Bellerophon Therapeutics, Inc.
Form 10-K
March 13, 2017

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, 2016
or
¨ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to
Commission file number 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.)
184 Liberty Corner Road, Suite 302 Warren, New Jersey	07059
(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	The NASDAQ Global Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. ¨ Yes 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. ¨ 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. x Yes ¨ No
Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). x Yes ¨ 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. ¨
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 ¨ (Do not check if a smaller reporting company)	Smaller reporting company x

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

As of June 30, 2016, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $11.9 million, based upon the closing price on the NASDAQ Global Market reported for such date. Shares of common stock held by each officer and director and by each person who 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 2, 2017: 32,039,496

DOCUMENTS INCORPORATED BY REFERENCE

The following documents (or parts thereof) are incorporated by reference into the following parts of this Form 10-K: Certain information required in Part III of this Annual Report on Form 10-K is incorporated from the registrant's Proxy Statement for the Annual Meeting of Stockholders to be held on May 4, 2017.

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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 refe 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 LLC into shares of common stock of Bellerophon Therapeutics, Inc.

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. The words “may,” “will,” “should,” “expects,” “plans,” “anticipates,” “could,” “intends,” “target,” “projects,” “contemplates,” “believes,” “estimates,” “predicts,” “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 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;
- our ability to obtain adequate financing to meet our future operational and capital needs;
- our ability to continue as a going concern within one year beyond the filing of this Annual Report on Form 10-K.
- the timing of and our ability to obtain marketing approval of our product candidates, and the ability of our product candidates to meet existing or future regulatory standards;
- 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 the remaining 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 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.

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 diseases. Our focus is the continued development of our nitric oxide therapy for patients with pulmonary hypertension, or PH, using our proprietary delivery system, INOpulse, with pulmonary arterial hypertension, or PAH, representing the lead indication. Our INOpulse platform is based on our proprietary pulsatile nitric oxide delivery device.

In February 2016, we announced positive data from the final analysis of our Phase 2 long-term extension clinical trial of INOpulse for PAH, which was Part 2 of our Phase 2 clinical trial of INOpulse for PAH. The data indicated a sustainability of benefit to PAH patients who received INOpulse therapy at the 75 mcg/kg of ideal body weight/hour dose for an average of greater than 12 hours per day and were on long-term oxygen therapy, or LTOT. After reaching agreement with the U.S. Food and Drug Administration, or FDA, and the European Medicines Agency, or EMA, on our Phase 3 protocol, we are moving forward with Phase 3 development. In September 2015, the FDA agreed to a Special Protocol Assessment, or SPA, for our Phase 3 PAH program for INOpulse, which will include two confirmatory clinical trials. The first of the two Phase 3 trials, or INOvation-1, has been initiated with the first patient enrolled in June 2016. During January 2017, we received confirmation from the FDA of its acceptance of all modifications proposed by us to our Phase 3 program. Under the newly modified Phase 3 program, the ongoing one-year INOvation-1 study, and a second confirmatory randomized withdrawal study with approximately 40 patients who will be crossing over from the INOvation-1 study, can serve as the two adequate and well-controlled studies to support a New Drug Application,or NDA, submission for INOpulse in PAH subjects on LTOT. Both studies include an interim analysis approximately half-way through each study to assess for efficacy and futility. The interim analysis for the INOvation-1 study also includes a potential sample size reassessment.

We completed a randomized, placebo-controlled, double-blind, dose-confirmation Phase 2 clinical trial of INOpulse for PH-COPD in July 2014. We received results from this trial, and we have initiated further Phase 2 testing. In September 2015, an oral presentation of late-breaking data from a clinical trial sponsored by us was presented at the European Respiratory Society International Congress 2015 in Amsterdam. The data showed that INOpulse improved vasodilation in patients with PH-COPD. In July 2016, the results were published in the International Journal of COPD in an article titled "Pulmonary vascular effects of pulsed inhaled nitric oxide in COPD patients with pulmonary hypertension". Building upon this and other work we have done during recent quarters, we have initiated Phase 2 testing for the use of the INOpulse device for PH-COPD patients to evaluate the potential benefit of chronic use on exercise capacity, and enrolled the first patient in October 2016.

We have begun clinical testing of the INOpulse therapy to treat PH associated with idiopathic pulmonary fibrosis, or PH-IPF, based on feedback from the medical community and the large unmet medical need for this condition. Our first patient was enrolled in our Phase 2 study in the second quarter of 2016. In addition, other opportunities for the application of our INOpulse platform include the following indications: chronic thromboembolic PH, or CTEPH, PH associated with sarcoidosis and PH associated with pulmonary edema from high altitude sickness.

