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

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2022

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	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.01 par value per share	**BLPH**	**The Nasdaq Capital 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 ☒ 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 ☒ 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. ☒ Yes ☐ No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). ☒ Yes ☐ No

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐ Accelerated filer ☐ Non-accelerated filer ☒ Smaller reporting company ☒ Emerging growth company ☐

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

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b).

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

As of June 30, 2022, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $8.8 million, based upon the closing price on the Nasdaq Capital Market reported for such date. Shares of common stock beneficially owned 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 30, 2023: 10,448,185

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 2023 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission.

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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" refer to Bellerophon Therapeutics, Inc. and its consolidated subsidiaries.

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," "potential" or "continue" or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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

- the timing of the ongoing and expected clinical trials of our 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;
- 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 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
- any of the other risks included in this Annual Report on Form 10-K, including those set forth under the heading "Risk Factors."

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.

SUMMARY OF PRINCIPAL RISK FACTORS

This summary briefly lists the principal risks and uncertainties facing our business, which are only a select portion of those risks. A more complete discussion of those risks and uncertainties is set forth in Part I, Item 1A of this Annual Report, entitled Risk Factors. Additional risks not presently known to us or that we currently deem immaterial may also affect us. If any of these risks occur, our business, financial condition or results of operations could be materially and adversely affected.

Our business is subject to the following principal risks and uncertainties:

Risks Related to Our Financial Position and Need for Additional Capital

- We have incurred significant losses since inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.
- Our limited operating history may make it difficult for our stockholders to evaluate the success of our business to date and to assess our future viability.
- We will need substantial additional funding in order to alleviate the substantial doubt about our ability to continue as a going concern.
- Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to technologies or product candidates.
- We may not be able to utilize all of our net operating loss carryforwards.

Risks Related to Our Business and Industry

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

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

- If we are unable to develop, obtain marketing approval for or successfully commercialize our product candidates, either alone or through a collaboration, or experience significant delays in doing so, our business could be materially harmed.
- We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates due based on the lengthy and uncertain outcome of clinical trials.
- We may experience problems with, failure of, or delays in obtaining INOpulse components.
- We have conducted, and may in the future conduct, clinical trials for certain of our product candidates at sites outside the United States, and the FDA may not accept data from trials conducted in such locations.
- Some of our clinical trials have failed and others may fail to demonstrate safety and efficacy.

- If we experience any of a number of possible unforeseen events in connection with clinical trials of our product candidates, potential marketing approval or commercialization of our product candidates could be delayed or prevented.
- We may experience delays or difficulties in the enrollment of patients in clinical trials.
- We may not obtain orphan drug exclusivity for any of our product candidates and indications.
- Serious adverse events, or SAEs, or undesirable side effects of our product candidates may be identified.
- We may not be successful in our efforts to identify or discover additional potential product candidates.
- Even if one of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success, and the market opportunity for the product candidate may be smaller than we estimate.
- We may not be successful in commercializing any product candidates that we develop.
- Even if we are able to commercialize any product candidate that we develop, the product may become subject to unfavorable pricing regulations, third-party payor reimbursement practices or healthcare reform initiatives that could harm our business.
- Regulatory approval of generic versions of any of our products that receive marketing approval could adversely affect the sales of our products.
- Product liability lawsuits against us could divert our resources and cause us to incur substantial liabilities.
- Our INOpulse devices use lithium-ion battery cells, which have been observed to catch fire or vent smoke and flame, and these events may raise concerns about the batteries we use.
- The COVID-19 pandemic, and any other pandemic, epidemic or outbreak of an infectious disease, may materially and adversely affect our business and operations.

Risks Related to Our Dependence on Third Parties

- The intellectual property underlying INOpulse is exclusively licensed from Ikaria. If Ikaria terminates the license agreement, or fails to prosecute, maintain or enforce the underlying patents, our business will be materially harmed.
- We rely on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily.
- We currently rely on a single supplier, Ikaria, for our supply of nitric oxide for the clinical trials of INOpulse.
- Any failure by a third-party supplier or manufacturer to produce or deliver supplies for us or to provide necessary servicing may delay or impair our ability to complete our clinical trials or commercialize our product candidates.
- Our product candidates currently in development are exclusively licensed from third parties, and we may enter into additional agreements to in-license technology from third parties.
- We may seek to enter into collaborations with third parties for the development and commercialization of our product candidates. If we fail to enter into such collaborations, or such collaborations are not successful, we may not be able to capitalize on the market potential of our product candidates.

Risks Related to Our Intellectual Property

- If we fail to obtain and maintain sufficiently broad patent protection of our technology or if we are unable to obtain and maintain patent protection for our technology and products or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired.
- We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.
- If we fail to comply with our obligations under license agreements, we could lose rights that are important to our business.

- We may be subject to claims by third parties asserting that we or our employees have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.
- If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

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

- Even if we complete the necessary clinical trials, the expensive, time consuming and uncertain nature of the marketing approval process has and may continue to prevent us from obtaining approvals for the commercialization of some or all of our product candidates.
- Our failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad.
- Changes in law or policy could have a negative impact on the approval of our drug candidates.

Risks Related to Employee Matters and Managing Growth

- Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.
- Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

Risks Related to Ownership of Our Common Stock

- Our common stock may be delisted from The Nasdaq Capital Market if we fail to comply with continued listing standards.

PART I

Item 1. Business

Overview

We are a clinical-stage therapeutics company focused on developing innovative products 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 or at risk of pulmonary hypertension, or PH, using our proprietary pulsatile nitric oxide delivery platform, INOpulse.

In 2016, we began developing INOpulse for the treatment of pulmonary hypertension associated with fibrotic interstitial lung disease ("fILD"), which includes PH associated with idiopathic pulmonary fibrosis ("PH-IPF") as well as other pulmonary fibrosing diseases. During May 2017, we announced the 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 with acute exposure to iNO. The study assessed both the iNO 75 and iNO 30 dose.

During August 2017, we announced acceptance by the U.S. Food and Drug Administration (the "FDA") of our Investigational New Drug ("IND") application 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 PH. In January 2019, we announced top-line results from cohort 1 of our iNO-PF trial. The results suggested directional improvements in multiple clinically meaningful exploratory endpoints as measured by a wearable medical-grade activity monitor. In addition, these results suggested that iNO may have a favorable safety profile, supporting the continuation into cohort 2. In April 2019, we announced that we reached an agreement with the FDA on modifying the ongoing Phase 2b trial into a seamless Phase 2/3 trial, with cohort 3 serving as the pivotal study, as well as an agreement on the primary endpoint in cohort 3 of change in moderate to vigorous activity ("MVPA") from baseline to month 4, measured by Actigraphy. Actigraphy (medical wearable continuous activity monitoring) has the potential to provide highly sensitive objective real-world physical activity data that we expect to correlate with clinically meaningful patient functional abilities and health outcomes. Actigraphy is currently being utilized as the primary endpoint in multiple late-stage clinical programs in various cardiopulmonary diseases such as heart failure and chronic obstructive pulmonary disease ("COPD"). In December 2019, we announced top-line results from cohort 2 of the iNO-PF trial. Cohort 2 of iNO-PF suggested directionally favorable and potentially clinically meaningful placebo corrected improvement in MVPA, in subjects treated with iNO45 (45 mcg/kg IBW/hr) versus placebo. The improvement in MVPA was underscored by benefits in overall activity, as well as multiple patient reported outcomes. In March 2020, we announced that in consultation with the FDA, we had finalized some of the key elements of our planned pivotal Phase 3 study for fILD, including the use of MVPA as the primary endpoint for approval, the patient population of pulmonary fibrosis subjects at risk of PH, as well as the dose of iNO45. In December 2020, we announced the first patient enrollment in this Phase 3 study called REBUILD. In September 2022, the FDA informed us that it had no objection to our proposal to reduce the study size to 140 subjects which does not impact the trial's principal objective or endpoints and maintains power of >90% (p-value < 0.01) for the primary endpoint of MVPA based on the effect size observed in our Phase 2 study. The FDA did note that since our proposal to reduce the sample size was based on Phase 2b cohort 2 actigraphy data, there is always a concern that such sample size reduction may further limit the acquisition of information on other, more important clinical endpoints in the trial. The FDA agreement was based on its review of:

- Analysis conducted on cohort 2 (Phase 2) data utilizing the statistical analysis methodology to be used in REBUILD, including bi-weekly analysis of MVPA data and mixed models for repeated mearures ("MMRM") assessment of the last half of the blinded treatment period, which showed the trial would be >90% powered for $p<0.05$ at 80 total patients and >90% powered for a $p<0.01$ at 114 patients based on the effect size determined from cohort 2;
- Similar baseline MVPA distribution between cohort 2 and the first 80 randomized patients in REBUILD based on a blinded assessment; and
- Independent Data Monitoring Committee unblinded safety review of the first 85 randomized patients in REBUILD indicating no safety concern with regards to reduction of REBUILD to 140 patients.

During January 2023, we completed enrollment of the REBUILD study with a total of 145 patients enrolled. We expect to report pivotal top-line data results in mid-2023.

In 2018, we initiated an ancillary Phase 2 open-label intra-patient dose escalation study that utilizes right heart catheterization to assess the hemodynamic effect of INOpulse from a dose of iNO 30 to iNO 125 in PH-PF subjects. In February 2020, we announced the completion of the study and that the top-line results demonstrated that INOpulse achieved clinically and statistically meaningful cardiopulmonary improvements in pulmonary vascular resistance and mean pulmonary arterial pressure. The data suggested that inhaled nitric oxide was generally well tolerated and may yield a favorable risk-benefit profile across doses.

In 2018, we also initiated development of INOpulse for the treatment of PH associated with Sarcoidosis ("PH-Sarc"). Sarcoidosis is a multi-system disease which is characterized by the growth of granulomas (inflammatory cells) in one or more organs. The most frequent organs involved are the lungs and lymph nodes within the chest. Pulmonary hypertension may be present in as many as 74% of patients depending on the disease severity and how the pulmonary hypertension ("PH") is defined. The presence of PH in sarcoidosis is associated with a poor prognosis. There are a number of different mechanisms linking PH with sarcoidosis. The primary treatment for sarcoidosis is corticosteroids; however, the outcome of this treatment on the PH is unclear. There is no approved therapy for PH associated with sarcoidosis. Various PAH treatments have been tried including iNO and IV prostacyclin with some clinical and functional improvement. The study was a Phase 2 open-label dose escalation design that utilized right heart catheterization to assess the acute hemodynamic effect of INOpulse from a dose of iNO 30 to iNO 125 in PH-Sarc subjects. In December 2021, we announced the completion of the acute dose escalation phase of the study and that the top-line results demonstrated that INOpulse provided clinically meaningful improvements in pulmonary vascular resistance. Supported by the results from this study, on June 21, 2022, we submitted to the FDA an exploratory Phase 2 double-blinded placebo-controlled study to investigate the safety and efficacy of inhaled nitric oxide/INOpulse dosed chronically for six months in patients with PH-Sarc. Subsequently, on July 28, 2022, we received an FDA letter indicating that the FDA completed its review of our study protocol, with a minor recommendation to include safety stopping rules. We have agreed to incorporate this recommendation into our periodic safety reviews. We are now positioned to initiate this Phase 2 study and are currently assessing the next steps for the study.

We completed a randomized, placebo-controlled, double-blind, dose-confirmation Phase 2 clinical trial of INOpulse for pulmonary hypertension associated with chronic obstructive pulmonary disease, or PH-COPD, in July 2014. The results from this trial showed that iNO 30 was a potentially safe and effective dose for treatment of PH-COPD. Based on the results of this trial, we completed further Phase 2 testing to assess the targeted vasodilation provided by INOpulse in this patient population. We presented the results of this trial in September 2015 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 entitled "Pulmonary vascular effects of pulsed inhaled nitric oxide in COPD patients with pulmonary hypertension." During September 2017, we shared the results of our Phase 2a PH-COPD trial that was designed to evaluate the acute effects of pulsed inhaled nitric oxide, or iNO, on vasodilation as well as the chronic effect on hemodynamics and exercise tolerance. The trial showed a statistically significant increase (average 4.2%) in blood vessel volume on iNO compared to baseline ($p=0.03$), and a statistically significant correlation in Ventilation-Vasodilation ($p=0.01$). The chronic results demonstrated a statistically significant and clinically meaningful increase in six minute walk distance, or 6MWD, of 50.7m ($p=0.04$) as well as a decrease of 19.9% in systolic pulmonary arterial pressure ($p=0.02$), as compared to baseline. The data suggested that the dose may have a favorable safety profile. In May 2018, we announced that the

FDA concurred with the design of our planned Phase 2b study of INOpulse for treatment of PH-COPD. The study will assess the effect of INOpulse on various parameters including exercise capacity, right ventricular function and oxygen saturation, as well as other composite endpoints. We continue to evaluate alternatives for the funding and timing of this program.

On March 19, 2020, the FDA granted emergency expanded access ("EA") to allow for our INOpulse system to immediately be used as supportive treatment for a patient with COVID-19 under the care and supervision of the patient's physician. The clinical goal of this experimental treatment was to mitigate the hospitalized patient's disease progression and avoid the need to perform intubation. Under the emergency access program, 180 hospitalized patients with COVID-19 from 18 hospitals across the United States received treatment with INOpulse. In April 2020, we submitted an IND application to the FDA to study the iNO delivery system for the treatment of patients with COVID-19. The proposed randomized, placebo controlled study, called COViNOX, was designed to evaluate the efficacy and safety of INOpulse in patients diagnosed with COVID-19 who require supplemental oxygen before the disease progresses to necessitate mechanical ventilation support. The COViNOX protocol aimed to enroll up to 500 patients with COVID-19 who were to be treated with either INOpulse or placebo. The primary endpoint of the study required an assessment of the proportion of subjects who experienced respiratory failure or mortality during the 28-day study period, which would allow the trial to serve as a registrational study for approval. The IND application was accepted by the FDA in May 2020, and the trial was initiated with the first patient treated in July 2020. The first 100 patients completed their 28-day assessment periods in October 2020. In November 2020, we announced that the independent Data Monitoring Committee ("DMC") had completed its pre-specified interim analysis from the first 100 patients. Based on the finding of futility, we placed the COViNOX study on a clinical hold. Although new enrollment of subjects into the study was halted, the remaining 91 subjects already enrolled at the time the clinical hold was announced were allowed to complete the treatment course. Upon completion of the protocol defined monitoring period, the pre-specified efficacy and safety analysis of these 191 patients was reviewed by the DMC and the DMC concluded that there were no safety concerns that were attributed to INOpulse for COVID-19. Based on the COViNOX results, we put the trial on a permanent clinical hold and we are not planning additional studies for INOpulse for the treatment of COVID-19. In May 2021, we submitted notification of withdrawal of the COViNOX IND to the FDA.

In addition, other potential indications for our INOpulse platform include: chronic thromboembolic PH, or CTEPH 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 performance of IND-enabling studies, 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 our drug delivery system, 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.

Product	Indication	Stage of Development
INOpulse®	Indications under development	
	Fibrotic Interstitial Lung Disease at risk of Pulmonary Hypertension	Phase 3
	PH associated with chronic obstructive pulmonary disease	Phase 2
	PH associated with sarcoidosis	Phase 2
	Additional indications:	
	Pulmonary arterial hypertension	
	Chronic thromboembolic PH	
	PH associated with pulmonary edema from high altitude sickness	

From the inception of our business through December 31, 2022, $340.3 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 CTEPH, PH-Sarc 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. In April 2018, we expanded the scope of our license from PH-IPF to PH in patients with Pulmonary Fibrosis ("PH-PF"), which includes idiopathic interstitial pneumonias, chronic hypersensitivity pneumonitis, occupational and environmental lung disease, with a royalty equal to 1% of net sales of any commercial products for PH-PF.

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 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 700,000 patients have been treated with inhaled nitric oxide worldwide since its approval in 1999. 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 that 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 began 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 one or 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 conducted, all eight patients who were experienced with the use of the INOpulse DS device responded positively to the modifications in the INOpulse device. 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 in part on patents we have exclusively licensed from Ikaria for the treatment of PAH, PH-COPD, PH-PF, CTEPH, PH-Sarc and PH associated with pulmonary edema from high altitude sickness which, collectively, we refer to as the Bellerophon indications. The licensed patents from Ikaria 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 provisional and non-provisional patent applications relating to the use of nitric oxide that if pursued and issued would expire as late as 2043.

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, or the EU. 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 fILD

We are developing INOpulse for the treatment of patients with fibrotic interstitial lung disease ("fILD") at a risk for pulmonary hypertension, which includes PH associated with idiopathic pulmonary fibrosis as well as other pulmonary fibrosing diseases. All interstitial lung diseases ("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 disease 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 vasculature both directly and indirectly via hypoxia, 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 idiopathic pulmonary fibrosis ("IPF"), a progressive disease of unknown etiology associated with growth of fibrotic tissue in the lungs causing hypoxemia, dyspnea, fatigue and cough. 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. There are two therapies that are currently approved to treat IPF, Nintedanib and Pirfenidone, each of which costs approximately $100,000 per year. PH with IPF increases mortality, with a median survival of only two to three years. The presence of PH correlates most closely with the need for oxygen therapy. However, there are currently no treatments approved to treat PH associated with IPF.

iNO may improve outcomes in PH-PF including 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 in subjects with PH-IPF. In addition, the combined inhalation of nitric oxide and oxygen produced both 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 patients with PH-PF including PH-IPF.

INOpulse for PH-Sarcoidosis

In 2018, we also initiated development of INOpulse for the treatment of PH associated with Sarcoidosis ("PH-Sarc"). Sarcoidosis is a multi-system disease which is characterized by the growth of granulomas (inflammatory cells) in one or more organs. The most frequent organs involved are the lungs and lymph nodes within the chest. Pulmonary hypertension may be present in as many as 74% of patients depending on the disease severity and how the pulmonary hypertension ("PH") is defined. The presence of PH in sarcoidosis is associated with a poor prognosis. There are a number of different mechanisms linking PH with sarcoidosis. The primary treatment for sarcoidosis is corticosteroids; however, the outcome of this treatment on the PH is unclear. There is no approved therapy for PH associated with sarcoidosis. Various PAH treatments have been tried including iNO and IV prostacyclin with some clinical and functional improvement.

The study was a Phase 2 open-label dose escalation design that utilized right heart catheterization to assess the acute hemodynamic effect of INOpulse from a dose of iNO 30 to iNO 125 in PH-Sarc subjects. In December 2021, we announced the completion of the acute dose escalation phase of the study and that the top-line results demonstrated that INOpulse provided clinically meaningful improvements in pulmonary vascular resistance.

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. In order to confirm the dose with our proprietary INOpulse device, we conducted a Phase 2 acute dose ranging randomized placebo-controlled trial in 159 patients with the INOpulse DS device, with doses ranging from iNO 3 to iNO 75. 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 that we sponsored 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 subsequent work with acute testing, we 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. During September 2017, we shared the results of our Phase 2a PH-COPD trial that was designed to evaluate the acute effects of iNO on vasodilation as well as the chronic effect on hemodynamics and exercise tolerance. The trial showed a statistically significant increase (average 4.2%) in blood vessel volume on iNO compared to baseline ($p=0.03$), and a statistically significant correlation in Ventilation-Vasodilation ($p=0.01$). The chronic results demonstrated a statistically significant and clinically meaningful increase in 6MWD of 50.7m ($p=0.04$) as well as a decrease of 19.9% in systolic pulmonary arterial pressure ($p=0.02$), as compared to baseline. In May 2018, we announced that the FDA concurred with the design of our planned Phase 2b trial of INOpulse for treatment of PH-COPD. The study will assess the effect of INOpulse on various parameters, including exercise capacity, right ventricular function and oxygen saturation, as well as other composite endpoints. We are currently evaluating alternatives for the funding and timing of this program.

Our Strategy

Our goal is to become a leader in developing and commercializing innovative products 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 fILD. We have completed our Phase 2b PH-PF program for INOpulse, which included 85 patients in two cohorts to evaluate two different doses of iNO for periods of eight to 16 weeks. We also completed Phase 2 studies for INOpulse in each of fILD to evaluate the acute hemodynamic benefit and PH-COPD to evaluate the effect of chronic use on exercise capacity and completed a Phase 2 dose escalation study for PH-Sarc.

- *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 and PH associated with pulmonary edema from high 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 the treatment of a variety of conditions and, as reported by Ikaria, over 700,000 patients have been treated with inhaled nitric oxide worldwide since its approval in 1999. 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 2018. 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, 3 and 5 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. 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 COPD and ILD (including fILD and IPF), among others. Group 5 PH consists of PH associated with blood, systematic and metabolic disorders. This Group includes patients with PH-Sarc.

INOpulse for fILD

We are developing INOpulse for the treatment of patients with fibrotic interstitial lung disease ("fILD") at a risk for pulmonary hypertension, which includes PH associated with idiopathic pulmonary fibrosis as well as other pulmonary fibrosing diseases. fILD, also referred to as pulmonary fibrosis, is a general category that includes many different lung conditions. All fILDs affect the interstitium, a lace-like network of tissue that extends throughout both lungs and is the infrastructure that supports the small airways, blood vessels, and gas exchange units. The interstitium under normal and healthy conditions is a very thin layer, however, it becomes dense and thick in conditions such as in ILD. This thickening may become very dense and consolidated leading to lung scarring, otherwise known as fibrosis. Typically, fILDs are chronic and progressive leading to destruction of the airways, blood vessels and lung tissue. This causes insufficient ability for the lungs to oxygenate blood, caused by imbalance in mediators and chronic inflammation. While fILD is primarily a respiratory disease, it can also affect the pulmonary vasculature, 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 and death.

Disease Background and Market Opportunity

One of the largest and most serious subsets of fILDs is idiopathic pulmonary fibrosis ("IPF"), a progressive disease of unknown etiology associated with growth of fibrotic tissue in the lungs causing hypoxemia, dyspnea, fatigue and cough. 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. There are two therapies that are currently approved to treat IPF, Nintedanib and Pirfenidone, each of which costs approximately $100,000 per year. PH with IPF increases mortality, with a median survival of only two to three years. The presence of PH correlates most closely with the need for oxygen therapy. However, there are currently no treatments approved to treat PH associated with IPF.

Scientific Rationale for Use of INOpulse for fILD

Like endogenous pulmonary nitric oxide, inhaled nitric oxide works by selectively relaxing lung vascular smooth muscles, causing dilation of pulmonary blood vessels and consequently increased pulmonary blood flow. This reduces the elevated pulmonary artery pressure in patients at risk of PH associated with fILD.

iNO may also improve outcomes in fILD including 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 in IPF patients with pulmonary hypertension. However, the arterial oxygen partial pressure ("PaO2") did not improve. The combined inhalation of nitric oxide and oxygen produced both 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 patients with fILD, including IPF.

Clinical Development Program

During May 2017, we announced the 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 with acute exposure to iNO, and assessed both the iNO 75 and iNO 30 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 PH. In January 2019, we announced top-line results from cohort 1 of our iNO-PF study. The Phase 2 trial was designed as an exploratory study to identify optimal endpoints to progress into pivotal Phase 3 trial. The results suggested benefit in multiple clinically meaningful activity parameters as measured by a wearable medical-grade activity monitor:

- subjects on iNO demonstrated an increase of 8% in moderate activity versus a 26% decrease for subjects on placebo (p=0.04);

- subjects on iNO showed no decline in their overall activity levels versus a 12% decline for subjects on placebo (p=0.05);

Clinically meaningful improvements were also demonstrated in the following key areas:

- subjects on iNO showed an increase of 15% in NT-ProBNP versus a 42% increase for subjects on placebo (NT-ProBNP is a peptide marker of right ventricular failure, with higher levels indicative of disease worsening);

- subjects on iNO demonstrated improved oxygen saturation by 9% versus a worsening of 11% for placebo.

In addition, the preliminary data suggested that iNO may present a favorable safety profile supporting the continuation into cohort 2.

In April 2019, we announced that we reached an agreement with the FDA on modifying the ongoing Phase 2b trial into a seamless Phase 2/3 trial, with cohort 3 serving as the pivotal study, as well as an agreement on the primary endpoint in cohort 3 of change in MVPA from baseline to week 16, measured by Actigraphy. Actigraphy (medical wearable continuous activity monitoring) has the potential to provide highly sensitive objective real-world physical activity data that we expect to correlate with clinically meaningful patient functional abilities and health outcomes. Actigraphy is currently being utilized as the primary endpoint in multiple late-stage clinical programs in various cardiopulmonary diseases such as heart failure and COPD.

In May 2019, we presented additional positive data from cohort 1 at the American Thoracic Society 115th International Conference:

- 23% of subjects on iNO had a clinically significant improvement in MVPA, compared to 0% of subjects on placebo. This represents a placebo corrected difference of 23% - a clinically significant improvement is > 15% increase in MVPA from baseline;

- 39% of subjects on iNO had a clinically significant decline in MVPA, compared to 71% of subjects on placebo. This represents a placebo corrected difference of 32% - a clinically significant improvement is >15% decrease in MVPA from baseline;

- Proportion of awake time spent in MVPA improved by 38% (16% increase on iNO vs. 22% decrease on placebo; p=0.04), (p-value based on t-test on available data; exploratory endpoint; post-hoc analysis not adjusted for multiplicity);

- Calorie expenditure improved by 12% (6% decrease on iNO vs. 18% decrease on placebo; p=0.05), (p-value based on t-test on available data; exploratory endpoint; post-hoc analysis not adjusted for multiplicity);

- Subjects on open-label extension demonstrated consistent improvements in MVPA and overall activity, with subjects transitioning from placebo to open-label experiencing a reversal from worsening to improving.

In September 2019, we announced that that we received an Orphan Drug Designation for nitric oxide for the treatment of IPF. Orphan drug designation provides us access to various development incentives, including tax credits for qualified clinical trial expenditures and waivers for certain FDA user fees. Orphan Drug Designation also provides up to seven years of marketing exclusivity if regulatory approval is received.

In October 2019, we presented additional positive responder analysis data from cohort 1, as well as new long-term results for subjects on open-label extension ("OLE") at the American College of Chest Physicians Conference:

- Responder analysis:
    - 85% of subjects on placebo declined in MVPA, overall activity and non-sedentary activity;
    - 46% of subjects on INOpulse improved in MVPA, 62% in overall activity and 39% in non-sedentary activity (compared to only 15% of subjects on placebo in each category).
- OLE:
    - Collectively, subjects (with an average of 27 weeks of OLE data) demonstrated maintenance of MVPA, overall activity and non-sedentary activity;
    - Subjects randomized to active treatment in the blinded portion of the trial continued to maintain their activity levels when transitioning to OLE over 27 weeks of open-label treatment;
    - Subjects randomized to placebo in the blinded portion of the trial transitioned from a decline during blinded treatment to stabilization of activity levels (MVPA, overall activity and non-sedentary activity) over 27 weeks of open-label treatment.

In December 2019, we announced top-line results from Cohort 2 of iNO-PF. Cohort 2 suggested directionally favorable and possibly clinically meaningful placebo corrected improvement in MVPA, defined as walking, stairs, yardwork, and similar activities, in subjects treated with iNO45 (45 mcg/kg IBW/hr) versus placebo. The improvements in MVPA were supported by potential benefits in overall activity, as well as patient reported outcomes. Subjects on iNO showed a placebo corrected benefit in the following top-line parameters:

- MVPA improved by 14 minutes per day (p=0.02), representing a 20% improvement, after 4 months (p-value based on t-test on available data; exploratory endpoint; post-hoc analysis not adjusted for multiplicity);
- Overall activity improved by 100 counts/min, representing a 7% improvement;
- St. George Respiratory Questionnaire ("SGRQ") Total score improved by 3 points;
- SGRQ Impacts score improved by 5 points;
- SGRQ Activity score improved by 6 points;

- University of California, San Diego Shortness of Breath Questionnaire improved by 5 points;

- Data indicated that iNO45 showed a favorable safety profile.

In addition, a longitudinal analysis based on all available data, as planned for Phase 3 for multiple endpoints showed:

- a 20% benefit in MVPA and 7% benefit in overall activity after 4 months (analysis based on MMRM model with change from month 1; no baseline covariate; data log-transformed for analysis);

- SGRQ total score improved by 4 points, Impacts score improved by 6 points and Activity score improved by 6 points;

- University of California, San Diego Shortness of Breath Questionnaire improved by 5 points.

In March 2020, we announced that in consultation with the FDA, we had finalized the key elements of our planned pivotal Phase 3 study for fILD, including the use of MVPA as the primary endpoint for approval, the patient population of pulmonary fibrosis subjects at risk of PH, as well as the dose of iNO45.

