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

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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.

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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

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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.

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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.

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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.

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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.

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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

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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

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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

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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.

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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.

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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 d