

Bellerophon Therapeutics, Inc.
Form S-3
June 25, 2018

As filed with the Securities and Exchange Commission on June 25, 2018

Registration No. 333-

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM S-3

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

BELLEROPHON THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Delaware 47-3116175
(State or other jurisdiction of (I.R.S. Employer
incorporation or organization) Identification No.)

184 Liberty Corner Road, Suite 302
Warren, New Jersey 07059
(908) 574-4770
(Address, including zip code, and telephone number, including area
code, of registrant's principal executive offices)

Fabian Tenenbaum
President and Chief Executive Officer
Bellerophon Therapeutics, Inc.
184 Liberty Corner Road, Suite 302
Warren, New Jersey 07059
(908) 574-4770
(Name, address, including zip code, and telephone number, including area
code, of agent for service)

Copies to:

Kenneth R. Koch, Esq.
Jeffrey P. Schultz, Esq.
Mintz, Levin, Cohn, Ferris, Glovsky and Popeo P.C.
Chrysler Center, 666 Third Avenue
New York, NY 10017
Tel: (212) 935-3000

Edgar Filing: Bellerophon Therapeutics, Inc. - Form S-3

Approximate date of commencement of proposed sale to the public: From time to time after the effective date of this registration statement as determined by the registrant.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box:

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box:

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

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 Smaller reporting company

(Do not check if a smaller reporting company)

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered	Proposed Maximum Offering Price per Unit	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee (1)
Common Stock, \$0.01 par value	(2)	(3)	(3)	0
Preferred Stock, \$0.01 per value	(2)	(3)	(3)	0
Debt Securities	(2)	(3)	(3)	0
Warrants	(2)	(3)	(3)	0
Rights	(2)	(3)	(3)	0
Units	(2)	(3)	(3)	0
Total			\$ 100,000,000	\$ 12,450.00

(1) Calculated pursuant to Rule 457(o) under the Securities Act of 1933, as amended, based on the proposed maximum aggregate offering price.

(2) There are being registered hereunder such indeterminate number of shares of common stock, such indeterminate number of shares of preferred stock, such indeterminate principal amount of debt securities, such indeterminate number of warrants and rights to purchase common stock or debt securities, and such indeterminate number of units, as shall have an aggregate initial offering price not to exceed \$100,000,000. If any debt securities are issued at an original issue discount, then the offering price of such debt securities shall be in such greater principal amount as shall result in an aggregate initial offering price not to exceed \$100,000,000, less the aggregate dollar amount of all securities previously issued hereunder. Any securities registered hereunder may be sold separately or as units with other securities registered hereunder. The proposed maximum initial offering price per unit will be determined, from time to time, by the registrant in connection with the issuance by the registrant of the securities registered hereunder. The securities registered also include such indeterminate number of shares of common stock and amount of debt securities as may be issued upon conversion of or exchange for debt securities that provide for conversion or exchange, upon exercise of warrants or rights or pursuant to the anti-dilution provisions of any such securities. In addition, pursuant to Rule 416 under the Securities Act of 1933, as amended, the shares being registered hereunder include such indeterminate number of shares of common stock as may be issuable with respect to the shares being registered hereunder as a result of stock splits, stock dividends or similar transactions.

(3) The proposed maximum aggregate offering price per class of security will be determined from time to time by the registrant in connection with the issuance by the registrant of the securities registered hereunder and is not specified as to each class of security pursuant to General Instruction II.D. of Form S-3 under the Securities Act of 1933, as amended.

THE REGISTRANT HEREBY AMENDS THIS REGISTRATION STATEMENT ON SUCH DATE OR DATES AS MAY BE NECESSARY TO DELAY ITS EFFECTIVE DATE UNTIL THE REGISTRANT SHALL FILE A FURTHER AMENDMENT WHICH SPECIFICALLY STATES THAT THIS REGISTRATION STATEMENT SHALL THEREAFTER BECOME EFFECTIVE IN ACCORDANCE WITH SECTION 8(a) OF THE SECURITIES

ACT OF 1933, AS AMENDED, OR UNTIL THE REGISTRATION STATEMENT SHALL BECOME EFFECTIVE ON SUCH DATE AS THE SECURITIES AND EXCHANGE COMMISSION, ACTING PURSUANT TO SAID SECTION 8(a), MAY DETERMINE.

THE INFORMATION IN THIS PROSPECTUS IS NOT COMPLETE AND MAY BE CHANGED. WE MAY NOT SELL THESE SECURITIES UNTIL THE REGISTRATION STATEMENT FILED WITH THE SECURITIES AND EXCHANGE COMMISSION IS EFFECTIVE. THIS PROSPECTUS IS NOT AN OFFER TO SELL THESE SECURITIES AND IS NOT SOLICITING AN OFFER TO BUY THESE SECURITIES IN ANY STATE WHERE THE OFFER OR SALE IS NOT PERMITTED.

SUBJECT TO COMPLETION, DATED June 25, 2018

PROSPECTUS

BELLEROPHON THERAPEUTICS, INC.