In 2018, we also implemented an open-label intra-patient acute dose escalation trial utilizing right heart catheterization to assess the hemodynamic effect of INOpulse from a dose of iNO 30 to iNO 125 in PH-PF subjects. In February 2020, we announced the completion of the study and that the top-line results from PHPF-002 demonstrated that INOpulse achieved clinically and statistically meaningful cardiopulmonary improvements in multiple pre-specified hemodynamic parameters (statistical analysis was conducted based on available data from the 9 fILD study participants using Wilcoxon Log Rank test to compare results for each dose to baseline as well as the prior dose; the study did not pre-specify a statistical analysis methodology and the results were not adjusted for multiplicity):

- Pulmonary vascular resistance reduced by 21% (average reduction of 125 dyne*sec*cm^{-5}; baseline of 583 dyne*sec*cm^{-5}); doses of iNO 30 ($p<0.01$), iNO 45 ($p<0.01$) and iNO 75 ($p=0.01$) were statistically significant as compared to baseline, with increased benefit ($p<0.01$) on dose escalation from iNO30 (30 mcg/kg IBW/hr) to iNO45 (45 mcg/kg IBW/hr);

- Mean pulmonary arterial pressure reduced by 12% (average reduction of 4 mmHg; baseline of 34.7 mmHg); doses of iNO 30 ($p=0.02$), iNO 45 ($p=0.03$) and iNO 75 ($p=0.01$) were statistically significant as compared to baseline;

- Data suggested that iNO was generally well-tolerated and may yield a favorable risk-benefit profile across doses.

INOpulse for PH-Sarcoidosis

We are also developing INOpulse for PH-Sarcoidosis. We believe the mechanism of action of inhaled nitric oxide as a targeted pulmonary vasodilator, and thus INOpulse, can be effective in treating PH related to other conditions including PH associated with sarcoidosis. Sarcoidosis is a multi-system disease which is characterized by the growth of granulomas (inflammatory cells) in one or more organs. The most frequent organs involved are the lungs and lymph nodes within the chest. Pulmonary hypertension may be present in as many as 74% of patients depending on the disease severity and how the pulmonary hypertension ("PH") is defined. The presence of PH in sarcoidosis is associated with a poor prognosis. There are a number of different mechanisms linking PH with sarcoidosis. The primary treatment for sarcoidosis is corticosteroids; however, the outcome of this treatment on the PH is unclear. There is no approved therapy for PH associated with sarcoidosis. Various PAH treatments have been tried including iNO and IV prostacyclin with some clinical and functional improvement.

In 2018, we also initiated development of INOpulse for the treatment of PH-Sarc. The study was a Phase 2 open-label dose escalation design that utilized right heart catheterization to assess the acute hemodynamic effect of INOpulse from a dose of iNO 30 to iNO 125 in PH-Sarc subjects. In December 2021, we announced the completion of the acute dose escalation phase of the study and that the top-line results demonstrated that INOpulse provided clinically meaningful improvements in pulmonary vascular resistance (statistical analysis was conducted based on available data from the 8 PH-Sarc study participants using Wilcoxon Log Rank test to compare results for each dose to baseline as well as the prior dose; the study did not pre-specify a statistical analysis methodology and the results were not adjusted for multiplicity):

- All eight subjects demonstrated decreases in mean pulmonary arterial pressure ("mPAP") and pulmonary vascular resistance ("PVR") across the doses of INOpulse utilized in the study.

- The dose of iNO45 (45 mcg/kg IBW/hr) resulted in a median drop of 20% (-54% to +22%) in PVR, compared to a median baseline PVR of 329 dyne/cm.sec-5. A reduction of 20% or more in PVR is generally considered to be clinically meaningful.

- Increasing to the highest dose, iNO125 (125 mcg/kg IBW/hr), demonstrated further improvement in PVR, with a median drop of 29% (-43% to -5%), achieving statistical significance from baseline (p=0.02) and from the preceding lower dose of iNO75 (75 mcg/kg IBW/hr) (p=0.02). During the study, seven out of eight patients escalated to the highest dose, iNO125.

- Along with the improvements in PVR, mPAP decreased by a median of 6-10% across the doses of iNO30 to iNO125, compared to a median baseline mPAP of 37.2 mmHg.

- No treatment-emergent adverse events or serious adverse events occurred during the acute hemodynamic dose escalation phase of the study.

INOpulse for PH-COPD

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

Disease Background and Market Opportunity

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

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

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

Scientific Rationale for Use of INOpulse for PH-COPD

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

PH-COPD patients generally have hypoxemia as a result of deteriorating lung function, which can be treated with supplemental oxygen therapy. However, these patients are not treated with currently approved PAH-specific drugs because these drugs can worsen hypoxemia. This worsening can occur when these drugs, which are systemically bioavailable, cause indiscriminate pulmonary vasodilation, even in poorly ventilated alveoli, resulting in lower average blood oxygenation levels. We believe that pulsed nitric oxide, as a locally active selective pulmonary vasodilator, can avoid the indiscriminate vasodilation associated with drugs that are systemically bioavailable. The INOpulse technology, by targeting the delivery of the pulse to the well ventilated alveoli, has the potential to drop pulmonary arterial pressure while avoiding the lowering of blood oxygen levels.

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

Clinical Development Program

INOpulse for PH-COPD is designated as a drug-device combination by the FDA and is being reviewed by the Division of Cardiovascular and Renal Products in the Center for Drug Evaluation and Research (“CDER”) with consultation from the Division of Pulmonary, Allergy, and Rheumatology Products and the Center for Devices and Radiological Health (“CDRH”). In our IND for PH-COPD, we referenced all of the information in our IND for PAH. The data referenced in our IND, as well as the years of use of the marketed product, demonstrate that nitric oxide is generally well tolerated. The FDA has agreed that the IND package is adequate for supporting Phase 2 clinical development of INOpulse for PH-COPD. The FDA also agreed that no additional pre-clinical studies are needed to support product approval.

We completed a randomized, placebo-controlled, double-blind, dose-confirmation Phase 2 clinical trial of INOpulse for PH-COPD in July 2014. We have received results from this trial, and have initiated further Phase 2 testing to demonstrate the potential benefit on exercise capacity. In September 2015, an oral presentation of late-breaking data from a clinical trial that we sponsored 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 over 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, with the first patient enrolled in October 2016. During September 2017, we shared the results of our Phase 2a PH-COPD study designed to evaluate the acute effects of pulsed inhaled nitric oxide, or iNO, on vasodilation as well as the chronic effect on hemodynamics and exercise tolerance. In May 2018, we announced that we reached agreement with the FDA on the design of our planned Phase 2b study of INOpulse for treatment of PH-COPD. The study will assess the effect of INOpulse on various parameters including exercise capacity, right ventricular function, oxygen saturation as well as other composite endpoints. We continue to evaluate alternatives for the funding and timing of this program.

INOpulse for Pulmonary Arterial Hypertension

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. 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.

Clinical Development Program

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 initiated the first of the two Phase 3 trials. The INOvation-1 trial was initiated with the first patient enrolled in June 2016. As agreed upon with the FDA, a pre-specified interim analysis was conducted by the Data Monitoring Committee, or DMC, in August 2018, after half of the planned subjects completed 16 weeks of blinded treatment. The data showed INOpulse provided clinically meaningful improvements in pulmonary vascular resistance (18%), cardiac output (0.7 L/min) and NT Pro-BNP. In addition, subjects on PAH background mono-therapy showed a 23 meter improvement in 6MWD, while subjects that were not on prostanoid background therapy showed a 17 meter improvement in 6MWD. However, the DMC determined that the overall change in 6MWD, the primary endpoint of the trial, was insufficient to support the continuation of the study. Accordingly, based on the DMC's recommendation, we discontinued the trial in August 2018. The trial results showed 6MWD was improved when subjects were on less background therapies and more patients deteriorated in 6MWD on placebo as compared to iNO. During the trial, however, the data suggested that INOpulse may have a favorable safety profile.

INOpulse for Other Pulmonary Hypertension Conditions

PH disease is often classified according to the WHO classification system which groups patients with PH according to the underlying etiologies, or causes, of the PH. In this system, PAH is defined as Group 1 and COPD and ILD (including fILD and IPF) are classified under Group 3, PH due to lung disease and/or hypoxemia. Group 5 PH

consists of PH associated with blood, systematic and metabolic disorders. This Group includes patients with PH-Sarc. We believe the mechanism of action of inhaled nitric oxide as a targeted pulmonary vasodilator, and thus INOpulse, can be effective in treating PH related to other conditions, including CTEPH and PH associated with pulmonary edema from high altitude sickness.

In 2013, riociguat (Adempas) was the first drug therapy approved for treating CTEPH, although other PAH medications are sometimes used to treat this condition. Patients with sarcoidosis are often treated with steroids or other anti-inflammatory medications, however, there are no therapies approved to treat the PH associated with this disease. Pulmonary edema from high altitude sickness is typically treated with oxygen therapy, however, there are no current treatments for PH associated with this disease.

Our current license from Ikaria covers the development of the Bellerophon indications as noted above.

Relationship with Ikaria after the Spin-Out

The development of our programs was initiated under the leadership of our scientific and development team while at Ikaria. Ikaria's lead product, INOmax, is an inhaled nitric oxide product used for the 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.

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. 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.

Exclusive Cross-License, Technology Transfer and Regulatory Matters Agreement

In February 2014, we entered into an exclusive cross-license, technology transfer and regulatory matters agreement with Ikaria. Pursuant to the terms of the license agreement, Ikaria granted to us a fully paid-up, non-royalty bearing, exclusive license under specified intellectual property rights controlled by Ikaria to engage in the development, manufacture and commercialization of nitric oxide, devices to deliver nitric oxide and related services for or in connection with out-patient, chronic treatment of patients with PAH, PH-COPD or PH-IPF. In July 2015, we entered into an amendment to the license agreement to expand the scope of our license to allow us to develop our INOpulse program for the treatment of three additional indications: CTEPH, PH associated with sarcoidosis and PH associated with pulmonary edema from high altitude sickness. Subject to the terms set forth therein, the amendment to the license agreement also provides that the Company will pay Ikaria a royalty equal to 5% of net sales of any commercialized products for the 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.

In April 2018, we expanded the scope of our license from PH-IPF to PH in patients with Pulmonary Fibrosis ("PH-PF"), which includes idiopathic interstitial pneumonias, chronic hypersensitivity pneumonitis, occupational and environmental lung disease, with a royalty equal to 1% of net sales of any commercial products for PH-PF.

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

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

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

Ikaria retains the right to develop and commercialize inhaled nitric oxide products, including pulsed products, in all indications other than the Bellerophon indications.

In February 2014, we also entered into drug and device clinical supply agreements with Ikaria. In November 2015, we entered into an amendment to the drug supply agreement. See “Manufacturing” below for a description of the drug and device clinical supply agreements.

In January 2023, we entered into a license agreement (the “License Agreement”) with Baylor BioSciences, Inc. (“Baylor”), pursuant to which Baylor received exclusive rights to develop and commercialize INOpulse within mainland China, Taiwan, Hong Kong and Macau (collectively, “Greater China”) for diseases associated with pulmonary hypertension, including the lead indication of fibrotic interstitial lung disease (“fILD”), as well as PAH, PH-Sarcoidosis, and PH-COPD, CTEPH and PH associated with pulmonary edema from high altitude sickness. Under the terms of the License Agreement, a license payment of $6 million, net of taxes and customary closing costs, is payable by Baylor within 90 days. Additionally, we are entitled to royalties of 5% on net sales by Baylor resulting from all of the licensed INOpulse indications within Greater China.

Manufacturing

INOpulse Drug Product

In February 2014, we and a subsidiary of Ikaria entered into a drug supply agreement which was subsequently amended in November 2015. Under this agreement, Ikaria has agreed to use commercially reasonable efforts to supply inhaled nitric oxide for us in our clinical trials, and we have agreed to purchase our clinical supply of inhaled nitric oxide from Ikaria. We have also granted Ikaria a right of first negotiation in the event that we desire to enter into a commercial supply agreement with a third party for supply of nitric oxide for inhalation. The drug supply agreement will expire on a product-by-product basis on the date we discontinue clinical development of such product. In addition, either party may terminate the drug supply agreement in the event of an uncured material breach by the other party.

Ikaria manufactures pharmaceutical-grade nitric oxide at its facility in Port Allen, Louisiana. This facility, which we believe is operated in compliance with current Good Manufacturing Practices, or cGMP, is the only FDA-approved site in the world for manufacturing medical nitric oxide.

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

The filling process has been developed by Ikaria as a high-throughput batch fill process that leverages several technologies that Ikaria has developed, and we have licensed, to fill the cartridge (containers) at a high pressure and purity.

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

INOpulse Drug Delivery Systems

In February 2015, we entered into an agreement with Flextronics Medical Sales and Marketing Ltd., a subsidiary of Flextronics International Ltd., or Flextronics, to manufacture and service the INOpulse device. In June 2018, we entered into a similar agreement with Benchmark Electronics, Inc. to manufacture and service additional INOpulse devices.

PH patients have the potential for rebound PH, which is a sudden and serious increase in pulmonary arterial pressure that results from therapy withdrawal. However, in the PAH Phase 2 trial and Phase 2 PH-PF trial, all patients were tested for rebound PH and we found no adjudicated cases of rebound PH with this testing. Though the likelihood of rebound PH is very low, all of our patients are provided with a backup system.

Competition

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

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

Currently, there are no approved therapies for treating PH-COPD, and the only generally accepted treatments are LTOT, pulmonary rehabilitation and lung transplant, and we are not aware of any therapies for PH-COPD in advanced clinical development. Currently, we are aware of 14 drugs approved for the treatment of PAH and also other potential therapies in clinical development, however, only one of these therapies, inhaled trespostinil, is currently approved for the treatment of PH associated with fILD and none are currently approved for the treatment of PH associated with sarcoidosis.

Patents and Proprietary Rights

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

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

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

A third party may hold intellectual property, including patent rights that are important or necessary to the development of our programs. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our product candidates, in which case we would be required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially. For example, if we want to expand the indications for which we could develop and commercialize pulsed nitric oxide beyond the Bellerophon indications, we will need to obtain a license from Ikaria.

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

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

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

INOpulse

As of December 31, 2022, we hold exclusive licenses from Ikaria to at least 100 patents and pending patent applications in both the United States and foreign countries including Australia, Brazil, Canada, China, Eurasia, Europe,

Hong Kong, India, Indonesia, Israel, Japan, Korea, Mexico, the Philippines, Russia, Singapore and South Africa. Certain of these issued patents and patent applications, if issued, will expire as late as 2033. These patent rights have been exclusively licensed for the treatment of patients with Bellerophon indications and cover methods of delivery and the drug delivery device, as well as important safety features and the ornamental design of the drug delivery device.

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

Another important basis for patent exclusivity is based on an in-licensed portfolio of patents, directed to novel nasal cannula features that we believe are necessary for the accurate, safe and efficacious administration of pulsed nitric oxide. The patent family consists of seven issued U.S. patents and issued patents in Australia, Brazil, China, Eurasia, Europe, Hong Kong, Israel, Japan, Korea, Mexico and South Africa, as well as pending applications in the United States as well as Australia, Canada, Europe, Israel, India, Japan, Korea, Mexico and South Africa. Each of these patents and patent applications, if issued, will expire in 2033 in the United States and abroad.

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

Several other patent families directed to device and safety features are issued and pending. One U.S. issued patent directed to the valve configuration of our proprietary drug delivery device and the shape of the nitric oxide pulses will expire in 2039. Furthermore, design patents covering the ornamental designs of the intended commercial device and clinical device have been granted.

We have also filed several Company-owned patent applications relating to the use and administration of nitric oxide and devices for administering nitric oxide. These Company-owned patent families are currently pending as international PCT patent applications, US applications and/or applications in foreign countries including Argentina, Australia, Brazil, Canada, China, Eurasia, Europe, Hong Kong, India, Indonesia, Israel, Japan, Korea, Mexico, New Zealand, the Philippines, Singapore, South Africa and/or Taiwan, and any patents that issue in these families will expire in 2039, 2040, 2041 or 2043. The patent families relate to the use of inhaled nitric oxide for the improvement of right and/or left ventricular function, the use of inhaled nitric oxide for the treatment of PH-ILD, the use of inhaled nitric oxide and oxygen for the treatment of PH, and treating PH by maintaining dosing frequency and/or minimizing skipped breaths during pulsed administration of inhaled nitric oxide. Additional patent families relate to methods of administering pulsed nitric oxide, administration of nitric oxide for improvement of severe hypoxemia, administration of nitric oxide in combination with PDE-5 inhibitors, administration of nitric oxide to improve activity levels in patients having lung-related impairment, improvement in pulmonary arterial compliance with inhaled nitric oxide treatment, use of inhaled nitric oxide treatment of infection (including infection with SARS-CoV2) and treatment of COVID-19, use of inhaled nitric oxide for decreasing pulmonary arterial pressure and pulmonary vascular resistance and methods for pulsatile delivery of a gaseous drug.

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

Patent Term

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

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

Trade Secrets

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

Trademarks

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

Government Regulation

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

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a

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

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

- completion of pre-clinical laboratory tests, animal studies and formulation studies in compliance with applicable good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND which must take effect before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, at each clinical site before a clinical trial may be initiated at that site;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;
- preparation and submission to the FDA of an NDA;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity; and
- FDA review and approval of the NDA.

Pre-Clinical Studies

Pre-clinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as *in vitro* and animal studies to assess the toxicity, safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of pre-clinical and other non-clinical studies is subject to FDA regulations, including GLP regulations. An IND sponsor must submit the results of the pre-clinical studies, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, to the FDA as part of an IND. Some long-term pre-clinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to the proposed clinical trial and places the IND on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

After the IND becomes effective, the sponsor continues to perform nonclinical studies including those related to the development of a manufacturing process that is capable of consistently producing quality batches of the drug candidate and the development of methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to support the eventual shelf life and storage of the drug.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written protocols detailing, among other things, the objectives of the clinical trial, the

parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each phase of a clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

In addition, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations.

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

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

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

- Phase 3: The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product.

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

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse effects, or SAEs, occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted. In addition, the sponsor of a clinical trial must register and post information about the trial on the National Institutes of Health's ClinicalTrials.gov website. Information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. Sponsors are also obligated to disclose the results of their clinical trials after completion, although in some cases disclosure of the results of these trials can be delayed for up to two years after the trial completion date. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

Traditional and Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full, or pivotal, clinical trials that must contain substantial evidence of the safety and efficacy of the proposed new product. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the applicant to rely, in part, on the FDA's previous findings of safety and efficacy for a drug product previously approved under an NDA, published literature, or a combination of both. Specifically, Section 505(b)(2) permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. If the 505(b)(2) applicant can establish that reliance on studies conducted for a previously-

approved product or FDA's previous findings regarding safety or effectiveness is appropriate, the applicant may eliminate the need to conduct certain pre-clinical studies or clinical trials of the new product. Thus, Section 505(b)(2) often provides an alternate and potentially more expeditious pathway to FDA approval via NDA for new or improved formulations or new uses of previously approved products.

Unlike the abbreviated new drug, or ANDA, pathway used by developers of generic versions of innovator drugs, which does not allow applicants to submit new clinical data other than bioavailability or bioequivalence data, the 505(b)(2) NDA pathway does not preclude the possibility that a follow-on applicant would need to conduct additional clinical trials or nonclinical studies; for example, a 505(b)(2) applicant may be seeking approval to market a new dosage form of a previously approved drug or for the treatment of a different patient population, which would require new clinical data to demonstrate safety or effectiveness. The FDA will generally require companies to perform additional studies to support any differences from the previously approved product, called a listed drug. The FDA may then approve the new drug candidate for all or some of the label indications for which the listed drug has been approved, or for any new indication sought by the 505(b)(2) applicant, as applicable. Accordingly, a 505(b)(2) NDA is subject to the same patent certification requirements as an ANDA with respect to the previously-approved drug being referenced, and it may be eligible for the three-year period of marketing exclusivity based on the submission of new clinical data that are essential to the approval of the new 505(b)(2) drug product. For more information, see section below entitled *Hatch-Waxman Act and Marketing Exclusivity*.

Submission of an NDA to the FDA

Assuming successful completion of clinical trials and other requirements, the results of the non-clinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug candidate for one or more indications. Under federal law, the submission of most NDAs is additionally subject to a user fee, which for FY2023 exceeds $3.2 million for NDAs that require clinical trials, and the sponsor of an approved NDA is also subject to annual program fee of $393,933. These fees are typically increased annually.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor by the 74th day after the FDA's receipt of the submission whether the application will be filed because it is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or PDUFA, the FDA has agreed to specified performance goals in the review process of NDAs. For most applications involving first-in-kind molecular entities, FDA has ten months from the date of filing in which to complete its initial review of a standard application and respond to the applicant, and six months from the date of filing for an application with "priority review" products are meant to be reviewed within six months of filing. Priority review can be applied to drugs intended to treat a serious condition and that the FDA determines offer major advances in treatment by providing a significant improvement in safety or effectiveness, or that provide a treatment where no adequate therapy exists. Even if the NDA is filed by the FDA, however, companies cannot be sure that any approval will be granted on a timely basis, if at all. Moreover, the FDA does not always meet its PDUFA goal dates, and the review process for both standard and priority new drug applications may be extended by the FDA for various reasons, including for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will often inspect one or more clinical sites to assure compliance with GCP.

The FDA may refer an application for a novel drug to an advisory committee. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a

recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations when making decisions.

Special Protocol Assessment

A sponsor of an IND may request that the FDA evaluate within 45 days certain protocols and issues relating to the protocols to assess whether they are adequate to meet scientific and regulatory requirements for approval. If the trials were the subject of discussion at an end-of-Phase 2 meeting with the FDA, an SPA may be requested for clinical protocols for Phase 3 trials whose data is intended to form the primary basis for an efficacy claim. If the sponsor and the FDA reach a written agreement regarding the protocol, the SPAs will be considered binding on the FDA and will not be changed unless the sponsor fails to follow the agreed-upon protocol, data supporting the request are found to be false or incomplete, or the FDA determines that a substantial scientific issue essential to determining the safety or effectiveness of the drug was identified after the testing began. Even if an SPA is agreed to, approval of the NDA is not guaranteed since a final determination that an agreed-upon protocol satisfies a specific objective, such as the demonstration of efficacy, or supports an approval decision, will be based on a complete review of all the data in the NDA.

Expedited Review Programs and Accelerated Approval

The FDA has various programs, including Fast Track, priority review, breakthrough therapy designation, and accelerated approval, which are intended to expedite or simplify the process for reviewing drugs, and/or provide for approval on the basis of surrogate endpoints. Even if a drug qualifies for one or more of these programs, the FDA may later decide that the drug no longer meets the conditions for qualification or that the time period for FDA review or approval will not be shortened. Generally, drugs that may be eligible for these programs are those for serious or life threatening conditions, those with the potential to address unmet medical needs, and those that offer meaningful benefits over existing treatments. For example, Fast Track is a process designed to facilitate the development, and expedite the review, of drugs to treat serious diseases and fill an unmet medical need. The request may be made at the time of IND submission and generally no later than the pre-NDA meeting. The FDA will respond within 60 calendar days of receipt of the request. Priority review, which is requested at the time of NDA submission, is designed to give drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists an initial review within six months as compared to a standard review time of ten months. Although Fast Track and priority review do not affect the standards for approval, the FDA will attempt to facilitate early and frequent meetings with a sponsor of a Fast Track designated drug and expedite review of the application for a drug designated for priority review.

In contrast, accelerated approval provides an earlier pathway to approval of drugs to treat serious or life-threatening diseases and that that generally provide a meaningful therapeutic advantage to patients over existing treatments and demonstrate an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. The FDA may also grant accelerated approval for such a drug when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval when the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate long-term clinical benefit of a drug. Discussions with the FDA about the feasibility of an accelerated approval typically begin early in the development of the drug in order to identify, among other things, an appropriate endpoint. The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or to confirm the

predicted clinical benefit of the product during post-marketing studies, would allow the FDA to withdraw approval of the drug. Products granted accelerated approval also are subject to additional requirements for the pre-dissemination review by the FDA of proposed promotional materials both during the NDA review process and for 120 days after marketing approval.

In 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act, or FDASIA. This law established a new designation for drugs as "breakthrough therapies." A product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s), such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to products designated as breakthrough therapies, including: holding meetings with the sponsor throughout the development process; providing timely advice to the sponsor regarding development and approval, including working with the sponsor on an alternative clinical trial design; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and initiating a rolling review of the NDA. Although a request for breakthrough therapy designation may be submitted with the sponsor's original IND, typically the timing of such requests follows the completion of Phase 1 or Phase 2 studies, due to the statutory criterion that the FDA make these determinations based on preliminary clinical evidence.

The FDA's Decision on an NDA

The approval process is lengthy and often difficult, and the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical or other data and information. On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter, or CRL, generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

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

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

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for that are now assessed as program fees for certain NDA-approved drugs. The most recent, 2017 reauthorization of PDUFA restructured the prescription drug user fee program to eliminate the previously collected establishment and supplemental application fees.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and some state agencies, and are subject to periodic unannounced inspections by the FDA for compliance with cGMP and other requirements. Changes to the manufacturing process, specifications or container closure system for an approved drug product are strictly regulated and often require prior FDA approval before being implemented. Compliance with cGMPs requires, among other things, the investigation and correction of any deviations from cGMP and the imposition of reporting and documentation requirements upon the sponsor and the manufacturer. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance and ensure ongoing compliance with other statutory requirements the FDCA, such as the requirements for making manufacturing changes to an approved NDA.

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

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

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

In addition, the distribution of prescription pharmaceutical products is subject to a variety of federal and state laws, the most recent of which is still in the process of being phased in to the U.S. supply chain and regulatory framework. The Prescription Drug Marketing Act of 1987, or PDMA, was the first federal law to set minimum standards for the registration and regulation of drug distributors by the states and to regulate the distribution of drug samples. Today, both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution. Congress more recently enacted the Drug Supply Chain Security Act, or DSCSA, which made significant amendments to the FDCA, including by replacing certain provisions from the PDMA pertaining to wholesale distribution of prescription drugs with a more comprehensive statutory scheme. The DSCSA now requires uniform national standards for wholesale distribution and, for the first time, for third-party

logistics providers; it also provides for preemption of certain state laws in the areas of licensure and prescription drug traceability. The product tracing provisions of the DSCSA were negotiated over many years by groups representing all supply chain stakeholders. Accordingly, the comprehensive system envisioned by this law is being implemented both by the FDA and those various stakeholders towards the shared goal of building an interoperable electronic system to identify and trace prescription drugs distributed in the United States for enhanced supply chain security. The DSCSA mandates phased-in and resource-intensive obligations for pharmaceutical manufacturers, repackagers, wholesale distributors, and dispensers (primarily pharmacies) over a 10-year period that is expected to culminate in November 2023.

Hatch-Waxman Act and Marketing Exclusivity

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

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

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

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. In cases where such exclusivity has been granted, an ANDA may not be submitted to the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication.

The Hatch-Waxman Amendments also amended the FDCA to create Section 505(b)(2) of the FDCA, and as previously described in "*Traditional and Section 505(b)(2) NDAs*," Section 505(b)(2) permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. Due to the inclusion of new clinical investigations conducted to demonstrate the safety and efficacy of the new product that relies in part on am FDA-approved listed drug, new drug applications submitted under Section 505(b)(2) are also eligible for three-year exclusivity, or in certain rare cases, five-year new chemical entity exclusivity. Accordingly, when it comes to the various forms of marketing and data exclusivity available to NDA applicants under the FDCA, a 505(b)(2) application is more similar to a traditional NDA than a generic drug application. However, the 505(b)(2) NDA follows similar procedures as an ANDA with respect to the required patent certifications, the application of the 30-month stay, and other regulatory requirements of Hatch-Waxman that may be triggered based on the nature of the listed drug being relied upon by the 505(b)(2) applicant.

Hatch-Waxman Patent Certification and the 30-Month Stay

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

Specifically, under FDA's regulations implementing the Hatch-Waxman provisions, as amended, an ANDA or 505(b)(2) applicant must certify with respect to each listed patent that:

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

If a Paragraph I or II certification is filed, the FDA may make approval of the application effective immediately upon completion of its review. If a Paragraph III certification is filed, the approval may be made effective on the patent expiration date specified in the application, although a tentative approval may be issued before that time. If an application contains a Paragraph IV certification, a series of events will be triggered, the outcome of which will determine the effective date of approval of the ANDA or 505(b)(2) application. The ANDA or Section 505(b)(2) application also will not be approved until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, identified in the Orange Book for the listed drug has expired.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the follow-on applicant does not challenge the listed patents or indicate that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the ANDA applicant is not seeking approval).