We have devoted all of our resources to our therapeutic discovery and development efforts, including conducting clinical trials for our product candidates, protecting our intellectual property and the general and administrative support of these operations. We have devoted significant time and resources to developing and optimizing INOpulse which operates through the administration of nitric oxide as brief, controlled pulses that are timed to occur at the beginning of a breath.

To date, we have generated no revenue from product sales. We expect that it will be several years before we commercialize a product candidate, if ever.

Our Development Program

The following table summarizes key information about INOpulse and indications for which we have worldwide commercialization rights.

From the inception of our business through December 31, 2016, $243.9 million was invested in our development programs. Prior to our February 2015 initial public offering, or IPO, our sole source of funding was investments in us by our former parent company, Ikaria, Inc. (a subsidiary of Mallinckrodt plc), or Ikaria. As used herein, unless the context otherwise requires, references to "Ikaria" refer to Ikaria, Inc. and its subsidiaries and any successor entity.

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 FDA and certain other regulatory authorities to treat persistent PH of the newborn. Ikaria has marketed continuous-flow inhaled nitric oxide as INOmax for hospital use in this indication since FDA approval in 1999. In October 2013, Ikaria transferred to us exclusive worldwide, royalty-free rights to develop and commercialize pulsed nitric oxide in PAH, PH associated with chronic obstructive pulmonary disease, or PH-COPD, and PH associated with idiopathic pulmonary fibrosis, or PH-IPF. In July 2015, we expanded the scope of our license to allow us to develop our INOpulse program for the treatment of chronic thromboembolic PH, or CTEPH, PH associated with sarcoidosis and PH associated with pulmonary edema from high altitude sickness with a royalty equal to 5% of net sales of any commercial products for these three additional indications. In November 2015, we entered into an amendment to our exclusive cross-license, technology transfer and regulatory matters agreement with Ikaria that included a royalty equal to 3% of net sales of any commercial products for PAH. Our INOpulse program is built on scientific and technical expertise developed for the therapeutic delivery of inhaled nitric oxide. In 2010 and 2012, respectively, Ikaria submitted investigational new drug applications, or INDs, for INOpulse for the treatment of patients with PAH and PH-COPD. PAH is a form of PH that is closely related to persistent PH of the newborn. 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 vessels and results in vascular smooth muscle relaxation, an important factor in regulating blood pressure. Relaxation of the muscles of the blood vessels 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 600,000 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 previous Phase 2 INOpulse clinical trials, we used the first generation INOpulse device, which we refer to as the INOpulse DS device. Beginning with our Phase 3 trial of INOpulse for PAH in 2016, we have begun using our second generation device, which we refer to as the INOpulse device. The INOpulse device has approximately the same dimensions as a paperback book and weighs approximately 2.5 pounds. The INOpulse device has a simple and intuitive user interface and a battery life of approximately 16 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 most patients will use two cartridges a day. The INOpulse device incorporates our proprietary triple-lumen nasal

cannula, safety systems and proprietary software algorithms. The triple-lumen nasal cannula 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 configured to be highly portable and compatible with long-term oxygen therapy, or LTOT, systems via nasal cannula delivery.

The INOpulse device 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 INOpulse device, and several of these patients indicated that the ability to take the INOpulse device outside the home would likely reduce concerns with maintaining compliance. We conducted two studies to assess the environmental and the expiratory concentration of nitrogen dioxide associated with use of the INOpulse delivery system. Both studies found that the nitrogen dioxide levels were below the National Ambient Air Quality Standards.

Our technology is based on patents we have exclusively licensed from Ikaria for the treatment of PAH, PH-COPD, PH-IPF, CTEPH, PH associated with sarcoidosis and PH associated with pulmonary edema from altitude sickness which, collectively, we refer to as the Bellerophon indications. 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 in the United States and abroad. We have also licensed several other patent applications from Ikaria for certain of the innovations included in the INOpulse device and certain of the resulting patents, if issued, would expire as late as 2030 in the United States.