\$100,000,000

COMMON STOCK
PREFERRED STOCK
DEBT SECURITIES
WARRANTS
RIGHTS
UNITS

This prospectus will allow us to issue, from time to time at prices and on terms to be determined at or prior to the time of the offering, up to \$100,000,000 of any combination of the securities described in this prospectus, either individually or in units. We may also offer common stock or preferred stock upon conversion of or exchange for the debt securities; common stock or preferred stock or debt securities upon the exercise of warrants or rights.

This prospectus describes the general terms of these securities and the general manner in which these securities will be offered. We will provide you with the specific terms of any offering in one or more supplements to this prospectus. The prospectus supplements will also describe the specific manner in which these securities will be offered and may also supplement, update or amend information contained in this document. You should read this prospectus and any prospectus supplement, as well as any documents incorporated by reference into this prospectus or any prospectus supplement, carefully before you invest.

Our securities may be sold directly by us to you, through agents designated from time to time or to or through underwriters or dealers. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus and in the applicable prospectus supplement. If any underwriters or agents are involved in the sale of our securities with respect to which this prospectus is being delivered, the names of such underwriters or agents and any applicable fees, commissions or discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds that we expect to receive from such sale will also be set forth in a prospectus supplement.

Our common stock is listed on the Nasdaq Global Market, under the symbol "BLPH." On June 22, 2018, the last reported sale price of our common stock on the Nasdaq Global Market was \$2.87 per share.

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks that we have described on page 7 of this prospectus under the caption "Risk Factors." We may include specific risk factors in supplements to this prospectus under the caption "Risk Factors." This prospectus may not be used to sell our securities unless accompanied by a prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is _____, 2018.

3

TABLE OF CONTENTS

	Page
ABOUT THIS PROSPECTUS	i
PROSPECTUS SUMMARY	<u>1</u>
RISK FACTORS	<u>7</u>
CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS	<u>8</u>
RATIO OF EARNINGS TO FIXED CHARGES	<u>10</u>
USE OF PROCEEDS	<u>11</u>
PLAN OF DISTRIBUTION	<u>12</u>
DESCRIPTION OF CAPITAL STOCK	<u>14</u>
DESCRIPTION OF DEBT SECURITIES	<u>19</u>
DESCRIPTION OF WARRANTS	<u>22</u>
DESCRIPTION OF RIGHTS	<u>24</u>
DESCRIPTION OF UNITS	<u>26</u>
LEGAL MATTERS	<u>28</u>
EXPERTS	<u>28</u>
WHERE YOU CAN FIND MORE INFORMATION	<u>28</u>
INCORPORATION OF INFORMATION BY REFERENCE	<u>28</u>
PART II INFORMATION NOT REQUIRED IN PROSPECTUS	<u>30</u>
EXHIBIT INDEX	<u>35</u>

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a “shelf” registration process. Under this shelf registration process, we may offer shares of our common stock, preferred stock, various series of debt securities and/or warrants or rights to purchase any of such securities, either individually or in units, in one or more offerings, with a total value of up to \$100,000,000. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will contain specific information about the terms of that offering.

This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of the offering of the securities, you should refer to the registration statement, including its exhibits. The prospectus supplement may also add, update or change information contained or incorporated by reference in this prospectus. However, no prospectus supplement will offer a security that is not registered and described in this prospectus at the time of its effectiveness. This prospectus, together with the applicable prospectus supplements and the documents incorporated by reference into this prospectus, includes all material information relating to the offering of securities under this prospectus. You should carefully read this prospectus, the applicable prospectus supplement, the information and documents incorporated herein by reference and the additional information under the heading “Where You Can Find More Information” before making an investment decision.

You should rely only on the information we have provided or incorporated by reference in this prospectus or any prospectus supplement. We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus. No dealer, salesperson or other person is authorized to give any information or to represent anything not contained or incorporated by reference in this prospectus. You must not rely on any unauthorized information or representation. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. You should assume that the information in this prospectus or any prospectus supplement is accurate only as of the date on the front of the document and that any information we have incorporated herein by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus or any sale of a security.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference in the accompanying prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

This prospectus may not be used to consummate sales of our securities, unless it is accompanied by a prospectus supplement. To the extent there are inconsistencies between any prospectus supplement, this prospectus and any documents incorporated by reference, the document with the most recent date will control.

We were incorporated under the laws of the State of Delaware on October 17, 2013 under the name Ikaria Development LLC. We changed our name to Bellerophon Therapeutics LLC on January 27, 2014. On February 12, 2015, we converted from a Delaware limited liability company into a Delaware corporation and changed our name to Bellerophon Therapeutics, Inc. We currently have three wholly-owned subsidiaries: Bellerophon BCM LLC, a Delaware limited liability company; Bellerophon Pulse Technologies LLC, a Delaware limited liability company; and Bellerophon Services, Inc., a Delaware corporation.

Unless the context otherwise requires, “Bellerophon,” “the Company,” “we,” “us,” “our” and similar terms refer to Bellerophon Therapeutics, Inc.