If the ANDA applicant or 505(b)(2) applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA owner and patent holders once the ANDA or 505(b)(2) NDA has been accepted for filing by the FDA. The NDA owner and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) NDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA or 505(b)(2) applicant. Alternatively, if the listed patent holder does not file a patent infringement lawsuit within the required 45-day period, the follow-on applicant's ANDA or 505(b)(2) NDA will not be subject to the 30-month stay.

Orphan Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product). A company must

request orphan product designation before submitting an NDA for the relevant drug candidate (which may be a traditional new chemical entity or a 505(b)(2) NDA candidate). If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation, the product will be entitled to orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. If a designated orphan drug ultimately receives marketing approval for an indication broader than what was described in its orphan drug designation request, it may not be entitled to exclusivity under the Orphan Drug Act.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act, or PREA, amendments to the FDCA, an NDA or supplement to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted in 2012, made permanent PREA to require that a sponsor who is planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration submit an initial Pediatric Study Plan, or PSP, within 60 days of an end-of-Phase II meeting or, if there is no such meeting, as early as practicable before the initiation of the Phase III or Phase II/III study. Unless otherwise required by regulation, PREA does not apply to any drug for an indication where orphan designation has been granted, although FDA has recently taken steps to limit what it considers abuse of this statutory exemption in PREA by announcing that it does not intend to grant any additional orphan drug designations for rare pediatric subpopulations of what is otherwise a common disease.

The sponsor or the FDA may request a deferral of pediatric studies for some or all of the pediatric subpopulations. A deferral may be granted for several reasons, including a finding that the drug or biologic is ready for approval for use in adults before pediatric studies are complete or that additional safety or effectiveness data needs to be collected before the pediatric studies begin. The FDA must send a non-compliance letter to any sponsor that fails to submit the required assessment, keep a deferral current or fails to submit a request for approval of a pediatric formulation.

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

Patent Term Restoration and Extension

A patent claiming a prescription drug or medical device for which FDA approval is granted may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review provided that certain statutory and regulatory requirements are met. The length of the patent term extension is related to the length of time the drug is under regulatory review while the patent is in force. The restoration period granted on a patent covering a new prescription drug product is typically one-half the time between the date a clinical investigation on human beings is begun and the

submission date of an application for premarket approval of the product, plus the time between the submission date of an application for approval of the product and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the NDA approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Review and Approval of Medical Devices in the United States

Medical devices are strictly regulated by the FDA in the United States. Under the FDCA, a medical device is defined as "an instrument, apparatus, implement, machine, contrivance, implant, *-in vitro-* reagent, or other similar or related article, including a component, part or accessory which is, among other things: intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes." This definition provides a clear distinction between a medical device and other FDA regulated products such as drugs. If the primary intended use of a medical product is achieved through chemical action or by being metabolized by the body, the product is usually a drug or biologic. If not, it is generally a medical device.

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

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

Class II devices are moderate risk devices and are subject to the FDA's general controls, and any other special controls, such as performance standards, post-market surveillance, and FDA guidelines, deemed necessary by the FDA to provide reasonable assurance of the devices' safety and effectiveness. Premarket review and clearance by the FDA for most Class II devices is accomplished through the 510(k) process, although some Class II devices are exempt from the 510(k) requirements. To obtain 510(k) clearance, a sponsor must submit to the FDA a premarket notification demonstrating that the device is substantially equivalent to a device that is already legally marketed in the United States and for which a PMA was not required (i.e., a Class II device). The device to which the sponsor's device is compared for the purpose of determining substantial equivalence is called a "predicate device." The FDA's goal is to make a substantial equivalence determination within 90 days of FDA's receipt of the 510(k) application, but it often takes longer if the FDA requests additional information. Most 510(k)s do not require supporting data from clinical trials, but the FDA may request such data. After a device receives 510(k) clearance, any modification that could significantly affect its safety or effectiveness, or that would constitute a major change in its intended use, will require a new clearance or possibly a pre-market approval. Premarket notifications are subject to user fees, unless a specific exemption applies.

Class III devices are deemed by the FDA to pose the greatest risk to patients, such as those for which reasonable assurance of the device's safety and effectiveness cannot be assured solely by the general controls and special controls described above and that are life-sustaining or life-supporting. All Class III devices must be reviewed and approved by the FDA through the PMA process. A PMA must be supported by extensive data including, but not limited to, technical, preclinical, clinical trials, manufacturing and labeling to demonstrate to the FDA's satisfaction the safety

and effectiveness of the device for its intended use. After a PMA is sufficiently complete, the FDA will accept the application for filing and begin an in-depth review of the submitted information. By statute, the FDA has 180 days to review the accepted application, although review of the application generally can take between one and three years. During this review period, the FDA may request additional information or clarification of information already provided. Also during the review period, an advisory panel of experts from outside the FDA may be convened to review and evaluate the application and provide recommendations to the FDA as to the approvability of the device. Although the FDA is not bound by the advisory panel decision, it considers such recommendations when making final decisions on approval. In addition, the FDA will conduct a preapproval inspection of the manufacturing facility to ensure compliance with the QSR. New premarket approval applications or premarket approval application supplements are also required for product modifications that affect the safety and efficacy of the device. PMA (and supplemental PMAs) are subject to significantly higher user fees than are 510(k) premarket notifications.

Medical device types that the FDA has not previously classified as Class I, II or III are automatically classified into Class III regardless of the level of risk they ultimately pose to patients and/or users. The Food and Drug Administration Modernization Act of 1997 established a new route to market for low to moderate risk medical devices that are automatically placed into Class III due to the absence of a predicate device, called the "Request for Evaluation of Automatic Class III Designation," or the de novo classification procedure. This procedure allows a manufacturer whose novel device is automatically classified into Class III to request down-classification of its medical device into Class I or Class II based on a benefit-risk analysis demonstrating the device actually presents low or moderate risk, rather than requiring the submission and approval of a PMA application. Prior to the enactment of the Food and Drug Administration Safety and Innovation Act of 2012, or FDASIA, a medical device could only be eligible for de novo classification if the manufacturer first submitted a 510(k) premarket notification and received a determination from the FDA that the device was not substantially equivalent. FDASIA streamlined the de novo classification pathway by permitting manufacturers to request de novo classification directly without first submitting a 510(k) premarket notification to the FDA and receiving a not substantially equivalent determination. Under FDASIA, the FDA is required to classify the device within 120 days following receipt of the de novo application however, the most recent FDA premarket review goals state that in fiscal year 2023, FDA will attempt to issue a decision on 65% of all de novo classification requests received within 150 days of receipt. If the manufacturer seeks reclassification into Class II, the manufacturer must include a draft proposal for special controls that are necessary to provide a reasonable assurance of the safety and effectiveness of the medical device. In addition, the FDA may reject the reclassification petition if it identifies a legally marketed predicate device that would be appropriate for a 510(k) or determines that the device is not low to moderate risk or that general controls would be inadequate to control the risks and special controls cannot be developed. De novo reclassification requests are also subject to user fees, unless a specific exemption applies.

Post-Marketing Restrictions and Enforcement

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

- submitting and updating establishment registration and device listings with the FDA;
- compliance with the QSR, which requires manufacturers to follow stringent design, testing, control, documentation, record maintenance, including maintenance of complaint and related investigation files, and other quality assurance controls during the manufacturing process;
- unannounced routine or for-cause device facility inspections by the FDA, which may include our suppliers' facilities; and
- labeling regulations, which prohibit the promotion of products for uncleared or unapproved (or "off-label") uses and impose other restrictions relating to promotional activities;
- corrections and removal reporting regulations, which require that manufacturers report to the FDA field corrections or removals if undertaken to reduce a risk to health posed by a device or to remedy a violation of the FDCA that may present a risk to health; and

- post-market surveillance regulations, which apply to certain Class II or III devices when necessary to protect the public health or to provide additional safety and effectiveness data for the device.

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

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

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

- warning letters, fines, injunctions or civil penalties;
- recalls, detentions or seizures of products;
- operating restrictions;
- delays in the introduction of products into the market;
- total or partial suspension of production;
- delay or refusal of the FDA or other regulators to grant 510(k) clearance or PMA approvals of new products;
- withdrawals of 510(k) clearance or PMA approvals; or
- in the most serious cases, criminal prosecution.

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

Review and Approval of Combination Products in the United States

Products comprised of separate components (e.g., a drug and a device; a biologic and a device; a drug and a biologic; or a drug, device, and a biologic) are known as "combination products." Such products often raise regulatory, policy and review management challenges because they integrate components that are regulated under different types of regulatory requirements and by different FDA Centers, namely, CDER, CDRH, or the Center for Biologics Evaluation and Research. Differences in regulatory pathways for each component can impact the regulatory processes for all aspects of product development and management, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, user fees and post-approval modifications. Specifically, under regulations issued by the FDA, a combination product may be:

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

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

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

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

The FDA's Office of Combination Products ("OCP") was established in 2003 to provide prompt determination of the FDA Center with primary jurisdiction over the review and regulation of a combination product; ensure timely and effective premarket review by overseeing the timeliness of and coordinating reviews involving more than one center; ensure consistent and appropriate post-market regulation; resolve disputes regarding review timeliness; and review/revise agreements, guidance and practices specific to the assignment of combination products.

OCP, determines which Center will have primary jurisdiction (the "Lead Center") for the combination product based on the combination product's "primary mode of action" ("PMOA"). A mode of action is the means by which a product achieves an intended therapeutic effect or action. The PMOA is the mode of action that provides the most important therapeutic action of the combination product, or the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. The Lead Center has primary responsibility for the review and regulation of a combination product; however a second Center is often involved in the review process, especially to provide input regarding the "secondary" component(s). In most instances, the Lead Center applies its usual regulatory pathway. For example, a drug-device combination product assigned to CDER will typically be reviewed under an NDA, while a drug-device combination product assigned to CDRH is typically reviewed under through a 510(k), Premarket Approval Application ("PMA"), or de novo reclassification request.

Often it is difficult for OCP to determine with reasonable certainty the most important therapeutic action of the combination product. In those difficult cases, OCP will consider consistency with other combination products raising similar types of safety and effectiveness questions, or which Center has the most expertise to evaluate the most significant safety and effectiveness questions raised by the combination product. A sponsor may use a voluntary formal process, known as a Request for Designation, when the product classification is unclear or in dispute, to obtain a binding decision as to which center will regulate the combination product. If the sponsor objects to that decision, it may request that the agency reconsider that decision.

Combination products are subject to application User Fees based on the type of application submitted for the product's premarket approval or clearance. For example, a combination product for which an NDA is submitted is subject to the NDA fee under the Prescription Drug User Fee Act. Likewise, a combination product for which a PMA is submitted is subject to the PMA fee under the Medical Device User Fee and Modernization Act.

Since a combination product incorporates two or more components that have different regulatory requirements, a combination product manufacturer must comply with all cGMP and QSR requirements that apply to each component. The FDA has issued a combination product cGMP regulation, along with final guidance, describing two approaches a combination product manufacturer may follow to demonstrate compliance. Under these two options, the manufacturer demonstrates compliance with

1. All cGMP regulations applicable to each separate regulated component included in the combination product; or

2. Either the drug cGMPs or the QSR, as well as with specified provisions from the other of these two sets of requirements (also called the "streamlined approach").

We believe that our INOpulse product will be reviewed as NDAs by CDER with consulting review on the device component provided by CDRH. The QSR will apply to all manufacturing of our device components and we may be subject to additional QSR requirements applicable to medical devices, such as management responsibility, design controls, purchasing controls, and corrective and preventive action.

Review and Approval of Drug Products in the European Union

In addition to regulations in the United States, we are and will be subject, either directly or through our distribution partners, to a variety of regulations in other jurisdictions governing, among other things, clinical trials and future commercial sales and distribution of our products, if approved in those markets.

We must obtain the requisite approvals from regulatory authorities in non-U.S. countries prior to the commencement of clinical trials or marketing of a product in those countries. Moreover, the time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others. As of January 31, 2020, the United Kingdom (UK) is no longer a member state of the EU, and therefore a separate marketing authorization application ("MAA") and approval will be required to market a medicinal product in the UK.

As in the United States, medicinal products can be marketed in the EU only if a marketing authorization from the competent regulatory agencies has been obtained. Similar to the United States, the various phases of preclinical and clinical research in the EU are subject to significant regulatory controls. Also similar to the United States, when a drug-device combination product's principal intended action is accomplished by the drug constituent part, the EU regulates the combination product as a medicinal product.

Pursuant to the European Clinical Trials Directive, a system for the approval of clinical trials in the EU has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of an EU member state in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial after a competent ethics committee has issued a favorable opinion. Clinical trial applications must be accompanied by an investigational medicinal product dossier with supporting information prescribed by the European Clinical Trials Directive and corresponding national laws of the member states and further detailed in applicable guidance documents. In April 2014, the new Clinical Trials Regulation, (EU) No 536/2014 (Clinical Trials Regulation) was adopted and it is anticipated to come into application in late 2021. The Clinical Trials Regulation will be directly applicable in all the EU Member States, repealing the current Clinical Trials Directive 2001/20/EC. Conduct of all clinical trials performed in the European Union (EU) will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation becomes applicable. The extent to which ongoing clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the European Union. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the "EU portal"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned). Part II is assessed separately by each Member State concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

To obtain marketing approval of a drug in the EU, an applicant must submit an MAA either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization by the

European Commission that is valid for all EU member states, Iceland, Lichtenstein and Norway. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products (such as gene-therapy, somatic cell-therapy or tissue-engineered medicines) and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of certain diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. Under the centralized procedure the maximum timeframe for the evaluation of an MAA by the European Medicines Agency ("EMA") is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the Committee for Medicinal Products for Human Use ("CHMP"). Accelerated assessment might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. The timeframe for the evaluation of an MAA under the accelerated assessment procedure is of 150 days, excluding stop-clocks.

The decentralized procedure is available to applicants who wish to market a product in specific EU member states where such product has not received marketing approval in any EU member states before. The decentralized procedure provides for an applicant to apply to one-member state to assess the application (the reference member state) and specifically list other member states in which it wishes to obtain approval (concerned member states). Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labelling and package leaflet, to the reference member state and each concerned member state. The reference member state prepares a draft assessment report and drafts of the related materials within 210 days after receipt of a valid application which is then reviewed and approved commented on by the concerned member states. Within 90 days of receiving the reference member state's assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials.

In the EU, only products for which marketing authorizations have been granted may be promoted. A marketing authorization is valid for five years in principle and the marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the authorizing member state. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal. Any authorization which is not followed by the actual placing of the drug on the EU market (in case of centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid (the so-called sunset clause). Even if authorized to be marketed in the EU, prescription-only medicines may only be promoted to health care professionals, not the general public. All promotion should be in accordance with the particulars listed in the summary of product characteristics. Promotional materials must also comply with various laws, and codes of conduct developed by pharmaceutical industry bodies in the EU which govern (among other things) the training of sales staff, promotional claims and their justification, comparative advertising, misleading advertising, endorsements, and (where permitted) advertising to the general public. Failure to comply with these requirements could lead to the imposition of penalties by the competent authorities of the EU member states. The penalties could include warnings, orders to discontinue the promotion of the drug product, seizure of promotional materials, fines and possible imprisonment.

Rest of World Government Regulation

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of drug products. Whether or not it obtains FDA approval for a product, the company will have to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between and among countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other

countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Pharmaceutical Coverage, Pricing and Reimbursement

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

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

In Europe and other countries outside of the United States, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed to. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. In some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

Healthcare Law and Regulation

If our product candidates are approved in the United States, we will have to comply with various U.S. federal and state laws, rules and regulations pertaining to healthcare fraud and abuse, including anti-kickback laws and physician self-referral laws, rules and regulations. Violations of the fraud and abuse laws are punishable by criminal and civil sanctions, including, in some instances, exclusion from participation in federal and state healthcare programs, including Medicare and Medicaid. These laws include the following:

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

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

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

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

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

- the federal transparency requirements under the Physician Payments Sunshine Act require manufacturers of FDA-approved drugs, devices, biologics and medical supplies covered by Medicare or Medicaid to report, on an annual basis, to the Department of Health and Human Services information related to payments and other transfers of value to physicians, teaching hospitals, and certain advanced non-physician health care practitioners and physician ownership and investment interests; and

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

Some state laws require pharmaceutical or medical device companies to comply with the relevant industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures.

State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. We also may be subject to, or may in the future become subject to, U.S. federal and state, and foreign laws and regulations imposing obligations on how we collect, use, disclose, store and process personal information. Our actual or perceived failure to comply with such obligations could result in liability or reputational harm and could harm our business. Ensuring compliance with such laws could also impair our efforts to maintain and expand our customer base and thereby decrease our future revenues.

Health Care Reform and Potential Changes to Laws and Regulations

FDA and other regulatory authority policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. For example, in December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and devices and to spur innovation, but its ultimate implementation is uncertain. In addition, in August 2017, the FDA Reauthorization Act was signed into law, which reauthorized the FDA's user fee programs and included additional drug and device provisions that build on the Cures Act. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we otherwise may have obtained and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in health care systems with the stated goals of containing health care costs, improving quality and/or expanding access. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products and services, implementing reductions in Medicare and other health care funding and applying new payment methodologies. For example, in March 2010, the Patient Protection and Affordable Care Act ("ACA") was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced a new methodology by which rebates

owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care plans; imposed mandatory discounts for certain Medicare Part D beneficiaries as a condition for manufacturers' outpatient drugs coverage under Medicare Part D; and established a Center for Medicare Innovation at the U.S. Centers for Medicare and Medicaid Services ("CMS"), to test innovative payment and service delivery models to lower Medicare and Medicaid spending. As another example, the 2021 Consolidated Appropriations Act (P.L. 116-260) signed into law on December 27, 2020 incorporated extensive health care provisions and amendments to existing laws, including a requirement that all manufacturers of drug products covered under Medicare Part B report the product's average sales price, or ASP, to DHHS beginning on January 1, 2022, subject to enforcement via civil money penalties.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the ACA, and as a result certain sections of the ACA have not been fully implemented or effectively repealed. In particular, in December of 2018, a Texas U.S. District Court Judge ruled that the ACA is unconstitutional in its entirety because the individual mandate was repealed by Congress as part of the Tax Cuts and Jobs Act, effective January 1, 2019. In December 2019, the Fifth Circuit Court of Appeals upheld the district court's ruling that the individual mandate in the ACA was unconstitutional but remanded the case to the district court to determine whether other reforms enacted as part of the ACA but not specifically related to the individual mandate or health insurance could be severed from the rest of the ACA so as not to have the law declared invalid in its entirety. On March 2, 2020, the United States Supreme Court granted the petitions for writs of certiorari to review this case and allocated one hour for oral arguments, which occurred on November 10, 2020. A decision from the Supreme Court is expected to be issued in spring 2021. It is unclear how this litigation and other efforts to repeal and replace the ACA will affect the implementation of that law, the pharmaceutical industry more generally, and our business. We continue to evaluate the potential impact of the ACA and its possible repeal or replacement on our business.

Other legislative changes have been proposed and adopted in the United States since the ACA that may affect health care expenditures. For example, the 2020 Consolidated Appropriations Act (P.L. 116-94) includes a piece of bipartisan legislation called the Creating and Restoring Equal Access to Equivalent Samples Act of 2019 or the "CREATES Act." The CREATES Act aims to address the concern articulated by both the FDA and others in the industry that some brand manufacturers have improperly restricted the distribution of their products, including by invoking the existence of a REMS for certain products, to deny generic and biosimilar product developers access to samples of brand products. Because generic and biosimilar product developers need samples to conduct certain comparative testing required by the FDA, some have attributed the inability to timely obtain samples as a cause of delay in the entry of generic and biosimilar products. To remedy this concern, the CREATES Act establishes a private cause of action that permits a generic or biosimilar product developer to sue the brand manufacturer to compel it to furnish the necessary samples on "commercially reasonable, market-based terms." Whether and how generic and biosimilar product developments will use this new pathway, as well as the likely outcome of any legal challenges to provisions of the CREATES Act, remain highly uncertain and its potential effects on our future commercial products are unknown. Other new laws may result in additional reductions in Medicare and other health care funding, which could have an adverse effect on customers for our approved product and, accordingly, our financial operations.

In addition, the United States government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our future net revenue and results. For example, on August 16, 2022, President Biden signed into law the Inflation Reduction Act of 2022, which, among other things, includes policies that are designed to have a direct impact on drug prices and reduce drug spending by the federal government, which shall take effect in 2023. Under the Inflation Reduction Act, Congress authorized Medicare beginning in 2026 to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars. This provision is limited in terms of the number of pharmaceuticals whose prices can be negotiated in any given year and it only applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years. Drugs and biologics that have been approved for a single rare disease or condition are categorically excluded from price negotiation. Further, the new legislation provides that if pharmaceutical companies raise prices in Medicare faster than the rate of inflation, they must

pay rebates back to the government for the difference. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year. Decreases in third-party reimbursement for our product candidates or a decision by a third-party payor to not cover our product candidates could reduce physician usage of our product candidates, if approved, and have a material adverse effect on our future sales, results of operations and financial condition.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. We expect that additional state and federal health care reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for health care products and services. Moreover, if we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, our therapeutic candidates may lose any marketing approval that may have been obtained and we may not achieve or sustain profitability, which would adversely affect our business.

Sales and Marketing

We do not have a sales, marketing or distribution infrastructure and have limited experience in the sale, marketing and distribution of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. We expect to build a commercial infrastructure to allow us to market and sell certain of our product candidates when approved, if any, using a specialty sales force in the United States, and we may choose to establish commercialization capabilities in select countries outside the United States.

Employees

As of December 31, 2022, we had 18 full-time employees, of which 15 employees were engaged in research and development and three employees provided general and administrative support. Our employees are not represented by a labor union or covered by a collective bargaining agreement.

Our Corporate Information

We were incorporated under the laws of the State of Delaware on October 17, 2013 under the name Ikaria Development LLC. We changed our name to Bellerophon Therapeutics LLC on January 27, 2014. On February 12, 2015, we converted from a Delaware limited liability company into a Delaware corporation and changed our name to Bellerophon Therapeutics, Inc. We currently have three wholly-owned subsidiaries: Bellerophon BCM LLC, a Delaware limited liability company; Bellerophon Pulse Technologies LLC, a Delaware limited liability company; and Bellerophon Services, Inc., a Delaware corporation. Our website address is www.bellerophon.com. The information contained on, or that can be accessed through, our website does not constitute part of this Annual Report on Form 10-K. We have included our website address in this Annual Report on Form 10-K solely as an inactive textual reference.

Our executive offices are located at 184 Liberty Corner Road, Suite 302, Warren, New Jersey 07059, and our telephone number is (908) 574-4770. Effective April 1, 2023, our executive offices will be located at 20 Independence Blvd, Suite 402, Warren, New Jersey 07059.

Available Information

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

Item 1A. Risk Factors

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

Risks Related to Our Financial Position and Need for Additional Capital

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

Since inception, we have incurred significant operating losses. Our operating loss was approximately $22.4 million, $20.2 million and $26.3 million for the years ended December 31, 2022, 2021 and 2020, respectively. We do not know whether or when we will become profitable. We have not generated any revenues to date from product sales. We have not completed development of any product candidate and have devoted substantially all of our financial resources and efforts to research and development, including pre-clinical studies and clinical trials. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our deficit and working capital. We anticipate that our expenses will increase substantially if and as we:

- continue our research and clinical development of our product candidates;
- identify, develop and/or in-license additional product candidates;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- in the future, establish a manufacturing, sales, marketing and distribution infrastructure;
- maintain, expand and protect our intellectual property portfolio;
- add equipment and physical infrastructure to support our research and development;
- hire additional clinical, regulatory, quality control and scientific personnel; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and any future commercialization efforts.

To become and remain profitable, we must succeed in developing and eventually commercializing products that generate significant revenue. We do not expect to generate significant revenue unless and until we are able to obtain marketing approval for, and successfully commercialize, one or more of our product candidates. This will require us to be successful in a range of challenging activities, including completing pre-clinical studies and clinical trials of our product candidates, discovering additional product candidates, obtaining regulatory approval for our product candidates, manufacturing, marketing and selling any products for which we may obtain regulatory approval, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payors. We are in the early stages of most of these activities and have not yet commenced the other activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability.

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

there are any delays in completing our clinical trials or the development of any of our product candidates, our expenses could increase.

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

In addition, our recurring losses from operations, accumulated deficit and our need to raise additional financing in order to continue to fund our operations, has raised substantial doubt about our ability to continue as a going concern. We completed a registered direct offering and a sale of NOLs and entered into a licensing agreement during the first quarter of 2023 from which we have secured additional capital to continue our operations. Although we expect that these transactions will provide us with approximately $11.8 million, net of taxes and ordinary closing costs, we believe that our existing cash and cash equivalents are not sufficient to satisfy our operating cash needs for at least one year after the filing of this Annual Report on Form 10-K. Accordingly, we and our independent registered public accounting firm have concluded that substantial doubt about our ability to continue as a going concern exists.

Our limited operating history may make it difficult for our stockholders to evaluate the success of our business to date and to assess our future viability.

We were formed as a wholly-owned subsidiary of Ikaria in October 2013 and became a stand-alone company in February 2014 following the Spin-Out and, as such, have a limited independent operating history.

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

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

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

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue research and development and initiate and continue clinical trials of our product candidates and seek regulatory approval for these and potentially other product candidates. In addition, if we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. In particular, the costs that may be required for the manufacture of any product candidate that receives marketing approval may be substantial. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

We plan to use our current cash and cash equivalents primarily to fund our ongoing research and development efforts. We will be required to expend significant funds in order to advance development of our product candidates and any other potential product candidates. Our existing cash and cash equivalents will be used primarily to complete the Phase 3 trial of INOpulse for fILD and will not be sufficient to fund all of the efforts that we plan to undertake or the completion of clinical development or commercialization of any of our product candidates. Accordingly, we will be

required to obtain further funding through public or private equity offerings, debt financings, collaborations or licensing arrangements or other sources. Adequate additional funding may not be available to us on acceptable terms or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

We believe that our existing cash and cash equivalents as of December 31, 2022, and proceeds received and expected to become available from the subsequent registered direct offering, sale of our NOLs and R&D tax credits under the State of New Jersey's Technology Business Tax Certificate Transfer Program, and licensing agreement with Baylor will not be sufficient to satisfy our operating cash needs for at least one year after the filing of this Annual Report on Form 10-K. Accordingly, substantial doubt about our ability to continue as a going concern exists.

If we are unsuccessful in our efforts to raise additional financing for operations following top-line results for our REBUILD study, expected mid-year 2023, we may be required to significantly reduce or cease operations. The report of our independent registered public accounting firm on our audited financial statements for the year ended December 31, 2022 included a "going concern" explanatory paragraph indicating that we have sustained operating losses and believe that our existing cash and cash equivalents are not sufficient to satisfy operating cash needs which raises substantial doubt about our ability to continue as a going concern.

Our future capital requirements will depend on many factors, including:

- the timing, progress, and results of our ongoing and planned clinical trials of our product candidates;
- our ability to manufacture sufficient clinical supply of our products candidates and the costs thereof;
- discussions with regulatory agencies regarding the design and conduct of our clinical trials and the costs, timing and outcome of regulatory review of our product candidates;
- the cost and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;
- the costs of any other product candidates or technologies we pursue;
- our ability to establish and maintain strategic partnerships, licensing or other arrangements and the financial terms of such agreements;
- the revenue, if any, received from commercial sales of any product candidates for which we receive marketing approval; and
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims.

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

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. Our ability to raise additional funds

will depend, in part, on the success of our preclinical studies and clinical trials and other product development activities, regulatory events, our ability to identify and enter into in-licensing or other strategic arrangements, and other events or conditions that may affect our value or prospects, as well as factors related to financial, economic and market conditions, many of which are beyond our control. We cannot be certain that sufficient funds will be available to us when required or on acceptable terms, if at all. Raising additional capital through the sale of securities could cause significant dilution to our stockholders. If we are unable to secure additional funds on a timely basis or on acceptable terms, we may be required to defer, reduce or eliminate significant planned expenditures, restructure, curtail or eliminate some or all of our development programs or other operations, dispose of technology or assets, pursue an acquisition of our company by a third party at a price that may result in a loss on investment for our stockholders, enter into arrangements that may require us to relinquish rights to certain of our product candidates, technologies or potential markets, file for bankruptcy or cease operations altogether. Any of these events could have a material adverse effect on our business, financial condition and results of operations. Moreover, if we are unable to obtain additional funds on a timely basis, the substantial doubt about our ability to continue as a going concern will not be alleviated, potentially resulting in an increased risk of insolvency and loss of investment by our stockholders.