During January 2016, the European Patent Office issued a Notice of Intention to Grant a European Patent that provides protection for our INOpulse program. The patent, entitled "System of Administering a Pharmaceutical Gas to a Patient," covers the ability to provide a known amount of pharmaceutical gas to a patient regardless of the patient inspiration rate or volume and distinguishes the INOpulse® delivery system from others on the market. This patent was granted by the European Patent Office on March 30, 2016, and was subsequently validated in 30 European countries. Also during January 2016, we received European Conformity, or EC, Certification for our proprietary new, INOpulse® drug-device delivery system. This EC Certification grants CE marking on the INOpulse product, which confirms INOpulse compliance with the essential requirements of the relevant European health, safety and environment protection legislation of the European Union. This certification covers the design, development and manufacture of inhaled pulsatile nitric oxide drug delivery systems including our triple-lumen cannula and application software.

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 2011, the FDA 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, except in a limited number of specific situations such as another product being 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 that there are a total of at least 35,000 patients currently diagnosed with and being 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 2014 combined global sales for these therapies were over $4.6 billion with a compounded annual growth rate of approximately 7%. Most PAH patients are treated with multiple medications and many are on supportive therapy. We believe that 40 to 60% of PAH patients are on 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.

We completed a randomized, placebo-controlled, double-blind Phase 2 clinical trial of INOpulse for PAH in October 2014, which was Part 1 of the trial. In February 2016, we announced positive data from the final analysis of Part 2 of our Phase 2 clinical trial of INOpulse for PAH. The data reinforced the results from October 2014 and indicated a sustainability of benefit to PAH patients who received INOpulse therapy at the 75 mcg dose for an average of greater than 12 hours per day and were also treated with LTOT. After reaching agreement with the FDA, and the EMA on our Phase 3 protocol, we are moving forward with Phase 3 development. In September 2015, the FDA agreed to a SPA for our Phase 3 PAH program for INOpulse, which will include two confirmatory clinical trials. The INOvation-1 trial has been initiated with the first patient enrolled in June 2016. During January 2017, we received confirmation from the FDA of its acceptance of all modifications proposed by us to

our Phase 3 program. Under the newly modified Phase 3 program, the ongoing one-year INOvation-1 study, and a second confirmatory randomized withdrawal study with approximately 40 patients who will be crossing over from the INOvation-1 study, can serve as the two adequate and well-controlled studies to support a NDA filing for INOpulse in PAH subjects on LTOT. Both studies include an interim analysis approximately half-way through each study to assess for efficacy and futility. The interim analysis for the INOvation-1 study also includes a potential sample size reassessment.

INOpulse for PH-COPD

We are also developing INOpulse for the treatment of PH-COPD. COPD is a disease characterized by progressive and persistent airflow limitations. Patients with more severe COPD frequently have hypoxemia, or an abnormally low level of oxygen in the blood, and may be treated with LTOT. Despite treatment with oxygen, hypoxemia can progress and contribute to PH. 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 PH. PH-COPD patients have a lower median life expectancy and a higher rate of hospitalization than COPD patients with similar respiratory disease but without PH. Currently, there are no approved therapies for treating PH-COPD, and the only generally accepted treatments are LTOT, pulmonary rehabilitation and lung transplant. The overall COPD market in the United States was estimated to be approximately $32 billion in 2010 with a compounded annual growth rate of approximately 4% (Ford et al., Chest, 2015, Vol 147, pp 31-45).

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, which is a significant concern for these patients. 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. In September 2015, an oral presentation of late-breaking data from a clinical trial sponsored by us was presented at the European Respiratory Society International Congress 2015 in Amsterdam. The data showed that INOpulse improved vasodilation in patients with PH-COPD. In July 2016, the results were published in the International Journal of COPD in an article titled "Pulmonary vascular effects of pulsed inhaled nitric oxide in COPD patients with pulmonary hypertension". Building upon this and other work we have done during recent quarters, we have initiated additional Phase 2 testing for the use of the INOpulse device for PH-COPD patients to evaluate the potential benefit of chronic use on exercise capacity, and enrolled the first patient in October 2016.

INOpulse for PH-IPF

We are also developing INOpulse for the treatment of PH-IPF. IPF is a progressive disease of unknown etiology associated with growth of fibrotic tissue in the lungs causing hypoxemia, dyspnea, fatigue and cough. The median survival is only two to three years. Based on academic studies, we estimate the prevalence of IPF in the United States at approximately 90,000 patients (Raghu et al., Am J RespirCare Med, 2006, Vol 174, pp810-816), with 20-40% suffering from pulmonary hypertension (Rivera-Lebron, MD, MSCE, Advances in Pulmonary Hypertension, 2013, Vol 12, pp127-134). PH with IPF increases mortality. The presence of PH correlates most closely with the need for oxygen therapy. The two therapies that are currently approved for IPF, nintedanib and perfinidone cost approximately $100,000 per year (Pulmonary Fibrosis News, Oct 23, 2014).

