursuant to our license agreement with Ikaria, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering the INOpulse technology that we license from Ikaria, except in the event that Ikaria declines to prosecute or maintain certain licensed patents that are core to our business, elects to allow any of such patents to lapse or elects to abandon any such patents, in which case we would have step-in rights to assume control of the prosecution and/or maintenance of such patents, subject to Ikaria s right to prohibit us from taking such actions if it reasonably determines that such actions could materially impair its business, operations or intellectual property rights. Similarly, under the terms of any future agreements that we may enter into with other third parties, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering the technology that is licensed to us under such agreements. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the laws of non-U.S. countries may not protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than U.S. law does. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, and in some cases not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not issue as patents that protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our owned or licensed issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. The Leahy-Smith Act includes provisions that affect the way patent applications are prosecuted and affect patent litigation. The USPTO recently developed new regulations and procedures to govern administration of the Leahy-Smith Act. Many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our owned or licensed patent applications and the enforcement or defense of our owned or licensed issued patents, all of which could have a material adverse effect on our business and financial condition.

Moreover, we may be subject to third-party preissuance submissions of prior art to the USPTO, or become involved in opposition, derivation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging our owned or licensed patent rights or the patent rights of others. For example, Notices of Opposition to two European patents covering BCM that we licensed from BioLine have been filed with the European Patent Office. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection

Table of Contents

provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Even if our owned and licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us, or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner. We may not receive patent term extension under the Hatch-Waxman Act that we expect or our rights during the extension period may be more limited than the full scope of the patent, making it easier for our competitors to develop and market non-infringing technologies or products.

Table of Contents

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate, or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our owned or licensed patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file or participate in infringement claims, which can be expensive and time consuming. Any claims we or our licensors assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours or our licensor is invalid or unenforceable, in whole or in part, construe the patent s claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our owned or licensed patents at risk of being invalidated or interpreted narrowly.

Under the terms of our license agreement with Ikaria, in the event a third party is suspected of infringing any patent rights licensed to us by Ikaria, Ikaria has the initial right, but not the obligation, to initiate a legal action against such third party. In the event that Ikaria declines to take any action with respect to an alleged infringement of certain licensed patents that are core to our business, we have the right, in certain circumstances, to initiate a legal action against such third party, provided that, if Ikaria reasonably determines that our pursuit of any action with respect to infringement of any of such core patents could materially impair Ikaria s business operations or intellectual property rights, Ikaria may require us to not undertake or to cease any such action. Our inability to initiate a legal action against a third party suspected of infringing intellectual property rights important to our business may have a material adverse effect on our competitive business position and our business prospects.

If we fail to comply with our obligations under license agreements, we could lose rights that are important to our business.

We are party to a license agreement with BioLine relating to our BCM product candidate that imposes, and we may enter into additional license agreements that may impose, various diligence, milestone payment, royalty and other obligations on us. Under our existing license agreement with BioLine, we are obligated to pay royalties on the net sales of product candidates or related technologies to the extent they are covered by the agreement. We also have diligence and development obligations under this agreement. Moreover, under our license agreement with Ikaria, we have granted Ikaria a sole and exclusive worldwide license to any intellectual property rights that we control for use in Ikaria s nitric oxide business, are required to ensure that all of our products, if any, are used solely for the chronic treatment of PAH, PH-COPD and PH-IPF and to enter into written agreements with any customers that contain restrictions on the use of our products and termination rights in the event such restrictions are violated, and have agreed to pay 100% of the reasonable and documented costs incurred by Ikaria for the prosecution and maintenance of certain licensed patents that are core to our business and 10% of such costs incurred by Ikaria for all other licensed patents. If we fail to comply with our obligations under current or future license agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product that is covered by the agreement or face other penalties under the agreement. Such an occurrence could materially adversely affect the value of the product candidate being developed under any such agreement.

Table of Contents

For example, BioLine recently indicated to us that it believed that we had breached our license agreement in several ways. We were able to reach agreement with BioLine and resolve the dispute through an amendment to the license agreement that includes a release of claims by BioLine. However, had we not been able to reach resolution and had BioLine brought and prevailed in a lawsuit against us, one of the potential remedies could have been the termination of the license agreement and our consequent loss of rights to BCM. Termination of our license agreement with BioLine, or any future license agreements we may enter into, or reduction or elimination of our rights under such agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the pharmaceutical, biotechnology and medical device industries. We may become party to, or be threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including interference or derivation proceedings before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future.

If we are found to infringe a third party s intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

We may be subject to claims by third parties asserting that we or our employees have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at other pharmaceutical, biotechnology or medical device companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee s former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in timely obtaining such an agreement with each party who in fact develops intellectual property that we regard as our own. Even if timely obtained, such agreements may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, we may lose valuable intellectual property rights or personnel, in addition to paying monetary damages. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

Table of Contents

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for some of our technology and product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. Even if we are successful in prosecuting such claims, any remedy awarded may be insufficient to fully compensate us for the improper disclosure or misappropriation. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

Intellectual property rights do not necessarily address all potential threats to our competitive advantage.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business, or permit us to maintain our competitive advantage. The following examples are illustrative:

- Others may be able to develop and commercialize treatments that are similar to our product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed.

- We or our licensors might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed.

- We or our licensors might not have been the first to file patent applications covering certain of our inventions.

- Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.