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

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of public or private equity offerings, debt financings and/or license and development agreements with collaboration partners. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of our stockholders may be materially diluted, and the terms of such securities could include liquidation or other preferences or other rights such as anti-dilution rights that adversely affect the rights of our stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include restrictive covenants that limit our ability to take specified actions, such as incurring additional debt, making capital expenditures or declaring dividends.

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

We may not be able to utilize all of our net operating loss carryforwards.

The State of New Jersey's Technology Business Tax Certificate Program allows certain high technology and biotechnology companies to sell unused net operating loss ("NOL") carryforwards to other New Jersey-based corporate taxpayers. In accordance with this program, for the year ended December 31, 2022, we sold New Jersey NOL carryforwards, resulting in the recognition of $2.4 million of income tax benefit compared to $1.8 million for the year ended December 31, 2021. Subject to program availability and state approval, we have plans to sell additional NOLs and credits under the same program in following years as well. If there is an unfavorable change in the State of New Jersey's Technology Business Tax Certificate Program (whether as a result of a change in law, policy or otherwise) that terminates the program or eliminates or reduces our ability to use or sell our NOL carryforwards, or if we are unable to find a suitable buyer to utilize our New Jersey NOL carryforwards to the extent the NOLs expire before we are able to utilize them against our future taxable income, our future cash taxes may increase which might have an adverse effect on our future financial condition.

Risks Related to Our Business and Industry

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

The pharmaceutical, biotechnology and medical device industries are highly competitive. There are many pharmaceutical, biotechnology and medical device companies, public and private universities and research organizations actively engaged in the research and development of products that may be similar to our product candidates. In addition, other companies are increasingly looking at the cardiopulmonary disease market as a potential opportunity. For example, currently, there are 14 drugs approved for the treatment of PAH and there are also other potential therapies in clinical development, however, only one of these therapies are currently approved for the treatment of PH associated with fILD and none are currently approved for the treatment of PH associated with sarcoidosis. or COPD. In addition, there are multiple nitric oxide generation and delivery systems that are under development, primarily for the treatment of persistent pulmonary hypertension in a hospital setting. Many of our competitors, either alone or through their strategic partners, have substantially greater name recognition and financial, technical, manufacturing, marketing and human resources than we do and significantly greater experience and infrastructure in the research and clinical development of medical products, obtaining FDA and other regulatory approvals of those products, and commercializing those products around the world. Additional mergers and acquisitions in the pharmaceutical, biotechnology and medical device industries may result in even more resources being concentrated in our competitors. Large pharmaceutical and medical device companies in particular have extensive expertise in pre-clinical and clinical testing and in obtaining regulatory approvals for medical products. In addition, academic institutions, government agencies and other public and private organizations conducting research may seek patent protection with respect to potentially competitive products or technologies. These organizations may also establish exclusive collaborative or licensing relationships with our competitors. Accordingly, our competitors may be more successful than we may be in obtaining approval for inhaled nitric oxide products and achieving widespread market acceptance. We anticipate that we will face intense and increasing competition as new products and technologies become available.

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

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

It is also possible that Ikaria will seek to develop and commercialize inhaled nitric oxide products or product candidates in the Bellerophon indications. While a subsidiary of Ikaria has granted to us an exclusive license to develop and commercialize pulsed nitric oxide in the Bellerophon indications and the scope of that license includes certain technology developed or acquired by that subsidiary after the date of the license agreement, the license does not include technology developed or acquired by other subsidiaries or affiliates of Ikaria including Mallinckrodt's other subsidiaries. Because Ikaria, Mallinckrodt and its other subsidiaries and affiliates are not subject to any non-competition obligations in our favor, it is possible that these other subsidiaries or affiliates of Ikaria or Mallinckrodt may seek to develop or commercialize inhaled nitric oxide or other products or product candidates, using technology not exclusively licensed to us that are competitive with our products or product candidates, which could adversely affect our business, financial condition or results of operations.

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

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

We currently have no products approved for sale and have invested a significant portion of our efforts and financial resources in the development of our INOpulse for PAH, INOpulse for fILD, INOpulse for PH-COPD, INOpulse for PH-Sarc and INOpulse for COVID-19 product candidates. Our prospects are substantially dependent on our ability to develop, obtain marketing approval for and successfully commercialize these product candidates.

The success of our product candidates will depend on, among other things, our ability to successfully complete clinical trials of each product candidate. The clinical trial process is uncertain, and failure of one or more clinical trials can occur at any stage of testing. For example, although we believe our Phase 2 clinical trial of INOpulse for PH-COPD supports advancement into further Phase 2 testing, the primary endpoint for INOpulse for PH-COPD was not statistically significant for any of the doses tested. In November 2020, we halted our clinical trial on INOpulse for COVID-19 for futility.

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

- receipt of marketing approvals from the FDA or other applicable regulatory authorities;
- establishment of supply arrangements with third-party raw materials suppliers and manufacturers;
- establishment of arrangements with third-party manufacturers to obtain finished drug products that are appropriately packaged for sale;
- the performance of our future collaborators for one or more of our product candidates, if any;
- the extent of any required post-marketing approval commitments to applicable regulatory authorities;
- obtaining and maintaining patent, trade secret protection and regulatory exclusivity, both in the United States and internationally;
- protection of our rights in our intellectual property portfolio;
- launch of commercial sales if and when our product candidates are approved;
- a continued acceptable safety profile of our product candidates following any marketing approval;
- commercial acceptance, if and when approved, by patients, the medical community and third-party payors;
- establishing and maintaining pricing sufficient to realize a meaningful return on our investment; and
- competition with other products.

If we are unable to develop, obtain marketing approval for or successfully commercialize our INOpulse product candidates, either alone or through a collaboration, or experience significant delays in doing so, our business could be materially harmed.

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

The risk of failure of all of our product candidates is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of development, including failure to demonstrate efficacy in a clinical trial or across a broad population of patients, the occurrence of severe or medically or commercially unacceptable adverse events, failure to comply with protocols or applicable regulatory requirements and determination by the FDA or any comparable non-U.S. regulatory authority that a drug product is not approvable.

It is possible that even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of or intolerability caused by our product candidates, or mistakenly believe that our product candidates are toxic or not well tolerated when that is not in fact the case. Also, the exclusion criteria we define may not sufficiently rule out patients who are at a higher risk of being harmed by the treatment. For example, our exclusion criteria for pre-existing left heart dysfunction in our Phase 2 INOpulse clinical trials completed in 2014 may not rule out patients who may experience an adverse event related to left ventricular function due to exposure to nitric oxide. In addition, patients who are not excluded for reactive pulmonary vasculature when exposed to nitric oxide may still experience PH.

The outcome of pre-clinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results, particularly when earlier trials are small, open-label or non-placebo-controlled trials and in trials that have different endpoints than earlier trials. For example, for PAH, , a pre-specified interim analysis was conducted by the DMC, in August 2018, after half of the planned subjects completed 16 weeks of blinded treatment. The DMC determined that the overall change in 6MWD, the primary endpoint of the trial, was insufficient to support the continuation of the study and based on the DMC's recommendation, we discontinued the trial in August 2018. Many companies in the biotechnology, pharmaceutical and medical device industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we cannot be certain that we will not face such setbacks.

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

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

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

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

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

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

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

We have conducted, and may in the future choose to conduct, one or more of our clinical trials outside the United States. For example, our first of two Phase 3 clinical trials of INOpulse for PAH included sites outside of the United States, including Canada.

Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of this data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with GCP in the case of drug trials, or the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords greater protection to the human subjects, in the case of device trials. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. Generally, the patient population for any clinical trials conducted outside of the United States must be representative of the population for whom we intend to seek approval in the United States. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will be dependent upon its determination that the trials also complied with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from trials conducted outside of the United States.

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

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

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

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

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

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

If the FDA or other regulatory authority requires us to conduct additional testing or determines that an unacceptable amount of nitrogen dioxide is formed through the use of INOpulse, we may be required to alter the design of INOpulse, which may not be possible, and the clinical development timeline for INOpulse may be delayed or prove to be more costly than we currently anticipate.

We have experienced and may continue to experience a number of possible undesirable events in connection with clinical trials of our product candidates, potential marketing approval or commercialization of our product candidates could be delayed or prevented.

We have experienced and may continue to experience numerous undesirable events during, or as a result of, clinical trials that could delay or prevent marketing approval of our product candidates, including:

- clinical trials of our product candidates may produce unfavorable or inconclusive results;
- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, patient enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;

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

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

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

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

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

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

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

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

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

Product development costs for us will increase if we experience delays in testing or pursuing marketing approvals and we may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of our product candidates. We do not know whether any pre-clinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. For example, although we completed a Phase 2 clinical trial for INOpulse for PH-COPD in 2014, we only began further Phase 2 development in this indication in 2016. Significant pre-clinical study or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations. In addition, many of the factors that cause, or lead to, clinical trial delays may ultimately lead to the denial of marketing approval of any of our product candidates.

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

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

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

For example, we may experience difficulty enrolling our clinical trials, including, but not limited to, any future clinical trials of INOpulse for fILD, PH-Sarc, or any future clinical trials of INOpulse for PH-COPD because such trials may require that patients meet the restrictive enrollment criteria, such as having been diagnosed with both COPD and PH, be undergoing treatment with LTOT and not having significant left ventricular dysfunction.

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

We may not obtain orphan drug exclusivity for any of our product candidates and indications, or we may not receive the full benefit of orphan drug exclusivity even if we obtain such exclusivity.

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

under a limited number of situations including a showing that another product is clinically superior. We have not yet applied for orphan drug designation in any jurisdictions outside of the United States.

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

Serious adverse events, or SAEs, or undesirable side effects or other unexpected properties of our product candidates have been identified in past clinical trials and may be identified during development of other treatments that could delay or prevent the product candidate's marketing approval.

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

For example, in our Phase 2 clinical trial for INOpulse for PAH completed in October 2014, SAEs were reported for four patients in the 25 mcg/kg ideal body weight/hour, or mcg, low-dose active treatment arm, including bacteremia, myelodysplastic syndrome, increased shortness of breath, and dyspnea, one of which was assessed as possibly related to trial therapy. In the 75 mcg high-dose active treatment arm, nine patients had SAEs. The most common SAEs reported were syncope and bronchitis/tracheobronchitis, one of which was assessed as possibly related to trial therapy. Discontinuation of trial therapy due to adverse events occurred for two patients in the 75 mcg arm and one subject in the 25 mcg arm. Additional or more SAEs, undesirable side effects or other unexpected properties of INOpulse for PAH or our other product candidates could arise or become known during further clinical development. If such an event occurs during development, clinical trials for our product candidates could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us or our collaborators to cease further development, require us to conduct additional clinical trials or other tests or studies or deny approval of the applicable product candidate.

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

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

A significant portion of the research that we are conducting involves the development of innovative approaches to the pulsed delivery of nitric oxide. Our drug-device discovery efforts may not be successful in creating drugs or devices that have commercial value or therapeutic utility. Our research programs may initially show promise in creating potential product candidates, yet fail to yield viable product candidates for clinical development for a number of reasons, including that potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be product candidates that will receive marketing approval and achieve market acceptance.

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

Pursuant to the terms of our license agreement with Ikaria, we only have the right to develop and commercialize pulsed nitric oxide for the Bellerophon indications; Ikaria retains the right to develop and commercialize inhaled nitric oxide products, including pulsed products, for all other indications.

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

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

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

- regulatory authorities may withdraw their approval of the product or seize the product;
- we may be required to recall the product or change the way the product is administered;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- we may be required to create a handout, sometimes referred to as a Medication Guide, outlining the risks of the previously unidentified side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

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

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

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

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

- the efficacy and safety of the product;
- the potential advantages of the product compared to alternative treatments;
- the prevalence and severity of any side effects;
- the clinical indications for which the product is approved;
- whether the product is designated under physician treatment guidelines as a first-line therapy or as a second- or third-line therapy;
- limitations or warnings, including distribution or use restrictions, contained in the product's approved labeling;
- our ability to offer the product for sale at competitive prices;
- our ability to establish and maintain pricing sufficient to realize a meaningful return on our investment;
- our ability to prevent use of our INOpulse for PH-COPD device by fILD patients due to expected pricing differences;
- the product's convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try, and of physicians to prescribe, the product;
- the strength of sales, marketing and distribution support;
- the approval of other new products for the same indications;
- changes in the standard of care for the targeted indications for the product;

- the timing of market introduction of our approved products as well as competitive products and other therapies;

- availability and amount of reimbursement from government payors, managed care plans, private health coverage insurers and other third-party payors;

- adverse publicity about the product or favorable publicity about competitive products; and

- potential product liability claims.

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

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

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

If a potential partner has development or commercialization expertise or financial resources that we believe is particularly relevant to one of our product candidates, then we may seek to collaborate with that potential partner even if we believe we could otherwise develop and commercialize the product independently. We may partner with third parties to commercialize our product candidates in certain countries outside the United States. As a result of entering into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues may be lower, perhaps substantially lower, than if we were to directly market and sell products in those markets. Furthermore, we may be unsuccessful in entering into the necessary arrangements with third parties or may be unable to do so on terms that are favorable to us. In addition, we may have little or no control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our product candidates effectively.

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

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

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

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

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

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

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

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

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

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

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

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

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

- improper use or failure of INOpulse may result in rebound PH, which can be fatal in some patients;
- rebound PH may also occur if both the primary and back-up devices fail before we can replace them, if the built-in back-up with a device does not work properly or if the patient does not carry or have access to his or her back-up device; and
- rebound PH can also occur in patients who were not previously considered at risk for this reaction and who may not have been provided an adequate back-up device.
- Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:
- decreased demand for products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;

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

Although we maintain general liability insurance of $2.0 million in the aggregate, umbrella insurance in the amount of $10.0 million in the aggregate and clinical trial liability insurance of $20.0 million in the aggregate, this insurance may not fully cover potential liabilities that we may incur. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if and when we begin the commercial sale of any product candidate that receives marketing approval. In addition, insurance coverage is becoming increasingly expensive. If we are unable to obtain or maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could adversely affect our business, financial condition, results of operations and prospects.

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

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

The COVID-19 pandemic, and any other pandemic, epidemic or outbreak of an infectious disease, may materially and adversely affect our business and operations.

The COVID-19 pandemic is continuing to affect the United States and global economies and may affect our operations and those of third parties on which we rely, including by causing disruptions to our investigational product supply chain and the conduct of future clinical trials. Additionally, while the potential economic impact brought by, and the duration of the COVID-19 pandemic, are difficult to assess or predict, the impact of the COVID-19 pandemic on the global financial markets may reduce our ability to access capital, which could negatively impact our short-term and long-term liquidity. In addition, the loss of any of our employees as a result of COVID-19 or another pandemic may have a material adverse effect on our operations. Any continued and prolonged public health crisis such as the COVID-19 pandemic could have a material negative impact on our business, financial condition, and operating results.

Risks Related to Our Dependence on Third Parties

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

We have licensed the intellectual property underlying INOpulse from Ikaria. The license agreement prohibits us from sublicensing to any competitor of Ikaria any intellectual property licensed to us by Ikaria. In addition, we are required to ensure that all of our products candidates are used solely for the chronic treatment of the Bellerophon

indications and to enter into written agreements with any customers that contain restrictions on the use of our products and termination rights in the event such restrictions are violated.

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

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

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

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

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we design our clinical trials and will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with GCPs for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified time frames. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

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

We also expect to rely on other third parties to store and distribute drug and device supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of

our product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We currently rely on Ikaria, as our single source supplier, for our supply of nitric oxide for the clinical trials of INOpulse. Ikaria's inability to continue manufacturing adequate supplies of nitric oxide, or its refusal to supply us with commercial quantities of nitric oxide on commercially reasonable terms, or at all, due to the bankruptcy filing of Ikaria's parent company Mallinckrodt plc or otherwise could result in a disruption in the supply of, or impair our ability to market, INOpulse.

We have a drug clinical supply agreement with Ikaria, pursuant to which Ikaria will manufacture and supply our requirements for nitric oxide for inhalation and corresponding placebo for use in clinical trials of INOpulse. Ikaria manufactures pharmaceutical-grade nitric oxide at its facility in Port Allen, Louisiana. Ikaria's Port Allen facility is subject to the risks of a natural disaster or other business disruption, including the widespread outbreak of infectious diseases as the outbreak of the coronavirus known as COVID-19. We maintain under controlled storage conditions a two-to-three-month supply of clinical trial drug product, but there can be no assurance that we would be able to meet our requirements for INOpulse if there were a catastrophic event or failure of Ikaria's manufacturing system. Because Ikaria's Port Allen facility is one of the few FDA-inspected sites that can manufacture nitric oxide for INOpulse and because the manufacture of a pharmaceutical gas requires specialized equipment and expertise, there are few third-party manufacturers to which we could contract this work in a short period of time. Therefore, any disruption in Ikaria's Port Allen facility, or the failure by Ikaria for any other reason to provide us with nitric oxide, could materially and adversely affect supplies of nitric oxide for INOpulse and our ongoing and planned clinical trials. In addition, Ikaria's parent company, Mallinckrodt plc, filed for Chapter 11 bankruptcy protection in October 2020. While we have been assured by Ikaria and believe that there will be no disruption in Ikaria's ability to fulfill its supply obligations to us, there can be no assurance that there will not be a disruption or delay in such manufacture and supply of nitric oxide for our use. Any such disruption would force us to seek nitric oxide from an alternative source, which may not be available on commercially reasonable terms. In addition, we do not currently have any arrangements with Ikaria to provide us with commercial quantities of nitric oxide. If we are unable to arrange for Ikaria to provide such quantities on commercially reasonable terms, or at all, we may not be able to successfully produce and market INOpulse or may be delayed in doing so.

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

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

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

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

We have exclusively licensed INOpulse, for certain indications and settings, and subject to certain retained rights of the licensor, from Ikaria. We may also enter into additional license agreements as part of the development of our business in the future. Such licensors, if any, may be responsible for prosecution of certain patent applications and maintenance of certain patents. Such licensors may not successfully prosecute such patent applications or maintain such patents, which we have licensed and on which our business depends. Our licensors may fail to pursue litigation against third-party infringers, may fail to prove infringement, or may fail to defend against counterclaims of patent invalidity or unenforceability. If these in-licenses are terminated, or if the underlying patents fail to provide the intended market exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products identical to ours. This could have a material adverse effect on our competitive business position and our business prospects.

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

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

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

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

- intellectual property, technology and business matters, including failure to make required technology transfers and failure to comply with non-compete provisions applicable to Ikaria and us;
- labor, tax, employee benefit, indemnification and other matters arising from our separation from Ikaria;
- distribution and supply obligations;
- employee retention and recruiting;
- business combinations involving us;
- the nature, quality and pricing of transitional services Ikaria has agreed to provide us; and
- business opportunities that may be attractive to both Ikaria and us.

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

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

We may seek third-party collaborators for development and commercialization of our product candidates. Our likely collaborators for any marketing, distribution, development, licensing or broader collaboration arrangements

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

Collaborations involving our product candidates would pose certain risks to us, including:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- collaborators with marketing and distribution rights to one or more of our products may not commit sufficient resources to the marketing and distribution of such product or products;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our products or product candidates or that result in costly litigation or arbitration that diverts management attention and resources; and
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

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

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

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

with biotechnology and pharmaceutical companies for the development and potential commercialization of those product candidates.

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

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

Risks Related to Our Intellectual Property

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

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

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

operations or intellectual property rights. Similarly, under the terms of any future agreements that we may enter into with other third parties, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering the technology that is licensed to us under such agreements. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

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

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

Moreover, we may be subject to third-party preissuance submissions of prior art to the USPTO, or become involved in opposition, derivation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging our owned or licensed patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

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

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

patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

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

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

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

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

Under our license agreement with Ikaria, we have granted Ikaria a sole and exclusive worldwide license to any intellectual property rights that we control for use in Ikaria's nitric oxide business, and we are required to ensure that all of our products, if any, are used solely for the chronic treatment of Bellerophon indications and to enter into written agreements with any customers that contain restrictions on the use of our products and termination rights in the event such restrictions are violated. We have also agreed to pay 100% of the reasonable and documented costs incurred by Ikaria for the prosecution and maintenance of certain licensed patents that are core to our business and 10% of such costs incurred by Ikaria for all other licensed patents. If we fail to comply with our obligations under current or future license agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product that is covered by the agreement or face other penalties under the agreement. Such an occurrence could materially adversely affect the value of the product candidate being developed under any such agreement.

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

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

If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be

forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

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

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

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

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

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

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

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

In addition to seeking patents for some of our technology and product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. Even if we are successful in prosecuting such claims, any remedy awarded may be insufficient to fully compensate us for the improper disclosure or misappropriation. In addition, some

courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

We are increasingly dependent on information technology and our systems and infrastructure face certain risks, including cybersecurity and data storage risks.

Significant disruptions to our information technology systems or breaches of information security could adversely affect our business. Although we maintain cyber liability insurance of $2.0 million in the aggregate, this insurance may not fully cover potential liabilities that we may incur. In the ordinary course of business, we collect, store and transmit confidential information, and it is critical that we do so in a secure manner in order to maintain the confidentiality and integrity of such confidential information. Our information technology systems are potentially vulnerable to service interruptions and security breaches from inadvertent or intentional actions by our employees, partners, vendors, or from attacks by malicious third parties. Maintaining the secrecy of this confidential, proprietary, and/or trade secret information is important to our competitive business position. While we have taken steps to protect such information and invested in information technology, there can be no assurance that our efforts will prevent service interruptions or security breaches in our systems or the unauthorized or inadvertent wrongful access or disclosure of confidential information that could adversely affect our business operations or result in the loss, dissemination, or misuse of critical or sensitive information. A breach of our security measures or the accidental loss, inadvertent disclosure, unapproved dissemination or misappropriation or misuse of trade secrets, proprietary information, or other confidential information, whether as a result of theft, hacking, or other forms of deception, or for any other cause, could enable others to produce competing products, use our proprietary technology and/or adversely affect our business position. Further, any such interruption, security breach, loss or disclosure of confidential information could result in financial, legal, business, and reputational harm to us and could have a material effect on our business, financial position, results of operations and/or cash flow.

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

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

- Others may be able to develop and commercialize treatments that are similar to our product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed.
- We or our licensors might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed.
- We or our licensors might not have been the first to file patent applications covering certain of our inventions.
- Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.
- It is possible that our pending patent applications will not lead to issued patents.
- Issued patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors.
- Our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets.

- We may not develop additional proprietary technologies that are patentable.
- The patents of others may have an adverse effect on our business.
- Another party may be granted orphan drug exclusivity for an indication that we are seeking before us or may be granted orphan drug exclusivity for one of our products for another indication.

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

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

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

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

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

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

does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

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

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

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

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

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

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

- litigation involving patients taking our products;

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- untitled or warning letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of our products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

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

We will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations after we obtain FDA approval and begin to commercialize our products, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

After we obtain marketing approval, we will be subject to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be

presented false or fraudulent claims for payment by a federal government program, or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government;

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

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

- the federal transparency requirements under the Physician Payments Sunshine Act require manufacturers of FDA-approved drugs, devices, biologics and medical supplies covered by Medicare or Medicaid to report, on an annual basis, to the Department of Health and Human Services information related to payments and other transfers of value to physicians, teaching hospitals and certain advanced non-physician health care practitioners and physician ownership and investment interests; and

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

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

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

If we expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The Foreign Corrupt Practices Act, or the FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of such third party in order to assist the individual or business in obtaining or retaining business. The FCPA also

obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the company, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

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

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

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

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

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

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

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

Changes in law or policy could have a negative impact on the approval of our drug candidates.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. In the United States and in some other jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates or any potential future product candidates of ours, restrict or regulate post-approval activities, or affect our ability to profitably sell any product

candidates for which we obtain marketing approval. Increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements. Congress also must reauthorize the FDA's user fee programs every five years and often makes changes to those programs in addition to policy or procedural changes that may be negotiated between the FDA and industry stakeholders as part of this periodic reauthorization process. On September 30, 2022, President Biden signed into law the FDA User Fee Reauthorization Act of 2022, which includes the reauthorization of the Prescription Drug user Fee Act from fiscal year 2023 through 2027.

Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in health care systems with the stated goals of containing health care costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a focus of these efforts and has been significantly affected by major legislative initiatives. In March 2010, Congress passed the ACA, which substantially changed the way health care is financed by both the government and private insurers, and significantly impacts the United States pharmaceutical industry. As another example, the 2021 Consolidated Appropriations Act signed into law on December 27, 2020 incorporated extensive health care provisions and amendments to existing laws, including a requirement that all manufacturers of drug products covered under Medicare Part B report the product's average sales price, or ASP, to DHHS beginning on January 1, 2022, subject to enforcement via civil money penalties.

There remain judicial and Congressional challenges to certain aspects of the ACA, and as a result certain sections of the ACA have not been fully implemented or effectively repealed. However, following several years of litigation in the federal courts, in June 2021, the U.S. Supreme Court upheld the ACA when it dismissed a legal challenge to the law's constitutionality. Further, legislative and regulatory changes under the ACA remain possible, although the new federal administration under President Biden has signaled that it plans to build on the ACA and expand the number of people who are eligible for health insurance subsidies under it. It is unknown what form any such changes or any law would take, and how or whether it may affect the pharmaceutical industry as a whole or our business in the future. We expect that changes or additions to the ACA, the Medicare and Medicaid programs, such as changes allowing the federal government to directly negotiate drug prices, and changes stemming from other healthcare reform measures, especially with regard to healthcare access, financing or other legislation in individual states, could have a material adverse effect on the healthcare industry in the United States.

The uncertainty around the future of the ACA, and in particular the impact to reimbursement levels, may lead to uncertainty or delay in the purchasing decisions of our customers, which may in turn negatively impact our product sales. If there are not adequate reimbursement levels, our business and results of operations could be adversely affected.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year pursuant to the Budget Control Act of 2011, which began in 2013 and will remain in effect through 2030 unless additional Congressional action is taken. However, the Medicare sequester reductions under the Budget Control Act of 2011 was suspended from May 1, 2020 through December 31, 2020 due to the COVID-19 pandemic, pursuant to provisions of the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, which also extended the sequester by one year, through 2030, in order to offset the added expense of the 2020 cancellation. The suspension was subsequently extended through March 31, 2022, with a reduction of the suspension to 1% sequester through June 30, 2022. Effective July 1, 2022, the reduction of 2% was reimposed.

In addition, the Drug Supply Chain Security Act enacted in 2013 imposed obligations on manufacturers of pharmaceutical products related to product tracking and tracing, and in February 2022, FDA released proposed regulations to amend the national standards for licensing of wholesale drug distributors by the states; establish new minimum standards for state licensing third-party logistics providers; and create a federal system for licensure for use in the absence of a State program, each of which is mandated by the DSCSA. As another example, on December 20, 2019, President Trump signed the Further Consolidated Appropriations Act for 2020 into law (P.L. 116-94) that includes a piece of bipartisan legislation called the CREATES Act. The CREATES Act aims to address the concern articulated by both the FDA and others in the industry that some brand manufacturers have improperly restricted the distribution of their products, including by invoking the existence of a REMS for certain products, to deny generic and biosimilar product developers access to samples of brand products. The CREATES Act establishes a private cause of action that

permits a generic or biosimilar product developer to sue the brand manufacturer to compel it to furnish the necessary samples on "commercially reasonable, market-based terms." Whether and how generic and biosimilar product developments will use this new pathway, as well as the likely outcome of any legal challenges to provisions of the CREATES Act, remain highly uncertain and its potential effects on our future commercial products are unknown. Other legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We are unsure whether additional legislative changes will be enacted, or whether the current regulations, guidance or interpretations will be changed, or whether such changes will have any impact on our business.

Additionally, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices considering the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. For example, state legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In December 2020, the U.S. Supreme Court held unanimously that federal law does not preempt the states' ability to regulate pharmaceutical benefit managers and other members of the health care and pharmaceutical supply chain, an important decision that may lead to further and more aggressive efforts by states in this area.