PROSPECTUS SUMMARY

The following is a summary of what we believe to be the most important aspects of our business and the offering of our securities under this prospectus. We urge you to read this entire prospectus, including the more detailed consolidated financial statements, notes to the consolidated financial statements and other information incorporated by reference from our other filings with the SEC or included in any applicable prospectus supplement. Investing in our securities involves risks. Therefore, carefully consider the risk factors set forth in any prospectus supplements and in our most recent annual and quarterly filings with the SEC, as well as other information in this prospectus and any prospectus supplements and the documents incorporated by reference herein or therein, before purchasing our securities. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities.

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.

Our Development Program

The following table summarizes key information about our primary development product, INOpulse, and indications for which we have worldwide commercialization rights.

From the inception of our business through December 31, 2017, \$261.7 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. We have also expanded our patent portfolio by filing several Company-owned patent applications relating to the use of nitric oxide that will expire as late as 2038.

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. In January 2018, we announced our INOvation-1 study enrollment exceeded 100 patients, representing more than half of the anticipated enrollment.

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. In May 2018, we announced that we reached agreement with the FDA on all key aspects of our planned Phase 2b study of INOpulse for treatment of PH-COPD.

INOpulse for PH-ILD

We are also developing INOpulse for the treatment of PH-ILD. ILD is a general category that includes many different lung conditions. All ILDs affect the interstitium, a lace-like network of tissue that extends throughout both lungs. ILDs are a chronic progressive disease of destruction of the airways and lung tissue. This results in scarring, thickening of the lung tissue causing insufficient ability for the lungs to oxygenate blood to be delivered to the body, caused by imbalance in mediators and chronic inflammation. While ILD is primarily a respiratory disease, it can also affect the pulmonary blood circulation, resulting in vascular remodeling and pulmonary hypertension. Chronic elevation of the pulmonary artery pressures puts stress on the right ventricle and can lead to right ventricular failure. One of the largest and most serious subsets of ILDs is IPF, 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, with 20-40% suffering from pulmonary hypertension. 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 Pirfenidone, cost approximately \$100,000 per year.

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.

During May 2017, we announced completion of our Phase 2 clinical trial using INOpulse therapy to treat PH-IPF. The clinical data showed that INOpulse was associated with clinically meaningful improvements in hemodynamics and exercise capacity in difficult-to-treat PH-IPF patients. The PH-IPF trial was a proof of concept study (n=4) designed to evaluate the ability of pulsed inhaled nitric oxide, or iNO, to provide selective vasodilation as well as to assess the potential for improvement in hemodynamics and exercise capacity in PH-IPF patients. The clinical trial met its primary endpoint showing an average of 15.3% increase in blood vessel volume (p<0.001) during acute inhalation of iNO as well as showing a significant association between ventilation and vasodilation, demonstrating the ability of INOpulse to provide selective vasodilation to the better ventilated areas of the lung. The trial showed consistent benefit in hemodynamics with a clinically meaningful average reduction of 14% in systolic pulmonary arterial pressure (sPAP) with acute exposure to iNO. It also assessed the chronic effects of iNO on exercise capacity showing an average 75 meter improvement in 6MWD, and consistent improvement of approximately 80 m% in composite endpoints of 6MWD and oxygen saturation with four weeks of treatment. The study assessed both the iNO 75 and iNO 30 dose, supporting iNO 30 as a potentially safe dose. During August 2017, we announced FDA acceptance of

our IND for our Phase 2b (iNO-PF) clinical trial using INOpulse therapy in a broad population of patients with pulmonary fibrosis, or PF, at both low and intermediate/high risk of PF. PH. In January 2018, we announced the first patient enrollment in our iNO-PF Phase 2b trial.

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.

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. We also completed Phase 2 studies for INOpulse in PH-COPD looking at the effect of chronic use on exercise capacity and in PH-IPF consisting of an exploratory acute hemodynamic 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.

The Spin-Out

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.

The development of our programs was initiated under the leadership of our scientific and development team while at Ikaria. Ikaria’s lead product, INOmax, is an inhaled nitric oxide product used for treatment of persistent PH of the newborn. Our understanding of the medical applications of nitric oxide and associated delivery devices, as well as our

innovative approach to the pulsed delivery of nitric oxide, originated at Ikaria, and we in-licensed BCM while we were a part of Ikaria.

In October 2013, Ikaria completed an internal reorganization of certain assets and subsidiaries, in which it transferred to us exclusive worldwide royalty-free rights to develop and commercialize pulsed nitric oxide in PAH, PH-COPD and PH-IPF. 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. In April 2018, we amended the cross-license to (i) remove previous references to IPF and replacing them with references to PF and (ii) include a provision pursuant to which the Company agrees to pay to Ikaria one percent (1%) of PF net sales.

Following the internal reorganization, in February 2014, Ikaria distributed all of our then outstanding units to its stockholders through the payment of a special dividend on a pro rata basis based on each stockholder's ownership of Ikaria capital stock. We refer to Ikaria's distribution of our then outstanding units to its stockholders as the Spin-Out.

Shortly after the Spin-Out, Ikaria was acquired by entities affiliated with Madison Dearborn Partners. On April 16, 2015, Mallinckrodt plc, or Mallinckrodt, announced that it had completed its acquisition of Ikaria.

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

Corporate Information