Table of Contents

- It is possible that our pending patent applications will not lead to issued patents.

- Issued patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors.

- Our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets.

- We may not develop additional proprietary technologies that are patentable.

- The patents of others may have an adverse effect on our business.

- Another party may be granted orphan exclusivity for an indication that we are seeking before us or may be granted orphan exclusivity for one of our products for another indication.

Risks Related to Regulatory Approval of Our Product Candidates and Other Legal Compliance Matters

Even if we complete the necessary clinical trials, the marketing approval process is expensive, time consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and similar regulatory authorities outside the United States. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. Our product candidates are in the early stages of development and are subject to the risks of failure inherent in drug and device development. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in conducting and managing the clinical trials, and in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process. Securing marketing approval requires the submission of extensive pre-clinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate s safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional pre-clinical, clinical or other studies. In addition, varying interpretations of the data obtained from pre-clinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable. If we experience delays

Table of Contents

in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

Our failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad, and any approval we are granted for our product candidates in the United States would not assure approval of product candidates in foreign jurisdictions.

In order to market and sell our products in the European Union and many other jurisdictions, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

Even if we obtain marketing approval for our product candidates, the terms of approvals and ongoing regulation of our products may limit how we manufacture and market our products and compliance with such requirements may involve substantial resources, which could materially impair our ability to generate revenue.

Even if marketing approval of a product candidate is granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation, including the requirement to implement a risk evaluation and mitigation strategy or to conduct costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. We must also comply with requirements concerning advertising and promotion for any of our product candidates for which we obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product s approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved. In addition, manufacturers of approved products and those manufacturers facilities are required to ensure that quality control and manufacturing procedures conform to cGMP, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We and our contract manufacturers could be subject to periodic unannounced inspections by the FDA and other regulatory authorities to monitor and ensure compliance with cGMP.

Accordingly, assuming we receive marketing approval for one or more of our product candidates, we and our contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we are not able to comply with post-approval regulatory requirements, we could have the marketing approvals for our products withdrawn by regulatory authorities and our ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Thus, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Table of Contents

Any product candidate for which we obtain marketing approval will be subject to strict enforcement of post-marketing requirements and we could be subject to substantial penalties, including withdrawal of our product from the market, if we fail to comply with all regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include, but are not limited to, restrictions governing promotion of an approved product, submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping.

The FDA and other federal and state agencies, including the Department of Justice, closely regulate compliance with all requirements governing prescription drug and device products, including requirements pertaining to marketing and promotion of drugs and devices in accordance with the provisions of the approved labeling and manufacturing of products in accordance with cGMP requirements. Violations of such requirements may lead to investigations alleging violations of the Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act and other federal and state health care fraud and abuse laws as well as state consumer protection laws. Our failure to comply with all regulatory requirements, and later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, may yield various results, including:

- litigation involving patients taking our products;
- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- untitled or warning letters;
- withdrawal of the products from the market;

- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of our products;
- product seizure; or

Table of Contents

- injunctions or the imposition of civil or criminal penalties.

Non-compliance by us or any future collaborator with regulatory requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with regulatory requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

Our relationships with customers and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;

- the federal False Claims Act imposes criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented false or fraudulent claims for payment by a federal government program, or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

- the federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA, requires applicable manufacturers of covered drugs, devices, biologics and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests; and

Table of Contents

- analogous state laws and regulations such as state anti-kickback and false claims laws and analogous non-U.S. fraud and abuse laws and regulations, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and non-U.S. laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain product candidates and products outside of the United States and require us to develop and implement costly compliance programs.

If we expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The Foreign Corrupt Practices Act, or the FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of such third party in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the company, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the medical device industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing or selling certain product candidates and products outside of the United States, which could limit our growth potential and increase our development costs.

93

Table of Contents

The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The Securities and Exchange Commission, or the SEC, also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA s accounting provisions.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

Currently, we do not operate any research and development or production facilities, including laboratory, development or manufacturing facilities. However, if we decided to operate our own research and development and production facilities, we would be subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Such operations may involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and wastes, we would not be able to eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use or disposal of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we would increase our level of workers compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not expect to maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our possible future storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Table of Contents

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are dependent on the scientific, business development and clinical expertise of our management team, including Jonathan Peacock, our chief executive officer, Manesh Naidu, our chief business officer, Reinilde Heyrman, our chief clinical development officer, and Martin Meglasson, our chief scientific officer. We recently hired our chief executive officer. Leadership transitions can be inherently difficult to manage and may cause some disruptions in our business.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. Any of our employees may terminate their employment with us at any time. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. We do not maintain key person insurance for any of our executives or other employees. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical, biotechnology and medical device companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, to provide accurate information to the FDA, to comply with federal and state healthcare fraud and abuse laws and regulations, to report financial information or data accurately, to disclose unauthorized activities to us or to comply with our code of business conduct and ethics. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, false claims, inappropriate promotion, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. The precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

In addition, during the course of our operations, our directors, executives and employees may have access to material, non-public information regarding our business, our results of operations or potential transactions we are considering. We may not be able to prevent a director, executive or employee from violating our insider trading policies and trading in our common stock on the basis of, or while having access to, material, non-public information. If a director, executive or employee was to be investigated, or an action was to be brought against a director, executive

or employee for insider trading, it could have a negative impact on our