At the federal level, DHHS has solicited feedback on various measures intended to lower drug prices and reduce the out of pocket costs of drugs and has implemented others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage plans the option to use step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. In addition, in September 2020, the FDA finalized a rulemaking to establish a system whereby state governmental entities could lawfully import and distribute prescription drugs sourced from Canada. Those new regulations became effective on November 30, 2020, although the impact of such future programs is uncertain in part because lawsuits have been filed challenging the government's authority to promulgate them. The final regulations may also be vulnerable to being overturned by a joint resolution of disapproval from Congress under the procedures set forth in the Congressional Review Act, which could be applied to regulatory actions taken by the Trump administration on or after August 21, 2020 (i.e., in the last 60 days of legislative session of the 116th Congress). Congress and the executive branch have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, in July 2020, President Trump announced four executive orders related to prescription drug pricing that attempted to implement several of his Administration's proposals, including a policy that would tie Medicare Part B drug prices to international drug prices; one that directed DHHS to finalize the Canadian drug importation proposed rule previously issued by DHHS (which has since been finalized, as noted above) and made other changes allowing for personal importation of drugs from Canada; one that directed DHHS to finalize the rulemaking process on modifying the anti-kickback law safe harbors for plans, pharmacies, and pharmaceutical benefit managers after DHHS confirms that the action is not projected to increase federal spending, Medicare beneficiary premiums, or patients' total out-of-pocket costs (which DHHS finalized in November 2020, also making those rules subject to potentially being overturned under the Congressional Review Act); and one that reduces costs of insulin and epinephrine auto-injectors to patients of federally qualified health centers. President Trump also issued another executive order on September 13, 2020 that directed DHHS to undertake rulemaking in order to test an international reference pricing model for prescription drug products, which was also implemented by DHHS and then challenged in federal court by industry groups in December 2020. The probability of success of these newly announced policies and their impact on the U.S. prescription drug marketplace is unknown. There are likely to be continued political and legal challenges associated with implementing these reforms as they are currently envisioned, and the January 20, 2021 transition to a new Democrat-led presidential administration created further uncertainty. Following his inauguration, President Biden took immediate steps to order a regulatory freeze on all pending substantive executive actions in order to permit incoming department and agency heads to review whether questions of fact, policy, and law may be implicated and to determine how to proceed. The implementation of cost containment measures or other health care reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products. Current and future health care legislation could have a significant impact on our business. There is uncertainty with respect to the impact these changes, if any, may have, and

any changes likely will take time to unfold. In addition, it is possible that additional governmental action is taken to address the COVID-19 pandemic. Any additional federal or state health care reform measures could limit the amounts that third-party payers will pay for health care products and services, and, in turn, could significantly reduce the projected value of certain development projects and reduce our profitability.

Inadequate funding for the FDA, the SEC and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including enabling us to raise capital in order to fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including in December 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Risks Related to Employee Matters and Managing Growth

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

We are dependent on the scientific, business development and clinical expertise of our management team. Leadership transitions can be inherently difficult to manage and may cause some disruptions in our business.

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

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

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

In addition, during the course of our operations, our directors, executives and employees may have access to material, non-public information regarding our business, our results of operations or potential transactions we are considering. We may not be able to prevent a director, executive or employee from violating our insider trading policies and trading in our common stock on the basis of, or while having access to, material, non-public information. If a director, executive or employee was to be investigated, or an action was to be brought against a director, executive or employee for insider trading, it could have a negative impact on our reputation and our stock price. Such a claim, with or without merit, could also result in substantial expenditures of time and money, and divert attention of our management team from other tasks important to the success of our business.

Risks Related to Ownership of Our Common Stock

If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price or trading volume of our stock could decline.

The trading market for our common stock relies, in part, on the research and reports that industry or financial analysts publish about us or our business. If no, or few, analysts commence coverage of us, the trading price of our stock would likely decrease. Even if we do obtain analyst coverage, if one or more of the analysts covering our business do not publish favorable reports or downgrade their evaluations of our stock, the price of our stock could decline. If one or more analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price or trading volume to decline.

The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for our stockholders.

Our stock price may be volatile. The stock market in general, and the market for pharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may not be able to sell their shares of common stock at or above the price they paid for their shares. The market price for our common stock may be influenced by many factors, including:

- actual or anticipated results from and any delays in our clinical trials, including our expected and ongoing clinical trials of our INOpulse product candidates, as well as results of regulatory input on our clinical trial programs and regulatory reviews relating to the approval of our product candidates;

- the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;

- failure or discontinuation of any of our clinical development programs;
- the level of expenses related to any of our product candidates or clinical development programs;
- commencement or termination of any collaboration or licensing arrangement;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures and capital commitments;
- additions or departures of key scientific or management personnel;
- variations in our financial results or those of companies that are perceived to be similar to us;
- new products, product candidates or new uses for existing products introduced or announced by our competitors, and the timing of these introductions or announcements;
- results of clinical trials of product candidates of our competitors;
- general economic and market conditions and other factors that may be unrelated to our operating performance or the operating performance of our competitors, including changes in market valuations of similar companies;
- regulatory or legal developments in the United States and other countries;
- changes in the structure of healthcare payment systems;
- conditions or trends in the pharmaceutical, biotechnology and medical device industries;
- actual or anticipated changes in earnings estimates, development time lines or recommendations by securities analysts;
- announcement or expectation of additional financing efforts;
- sales of common stock by us or our stockholders in the future, as well as the overall trading volume of our common stock; and
- the other factors described in this "Risk Factors" section.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

In the past, following periods of volatility in the market price of a company's securities, securities class-action litigation often has been instituted against that company. Such litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert management's attention and resources, which could seriously harm our business, financial condition, results of operations and prospects.

An active trading market for our common stock may not be sustained.

Our shares of common stock began trading on the Nasdaq Global Market on February 13, 2015. On August 28, 2019, we received approval from the Listing Qualifications Department of The Nasdaq Stock Market ("Nasdaq") to transfer the listing of our common stock from the Nasdaq Global Market to the Nasdaq Capital Market. Our common stock was transferred to the Nasdaq Capital Market effective as of August 30, 2019. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares may not continue to develop or be sustained. If an active market for our common stock does not continue to develop or is not sustained, it may be difficult for investors to sell shares without depressing the market price for the shares, or at all.

Our common stock may be delisted from The Nasdaq Capital Market if we fail to comply with continued listing standards.

Our common stock is currently traded on The Nasdaq Capital Market under the symbol "BLPH." If we fail to meet any of the continued listing standards of The Nasdaq Capital Market, our common stock could be delisted from The Nasdaq Capital Market. These continued listing standards include specifically enumerated criteria, such as:

- a $1.00 minimum closing bid price;
- stockholders' equity of $2.5 million;
- 500,000 shares of publicly-held common stock with a market value of at least $1 million;
- 300 round-lot stockholders; and
- compliance with Nasdaq's corporate governance requirements, as well as additional or more stringent criteria that may be applied in the exercise of Nasdaq's discretionary authority.

If we fail to comply with Nasdaq's continued listing standards, we may be delisted and our common stock will trade, if at all, only on the over-the-counter market, such as the OTC Bulletin Board or OTCQX market, and then only if one or more registered broker-dealer market makers comply with quotation requirements. In addition, delisting of our common stock could depress our stock price, substantially limit liquidity of our common stock and materially adversely affect our ability to raise capital on terms acceptable to us, or at all. Further, delisting of our common stock would likely result in our common stock becoming a "penny stock" under the Exchange Act.

We have broad discretion in the use of our cash and cash equivalents and may not use them effectively.

Our management has broad discretion in the application of our cash and cash equivalents and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value.

We are incurring significant increased costs and demands upon management as a result of operating as a public company.

As a public company, and particularly if and after we cease to be a "smaller reporting company," we incur significant legal, accounting, and other expenses. We ceased to be an "emerging growth company," as defined in the JOBS Act, on December 31, 2020. As a result, we expect to incur additional expenses and to devote increased management time toward ensuring compliance with those requirements applicable to companies that are not emerging growth companies. We are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, which require, among other things, that we file with the SEC annual, quarterly and current reports with respect to our business and financial condition. In addition, the Sarbanes-Oxley Act, as well as rules subsequently adopted by the SEC and The Nasdaq Capital Market to implement provisions of the Sarbanes-Oxley Act, imposes significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Further, in 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that required the SEC to adopt additional rules and regulations in these areas such as "say on pay" and proxy access. Stockholder activism, the current political environment, and the current high level of government intervention and regulatory reform may result in substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate.

We expect the rules and regulations applicable to public companies to continue to substantially increase our legal and financial compliance costs and to make some activities more time-consuming and costly. If public company rules and regulations divert the attention of our management and personnel from other business concerns, our business, financial condition, and results of operations could be adversely affected. Increased costs associated with public company expenses will decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our products or services. For example, public company rules and regulations make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to incur substantial costs to maintain the same or similar coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements, the impact of which could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees, or as executive officers.

Our certificate of incorporation provides that the doctrine of "corporate opportunity" will not apply to any of our stockholders or directors, except in limited circumstances, which may adversely affect our business or prospects.

Our certificate of incorporation provides that the doctrine of "corporate opportunity" will not apply to any of our stockholders or directors, other than any stockholder or director that is an employee of ours. The doctrine of corporate opportunity generally provides that a corporate fiduciary may not develop an opportunity using corporate resources, acquire an interest adverse to that of the corporation or acquire property that is reasonably incident to the present or prospective business of the corporation or in which the corporation has a present or expectancy interest, unless that opportunity is first presented to the corporation and the corporation chooses not to pursue that opportunity. The doctrine of corporate opportunity is intended to preclude officers or directors from personally benefiting from opportunities that belong to the corporation. We have renounced any prospective corporate opportunity so that our stockholders and directors (other than those that are employees of ours) and their respective representatives have no duty to communicate or present corporate opportunities to us, including any opportunity that becomes known to Ikaria and its directors, and have the right to either hold any corporate opportunity for its (and its representatives') own account and benefit or to recommend, assign or otherwise transfer such corporate opportunity to persons other than us, including to Ikaria. As a result, our stockholders, directors and their respective affiliates will not be prohibited from investing in competing businesses or doing business with our customers. Therefore, we may be in competition with our stockholders, directors or their respective affiliates, and we may not have knowledge of, or be able to pursue, a transaction that could potentially be beneficial to us. Accordingly, we may lose a corporate opportunity or suffer competitive harm, which could negatively impact our business or prospects.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation or our bylaws, or any action asserting a claim against us that is governed by the internal affairs doctrine. This provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find this provision in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition.

Provisions in our certificate of incorporation, our bylaws or Delaware law might discourage, delay or prevent a change in control of our company or changes in our management and, therefore, depress the trading price of our common stock.

Provisions of our certificate of incorporation, our bylaws or Delaware law may discourage, delay or prevent a merger, acquisition or other change in control that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions may also prevent or frustrate attempts by our stockholders to change the composition of our board of directors or to replace or remove our management. These provisions include:

- limitations on the removal of directors;
- a classified board of directors so that not all members of our board are elected at one time;
- advance notice requirements for stockholder proposals and nominations;
- limitations on the ability of stockholders to call and bring business before special meetings and to take action by written consent in lieu of a meeting;
- limitations on the liability of, and the provision of indemnification to, our director and officers; and
- the ability of our board of directors to authorize the issuance of blank check preferred stock, which could be issued with voting, liquidation, dividend and other rights superior to our common stock.

In addition, we are subject to Section 203 of the Delaware General Corporation Law, which prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder, generally a person which together with its affiliates owns, or within the last three years has owned, 15% of our voting stock, for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner.

The existence of the foregoing provisions and anti-takeover measures could limit the price that investors might be willing to pay in the future for shares of our common stock. They could also deter potential acquirers of our company, thereby reducing the likelihood that investors could receive a premium for their shares of our common stock in an acquisition.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be the sole source of gain for our stockholders.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our principal facilities consist of approximately 22,000 square feet of office space at our headquarters located in Warren, New Jersey and approximately 3,640 square feet of office space and research lab facilities also located in Warren, New Jersey. Both the office space and the laboratory space are under leases that expire in 2023. Subsequent to December 31, 2022, we decided not to renew the lease associated with our current corporate headquarters and intend to vacate the premises upon expiration of the existing lease in March 2023. We did agree to a short-term lease extension of the existing laboratory space through August 2023. The existing laboratory space includes adequate office space to meet our needs and will serve as our corporate headquarters through August 2023. We believe that this space will be adequate during this time and suitable additional space will be available at commercially reasonably terms as needed.

Item 3. Legal Proceedings

We are not presently a party to any material litigation or regulatory proceeding, and we are not aware of any pending or threatened litigation or regulatory proceeding against us that could have a material adverse effect on our business, operating results, financial condition or cash flows.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our Common Stock is traded on The Nasdaq Stock Market under the symbol "BLPH".

Stockholders

As of March 30, 2023, we had 10,448,185 outstanding shares of common stock and approximately 155 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

Dividends

We have not declared or paid any cash dividends on our common stock since our inception. We do not plan to pay dividends in the foreseeable future. We currently intend to retain all available funds and any future earnings, if any, for use in the operation of our business. Any future determination to declare cash dividends will be made at the discretion of our board of directors, subject to applicable laws, and will depend on our financial condition, results of operations, capital requirements, general business conditions and other factors that our board of directors may deem relevant, and subject to the restrictions contained in any financing instruments. Consequently, stockholders will need to sell shares of our common stock to realize a return on their investment, if any.

Recent Sales of Unregistered Securities

None.

Issuer Purchases of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

Item 6. [RESERVED]

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

The following discussion and analysis of our financial condition and results of operations should be read together with our financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties and should be read together with the "Risk Factors" section of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. This section of this Annual Report on Form 10-K generally discusses 2022 and 2021 items and year to-year comparisons between 2022 and 2021. Discussions of 2020 items and year to-year comparisons between 2021 and 2020 that are not included in this Form 10-K can be found in "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Part II, Item 7 of the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2021.

Overview

Business

We are a clinical-stage therapeutics company focused on developing innovative products that address significant unmet medical needs in the treatment of cardiopulmonary. Our focus is the continued development of our nitric oxide therapy for patients with or at risk of pulmonary hypertension, or PH, using our proprietary pulsatile nitric oxide delivery platform, INOpulse.

In 2016, we began developing INOpulse for the treatment of pulmonary hypertension associated with fibrotic interstitial lung disease ("fILD"), which includes PH associated with idiopathic pulmonary fibrosis ("PH-IPF") as well as other pulmonary fibrosing diseases. During May 2017, we announced the completion of our Phase 2 clinical trial using INOpulse therapy to treat PH-IPF. The clinical data showed the 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 with acute exposure to iNO. The study assessed both the iNO 75 and iNO 30 dosage.

In January 2019, we announced top-line results from cohort 1 of our iNO-PF trial. The results suggested directional improvements in multiple clinically meaningful exploratory endpoints as measured by a wearable medical-grade activity monitor. In addition, these results suggested that iNO may have a favorable safety profile, supporting the continuation into cohort 2. In April 2019, we announced that we reached an agreement with the FDA on modifying the ongoing Phase 2b trial into a seamless Phase 2/3 trial, with cohort 3 serving as the pivotal study, as well as an agreement on the primary endpoint in cohort 3 of change in moderate to vigorous physical activity ("MVPA") from baseline to month 4, measured by Actigraphy. Actigraphy (medical wearable continuous activity monitoring) has the potential to provide highly sensitive objective real-world physical activity data that we expect to correlate with clinically meaningful patient functional abilities and health outcomes. Actigraphy is currently being utilized as the primary endpoint in multiple late-stage clinical programs in various cardiopulmonary diseases such as heart failure and chronic obstructive pulmonary disease ("COPD"). In December 2019, we announced top-line results from cohort 2 of the iNO-PF trial. Cohort 2 of iNO-PF suggested directionally favorable and potentially clinically meaningful placebo corrected improvement in MVPA, in subjects treated with iNO45 (45 mcg/kg IBW/hr) versus placebo. The improvement in MVPA was underscored by benefits in overall activity, as well as multiple patient reported outcomes. In March 2020, we announced that in consultation with the FDA, we had finalized some of the key elements of our planned pivotal Phase 3 study for fILD, including the use of MVPA as the primary endpoint for approval, the patient population of pulmonary

fibrosis subjects at risk of PH, as well as the dose of iNO45. In December 2020, we announced the first patient enrollment in this Phase 3 study called REBUILD. In September 2022, the FDA informed us that it had no objection to our proposal to reduce the study size to 140 subjects which does not impact the trial's principal objective or endpoints and maintains power of >90% (p-value < 0.01) for the primary endpoint of MVPA based on the effect size observed in our Phase 2 study. The FDA did note that since our proposal to reduce the sample size based on Phase 2b cohort 2 actigraphy data, there is always a concern that such a sample size reduction may further limit the acquisition of information on other, more important clinical endpoints in the trial. The FDA agreement was based on review of:

- Analysis conducted on cohort 2 (Phase 2) data utilizing the statistical analysis methodology to be used in REBUILD, including bi-weekly analysis of MVPA data and MMRM assessment of the last half of the blinded treatment period, which showed the trial would be >90% powered for p<0.05 at 80 total patients and >90% powered for a p<0.01 at 114 patients based on the effect size determined from cohort 2;
- Similar baseline MVPA distribution between cohort 2 and the first 80 randomized patients in REBUILD based on a blinded assessment; and
- Independent Data Monitoring Committee unblinded safety review of the first 85 randomized patients in REBUILD indicating no safety concern with regards to reduction of REBUILD to 140 patients.

During January 2023, we completed enrollment of the REBUILD study with a total of 145 patients enrolled. We expect to report pivotal top-line data results in mid-2023.

In 2018, we initiated an ancillary Phase 2 open-label intra-patient dose escalation study that utilizes right heart catheterization to assess the hemodynamic effect of INOpulse from a dose of iNO 30 to iNO 125 in PH-PF subjects. In February 2020, we announced the completion of the study and that the top-line results demonstrated that INOpulse achieved clinically and statistically meaningful cardiopulmonary improvements in pulmonary vascular resistance and mean pulmonary arterial pressure. The data suggested that inhaled nitric oxide was generally well-tolerated and may yield a favorable risk-benefit profile across doses.

In 2018, we also initiated development of INOpulse for the treatment of PH associated with Sarcoidosis ("PH-Sarc"). Sarcoidosis is a multi-system disease which is characterized by the growth of granulomas (inflammatory cells) in one or more organs. The most frequent organs involved are the lungs and lymph nodes within the chest. Pulmonary hypertension may be present in as many as 74% of patients depending on the disease severity and how the pulmonary hypertension ("PH") is defined. The presence of PH in sarcoidosis is associated with a poor prognosis. There are a number of different mechanisms linking PH with sarcoidosis. The primary treatment for sarcoidosis is corticosteroids; however, the outcome of this treatment on the PH is unclear. There is no approved therapy for PH associated with sarcoidosis. Various PAH treatments have been tried including iNO and IV prostacyclin with some clinical and functional improvement. The study was a Phase 2 open-label dose escalation design that utilized right heart catheterization to assess the acute hemodynamic effect of INOpulse from a dose of iNO 30 to iNO 125 in PH-Sarc subjects. In December 2021, we announced the completion of the acute dose escalation phase of the study and that the top-line results demonstrated that INOpulse provided clinically meaningful improvements in pulmonary vascular resistance. Supported by the results from this study, on June 21, 2022, we submitted to the FDA an exploratory Phase 2 double-blinded placebo-controlled study to investigate the safety and efficacy of inhaled nitric oxide/INOpulse dosed chronically for six months in patients with PH-Sarc. Subsequently, on July 28, 2022, we received an FDA letter indicating that the FDA completed its review of our study protocol, with a minor recommendation to include safety stopping rules. We have agreed to incorporate this recommendation into our periodic safety reviews. We are now positioned to initiate this Phase 2 study and are currently assessing the next steps for the study.

We completed a randomized, placebo-controlled, double-blind, dose-confirmation Phase 2 clinical trial of INOpulse for pulmonary hypertension associated with chronic obstructive pulmonary disease, or PH-COPD, in July 2014. The results from this trial showed that iNO 30 was a potentially safe and effective dose for treatment of PH-COPD. Based on the results of this trial, we completed further Phase 2 testing to assess the targeted vasodilation provided by INOpulse in this patient population. We presented the results of this trial in September 2015 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 entitled "Pulmonary vascular effects of pulsed inhaled nitric oxide in COPD patients with pulmonary hypertension."

During September 2017, we shared the results of our Phase 2a PH-COPD trial that was designed to evaluate the acute effects of pulsed inhaled nitric oxide, or iNO, on vasodilation as well as the chronic effect on hemodynamics and exercise tolerance. The trial showed a statistically significant increase (average 4.2%) in blood vessel volume on iNO compared to baseline (p=0.03), and a statistically significant correlation in Ventilation-Vasodilation (p=0.01). The chronic results demonstrated a statistically significant and clinically meaningful increase in six minute walk distance, or 6MWD, of 50.7m (p=0.04) as well as a decrease of 19.9% in systolic pulmonary arterial pressure (p=0.02), as compared to baseline. The data suggested that the dose may have a favorable safety profile. In May 2018, we announced that the FDA concurred with the design of our planned Phase 2b study of INOpulse for treatment of PH-COPD. The study will assess the effect of INOpulse on various parameters including exercise capacity, right ventricular function and oxygen saturation, as well as other composite endpoints. We continue to evaluate alternatives for the funding and timing of this program.

On March 19, 2020, the FDA granted emergency expanded access ("EA") to allow for our INOpulse system to immediately be used as supportive treatment for a patient with COVID-19 under the care and supervision of the patient's physician. The clinical goal of this experimental treatment was to mitigate the hospitalized patient's disease progression and avoid the need to perform intubation. Under the emergency access program, 180 hospitalized patients with COVID-19 from 18 hospitals across the United States received treatment with INOpulse. In April 2020, we submitted an IND application to the FDA to study the iNO delivery system for the treatment of patients with COVID-19. The proposed randomized, placebo controlled study, called COViNOX, was designed to evaluate the efficacy and safety of INOpulse in patients diagnosed with COVID-19 who require supplemental oxygen before the disease progresses to necessitate mechanical ventilation support. The COViNOX protocol aimed to enroll up to 500 patients with COVID-19 who were to be treated with either INOpulse or placebo. The primary endpoint of the study required an assessment of the proportion of subjects who experienced respiratory failure or mortality during the 28-day study period, which would allow the trial to serve as a registrational study for approval. The IND application was accepted by the FDA in May 2020, and the trial was initiated with the first patient treated in July 2020. The first 100 patients completed their 28-day assessment periods in October 2020. In November 2020, we announced that the independent Data Monitoring Committee ("DMC") had completed its pre-specified interim analysis from the first 100 patients. Based on the finding of futility, we placed the COViNOX study on a clinical hold. Although new enrollment of subjects into the study was halted, the remaining 91 subjects already enrolled at the time the clinical hold was announced were allowed to complete the treatment course. Upon completion of the protocol defined monitoring period, the pre-specified efficacy and safety analysis of these 191 patients was reviewed by the DMC and the DMC concluded that there were no safety concerns that were attributed to INOpulse for COVID-19. Based on the COVINOX results, we put the trial on a permanent clinical hold and we are not planning additional studies for INOpulse for the treatment of COVID-19. In May 2021, we submitted notification of withdrawal of the COViNOX IND to the FDA.

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 our drug delivery system, 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 may be several years before we commercialize a product candidate, if ever.

Impact of the COVID-19 Pandemic

The COVID-19 pandemic is continuing to affect the United States and global economies and may affect our operations and those of third parties on which we rely, including by causing disruptions to our investigational product supply chain and the conduct of future clinical trials. Additionally, while the potential economic impact brought by, and the duration of the COVID-19 pandemic, are difficult to assess or predict, the impact of the COVID-19 pandemic on the global financial markets may reduce our ability to access capital, which could negatively impact our short-term and long-term liquidity. In addition, the loss of any of our employees as a result of COVID-19 or another pandemic may have a material adverse effect on our operations. Any continued and prolonged public health crisis such as the COVID-19 pandemic could have a material negative impact on our business, financial condition, and operating results.

Financial Operations Overview

License Agreement with Baylor BioSciences, Inc.

In January 2023, we entered into a License Agreement with Baylor, pursuant to which Baylor received exclusive rights to develop and commercialize INOpulse within Greater China for diseases associated with pulmonary hypertension, including the lead indication of fibrotic interstitial lung disease ("fILD"), as well as PAH, PH-Sarcodosis, and PH-COPD, CTEPH and PH associated with pulmonary edema from high altitude sickness. Under the terms of the License Agreement, a license payment of $6 million, net of taxes and customary closing costs, is payable by Baylor within 90 days. Additionally, we are entitled to royalties of 5% on net sales by Baylor resulting from all of the licensed INOpulse indications within Greater China.

Registered Direct Offering

On March 3, 2023, we entered into a subscription agreement with an institutional investor, pursuant to which we agreed to issue and sell in a registered direct offering (the "Offering") (i) an aggregate of 718,474 shares (the "Shares") of our common stock and (ii) pre-funded warrants (the "Pre-Funded Warrants") to purchase up to 1,781,526 shares of common stock. We closed the Offering on March 7, 2023 with the Shares sold to the purchaser at a price per share of $2.00 per share. The Pre-Funded Warrants were sold at an offering price of $1.99 per Pre-Funded Warrant, which represents the per share offering price for the common stock less a $0.01 per share exercise price for each such Pre-Funded Warrant. No underwriter or placement agent participated in the Offering and the proceeds from the Offering were approximately $5 million.

The Pre-Funded Warrants are exercisable at any time after the date of issuance. A holder of Pre-Funded Warrants may not exercise the warrant if the holder, together with its affiliates, would beneficially own more than 9.99% of the number of shares of common stock outstanding immediately after giving effect to such exercise. A holder of Pre-Funded Warrants may increase or decrease this percentage, but not in excess of 19.99%, by providing at least 61 days prior notice to us.

The Offering was made pursuant to the Company's shelf registration statement previously filed with the Securities and Exchange Commission (the "SEC"), originally filed on June 26, 2020 (File No. 333-239473), which the SEC declared effective on July 2, 2020, and a related prospectus supplement.

Completion of Sale under the State of New Jersey's Technology Business Tax Certificate Transfer Program

During January 2023, we completed a subsequent sale of our NOLs and R&D credits under the State of New Jersey's Technology Business Tax Certificate Transfer Program. We sold $19.7 million of state NOLs and $0.1 million of R&D credits for net proceeds of approximately $1.7 million.

Financial Operations Overview

Prior to February 2014, we were a wholly-owned subsidiary of Ikaria, Inc. (a subsidiary of Mallinckrodt plc), or Ikaria. As part of an internal reorganization of Ikaria in October 2013, Ikaria transferred to us exclusive worldwide rights, with no royalty obligations, to develop and commercialize pulsed nitric oxide in PAH, PH-COPD and PH-IPF. Following the internal reorganization, in February 2014, Ikaria 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, which we refer to as the Spin-Out, and as a result we became a stand-alone company. 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 expanded the scope of our license from PH-IPF to PH in patients with Pulmonary Fibrosis ("PH-PF"), which includes idiopathic interstitial pneumonias, chronic hypersensitivity pneumonitis, occupational and environmental lung disease, with a royalty equal to 1% of net sales of any commercial products for PH-PF.

Revenue

To date, we have not generated any revenue from product sales and may not generate any revenue from product sales for the next several years, if ever. In the future, we may generate revenue from a combination of product sales, license fees and milestone payments in connection with strategic partnerships, and royalties from the sale of products developed under licenses of our intellectual property. Our ability to generate revenue and become profitable depends primarily on our ability to successfully develop and commercialize or partner our product candidates as well as any product candidates we may advance in the future. We expect that any revenue we may generate will fluctuate from quarter to quarter as a result of the timing and amount of any payments we may receive under future partnerships, if any, and from sales of any products we successfully develop and commercialize, if any. If we fail to complete the development of any of our product candidates currently in clinical development or any future product candidates in a timely manner, or to obtain regulatory approval for such product candidates, our ability to generate future revenue, and our business, results of operations, financial condition and cash flows and future prospects would be materially adversely affected.

Research and Development Expenses

Research and development expenses consist of costs incurred in connection with the development of our product candidates, including upfront and development milestone payments, related to in-licensed product candidates and technologies.

Research and development expenses primarily consist of:

- employee-related expenses, including salary, benefits and stock-based compensation expense;
- expenses incurred under agreements with contract research organizations, investigative sites that conduct our clinical trials and consultants that conduct a portion of our pre-clinical studies;
- expenses relating to vendors in connection with research and development activities;
- the cost of acquiring and manufacturing clinical trial materials;
- facilities, depreciation and allocated expenses;
- lab supplies, reagents, active pharmaceutical ingredients and other direct and indirect costs in support of our pre-clinical and clinical activities;
- device development and drug manufacturing engineering;
- license fees related to in-licensed products and technology; and
- costs associated with non-clinical activities and regulatory approvals.