iNO may improve outcomes in PH-IPF by both improving Ventilation-Perfusion, or V/Q, matching with increases in arterial oxygenation and by lowering pulmonary artery pressures. It has been shown (Yoshida et al., Eur Respir J 1997: 10: 2051-2054) that inhalation of nitric oxide significantly reduced the mean pulmonary arterial pressure and the pulmonary vascular resistance as compared with room air alone. However, the arterial oxygen tension (PaO2) did not improve. The combined inhalation of nitric oxide and oxygen produced a significant decrease of pulmonary arterial pressure ($p<0.01$) as well as an improvement ($p<0.05$) in PaO2 as compared to oxygen alone. These findings support the potential for the combined use of nitric oxide and oxygen for treating idiopathic pulmonary fibrosis patients with pulmonary hypertension. We also initiated our Phase 2 study in PH-IPF consisting of an exploratory acute hemodynamic study, for which the first patient was enrolled in second quarter of 2016, to be followed by an exercise capacity study.

BCM

In December 2011, we initiated a clinical trial of BCM, which we refer to as our PRESERVATION I trial, and completed enrollment in December 2014. Top-line results from the randomized, double-blind, placebo-controlled clinical trial were announced in July 2015. Topline results showed no statistically significant treatment differences between patients treated with BCM and patients treated with placebo for both the primary and the secondary endpoints. Following the results, we are considering further exploratory work but we do not intend to proceed with further clinical development of BCM at this point until and unless we can determine an alternative path forward. We continue to maintain the patent portfolio, including the composition of matter and method manufacturing patents that we have in-licensed from BioLineRx Ltd. In addition, we continue with trial management and close out activities for the PRESERVATION I trial in accordance with GCP requirements.

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 diseases. The key elements of our strategy to achieve this goal include:

- Advance the clinical development of INOpulse. One of our lead indications for our product candidate is INOpulse for PAH. Our Phase 3 PAH program for INOpulse will include two confirmatory clinical trials including the ongoing INOvation-1 trial and a second confirmatory randomized withdrawal study. The INOvation-1 trial has been initiated with the first patient enrolled in June 2016. We also initiated our second Phase 2 study for INOpulse in PH-COPD looking at the effect of chronic use on exercise capacity, for which the first patient was enrolled in October 2016. We also initiated our Phase 2 studies in PH-IPF consisting of an exploratory acute hemodynamic study, for which the first patient was enrolled in second quarter of 2016, to be followed by an exercise capacity study.

- Leverage our historical core competencies to expand our pipeline. Our employees have years of institutional experience in the use of inhaled nitric oxide in treating PH and in the development of drug-device combination product candidates. If we successfully advance INOpulse, we expect to develop INOpulse for treatment of CTEPH, PH associated with sarcoidosis and PH associated with pulmonary edema from altitude sickness and, subject to obtaining additional license rights from Ikaria, potentially other outpatient PH 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 may 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 vessels 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. PH patients can have a deficiency in endogenous nitric oxide production in their

lungs. When administered by inhalation to patients with PH, 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 PH. 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, oxygen levels within blood 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 PH 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 Japan). Inhaled nitric oxide is widely used in the hospital setting for a variety of conditions and, as reported by Ikaria, over 600,000 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.

Introduction to Pulmonary Hypertension

PH 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 PH that was updated most recently in 2013. The WHO classification has five broad PH 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 PH is comprised of patients with 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 and PH patients can have a deficiency in endogenous nitric oxide production in their lungs, patients in Group 1 will benefit from INOpulse. Group 3 PH consists of PH 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 of other therapies 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.

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. The currently approved PAH medications slow down disease progression, but do not prevent the underlying disease. 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. Currently, the only definitive treatment for PAH is a lung transplant, which is only available to a minority of patients due to the strict requirements and availability of viable lungs for transplant. 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 the REVEAL registry, a registry study of PAH based in the United States, indicate that approximately 40% of patients are treated with oxygen for hypoxemia. A more recent assessment of the use of oxygen in the REVEAL registry found that 57% of PAH patients were on LTOT. Approximately 60% of the patients from Part 1 of our Phase 2 clinical trial completed in October 2014 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 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 by a third party at an academic center in Spain in 11 patients, seven of whom had severe PAH and four of whom had severe chronic thromboembolic PH, 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 their WHO functional class status. At baseline, most of these patients had significant impairment of six-minute

walk distance, or 6MWD, 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 6MWD 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 6MWD 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 subject to review by the Division of Cardiovascular and Renal