We expense research and development costs as incurred.

Conducting a significant amount of research and development is central to our business model. Product candidates in late stages of clinical development generally have higher development costs than those in earlier stages of clinical development primarily due to the increased size and duration of late-stage clinical trials. Subject to the availability of requisite financing, we plan to increase our research and development expenses for ongoing clinical programs for the foreseeable future as we seek to continue multiple clinical trials for our product candidates, including to potentially advance INOpulse for PH-COPD and seek to identify additional early-stage product candidates.

We track external research and development expenses and personnel expenses on a program-by-program basis. We use our employee and infrastructure resources, including regulatory, quality, clinical development and clinical operations, across our clinical development programs and have included these expenses in research and development infrastructure. Research and development laboratory expenses are also not allocated to a specific program and are included in research and development infrastructure. Engineering activities related to INOpulse and the manufacture of cylinders related to INOpulse are included in INOpulse engineering.

Drug and Delivery System Costs

*Dr*ug and delivery system costs include cartridge procurement, cartridge filling, delivery system manufacturing and delivery system servicing. These costs relate to all indications that utilize the INOpulse delivery system.

Research and Development Infrastructure

We invest in regulatory, quality, clinical development and clinical operations activities, which are expensed as incurred. These activities primarily support our clinical development programs.

INOpulse Engineering

We have invested a significant amount of funds in INOpulse, which is configured to be highly portable and compatible with available modes of long-term oxygen therapy via nasal cannula delivery. Our Phase 2 clinical trials of INOpulse for PAH and INOpulse for PH-COPD utilized the first generation INOpulse DS/DS-C device. We believe that our second generation INOpulse device, as well as a custom triple-lumen cannula, have significantly improved several characteristics of our INOpulse delivery system. We have also invested in design and engineering technology, through Ikaria, for the manufacture of our drug cartridges. We manufacture and service the INOpulse devices that we are using in our ongoing clinical trials of INOpulse for fILD and PH-Sarc by third party turnkey manufacturers.

General and Administrative Expenses

General and administrative expenses include salaries and costs related to executive, finance, and administrative support functions, patent filing, patent prosecution, professional fees for legal, insurance, consulting, investor relations, human resources, information technology and auditing and tax services not otherwise included in research and development expenses.

Results of Operations

Comparison of Years Ended December 31, 2022 and 2021

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021, together with the changes in these items in dollars and as a percentage.

(Dollar amounts in thousands)	Year Ended December 31, 2022	2021	$ Change	% Change
Research and development expenses:				
fILD, PH-Sarc and PH-COPD	$ 5,466	$ 3,470	$ 1,996	58 %
COVID-19	(5)	411	(416)	(101)%
Other clinical trials	1	9	(8)	(86)%
Drug and delivery system costs	2,751	1,388	1,363	98 %
Clinical programs	8,213	5,278	2,935	56 %
Research and development infrastructure	6,546	5,778	768	13 %
INOpulse engineering	1,603	1,959	(356)	(18)%
Total research and development expenses	16,362	13,015	3,347	26 %
General and administrative expenses	6,022	7,146	(1,124)	(16)%
Total operating expenses	22,384	20,161	2,223	11 %
Loss from operations	(22,384)	(20,161)	(2,223)	11 %
Change in fair value of common stock warrant liability	1	600	(599)	(100)%
Interest income and financing expenses, net	135	5	130	2,605 %
Pre-tax loss	(22,248)	(19,556)	(2,692)	14 %
Income tax benefit	2,417	1,800	617	34 %
Net loss	$ (19,831)	$ (17,756)	$ (2,075)	12 %

Total Operating Expenses. Total operating expenses for the year ended December 31, 2022 were $22.4 million compared to $20.2 million for the year ended December 31, 2021, an increase of $2.2 million, or 11%. This increase was due to an increase in research and development expenses primarily attributable to operations supporting the REBUILD study in the current year partially offset by a decrease in our general and administrative expenses.

Research and Development Expenses. Total research and development expenses for the year ended December 31, 2022 were $16.4 million compared to $13.0 million for the year ended December 31, 2021, an increase of $3.4 million, or 26%. The increase in research and development expenses was primarily attributable to operations supporting the REBUILD study. Total research and development expenses consisted primarily of the following:

- fILD, PH-Sarc and PH-COPD research and development expenses for the year ended December 31, 2022 were $5.5 million compared to $3.5 million for the year ended December 31, 2021, an increase of $2.0 million, or 58%. The increase was primarily due to the increase in patient enrollment and overall recruitment activities related to the Phase 3 fILD trial during the year ended December 31, 2022.

- COVID-19 expenses for the year ended December 31, 2022 were $0.0 million compared to $0.4 million for the year ended December 31, 2021, a decrease of $0.4 million, or 101%. The decrease is due to the timing of completion of the trial and close-out activities during the first quarter of 2021.

- Drug and delivery system costs for the year ended December 31, 2022 were $2.8 million compared to $1.4 million for the year ended December 31, 2021, an increase of $1.4 million, or 98%. Drug and delivery system costs are recorded at the time of purchase from our suppliers. The increase in the drug and delivery system costs was attributable to the increased device demand to support the increase in patient enrollment related to the Phase 3 trial activities of fILD during the year ended December 31, 2022.

- Research and development infrastructure expenses for the year ended December 31, 2022 were $6.6 million compared to $5.8 million for the year ended December 31, 2021, an increase of $0.8 million, or 13%. The increase was primarily due to an increase in contractor costs associated with the Phase 3 clinical trial for fILD during the year ended December 31, 2022.

- INOpulse engineering expenses for the year ended December 31, 2022 were $1.6 million compared to $2.0 million for the year ended December 31, 2021, a decrease of $0.4 million, or 18%. The decrease was primarily due to a reduction in expenses related to improvement of the delivery system manufacturing process and overall requirements to support the fILD study as it approached completion of patient enrollment during the year ended December 31, 2022.

General and Administrative Expenses. General and administrative expenses for the year ended December 31, 2022 were $6.0 million compared to $7.1 million for the year ended December 31, 2021, a decrease of $1.1 million, or 16%. The decrease was primarily due to reduced labor, stock-based compensation and general consulting costs.

Change in Fair Value of Common Stock Warrant Liability. Change in fair value of common stock warrant liability for the year ended December 31, 2022 was de minimis compared to income of $0.6 million for the year ended December 31, 2021. All liability classified warrants have expired as of December 31, 2022 and the change in the liability fair value during the year ended December 31, 2021 was due to a change in our stock price, volatility, and shorter remaining term.

Income Tax Benefit. Income tax benefit was $2.4 million for the year ended December 31, 2022, compared to $1.8 million for the year ended December 31, 2021, a decrease of $0.6 million, or 34%. In April 2022, we sold $25.1 million of state NOLs and $0.2 million of R&D tax credits under the State of New Jersey's Technology Business Tax Certificate Transfer Program for net proceeds of $2.2 million. In June 2021, we sold $16.4 million of state NOLs and $0.3 million of research and development tax credits under the State of New Jersey’s Technology Business Tax Certificate Transfer Program for net proceeds of $1.7 million. The proceeds from such sales are recorded as income tax benefit when sales occur and proceeds are received.

Liquidity and Capital Resources

In the course of our development activities, we have sustained operating losses and expect such losses to continue over the next several years. We expect to continue to incur significant expenses and operating losses for the foreseeable future as we continue to develop, conduct clinical trials of, and seek regulatory approval for our product candidates. Our primary uses of capital are, and we expect will continue to be, compensation and related expenses, third-party clinical research and development services, contract manufacturing services, laboratory and related supplies, clinical costs, legal and other regulatory expenses and general overhead costs.

If we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses. We do not have a sales, marketing, manufacturing or distribution infrastructure for a pharmaceutical product. To develop a commercial infrastructure, we will have to invest financial and management resources, some of which would have to be deployed prior to having any certainty of marketing approval.

We had unrestricted cash and cash equivalents of $6.9 million as of December 31, 2022. Our existing cash and cash equivalents as of December 31, 2022 will be used primarily to fund the Phase 3 trial of INOpulse for fILD.

We have evaluated whether there are any conditions and events, considered in the aggregate, that raise substantial doubt about our ability to continue as a going concern within one year beyond the filing of this Annual Report on Form 10-K.

As described in Note 12 – *Subsequent Events* of our consolidated financial statement included herein, we completed a registered direct offering and a sale of NOLs and entered into a licensing agreement during the first quarter of 2023, from which we received an aggregate of $11.6 million as of the date of this Annual Report. These subsequent transactions have been included in our evaluation of our current plans. Based on such evaluation and our current plans,

including funds expected to be available, we believe that our existing cash and cash equivalents are not sufficient to satisfy our operating cash needs for at least one year after the filing of this Annual Report on Form 10-K. Accordingly, substantial doubt about our ability to continue as a going concern exists.

We may continue to pursue potential sources of funding, including equity financing and previously were able to obtain funding from the sale of tax attributes during 2022 and 2021, including the sale of NOLs and R&D credits described below.

- The Technology Business Tax Certificate Transfer Program enables qualified, unprofitable New Jersey based technology or biotechnology companies to sell a percentage of NOL and research and development (R&D) tax credits to unrelated profitable corporations, subject to meeting certain eligibility criteria. We have sold $25.1 million of state NOLs and $0.2 million of research and development credits under the State of New Jersey's Technology Business Tax Certificate Transfer Program in April 2022 for net proceeds of $2.2 million. We have also sold an additional $16.4 million of state NOLs and $0.3 million of research and development credits under the State of New Jersey's Technology Business Tax Certificate Transfer Program for net proceeds of $1.7 million in June 2021. We plan to sell additional NOLs and R&D credits under the same program in the future subject to program availability and state approval. The proceeds from such sales are recorded as Income tax benefit when sales occur or proceeds are received.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity and debt financings, sales of state NOLs and R&D credits subject to program availability and approval, existing working capital and funding from potential future collaboration arrangements. To the extent that we raise additional capital through the future sale of equity or convertible debt, the ownership interest of our existing stockholders may be diluted, and the terms of such securities may include liquidation or other preferences or rights such as anti-dilution rights that adversely affect the rights of our existing stockholders. If we raise additional funds through strategic partnerships in the future, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, or are unable to sell our state NOLs and R&D credits, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Cash Flows

The following table summarizes our cash flows for the years ended December 31, 2022, and 2021:

	Year Ended December 31,	
(Dollar amounts in thousands)	**2022**	**2021**
Operating activities	$ (17,770)	$ (22,821)
Financing activities	(40)	—
Net change in cash, cash equivalents and restricted cash	$ (17,810)	$ (22,821)

Net Cash Used in Operating Activities

Cash used in operating activities for the year ended December 31, 2022 was $17.8 million, as compared to $22.8 million for the year ended December 31, 2021. The change in cash used in operating activities was primarily due to the increase in our operating expenses combined with the changes in operating assets and liabilities.

Net Cash Used in Financing Activities

Cash used in financing activities for the year ended December 31, 2022 was $0.04 million, which related to the tax withholding payments made for stock compensation.

Contractual Obligations and Commitments

The following is a summary of our contractual cash obligations as of December 31, 2022 (in thousands):

	Payments Due by Period			
Contractual Obligations	Total	Less than 1 year	1 to 3 years	3 to 5 years
Operating Lease Obligations[1]	$ 205	$ 205	$ —	$ —
Total	$ 205	$ 205	$ —	$ —

(1) Operating lease obligations include a lease agreement we entered into on August 6, 2015 for office space, a lease agreement we entered into on September 3, 2019 and excludes the extension agreement we entered into on January 6, 2023 for laboratory space, both locations are in Warren, New Jersey.

Royalty payments and success-based milestones associated with our license and supply agreements with Ikaria have not been included in the above table of contractual obligations as we cannot reasonably estimate if or when they will occur.

In the course of our normal business operations, we also enter into agreements with suppliers, contract service providers and others to assist in the performance of our research and development and manufacturing activities. We can elect to discontinue the work under these contracts and purchase orders at any time with notice, and such contracts and purchase orders do not contain minimum purchase obligations.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenue and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to research and development expense, stock-based compensation, and common stock warrants. We base our estimates on historical experience, known trends and events and various other factors that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in Note 2 of the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our financial statements.

Research and Development Expense

Research and development costs are expensed as incurred. These expenses include the costs of our proprietary research and development efforts, as well as costs incurred in connection with certain licensing arrangements. Upfront and milestone payments made to third parties in connection with research and development collaborations are expensed as incurred up to the point of regulatory approval. Payments made to third parties upon or subsequent to regulatory approval are capitalized and amortized over the remaining useful life of the related product. We expense the cost of purchased technology and equipment in the period of purchase if we believe that the technology or equipment has not demonstrated technological feasibility and does not have an alternative future use. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and are recognized as research and development expense as the related goods are delivered or the related services are performed.

As part of the process of preparing our financial statements, we are required to estimate a portion of our prepaid and accrued research expenses. This process involves reviewing open contracts and purchase orders, communicating with applicable personnel and third party service providers to identify services that have been performed on our behalf

and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual cost. We make such estimates of our incurred research and development expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated prepaid and accrued research and development expenses include:

- fees paid to contract research organizations in connection with clinical trials;
- fees paid to investigative sites in connection with clinical trials; and
- fees paid to contract manufacturers in connection with the production of clinical trial materials.

We base our expenses related to research and development and clinical trials on actual costs incurred in addition to our estimates of the services received and efforts expended pursuant to contracts with multiple third parties, including research institutions and contract research organizations that conduct and manage clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing the research and development service fees, we consider the terms of each agreement, the time period over which the services will be performed and the level of effort required to complete the service. If the actual timing of the performance of the services or the level of effort varies from our estimate, we adjust the accrual accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting amounts that are too high or too low in any particular period.

It is difficult to determine with certainty the duration and completion costs of our current or any future pre-clinical programs and any of our current or future clinical trials and any future product candidates we may advance, or if, when or to what extent we will generate revenue from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates. The duration, costs and timing of clinical trials and development of our product candidates will depend on a variety of factors, including the uncertainties of any future clinical trials and pre-clinical studies, uncertainties in clinical trial enrollment rate and significant and changing government regulation. In addition, the probability of success for each product candidate will depend on numerous factors, including competition, manufacturing capability and commercial viability. A change in the outcome of any of these variables with respect to the development of a product candidate could change significantly the costs and timing associated with the development of that product candidate. For example, if the FDA or other regulatory authority were to require us to conduct clinical trials beyond those that we currently anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant delays in enrollment in any of our clinical trials, we could be required to expend significant additional financial resources and time with respect to the development of that product candidate. We will determine which programs to pursue and how much to fund each program in response to the scientific and clinical success of each product candidate, as well as an assessment of each product candidate's commercial potential, including the likelihood of regulatory approval on a timely basis.

Common Stock Warrant Liability

We account for common stock warrants issued as freestanding instruments in accordance with applicable accounting guidance provided in Accounting Standards Codification, or ASC Topic 480, *Distinguishing Liabilities From Equity,* as either liabilities or as equity instruments depending on the specific terms of the warrant agreement. We classify warrant liability on the consolidated balance sheet as noncurrent liabilities, which are revalued at each balance sheet date subsequent to the initial issuance. Changes in the fair value of the warrants are reflected in the consolidated statement of operations as "Change in fair value of common stock warrant liability." We use the Black-Scholes-Merton pricing model to value the related warrant liability. Certain assumptions used in the model include expected volatility, dividend yield and risk-free interest rate. All liability classified warrants have expired as of December 31, 2022. Refer to

Note 6 of the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for a detailed description of our accounting for warrants.

Stock-Based Compensation

We issue stock-based awards to employees and non-employees in the form of stock options, restricted stock awards, or RSAs, and may issue restricted stock units, or RSUs.

We account for our stock-based compensation in accordance with ASC Topic 718 *Compensation- Stock Compensation*, which establishes accounting for share-based awards, including stock options and restricted stock, exchanged for services and requires companies to expense the estimated fair value of these awards over the requisite service period. We recognize stock-based compensation expense in operations based on the fair value of the award on the date of the grant. The resulting compensation expense is recognized on a straight-line basis over the requisite service period or sooner if the awards immediately vest. We use the Black-Scholes-Merton option pricing model to value our stock option awards. Refer to Note 8 of the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for a detailed description of our accounting for stock-based compensation.

Recently Issued Accounting Standards

Not Yet Adopted

In June 2022, the FASB issued ASU No. 2022-03: ASC Subtopic 820 - Value Measurement of Equity Securities Subject to Contractual Sale Restrictions ("ASU 2022-03"). ASU 2022-03 amends ASC 820 to clarify that a contractual sales restriction is not considered in measuring an equity security at fair value and to introduce new disclosure requirements for equity securities subject to contractual sale restrictions that are measured at fair value. ASU 2022-03 applies to both holders and issuers of equity and equity-linked securities measured at fair value. The amendments in ASU 2022-03 are effective for us for fiscal years beginning after December 15, 2023, and the interim periods within those fiscal years. Early adoption is permitted for both interim and annual financial statements that have not yet been issued or made available for issuance. We are evaluating the impact of this pronouncement on our consolidated financial statements and related disclosures.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to market risk related to changes in interest rates. As of December 31, 2022, we had unrestricted cash and cash equivalents of $6.9 million, consisting primarily of demand deposits with U.S. banking institutions. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in cash and cash equivalents. Due to the nature of our deposits and the low risk profile of our investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our deposits. At times, our deposits held at financial institutions exceeds the $250,000 limit insured by the Federal Deposit Insurance Corporation ("FDIC"). We have not been impacted by the recent insolvency announcement of Silicon Valley Bank ("SVB") and do not have any relationship with SVB that would have any impact on our future operations.

Item 8. Financial Statements and Supplementary Data

Index to Financial Statements

Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors
Bellerophon Therapeutics, Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Bellerophon Therapeutics, Inc. and subsidiaries (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, changes in stockholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2022, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 3 to the consolidated financial statements, the Company has sustained operating losses and believes that existing cash and cash equivalents are not sufficient to satisfy operating cash needs, which raises substantial doubt about its ability to continue as a going concern. Management's plans in regard to these matters are also described in Note 3. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

Critical audit matters are matters arising from the current period audit of the consolidated financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. We determined that there are no critical audit matters.

/s/ KPMG LLP

We have served as the Company's auditor since 2013.

Short Hills, New Jersey
March 31, 2023

BELLEROPHON THERAPEUTICS, INC.

Consolidated Balance Sheets

(Amounts in thousands, except share and per share data)

	As of December 31, 2022	As of December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 6,924	$ 24,736
Restricted cash	405	103
Prepaid expenses and other current assets	234	620
Total current assets	7,563	25,459
Restricted cash, non-current	—	300
Right of use assets, net	184	863
Property and equipment, net	2	67
Other non-current assets	186	186
Total assets	$ 7,935	$ 26,875
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 1,230	$ 1,192
Accrued research and development	2,655	1,397
Accrued expenses	1,313	1,711
Current portion of operating lease liabilities	203	752
Total current liabilities	5,401	5,052
Long term operating lease liabilities	—	203
Common stock warrant liability	—	1
Total liabilities	5,401	5,256
Commitments and contingencies		
Stockholders' equity:		
Common stock, $0.01 par value per share; 200,000,000 shares authorized and 9,645,711 and 9,545,451 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively	96	95
Preferred stock, $0.01 par value per share; 5,000,000 shares authorized, zero shares issued and outstanding at December 31, 2022 and December 31, 2021	—	—
Additional paid-in capital	254,516	253,771
Accumulated deficit	(252,078)	(232,247)
Total stockholders' equity	2,534	21,619
Total liabilities and stockholders' equity	$ 7,935	$ 26,875

The accompanying notes are an integral part of these consolidated financial statements.

BELLEROPHON THERAPEUTICS, INC.

Consolidated Statements of Operations and Comprehensive Loss

(Amounts in thousands, except share and per share data)

	Year Ended December 31,		
	2022	2021	2020
Operating expenses:			
Research and development	$ 16,362	$ 13,015	$ 17,890
General and administrative	6,022	7,146	8,386
Total operating expenses	22,384	20,161	26,276
Loss from operations	(22,384)	(20,161)	(26,276)
Change in fair value of common stock warrant liability	1	600	(327)
Interest income and financing expenses, net	135	5	(250)
Pre-tax loss	(22,248)	(19,556)	(26,853)
Income tax benefit	2,417	1,800	2,125
Net loss and comprehensive loss	$ (19,831)	$ (17,756)	$ (24,728)
Weighted average shares outstanding:			
Basic	9,550,872	9,502,793	7,797,130
Diluted	9,550,872	9,502,793	7,797,130
Net loss per share:			
Basic	$ (2.08)	$ (1.87)	$ (3.17)
Diluted	$ (2.08)	$ (1.87)	$ (3.17)

The accompanying notes are an integral part of these consolidated financial statements.

BELLEROPHON THERAPEUTICS, INC.

Consolidated Statements of Changes in Stockholders' Equity

(Amounts in thousands except share and per share data)

	Common Stock		Additional Paid in Capital	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount			
Balance at December 31, 2019	4,580,127	$ 46	$ 193,308	$ (189,763)	3,591
Net loss	—	—	—	(24,728)	(24,728)
Reverse stock split adjustment	(826)	—	—	—	—
Warrant exercises	254,760	3	3,054	—	3,057
Direct offerings	2,428,846	24	28,178	—	28,202
Public offering	2,211,538	22	26,472	—	26,494
Stock-based compensation	—	—	1,633	—	1,633
Issuance of common stock, restricted stock vesting	16,666	—	—	—	—
Balance at December 31, 2020	9,491,111	$ 95	$ 252,645	$ (214,491)	$ 38,249
Net loss	—	—	—	(17,756)	(17,756)
Stock-based compensation	—	—	1,126	—	1,126
Issuance of common stock, restricted stock vesting	54,340	—	—	—	—
Balance at December 31, 2021	9,545,451	$ 95	$ 253,771	$ (232,247)	21,619
Net loss	—	—	—	(19,831)	(19,831)
Stock-based compensation	—	—	785	—	785
Issuance of common stock, restricted stock vesting	145,500	1	—	—	1
Surrender of shares to the Company for the payment of tax withholding obligations	(45,240)	—	(40)	—	(40)
Balance at December 31, 2022	9,645,711	$ 96	$ 254,516	$ (252,078)	$ 2,534

The accompanying notes are an integral part of these consolidated financial statements.

BELLEROPHON THERAPEUTICS, INC.

Consolidated Statements of Cash Flows

(Amounts in thousands)

	Year Ended December 31,		
	2022	2021	2020
Cash flows from operating activities:			
Net loss	$ (19,831)	$ (17,756)	$ (24,728)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	65	102	147
Stock-based compensation	786	1,126	1,633
Change in fair value of common stock warrant liability	(1)	(600)	327
Financing expense	—	—	300
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	386	(200)	(15)
Accounts payable, accrued research and development, accrued expenses and other liabilities	825	(5,493)	2,452
Net cash used in operating activities	(17,770)	(22,821)	(19,884)
Cash flows from financing activities:			
Proceeds received from exercise of warrants	—	—	3,057
Proceeds from issuance of common stock in Public Offering, net of offering expenses	—	—	26,494
Payment of expenses related to the ATM sale agreement	—	—	(186)
Proceeds from issuance of common stock in Direct Offerings, net of offering expenses	—	—	28,202
Tax withholding payments for stock compensation	(40)	—	—
Net cash (used in) provided by financing activities	(40)	—	57,567
Net change in cash, cash equivalents and restricted cash	(17,810)	(22,821)	37,683
Cash, cash equivalents and restricted cash at beginning of year	25,139	47,960	10,277
Cash, cash equivalents and restricted cash at end of year	$ 7,329	$ 25,139	$ 47,960

The accompanying notes are an integral part of these consolidated financial statements.

BELLEROPHON THERAPEUTICS, INC.

Notes to Consolidated Financial Statements

(1) Organization and Nature of the Business

Bellerophon Therapeutics, Inc., or the Company, is a clinical-stage therapeutics company focused on developing innovative products that address significant unmet medical needs in the treatment of cardiopulmonary diseases. The focus of the Company's clinical program is the continued development of its nitric oxide therapy for patients with pulmonary hypertension, or PH, using its proprietary delivery system, INOpulse. The Company has 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.

The Company's business is subject to significant risks and uncertainties, including but not limited to:

- The risk that the Company will not achieve success in its research and development efforts, including clinical trials conducted by it or its potential collaborative partners.
- The expectation that the Company will experience operating losses for the next several years.
- Decisions by regulatory authorities regarding whether and when to approve the Company's regulatory applications as well as their decisions regarding labeling and other matters which could affect the commercial potential of the Company's products or product candidates.
- The risk that the Company will fail to obtain adequate financing to meet its future operational and capital needs post-top-line results, expected mid-year 2023, for which the Company may be required to significantly reduce or cease operations.
- The risk that key personnel will leave the Company and/or that the Company will be unable to recruit and retain senior level officers to manage its business.
- There are many uncertainties regarding the novel coronavirus ("COVID-19") pandemic, and the Company is closely monitoring the impact of the pandemic on all aspects of its business, including how the pandemic will impact its clinical trials, employees and suppliers. While the pandemic did not materially affect the Company's financial results and business operations in the Company's years ended December 31, 2022 and 2021, the extent to which the coronavirus impacts the Company's results will depend on future developments, which are highly uncertain and cannot be predicted. Further, should COVID-19 continue to spread, the Company's business operations could be delayed or interrupted. For instance, the Company's supply vendors may experience disruption which may impact the Company's clinical trials or any potential future clinical trials may suffer from lower than anticipated patient recruitment or enrollment.

(2) Summary of Significant Accounting Policies

(a) Basis of Presentation

The consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles or GAAP. Intercompany balances and transactions have been eliminated. The Company operates in one reportable segment and solely within the United States. Accordingly, no segment or geographic information has been presented.

The preparation of financial statements requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of costs and expenses during the reporting period, including prepaid and accrued

research and development expenses, stock-based compensation, common stock warrant liability and income taxes. Actual results could differ from those estimates.

On February 5, 2020, the Company filed a certificate of amendment to its amended and restated Certificate of Incorporation to effect a 1 - for - 15 reverse stock split of the Company's outstanding shares of common stock which became effective on February 7, 2020. The shares of common stock underlying the Company's outstanding options and warrants were also proportionately adjusted for the reverse stock split. In addition, the number of shares of common stock available for issuance under the Company's equity incentive plans and employee stock purchase plan were proportionately adjusted for the reverse stock split. Further, the per share exercise prices for options granted under such plans and warrants were proportionately adjusted for the reverse stock split. There was no change to our authorized number of shares or to our par value per share. The reverse stock split reduced the number of shares of the Company's common stock that were outstanding at February 10, 2020 from 69,053,548 to 4,603,460, after the cancellation of fractional shares. No fractional shares were issued in connection with the reverse stock split. Stockholders who otherwise held fractional shares of the Company's common stock as a result of the reverse stock split received a de minimis cash payment in lieu of such fractional shares. These consolidated financial statements give retroactive effect to such reverse stock split and all share and per share amounts have been adjusted accordingly.

(b) Cash and Cash Equivalents

The Company considers all highly liquid investments with an original maturity date of three months or less to be cash equivalents. All investments with maturities of greater than three months from date of purchase are classified as available-for-sale marketable securities.

(c) Stock-Based Compensation

The Company accounts for its stock-based compensation in accordance with applicable accounting guidance which establishes accounting for share-based awards, including stock options and restricted stock, exchanged for services and requires companies to expense the estimated fair value of these awards over the requisite service period. The Company recognizes stock-based compensation expense in operations based on the fair value of the award on the date of the grant. The resulting compensation expense is recognized on a straight-line basis over the requisite service period or sooner if the awards immediately vest. The Company determines the fair value of stock options issued using a Black-Scholes-Merton option pricing model. Certain assumptions used in the model include expected volatility, dividend yield, risk-free interest rate, estimated forfeitures and expected term. For restricted stock, the fair value is the closing market price per share on the grant date. See Note 8 - *Stock-Based Compensation* for a description of these assumptions.

(d) Common Stock Warrant Liability

The Company accounts for common stock warrants issued as freestanding instruments in accordance with applicable accounting guidance as either liabilities or as equity instruments depending on the specific terms of the warrant agreement. The Company classifies warrant liability on the consolidated balance sheet based on the warrants' terms as long-term liabilities, which are revalued at each balance sheet date subsequent to the initial issuance. Changes in the fair value of the warrants are reflected in the consolidated statement of operations as "Change in fair value of common stock warrant liability." The Company uses the Black-Scholes-Merton pricing model to value the related warrant liability. Certain assumptions used in the model include expected volatility, dividend yield and risk-free interest rate. All liability classified warrants have expired as of December 31, 2022. See Note 7 - *Fair Value Measurements* for a description of these assumptions.

(e) Income Taxes

The Company uses the asset and liability approach to account for income taxes as required by applicable accounting guidance, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases. Valuation allowances are provided when necessary to reduce deferred tax assets to the amount expected to be realized, on a more likely than not basis. The Company recognizes the benefit of an

uncertain tax position that it has taken or expects to take on income tax returns it files if such tax position is more likely than not to be sustained on examination by the taxing authorities, based on the technical merits of the position. These tax benefits are measured based on the largest benefit that has a greater than 50% likelihood of being realized upon ultimate resolution.

(f) Research and Development Expense

Research and development costs are expensed as incurred. These expenses include the costs of the Company's proprietary research and development efforts, as well as costs incurred in connection with certain licensing arrangements. Upfront and milestone payments made to third parties in connection with research and development collaborations are expensed as incurred up to the point of regulatory approval. Payments made to third parties upon or subsequent to regulatory approval are capitalized and amortized over the remaining useful life of the related product. The Company expenses the cost of purchased technology and equipment in the period of purchase if it believes that the technology or equipment has not demonstrated technological feasibility and it does not have an alternative future use. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and are recognized as research and development expense as the related goods are delivered or the related services are performed.

(g) Leases

A lease is a contract, or part of a contract, that conveys the right to control the use of explicitly or implicitly identified property, plant or equipment in exchange for consideration. Control of an asset is conveyed to the Company if the Company obtains the right to obtain substantially all of the economic benefits of the asset or the right to direct the use of the asset. The Company recognizes right of use ("ROU") assets and lease liabilities at the lease commencement date based on the present value of future, fixed lease payments over the term of the arrangement. Lease expense is recognized on a straight-line basis over the term of the lease. Lease liabilities are reduced at the time when the lease payment is payable to the vendor. Variable lease payments are recognized at the time when the event giving rise to the payment occurs and are recognized in the statement of operations in the same line item as expenses arising from fixed lease payments.

In accordance with Topic 842, leases are measured at present value using the rate implicit in the lease or, if the implicit rate is not determinable, the lessee's implicit borrowing rate. As the implicit rate is not typically available, the Company uses its implicit borrowing rate based on the information available at the lease commencement date to determine the present value of future lease payments. The implicit borrowing rate approximates the rate the Company would pay to borrow on a collateralized basis over a similar term an amount equal to the lease payments.

The Company does not recognize right of use assets or related lease liabilities with a lease term of twelve months or less on our consolidated balance sheet. Short-term lease costs are recorded in our consolidated statements of operations in the period in which the obligation for those payments was incurred. Short-term lease costs for the year ended December 31, 2022 were *de minimis*.

(h) New Accounting Pronouncements

Not Yet Adopted

In June 2022, the FASB issued ASU No. 2022-03: ASC Subtopic 820 - Value Measurement of Equity Securities Subject to Contractual Sale Restrictions ("ASU 2022-03"). ASU 2022-03 amends ASC 820 to clarify that a contractual sales restriction is not considered in measuring an equity security at fair value and to introduce new disclosure requirements for equity securities subject to contractual sale restrictions that are measured at fair value. ASU 2022-03 applies to both holders and issuers of equity and equity-linked securities measured at fair value. The amendments in ASU 2022-03 are effective for the Company for fiscal years beginning after December 15, 2023, and the interim periods within those fiscal years. Early adoption is permitted for both interim and annual financial statements that have not yet been issued or made available for issuance. The Company is evaluating the impact of this pronouncement on its consolidated financial statements and related disclosures.

(3) Liquidity and Going Concern

In the course of its development activities, the Company has sustained operating losses and expects such losses to continue over the next several years. The Company expects to continue to incur significant expenses and operating losses for the foreseeable future as it continues the development and clinical trials of, and seeks regulatory approval for, its product candidates. The Company's primary uses of capital are, and it expects will continue to be, compensation and related expenses, third-party clinical research and development services, contract manufacturing services, laboratory and related supplies, clinical costs, legal and other regulatory expenses and general overhead costs.

If the Company obtains regulatory approval for any of its product candidates, the Company expects to incur significant commercialization expenses. The Company does not have a sales, marketing, manufacturing or distribution infrastructure for a pharmaceutical product. To develop a commercial infrastructure, the Company will have to invest financial and management resources, some of which would have to be deployed prior to having any certainty of marketing approval.

The Company had unrestricted cash and cash equivalents of $6.9 million as of December 31, 2022. The Company's existing cash and cash equivalents as of December 31, 2022, will be used primarily to fund the Phase 3 trial of INOpulse for fILD.

The Company evaluated whether there are any conditions and events, considered in the aggregate, that raise substantial doubt about its ability to continue as a going concern within one year beyond the filing of this Annual Report on Form 10-K.

As described in Note 12 – *Subsequent Events*, the Company completed a registered direct offering and a sale of NOLs and entered into a licensing agreement during the first quarter of 2023. These subsequent transactions have been included in the Company's evaluation of its current plans. Based on such evaluation and the Company's current plans, including funds expected to be available, management believes that the Company's existing cash and cash equivalents are not sufficient to satisfy the Company's operating cash needs for at least one year after the filing of this Annual Report on Form 10-K. Accordingly, substantial doubt about the Company's ability to continue as a going concern exists.

The Company may continue to pursue potential sources of funding, including equity financing and previously was able to obtain funding from the sale of tax attributes during 2022 and 2021, including the below:

- The Technology Business Tax Certificate Transfer Program enables qualified, unprofitable New Jersey based technology or biotechnology companies to sell a percentage of NOL and research and development (R&D) tax credits to unrelated profitable corporations, subject to meeting certain eligibility criteria. The Company has sold $25.1 million of state NOLs and $0.2 million of research and development credits under the State of New Jersey's Technology Business Tax Certificate Transfer Program in April 2022 for net proceeds of $2.2 million. The Company has also sold an additional $16.4 million of state NOLs and $0.3 million of research and development credits under the State of New Jersey's Technology Business Tax Certificate Transfer Program for net proceeds of $1.7 million in June 2021. The Company plans to sell additional NOLs and R&D credits under the same program in the future subject to program availability and state approval. The proceeds from such sales are recorded as Income tax benefit when sales occur or proceeds are received.

Until such time, if ever, as the Company can generate substantial product revenues, it expects to finance its cash needs through a combination of equity and debt financings, sales of state NOLs and R&D credits subject to program availability and approval, existing working capital and funding from potential future collaboration arrangements. To the extent that the Company raises additional capital through the future sale of equity or convertible debt, the ownership interest of its existing stockholders may be diluted, and the terms of such securities may include liquidation or other preferences or rights such as anti-dilution rights that adversely affect the rights of its existing stockholders. If the Company raises additional funds through strategic partnerships in the future, it may have to relinquish valuable rights to its technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to it. If the Company is unable to raise additional funds through equity or debt financings when needed, or unable to sell its

state NOLs and R&D credits, it may be required to delay, limit, reduce or terminate its product development or future commercialization efforts or grant rights to develop and market product candidates that it would otherwise prefer to develop and market itself.

(4) Right of Use Assets and Leases

The Company has two operating leases in Warren, NJ, one for the use of an office and research facility and a second for the use of a laboratory. The office and research facility lease is for a term of four years with an expiration date of March 31, 2023, with the Company's right to extend the original term for one period of five years. The laboratory lease is for a term of three years and nine months with an expiration date of April 30, 2023. The office and research facility as well as the laboratory operating leases are included in "Right of use assets, net" on the Company's December 31, 2022 consolidated balance sheet and represents the Company's right to use the underlying assets for the respective lease term. The Company's obligation to make lease payments are included in "Current portion of operating lease liabilities" and "Long term operating lease liabilities" on the Company's December 31, 2022 and 2021 consolidated balance sheets. Operating lease expense is recognized on a straight-line basis over the respective lease term.

Subsequent to December 31, 2022, the Company decided not to renew the lease associated with its corporate headquarters and intends to vacate the premises upon expiration of the existing lease. The Company did agree to a short-term lease extension of the existing laboratory space through August 2023. The existing laboratory space is deemed to have adequate office space to meet the Company's needs and will serve as the Company's corporate headquarters.

The Company does not recognize right of use assets or related lease liabilities with a lease term of twelve months or less on our consolidated balance sheet. Short-term lease costs are recorded in our consolidated statements of operations in the period in which the obligation for those payments was incurred. Short-term lease costs for the year ended December 31, 2022 were *de minimis*.

Information related to the Company's right of use assets and related lease liabilities is as follows ($ amounts in thousands):

	For the Year Ended December 31, 2022	For the Year Ended December 31, 2021
Cash paid for operating lease liability	$ 783	$ 770
Operating lease expenses	$ 709	$ 707
Weighted average remaining lease term	0.26 years	1.26 years
Weighted average discount rate	4.92 %	4.93 %

Maturities of lease liabilities as of December 31, 2022 were as follows:	
2023	$ 205
Less imputed interest	(2)
Total operating lease liability	$ 203

Rent expenses for each of the years ended December 31, 2022 and 2021 were $0.7 million.

(5) Property and Equipment

Property and equipment as of December 31, 2022 and 2021 consist of the following (in thousands):

	December 31, 2022	December 31, 2021
Machinery and equipment	$ 2,048	$ 2,048
Leasehold improvements	204	204
Furniture and fixtures	276	276
Property and equipment, gross	2,528	2,528
Less accumulated depreciation	(2,526)	(2,461)
	$ 2	$ 67

Depreciation expense for each of the years ended December 31, 2022, 2021 and 2020 were $0.1 million.

(6) Common Stock Warrants

On November 29, 2016, the Company issued 1,142,838 warrants to purchase shares common stock to investors that were immediately exercisable with an original expiration date of 5 years from issuance at an exercise price of $12.00 per share (the "2016 Warrants"). On June 28, 2019, the Company entered into a warrant amendment (the "Warrant Amendment") with certain holders (the "Holders") of 839,899 of the 2016 Warrants to purchase common stock. Pursuant to the Warrant Amendment, the Company and the Holders agreed to eliminate provisions that had previously precluded equity classification treatment on the Company's consolidated balance sheets. In consideration of such amendment, the 839,899 warrants were extended by two (2) additional years (until November 29, 2023) and the fair market value of the amended warrants was reclassified from common stock warrant liability to stockholders' equity. The balance of the 2016 Warrants that were not amended could require cash settlement under certain circumstances, and therefore continued to be classified as liabilities and to be recorded at estimated fair value using a Black-Scholes-Merton pricing model. During the year ended December 31, 2021, all the previously outstanding liability classified warrants of the 2016 Warrants, which were not subject to the Warrant Amendment previously described, have expired, unexercised. As of December 31, 2022, there were 585,139 of the 2016 Warrants outstanding, all of which were equity classified. No warrants were exercised during the years ended December 31, 2022 and 2021.

On May 15, 2017, the Company issued to an investor warrants to purchase 66,666 shares of common stock that became exercisable commencing six months from their issuance with an expiration date five years from the initial exercise date at an exercise price of $22.50 per share. In addition, the Company issued to the placement agent warrants to purchase 4,000 shares that were immediately exercisable with an expiration date five years from issuance at an exercise price of $28.125 per share. As the warrants, under certain situations, could require cash settlement, the warrants were classified as liabilities and recorded at estimated fair value using a Black-Scholes-Merton pricing model. As of December 31, 2022, all of these warrants have expired, unexercised.

On September 29, 2017, the Company issued warrants to purchase 1,296,650 shares of common stock to investors that became exercisable commencing six months from their issuance with an expiration date of five years from the initial exercise date (or March 29, 2023) at an exercise price of $18.63 per share. As the warrants could not require cash settlement, the warrants were classified as equity. As of December 31, 2022, all of these warrants were outstanding.

The following table summarizes warrant activity for the year ended December 31, 2022 (fair value amount in thousands):

	Equity Classified	Liability Classified	
	Warrants	Warrants	Estimated Fair Value
Warrants outstanding as of December 31, 2021	1,881,789	70,666	$ 1
Expired	—	(70,666)	—
Change in fair value of common stock warrant liability recognized in consolidated statement of operations	—	—	(1)
Warrants outstanding as of December 31, 2022	1,881,789	—	$ —

The following table summarizes warrant activity for the year ended December 31, 2021 (fair value amount in thousands):

	Equity Classified	Liability Classified	
	Warrants	Warrants	Estimated Fair Value
Warrants outstanding as of December 31, 2020	1,881,789	146,837	$ 601
Expired	—	(76,171)	—
Change in fair value of common stock warrant liability recognized in consolidated statement of operations	—	—	(600)
Warrants outstanding as of December 31, 2021	1,881,789	70,666	$ 1

See Note 7 for determination of fair value of common stock warrant liability.

(7) Fair Value Measurements

Assets and liabilities recorded at fair value on the balance sheets are categorized based upon the level of judgment associated with the inputs used to measure the fair value. Level inputs are as follows:

- Level 1 - Values are based on unadjusted quoted prices for identical assets or liabilities in an active market which the company has the ability to access at the measurement date.
- Level 2 - Values are based on quoted market prices in markets where trading occurs infrequently or whose values are based on quoted prices of instruments with similar attributes in active markets.
- Level 3 - Values are based on prices or valuation techniques that require inputs that are both unobservable and significant to the overall fair value measurement. These inputs reflect management's own assumptions about the assumptions a market participant would use in pricing the asset.

The following table summarizes fair value measurements by level at December 31, 2022 for financial instruments measured at fair value on a recurring basis (in thousands):

	Level 1	Level 2	Level 3	Total
Common stock warrant liability	$ —	$ —	$ —	$ —

The following table summarizes fair value measurements by level at December 31, 2021 for financial instruments measured at fair value on a recurring basis (in thousands):

	Level 1	Level 2	Level 3	Total
Common stock warrant liability	$ —	$ —	$ 1	$ 1

The Company uses a Black-Scholes-Merton option pricing model to value its common stock warrants. The significant unobservable inputs used in calculating the fair value of common stock warrants represent management's best estimates and involve inherent uncertainties and the application of management's judgment. For volatility, the Company

uses its own historical volatility as a basis for its expected volatility to calculate the fair value of common stock warrants. The risk-free interest rate is based on U.S. Treasury notes with a term approximating the expected term of the common stock warrant. Any significant increases or decreases in the observable and unobservable inputs may result in significantly higher or lower fair value measurements.

As of December 31, 2022, there were no outstanding liability classified warrants.

The following are the weighted average assumptions used in estimating the fair value of warrants outstanding as of December 31, 2021:

	December 31, 2021			
Valuation assumptions:	Range			Weighted Average
Risk-free interest rate	0.39		%	0.39 %
Expected volatility	77.35 %	-	82.82 %	77.66 %
Expected term (in years)	0.4	-	0.9	0.8
Dividend yield	— %	-	— %	— %

(8) Stock-Based Compensation

Determining the appropriate fair value of stock-based awards requires the input of subjective assumptions, the expected term of the option and expected volatility. The Company uses the Black-Scholes-Merton option pricing model to value its stock option awards. The assumptions used in calculating the fair value of stock-based awards represent management's best estimates and involve inherent uncertainties and the application of management's judgment. The expected term of stock options is estimated using the "simplified method." The simplified method is based on the average of the vesting tranches and the contractual life of each grant. For volatility, the Company historically used comparable public companies as a basis for its expected volatility to calculate the fair value of option grants due to its limited history as a public company; however, during the year ended December 31, 2020, the Company had sufficient history of a public company and ceased using the comparable public company peer group as the basis for its expected volatility. The risk-free interest rate is based on U.S. Treasury notes with a term approximating the expected term of the option. For restricted stock, the fair value is the closing market price per share on the grant date. The estimation of the number of stock awards that will ultimately vest requires judgment, and to the extent actual results or revised estimates differ from the Company's current estimates, such amounts will be recorded as an adjustment in the period in which estimates are revised.

Incentive Plans

During 2014, the Company adopted the 2014 Equity Incentive Plan, or the 2014 Plan, which provided for the grant of options. Following the effectiveness of the Company's registration statement filed in connection with its IPO, no options may be granted under the 2014 plan. The awards granted under the 2014 Plan generally have a vesting period of between one to four years.

During 2015, the Company adopted the 2015 Equity Incentive Plan, or the 2015 Plan, which provides for the grant of options, restricted stock and other forms of equity compensation. As of December 31, 2022, the Company had 645,657 shares available for grant with an aggregate of 1,479,652 shares of common stock authorized under the 2015 Plan.

As of December 31, 2022, there was approximately $0.4 million of total unrecognized compensation expense related to unvested stock awards. This expense is expected to be recognized over a weighted-average period of 0.9 years.

No tax benefit was recognized during the years ended December 31, 2022, 2021 and 2020 related to stock-based compensation expense since the Company incurred operating losses and has established a full valuation allowance to offset all the potential tax benefits associated with its deferred tax assets.

Options

Compensation expense is measured based on the fair value of the option on the grant date and is recognized on a straight-line basis over the requisite service period, or sooner if vesting occurs sooner than on a straight-line basis. Options are forfeited if the employee ceases to be employed by the Company prior to vesting.

There were no options granted during the year ended December 31, 2022. The weighted average grant-date fair value of options issued during the years ended December 31, 2021 and 2020 was $2.76 and $9.28, respectively. The following are the weighted average assumptions used in estimating the fair value of options issued during the years ended December 31, 2021 and 2020.

	Year Ended	
	December 31, 2021	December 31, 2020
Valuation assumptions:		
Risk-free rate	1.30 %	0.33 %
Expected volatility	133.53 %	144.33 %
Expected term (years)	5.5	5.7
Dividend yield	— %	— %

A summary of option activity under the 2015 Plan and 2014 Plan for the years ended December 31, 2022, 2021 and 2020 is presented below:

	Bellerophon 2015 and 2014 Equity Incentive Plans			
	Options	Range of Exercise Price	Weighted Average Price	Weighted Average Remaining Contractual Life (in years)
Options outstanding as of December 31, 2019	663,501	$ 7.35 - 199.20	$ 24.15	8.3
Granted	77,263	10.12 - 12.58	10.12	
Forfeited	(507)	7.35 - 199.20	23.47	
Options outstanding as of December 31, 2020	740,257	$ 7.35 - 199.20	$ 22.69	7.5
Granted	97,483	3.10 - 4.06	3.11	
Forfeited	(220,391)	7.50 - 199.20	40.39	
Options outstanding as of December 31, 2021	617,349	$ 3.10 - 199.20	$ 13.28	7.0
Forfeited	(292,757)	7.35 - 199.20	14.11	
Cancelled	(2,554)	4.06 - 13.20	6.51	
Options outstanding as of December 31, 2022	322,038	$ 3.10 - 199.20	$ 12.58	6.7
Options vested and exercisable as of December 31, 2022	313,342	$ 3.10 - 199.20	$ 12.71	6.7

The intrinsic value of options outstanding, vested and exercisable as of December 31, 2022 was zero.

Restricted Stock

All restricted stock units granted under the 2015 Plan during the year ended December 31, 2022 were time-based restricted stock units as part of stock compensation for all employees and officers of the Company. Each granted stock unit awarded represents the right to receive Common Stock at the end of the vesting period equal to the number of restricted stock units granted and are subject to a risk of forfeiture if the award recipient is no longer employed by the Company for any reason prior to the lapse of the restriction.

A summary of restricted stock activity under the 2015 Plan for the years ended years ended December 31, 2022, 2021 and 2020 is presented below:

	Bellerophon 2015 Equity Incentive Plan			
	Shares	Weighted Average Fair Value	Aggregate Grant Date Fair Value (in millions)	Weighted Average Remaining Contractual Life (in years)
Restricted stock outstanding as of December 31, 2019	—	$ —	$ —	—
Granted	23,332	6.00	0.1	
Vested	(16,666)	(6.00)	(0.1)	
Expired	(6,666)	(6.00)	—	
Restricted stock outstanding as of December 31, 2020	—	$ —	$ —	—
Granted	54,340	3.69	0.2	
Vested	(54,340)	3.69	(0.2)	
Restricted stock outstanding as of December 31, 2021	—	$ —	$ —	—
Granted	370,000	2.30	0.9	
Vested	(145,500)	(2.35)	(0.1)	
Forfeited	(59,000)	2.36	(0.1)	
Restricted stock outstanding as of December 31, 2022	165,500	$ 2.23	$ 0.7	0.9

Ikaria Equity Incentive Plans for Periods Prior to February 12, 2014

Options

The Company has outstanding options that were assumed during its spin-out from Ikaria, Inc., or Ikaria. A summary of option activity under the assumed Ikaria 2007 stock option plan and the assumed Ikaria 2010 long term incentive plan for the years ended December 31, 2022, 2021 and 2020 is presented below:

	Ikaria Equity Incentive Plans for Periods Prior to February 12, 2014			
	Shares	Range of Exercise Price	Weighted Average Exercise Price	Weighted Average Remaining Contractual Life (in years)
Options outstanding, vested and exercisable as of December 31, 2019	3,463	$116.55 - 268.80	$ 136.81	2.3
Forfeited	(892)	116.55 - 124.05	119.17	
Expired	(63)	208.65	208.65	
Options outstanding, vested and exercisable as of December 31, 2020	2,508	$116.55 - 223.65	$ 123.87	1.5
Forfeited	(503)	124.05 - 131.55	130.39	
Expired	(907)	116.55	116.55	
Options outstanding, vested and exercisable as of December 31, 2021	1,098	$124.05 - 223.65	$ 126.94	1.2
Forfeited	(234)	124.05 - 223.65	135.95	
Options outstanding, vested and exercisable as of December 31, 2022	864	$124.05 - 131.55	$ 124.50	0.2

There were no options exercised during the years ended December 31, 2022, 2021 and 2020. The intrinsic value of options outstanding, vested and exercisable as of December 31, 2022 was zero.

Stock-Based Compensation Expense, Net of Estimated Forfeitures

The following table summarizes the stock-based compensation expense for the years ended December 31, 2022, 2021 and 2020. The following disclosures include stock-based compensation expense recognized under the 2015 Plan and the 2014 Plan (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Research and development	$ 463	$ 309	$ 376
General and administrative	323	817	1,257
Total expense	$ 786	$ 1,126	$ 1,633

There were no stock-based compensation expenses recognized during the years ended December 31, 2022, 2021 and 2020 under the assumed Ikaria 2007 stock option plan and the assumed Ikaria 2010 long term incentive plans.

(9) Income Taxes

Prior to its conversion to a Delaware corporation in February 2015, the Company was a Delaware limited liability company, or LLC, that passed through income and losses to its members for U.S. federal and state income tax purposes. As a result of its conversion to a Delaware corporation, the Company recognized deferred income taxes through income tax expense related to temporary differences that existed as of the date of its tax status change.

The Company's tax rate for 2022 and 2021 are (10.9%) and (9.2%), respectively, due to the fact that it sold its New Jersey state Net Operating Losses and Credits and recognized the sale as a benefit. The Company expects to generate additional losses and currently has a full valuation allowance against its deferred tax assets.

The Company may be subject to certain limitations in its annual utilization of NOL carry forwards to off-set future taxable income (and of tax credit carry forwards to off-set future tax expense) pursuant to Section 382 of the Internal Revenue Code, which could result in tax attributes expiring unused.

A reconciliation of the statutory federal income tax rate to the Company's effective tax rate for the years ended December 31, 2022, 2021 and 2020 is as follows:

	Year Ended December 31, 2022	Year Ended December 31, 2021	Year Ended December 31, 2020
U.S. federal statutory rate	21 %	21 %	21 %
State and local taxes, net of federal tax effect	(2.7)%	(1.9)%	(0.9)%
Research tax credits	7.1 %	3.8 %	4.5 %
Valuation allowance	(20.0)%	67.9 %	(22.8)%
Prior year adjustments	(3.0)%	(89.1)%	0.5 %
Sale of NOLs and R&D tax credits	(10.9)%	(9.2)%	(7.9)%
Expenses associated with common stock warrant liability (a)	— %	0.6 %	(0.3)%
Incentive stock options, non-deductible and permanent items	(2.4)%	(2.3)%	(2.0)%
	(10.9)%	(9.2)%	(7.9)%

(a) Represents change in fair value and attributable issuance costs

Deferred taxes as of December 31, 2022 and 2021 reflect the tax effects of the differences between the amounts recorded as assets and liabilities for financial reporting purposes and the comparable amounts recorded for income tax purposes.

Significant components of the deferred tax assets (liabilities) at December 31, 2022 are as follows (in thousands):

	December 31, 2022	
	Assets	(Liabilities)
Net operating loss carryforwards	$ 41,192	$ —
Research tax credit carryforwards	7,248	—
Property and equipment	26	—
Stock based compensation	184	—
Intangible assets	4,037	—
Lease liability	5	—
Capitalized Section 174 Costs	3,655	—
Accrued expenses	283	—
Subtotal	56,630	—
Valuation allowance	(56,630)	—
Total deferred tax assets (liabilities)	$ —	$ —
Net deferred tax assets	$ —	

Significant components of the deferred tax assets (liabilities) at December 31, 2021 are as follows (in thousands):

	December 31, 2021	
	Assets	(Liabilities)
Net operating loss carryforwards	$ 40,591	$ —
Research tax credit carryforwards	5,889	—
Property and equipment	17	—
Stock based compensation	660	—
Intangible assets	4,700	—
Lease liability	26	
Accrued expenses	298	—
Subtotal	52,181	—
Valuation allowance	(52,181)	—
Total deferred tax assets (liabilities)	$ —	$ —
Net deferred tax assets	$ —	

A valuation allowance is provided when it is more likely than not that some portion or all of the deferred tax assets will not be realized. As of December 31, 2022 and 2021, management believed that it was more likely than not that the deferred tax assets would not be realized, based on future operations, consideration of tax strategies and the reversal of deferred tax liabilities. The valuation allowance is required until the Company has sufficient positive evidence of taxable income necessary to support realization of its deferred tax assets. A valuation allowance release is recognized as an income tax benefit.

As of December 31, 2022, the Company has available net operating loss, or NOL, carry forwards for federal income tax reporting purposes of approximately $183.2 million and for state income tax reporting purposes of approximately $38.2 million, which expire at various dates between fiscal 2037 and 2040 for NOLs incurred for federal income tax prior to January 1, 2018. Losses incurred after this date have an indefinite life. The Company has sold $25.1 million of state NOLs and $0.2 million of research and development credits under the State of New Jersey's Technology Business Tax Certificate Transfer Program in April 2022 for net proceeds of $2.2 million. The Company also sold an additional $16.4 million of state NOLs and $0.3 million of research and development credits under the State of New Jersey's Technology business Tax Certificate Transfer Program for net proceeds of $1.7 million in June 2021. The Company plans to sell additional NOLs and R&D credits under the same program in the future subject to program availability and state approval.

As of December 31, 2022 and 2021, the Company had no material uncertain tax positions.

(10) Net Loss Per Share

	Twelve months ended December 31,		
	2022	2021	2020
Net loss	$ (19,831)	$ (17,756)	$ (24,728)
Weighted-average shares:			
Basic	9,550,872	9,502,793	7,797,130
Diluted	9,550,872	9,502,793	7,797,130
Net (loss) income per share:			
Basic	$ (2.08)	$ (1.87)	$ (3.17)
Diluted	$ (2.08)	$ (1.87)	$ (3.17)

For the year ended December 31, 2022, the total number of potential shares of common stock excluded from the diluted earnings per share computation because their inclusion would have been anti-dilutive was 2.4 million, which included 0.3 million options to purchase shares, 0.2 million restricted stock units to acquire shares and 1.9 million warrants to purchase shares.

For the year ended December 31, 2021, the total number of potential shares of common stock excluded from the diluted earnings per share computation because their inclusion would have been anti-dilutive was 2.6 million, which included 0.6 million options to purchase shares and 2.0 million warrants to purchase shares.

For the year ended December 31, 2020, the total number of potential shares of common stock excluded from the diluted earnings per share computation because their inclusion would have been anti-dilutive was 2.7 million, which included 0.7 million options to purchase shares and 2.0 million warrants to purchase shares.

Basic net loss per share is calculated by dividing net loss by the weighted average number of shares outstanding during the period, as applicable. Diluted net loss per share is calculated by dividing net loss, adjusted to reflect the impact of dilutive securities, by the weighted average number of shares outstanding, adjusted to reflect potentially dilutive securities using the treasury stock method, except when the effect would be anti-dilutive.

(11) Commitments and Contingencies

Legal Proceedings

The Company periodically becomes subject to legal proceedings and claims arising in connection with its business. The ultimate legal and financial liability of the Company in respect to all proceedings, claims and lawsuits, pending or threatened, cannot be estimated with any certainty.

As of the date of this report, the Company is not aware of any proceeding, claim or litigation, pending or threatened, that could, individually or in the aggregate, have a material adverse effect on the Company’s business, operating results, financial condition and/or liquidity.

Contractual Obligations

The following is a summary of the Company's contractual cash obligations as of December 31, 2022 (in thousands):

	Operating Lease (1)
2023	$ 205
2024	—
Thereafter	—
Total	$ 205

(1) Operating lease obligations include a lease agreement the Company entered into on August 6, 2015 for office space and a lease agreement the Company entered into on September 3, 2019 for laboratory space both in Warren, New Jersey.

Royalty payments and success-based milestones associated with the Company's license and supply agreements with Ikaria have not been included in the above table of contractual obligations as the Company cannot reasonably estimate if or when they will occur.

In the course of its normal business operations, the Company also enters into agreements with contract service providers and others to assist in the performance of its research and development and manufacturing activities. The Company can elect to discontinue the work under these contracts and purchase orders at any time with notice, and such contracts and purchase orders do not contain minimum purchase obligations.

License Agreement with Ikaria

In February 2014, the Company entered into a cross-license, technology transfer and regulatory matters agreement with a subsidiary of Ikaria. Pursuant to the terms of the license agreement, Ikaria granted to the Company a fully paid-up, non-royalty-bearing, exclusive license under specified intellectual property rights controlled by Ikaria to engage in the development, manufacture and commercialization of nitric oxide, devices to deliver nitric oxide and related services for or in connection with out-patient, chronic treatment of patients who have PAH, PH-COPD or PH associated with idiopathic pulmonary fibrosis, or PH-IPF. Pursuant to the terms of the license agreement, the Company granted Ikaria a fully paid-up, non-royalty-bearing, exclusive license under specified intellectual property rights that the Company controls to engage in the development, manufacture and commercialization of products and services for or used in connection with the diagnosis, prevention or treatment, whether in- or out-patient, of certain conditions and diseases other than PAH, PH-COPD or PH-IPF and for the use of nitric oxide to treat or prevent conditions that are primarily managed in the hospital. The Company agreed that, during the term of the license agreement, it will not, without the prior written consent of Ikaria, grant a sublicense under any of the intellectual property licensed to the Company under the license agreement to any of its affiliates or any third party, in either case, that directly or indirectly competes with Ikaria's nitric oxide business. In July 2015, the Company and Ikaria entered into an amendment to the license agreement to expand the scope of the Company's license to allow the Company to develop its INOpulse program for the treatment of three additional indications: chronic thromboembolic PH, or CTEPH, PH associated with sarcoidosis and PH associated with pulmonary edema from high altitude sickness. Subject to the terms set forth therein, the amendment to the license agreement also provides that the Company will pay Ikaria a royalty equal to 5% of net sales of any commercialized products for the three additional indications. In November 2015, the Company entered into an amendment to its 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 expanded the scope of our license from PH-IPF to PH in patients with Pulmonary Fibrosis (PH-PF), which includes idiopathic interstitial pneumonias, chronic hypersensitivity pneumonitis, occupational and environmental lung disease, with a royalty equal to 1% of net sales of any commercial products for PH-PF.

(12) Subsequent Events

License Agreement with Baylor Biosciences, Inc.

In January 2023, we entered into a license agreement (the "License Agreement") with Baylor BioSciences, Inc. ("Baylor"), pursuant to which Baylor received exclusive rights to develop and commercialize INOpulse within mainland China, Taiwan, Hong Kong and Macau (collectively, "Greater China") for diseases associated with pulmonary hypertension, including the lead indication of fibrotic interstitial lung disease (fILD), as well as PAH, PH-Sarcoidosis, and PH-COPD, CTEPH and PH associated with pulmonary edema from high altitude sickness. Under the terms of the License Agreement, a license payment of $6 million, net of taxes and customary closing costs, is payable by Baylor within 90 days. Additionally, we are entitled to royalties of 5% on net sales by Baylor resulting from all of the licensed INOpulse indications within Greater China.

Registered Direct Offering

On March 3, 2023, the Company entered into a subscription agreement with an institutional investor, pursuant to which the Company agreed to issue and sell in a registered direct offering (the "Offering") (i) an aggregate of 718,474 shares (the "Shares") of the Company's common stock, $0.01 par value per share ("Common Stock") and (ii) pre-funded warrants (the "Pre-Funded Warrants") to purchase up to 1,781,526 shares of Common Stock. The Company closed the Offering on March 7, 2023 with the Shares sold to the purchaser at a price per share of $2.00 per share. The Pre-Funded Warrants were sold at an offering price of $1.99 per Pre-Funded Warrant, which represents the per share offering price for the Common Stock less a $0.01 per share exercise price for each such Pre-Funded Warrant. No underwriter or placement agent participated in the Offering and the proceeds from the Offering were approximately $5 million.

The Pre-Funded Warrants are exercisable at any time after the date of issuance. A holder of Pre-Funded Warrants may not exercise the warrant if the holder, together with its affiliates, would beneficially own more than 9.99% of the number of shares of Common Stock outstanding immediately after giving effect to such exercise. A holder of Pre-Funded Warrants may increase or decrease this percentage, but not in excess of 19.99%, by providing at least 61 days prior notice to the Company.

The Offering was made pursuant to the Company's shelf registration statement previously filed with the Securities and Exchange Commission (the "SEC"), originally filed on June 26, 2020 (File No. 333-239473), which the SEC declared effective on July 2, 2020, and a related prospectus supplement.

Completion of Sale under the State of New Jersey's Technology Business Tax Certificate Transfer Program

During January 2023, the Company completed a subsequent sale of its NOLs and R&D credits under the State of New Jersey's Technology Business Tax Certificate Transfer Program. The Company sold $19.7 million of state NOLs and $0.1 million of R&D credits for net proceeds of approximately $1.7 million.

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2022. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2022, our principal executive officer and principal financial officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control Over Financial Reporting

Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and effected by the company's board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. The company's internal control over financial reporting includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2022. In making this assessment, management used the criteria set forth in the Internal Control - Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

Based on our assessment, management believes that, as of December 31, 2022, our internal control over financial reporting is effective based on those criteria**.**

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm regarding internal control over financial reporting. Effective April 27, 2020, the SEC adopted amendments to the "accelerated filer" and "large accelerated filer" definitions in Rule 12b-2 under the Exchange Act.

The amendments exclude from the accelerated and large accelerated filer definitions an issuer that is eligible to be a smaller reporting company and that had annual revenues of less than $100 million in the most recent fiscal year for which audited financial statements are available. We determined that our company does not meet the accelerated or large accelerated filer definitions as of December 31, 2022. For as long as we remain a non-accelerated filer, we intend to take advantage of the exemption permitting us not to comply with the requirement under Section 404(b) of the Sarbanes-Oxley Act of 2002 that our independent registered public accounting firm provide an attestation on the effectiveness of our internal control over financial reporting.

Changes in Internal Control Over Financial Reporting

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the fiscal quarter ended December 31, 2022 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The response to this item is incorporated by reference from the discussion responsive thereto under the captions "Management and Corporate Governance," "Delinquent Section 16(a) Reports," and "Code of Conduct and Ethics" in our Proxy Statement for the 2023 Annual Meeting of Stockholders (our "2023 Proxy Statement").

Directors and Executive Officers

The following table sets forth the name, age and position of each of our executive officers as of March 30, 2023.

Name	Age	Position
Peter Fernandes	68	Chief Executive Officer and Chief Regulatory, Safety & Quality Officer
Nicholas Laccona	34	Principal Financial and Accounting Officer and Secretary
Martin Dekker	50	Vice President of Engineering and Manufacturing
Parag Shah	46	Vice President of Business Operations
Bobae Kim	41	Vice President Regulatory Affairs and Quality Assurance
Naseem Amin, M.D.	61	Chairman of the Board of Directors
Scott P. Bruder, M.D., Ph.D.	61	Director
Mary Ann Cloyd	68	Director
Ted Wang	56	Director
Crispin Teufel	47	Director

Executive Officers

Peter Fernandes has served as our Chief Executive Officer since December 2022 having previously served as our Principal Executive Officer since November 2021 and as our Chief Regulatory, Safety & Quality Officer since May 2015. Prior to joining us, Mr. Fernandes was Vice President of Global Regulatory Affairs at Ikaria Inc., from October 2012 to May 2015, and in this capacity also led our regulatory group since its inception in February 2014. Previously, he led Regulatory Affairs and Quality Assurance for OptiNose, Inc. from October 2010 to September 2012, was Vice President US Drug Regulatory Affairs Respiratory and US DRA Respiratory Franchise Head for Novartis Pharmaceuticals from November 2007 to October 2010. He has also served as the Head of US Development Site and Vice President of Regulatory Affairs and Quality Assurance at Altana Pharma, a subsidiary of Nycomed Inc., and led the US Respiratory and GI Drug Regulatory Affairs group at Boehringer Ingelheim. Mr. Fernandes has over 30 years of experience leading cross functional global development teams covering respiratory and cardiovascular diseases with successful US and global submissions and approvals obtained for a number of well-known drugs e.g., Flomax, Spiriva, Omnaris. Mr. Fernandes also serves as Co-Chair of the Pulmonary Vascular Research Institute (PVRI) Innovative Drug Development Initiative that is instrumental in developing novel regulatory endpoints and clinical trial design for Pulmonary Hypertension (PH) in collaboration with academia, industry and regulators. Mr. Fernandes has an M. Pharm. from the Grant Medical College and a B. Pharm. from the K.M. K College of Pharmacy, both at the University of Bombay in India.

Nicholas Laccona has served as our Principal Financial and Accounting Officer and Secretary since October 2021. Mr. Laccona previously served as the Controller of the Company since August of 2020. Prior to joining the Company, Mr. Laccona served as Senior Manager, Audit at KPMG LLP from December 2014 through August 2020. Prior to that, Mr. Laccona served as an auditor with Sobel & Co., LLC. Mr. Laccona holds a Bachelor's degree from the University of Maryland, College Park, is a Certified Public Accountant and an active member of the America Institute of Certified Public Accountants.

Martin Dekker has served as our Vice President of Engineering and Manufacturing since January 2015. Prior to joining us, Mr. Dekker held several positions at Spacelabs Healthcare, a company that develops and manufactures medical devices, from November 1998 to January 2015, most recently as Director of Global Operations Engineering. During his time at Spacelabs Healthcare, Mr. Dekker led and co-designed new products, developed and launched transformative manufacturing technologies and championed cross-functional quality/engineering projects. He is a member of the Institute of Electrical and Electronic Engineers. Mr. Dekker received a B.S. in electronics from Noordelijke Hogeschool Leeuwarden, the Netherlands.

Parag Shah, Ph.D. has served as our Vice President of Business Operations since April 2016 with responsibilities for Project Management, Supply Distribution, Pre-Clinical and Business Development activities. Prior to joining us, Dr. Shah was Principal Scientist at Pfizer from 2004 through 2010 where he was responsible for leading multiple parenteral and liquid formulation development teams. In addition, Dr. Shah was a member of multiple Limited Duration Teams including serving as Pfizer's Team Lead for the Nanoparticle Network responsible for internal and external evaluation of nanoparticle technologies. Dr. Shah joined Ikaria as Parenteral Development Lead in 2010 and assumed additional responsibilities in 2012 as Director, Pharmaceutical Science, covering both Pharmaceutical Development and Clinical Supply Management. Dr. Shah received his Bachelor's degree from Carnegie Mellon and his Ph.D. in Chemical Engineering from The University of Texas at Austin.

Bobae Kim, has served as our Vice President, Regulatory Affairs and Quality Assurance since September 2022. Ms. Kim joined as Senior Director of Regulatory Affairs and Quality Assurance in September 2016. Prior to joining us, Ms. Kim served as Chief Technology Officer for Iluminage Beauty Inc, a joint venture of Syneron Candela and Unilever Ventures that develops and manufactures medical devices. Ms. Kim was responsible for identifying new technology, leading the design and developing new products as well as responsible for the Company's overall regulatory strategy including filing and obtaining regulatory approvals, maintaining their Quality Management System and the execution of their clinical development program to support safety, efficacy and usability. She holds a Regulatory Affairs Certificate (RAC) with Regulatory Affairs Professional Society since December 2017and is a Certified Clinical Research Associate (CCRA) with the Association of Clinical Research Professionals (ACRP) since April 2013. Ms. Kim received a Honors B.Sc. in Biochemistry from McMaster University, in Canada.

There are no family relationships among any of our executive officers.

Directors

Naseem Amin has served as the Chairman of our Board since May 2021, and has served as a member of our Board since June 2015. Dr. Amin has served as the Chief Executive Officer at GMP-Orphan since June 2017 and has served as the Chairman of Arix Bioscience plc, a global venture capital company focused on investing in life sciences, since April 2020. Dr. Amin had served as the Chief Scientific Officer of Smith and Nephew Plc until 2014. Previously, Dr. Amin was Senior Vice President, Business Development at Biogen Idec from 2005 to 2009 and was with Genzyme Corporation from 1999 to 2005, most recently as Head, International Business Development and where he has also led the clinical development of five currently marketed therapeutic products. Dr. Amin began his career at Baxter Healthcare Corporation, where he served as Director, Medical Marketing and Portfolio Strategy, Renal Division. Dr. Amin is a Venture Partner at Advent Life Sciences, serves as an Advisory Board member for Imperial College, Department of Biomedical Engineering, and serves as Chairman of OPEN-London, a non-profit organization focused on encouraging and mentoring South Asians from Pakistan who are interested in starting entrepreneurial companies. Dr. Amin received his medical degree from the Royal Free School of Medicine, London, and an MBA from the Kellogg Graduate School of Management, Northwestern University. We believe that Dr. Amin is qualified to serve on our Board because of his broad industry experience in the Biotech and Medical Device industry.

Scott Bruder has served as a member of our Board since May 2015. Dr. Bruder currently leads the Bruder Consulting & Venture Group with a global team that provides scientific, clinical, regulatory and development strategy services to medical device, regenerative medicine and biotechnology companies, investment banks, venture partners and private equity firms. Since 2011, Dr. Bruder has been an adjunct Professor of Biomedical Engineering at Case Western Reserve University, following 13 years as adjunct faculty in the Department of Orthopedic Surgery. Dr. Bruder currently serves on the Board of Directors of Kuros Biosciences AG, a Swiss Exchange listed biotechnology company, where he

leads the R&D Committee. Previously, he was the Chairman of the Board of Spinal Elements, a privately held, leading provider of innovative medical devices used during spinal surgical procedures. Dr. Bruder served as the Chief Medical and Scientific Officer of Stryker Corporation from 2012 until 2014, and was the Chief Science and Technology Officer for Becton, Dickinson and Company from 2007 until 2012. Previously, Dr. Bruder held a number of senior executive and scientific roles at Johnson & Johnson, Anika Therapeutics and Osiris Therapeutics. Dr. Bruder is a magna cum laude graduate from Brown University with a Sc.B. in Biology, and a graduate of Case Western Reserve University School of Medicine, where he simultaneously earned an M.D. and a Ph.D. in stem cell biology. We believe that Dr. Bruder is qualified to serve on our Board because of his experience in medical devices, biotechnology, life sciences, and biomedical engineering.

Mary Ann Cloyd has served as a member of our Board since February 2016. Since April 2018 she has served on the board of NCMIC Group, Inc., a mutual insurance and financial services company based in Des Moines, Iowa. Since May 2019 she has served on the board of Fresh Del Monte Produce, Inc., a producer and distributor of prepared fruit and vegetables, juices, beverages and snacks, and since 2020 as a director of Ekso Bionics, Holdings, Inc., a publicly traded company focused on exoskeleton technology. From 1990 to 2015, Ms. Cloyd was a partner at PricewaterhouseCoopers LLP ("PwC"), where she served multinational corporate clients in a variety of industries, including the biotechnology and pharmaceutical industries. She was the Leader of the PwC Center for Board Governance from 2012 to 2015. Ms. Cloyd has also served on both PwC's Global and U.S. Boards. On the U.S. Board, she chaired the Risk Management, Ethics & Compliance Committee and the Partner Admissions Committee, and on the Global Board, she served on the Risk and Operations Committee and the Clients Committee. Ms. Cloyd previously served on the Board of Trustees of the PwC Charitable Foundation, Inc., and she previously served as President of the Foundation. Ms. Cloyd is also on the Board of the Geffen Playhouse, where she serves as Vice Chair, the Caltech Associates and the Advisory Board of the UCLA Iris Cantor Women's Center. Ms. Cloyd earned a bachelor of business administration from Baylor University, summa cum laude. We believe that Ms. Cloyd is qualified to serve on our Board because of her experience in finance, senior management and corporate governance.

Dr. Ted Wang has served as a member of our Board since November 2017. Dr. Wang has served as the Chief Investment Officer of Puissance Capital Management LP, of which he was a founder, since January 2015. Prior to that, Dr. Wang was a Partner of Goldman, Sachs & Co. ("Goldman"), which he joined in 1996 and with which he served in many leadership positions, mostly recently as Co-Head of U.S. Equities Trading and Global Co-Head of One Delta Trading and a member of the Goldman Sachs Risk Committee. Prior to joining Goldman, Dr. Wang co-founded Xeotron Corp., a company specializing in DNA biochips in Texas. Dr. Wang serves on the board of Ekso Bionics Holdings, Inc., Viewray, Inc. and Tracon Pharmaceuticals, Inc. Dr. Wang holds a Ph.D. in Physics from the University of Minnesota, an M.B.A. from the University of Texas, Austin, and a B.S. from Fudan University, China. We believe that Dr. Wang is qualified to serve on our Board because of his financial expertise and years of experience.

Crispin Teufel was appointed to our Board effective March 18, 2019. Since 2017, Mr. Teufel has served as the Chief Executive Officer of Lincare Holdings Inc., the leading national provider of respiratory services in the home, and as its Chief Financial Officer since 2013. Mr. Teufel serves on the board of directors of the German-American Chamber of Commerce and was elected as their chairman of the board in November 2020. Mr. Teufel holds an MBA in Economics from Ruhr University Bochum, Germany, is a Certified Public Accountant and is a German Tax Advisor under Germany's Taxation and Ministry of Finance. We believe that Mr. Teufel is qualified to serve on our Board because of his managerial, financial and business experience.

Code of Ethics and Code of Conduct

We have adopted a written code of business conduct and ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. We have posted a current copy of the code on our website, www.bellerophon.com. If we make any substantive amendments to, or grant any waivers from, the code of business conduct and ethics for any officer or director, we will disclose the nature of such amendment or waiver on our website or in a current report on Form 8-K.

Delinquent Section 16(a) Reports

The information concerning compliance with Section 16(a) of the Securities Exchange Act of 1934 required by this Item is incorporated by reference to the "Delinquent Section 16(a) Reports" section of our 2023 Proxy Statement.

Item 11. Executive Compensation

The response to this item is incorporated by reference from the discussion responsive thereto under the caption "Executive Officer and Director Compensation" in our 2023 Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The response to this item is incorporated by reference from the discussion responsive thereto under the captions "Security Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information" in our 2023 Proxy Statement.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The response to this item is incorporated by reference from the discussion responsive thereto under the captions "Certain Relationships and Related Person Transactions" and "Management and Corporate Governance" in our 2023 Proxy Statement.

Item 14. Principal Accountant Fees and Services

The response to this item is incorporated by reference from the discussion responsive thereto under the caption "Independent Registered Public Accounting Firm" in our 2023 Proxy Statement.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(1) Financial Statements

Our consolidated financial statements are set forth in Part II, Item 8 of this Annual Report on Form 10-K and are incorporated herein by reference.

(2) Financial Statement Schedules

No financial statement schedules have been filed as part of this Annual Report on Form 10-K because they are not applicable or are not required or because the information is otherwise included herein.

(3) Exhibits

The exhibits filed as part of this Annual Report on Form 10-K are set forth on the Exhibit Index immediately following our financial statements. The Exhibit Index is incorporated herein by reference.

Item 16. Form 10-K Summary

None.

EXHIBIT INDEX

Exhibit Number	Description of Exhibit
2.1	Plan of Conversion (incorporated by reference to Exhibit 2.1 to the Registrant's Registration Statement on Form S 3 (File No. 333 239473) filed with the SEC on June 26, 2020)
2.2	Agreement and Plan of Merger (incorporated by reference to Exhibit 2.2 to the Registrant's Registration Statement on Form S 3 (File No. 333 239473) filed with the SEC on June 26, 2020)
3.1	Restated Certificate of Incorporation of the Registrant, as amended, dated July 30, 2018 (incorporated by reference to Exhibit 3.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36845) filed with the SEC on November 7, 2018)
3.2	Certificate of Amendment to the Restated Certificate of Incorporation of Bellerophon Therapeutics, Inc., filed with the Secretary of State of the State of Delaware on February 5, 2020 (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-36845) filed with the SEC on February 7, 2020)
3.3	Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-36845) filed with the SEC on February 25, 2015)
4.1	Specimen Stock Certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1/A (File No. 333-201474) filed with the SEC on February 3, 2015)
4.2	Form of Warrant Amendment, dated June 28, 2019 , between the Registrant and certain holders identified therein (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-36845) filed with the SEC on July 1, 2019)
4.3	Description of Securities Registered Under Section 12 of the Securities Exchange Act of 1934 (incorporated by reference to Exhibit 4.5 to the Registrant's Annual Report on Form 10-K (File No. 00136845) filed with the SEC on March 11, 2021)
4.4	Form of Senior Indenture (incorporated by reference to Exhibit 4.6 to the Registrant's Registration Statement on Form S 3 (File No. 333 239473) filed with the SEC on June 26, 2020)
4.5	Form of Subordinated Indenture (incorporated by reference to Exhibit 4.7 to the Registrant's Registration Statement on Form S 3 (File No. 333 239473) filed with the SEC on June 26, 2020)
10.1+	Assumed 2007 Ikaria Stock Option Plan (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.2+	Assumed 2010 Ikaria Long Term Incentive Plan (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.3+	2014 Equity Incentive Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.4+	Form of Option Agreement under 2014 Equity Incentive Plan (incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.5+	Amended and Restated 2015 Equity Incentive Plan (incorporated by reference to Appendix A to the Registrant's Definitive Proxy Statement (File No. 001-36845) filed with the SEC on March 20, 2017)
10.6+	Form of Incentive Stock Option Agreement under 2015 Equity Incentive Plan (incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form S-1/A (File No. 333-201474) filed with the SEC on February 3, 2015)
10.7+	Form of Nonstatutory Stock Option Agreement under 2015 Equity Incentive Plan (incorporated by reference to Exhibit 10.7 to the Registrant's Registration Statement on Form S-1/A (File No. 333-201474) filed with the SEC on February 3, 2015)

10.8† Drug Clinical Supply Agreement, dated as of February 9, 2014, between Bellerophon Pulse Technologies LLC and INO Therapeutics LLC (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)

10.9† Exclusive Cross-License, Technology Transfer and Regulatory Matters Agreement, dated February 9, 2014, between Bellerophon Pulse Technologies LLC and INO Therapeutics LLC, as amended on March 27, 2014 (incorporated by reference to Exhibit 10.14 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)

10.10 Registration Rights Agreement, dated February 12, 2015, among the Registrant, New Mountain Partners II (AIV-A), L.P., New Mountain Partners II (AIV-B), L.P., Allegheny New Mountain Partners, L.P., New Mountain Affiliated Investors II, L.P., ARCH Venture Fund VI, L.P., Venrock Partners, L.P., Venrock Associates IV, L.P., Venrock Entrepreneurs Fund IV, L.P., Linde North America, Inc., 5AM Ventures LLC and Aravis Venture I L.P. (incorporated by reference to Exhibit 10.16 to the Registrant's Annual Report on Form 10-K (File No. 001-36845) filed with the SEC on March 31, 2015)

10.11 Form of Indemnification Agreement between the Registrant and each of its executive officers and directors (incorporated by reference to Exhibit 10.17 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)

10.12 Form of Management Rights Letter between the Registrant and certain of its stockholders (incorporated by reference to Exhibit 10.23 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)

10.13+ Offer Letter, dated April 20, 2015, between Peter Fernandes and the Registrant (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36845) filed with the SEC on August 14, 2015)

10.14+ Offer Letter, dated December 8, 2014, between Martin Dekker and the Registrant (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36845) filed with the SEC on August 14, 2015)

10.15 Second Amendment to the Exclusive Cross-License, Technology Transfer, and Regulatory Matters Agreement between Bellerophon Pulse Technologies LLC and INO Therapeutics LLC, dated July 27, 2015 (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36845) filed with the SEC on November 12, 2015)

10.16 Form of Amendment to Agreement Not to Compete, entered into by Ikaria Acquisition LLC and each of the Registrant, Bellerophon BCM LLC, Bellerophon Pulse Technologies LLC and Bellerophon Services, Inc. dated July 27, 2015 (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36845) filed with the SEC on November 12, 2015)

10.17+ Offer Letter between Amy Edmonds and the Registrant dated February 14, 2014 (incorporated by reference to Exhibit 10.9 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-36845) filed with the SEC on November 12, 2015)

10.18+ Form of Restricted Stock Agreement under 2015 Equity Incentive Plan (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36845) filed with the SEC on December 4, 2015)

10.19 Second Amendment to Drug Clinical Supply Agreement and Third Amendment to Exclusive Cross-License, Technology Transfer, and Regulatory Matters Agreement, dated November 16, 2015, between Bellerophon Pulse Technologies LLC and INO Therapeutics LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36845) filed with the SEC on January 12, 2016)

10.20 Registration Rights Agreement, dated September 26, 2017, among the Registrant and the investors named therein (incorporated by reference to Exhibit 10.2 on Form 8-K filed with the SEC on September 27, 2017)

10.21 Form of Securities Purchase Agreement, dated as of March 30, 2020, by and among Bellerophon Therapeutics, Inc. and the Investors. (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36845) filed with the SEC on March 30, 2020)

10.22 Advisory Agreement, by and between Bellerophon Therapeutics, Inc. and Angel Pond Capital LLC, dated May 18, 2020 (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36845) filed with the SEC on May 20, 2020)

10.23	Subscription Agreement by and between Bellerophon Therapeutics, Inc. and Puissance Life Science Opportunities Fund VI, dated May 18, 2020 (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8 K (File No. 001 36845) filed with the SEC on May 20, 2020)
10.24	Open Market Sale Agreement, dated July 17, 2020, by and between Bellerophon Therapeutics, Inc. and Jefferies LLC (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36845) filed with the SEC on July 17, 2020)
10.25+	Form of Restricted Stock Unit Agreement under 2015 Equity Incentive Plan (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-36845) filed with the SEC on January 28, 2022)
21.1	Subsidiaries of the Registrant (incorporated by reference to Exhibit 21.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
23.1	Consent of KPMG LLP independent registered public accounting firm
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended
32	Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS	Inline XBRL Instance Document
101.SCH	Inline XBRL Taxonomy Schema Document
101.CAL	Inline XBRL Taxonomy Calculation Linkbase Document
101.LAB	Inline XBRL Taxonomy Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Presentation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
104	Cover Page Interactive Data File (Formatted as Inline XBRL and contained in Exhibit 101)

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* Schedules and exhibits have been omitted pursuant to Item 601(b)(2) of Regulation S-K. The Registrant hereby undertakes to furnish copies of any of the omitted schedules and exhibits upon request by the Securities and Exchange Commission.

† Confidential treatment has been granted as to certain portions, which portions have been omitted and separately filed with the Securities and Exchange Commission.

\+ Management contract or compensatory plan or arrangement filed in response to Item 15(a)(3) of the Instructions to the Annual Report on Form 10-K.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: March 31, 2023

BELLEROPHON THERAPEUTICS, INC.

By: /s/ Peter Fernandes
Peter Fernandes
Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Peter Fernandes Peter Fernandes	Chief Executive Officer (Principal Executive Officer)	March 31, 2023
/s/ Nicholas Laccona Nicholas Laccona	Principal Financial & Accounting Officer and Secretary (Principal Financial Officer and Principal Accounting Officer)	March 31, 2023
/s/ Naseem Amin Naseem Amin	Chairman	March 31, 2023
/s/ Scott P. Bruder Scott P. Bruder	Director	March 31, 2023
/s/ Mary Ann Cloyd Mary Ann Cloyd	Director	March 31, 2023
/s/ Crispin Teufel Crispin Teufel	Director	March 31, 2023
/s/ Ted Wang Ted Wang	Director	March 31, 2023