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Bellerophon Therapeutics (BLPH-NASDAQ)

BLPH's Novel Pulsed Inhaled NO Therapy Could Be First FDA-Approved Treatment for Terminal PH-Lung Diseases

Our DCF models only projected U.S. sales of INOpulse for the indications of PH-IPF, PH-COPD and PH-Sarcoidosis. We apply the following risk of regulatory failure rates to each of the programs; IPF 35% (i.e. 65% chance of FDA approval), COPD 50% and Sarcoidosis 65%. Our DCF, which uses a 12% discount rate and 2% terminal growth rate, **values BLPH at approximately $3.25/share**.

Current Price (08/06/19)	$0.65
Valuation	**$3.25**

OUTLOOK

Bellerophon is focused on the development and commercialization of a novel pulsed-delivery nitric oxide therapy to address serious and terminal chronic cardiovascular diseases with high unmet needs (and for which no FDA-approved treatments currently exist). The benefits of pulsed iNO includes a very rapid onset, clean safety profile and the fact that, unlike other medications, it largely confines its vasodilator effects to the pulmonary arteries. These are important characteristics as it means iNO provides almost immediate improvement in perfusion and blood oxygenation and does so without the potential systemic risks and complications associated with (less targeted) oral and intravenously delivered medications, which are sometimes used off-label to treat BLPH's targeted indications. BLPH has several mid-to-late stage clinical studies ongoing in three distinct clinical indications with multiple data readouts anticipated over the near term. These results should provide substantive additional insight into the clinical utility of the technology and related likelihood of eventual regulatory approval and, as such, could represent potential value-inflection events.

SUMMARY DATA

52-Week High	**$1.33**
52-Week Low	**$0.47**
One-Year Return (%)	**-69.73**
Beta	**1.06**
Average Daily Volume (sh)	**192,910**
Shares Outstanding (mil)	**69**
Market Capitalization ($mil)	**$44**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**48**
Insider Ownership (%)	**16**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2019 Estimate	**N/A**
P/E using 2020 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Growth**
Industry	**Med-Tech**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	0 A	0 A	0 A	0 A	0 A
2018	0 A	0 A	0 A	0 A	0 A
2019	0 A	0 E	0 E	0 E	0 E
2020					0 E

EPS

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$0.60 A	-$0.12 A	-$0.22 A	-$0.44 A	-$1.41 A
2018	$0.06 A	-$0.20 A	$0.17 A	-$0.02 A	$0.04 A
2019	$0.01 A	-$0.03 E	-$0.09 E	-$0.12 E	-$0.26 E
2020					-$0.44 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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SNAPSHOT

Bellerophon Therapeutics, Inc. (BLPH) is a clinical development-stage medical therapeutics company focused on the development and commercialization of a novel nitric oxide therapy which, if successfully fully developed and approved for sale, will address serious and terminal chronic cardiovascular diseases with high unmet needs. The company has several mid-to-late stage clinical studies ongoing in three distinct clinical indications with multiple data readouts anticipated over the near term. These results should provide substantive additional insight into the clinical utility of the technology and related likelihood of eventual regulatory approval (via the relatively streamlined and inexpensive 505(b)(2) NDA pathway) and, as such, could represent potential value-inflection events.

INOpulse, the company's flagship drug-device combination program, delivers (inhaled) pulsed nitric oxide to the lungs of patients suffering from diseases associated with pulmonary hypertension (PH), an uncurable condition that effects approximately 1% of the global population and for which there is great unmet need for more effective treatment options. Nitric oxide is produced by most cells in the human body including vascular endothelial cells, where it acts as a natural vasodilator (i.e. expander) of blood vessels.

Certain medical conditions such as PH are associated with reduced levels of nitric oxide and constriction of the pulmonary arteries. This can result in serious complications including a rise in blood pressure in the lungs, right ventricular failure (i.e. inability of the right heart ventricle, which is responsible for pumping blood into the lungs, to maintain sufficient blood flow through pulmonary circulation) and ultimately death. In addition to inhaled nitric oxide, current treatment for primary PH includes long-term oxygen therapy and the intravenously administered vasodilators epoprostenol (Flolan) and iloprost (Ventavis). This is in addition to a host of other available medications aimed at increasing blood oxygenation through opening and relaxing the blood vessels, stimulating production of endogenous vasodilators and enhancing blood flow.

Inhaled nitric oxide reaches the pulmonary arteries via alveoli, tiny sacs in the lungs responsible for gas exchange. The benefits of inhaled nitric oxide (iNO) as compared to other PH therapies includes a very rapid onset (which is similarly rapidly reversible) and the fact that, unlike other medications, it largely confines its vasodilator effects to the pulmonary arteries. These are important characteristics as it means iNO provides almost immediate improvement in perfusion and blood oxygenation and does so without the potential systemic risks and complications associated with (less targeted) oral and intravenously delivered medications.

Bellerophon licenses the INOpulse technology, which is protected by over 100 issued and pending patents, from Ikaria, Inc (a subsidiary of Mallinckrodt plc, NASDAQ: MNK), the company's former parent which markets the continuous-flow inhaled nitric oxide product, INOmax. INOmax, which has a current annual revenue run-rate of more than $600M, is used by hospitals for (the FDA-approved indication of) the treatment of term and near-term (> 34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.[1]

While the technology is similar, there are some important differences between the two products; INOmax delivers a continuous flow of iNO while INOpulse delivers the gas via pulsed action based on a patient's breathing pattern, INOmax uses significantly more NO than INOpulse (which relates to the difference in delivery), INOmax is used exclusively in the hospital while INOpulse is being developed for home use (i.e. ambulatory use), INOpulse is portable and lightweight while INOmax is not, and INOmax is indicated for the short-term (up to 14 days) treatment of neonates while INOpulse is aimed at adult patients with chronic PH-related diseases. INOpulse allows for safe long-term use of inhaled nitric oxide by administering the gas in relatively small volumes of short bursts, mitigating any risk of drug-related toxicity.

Unlike prostacyclin vasodilators which provide a much more systemic (i.e. indiscriminate) effect throughout the pulmonary arteries, INOpulse delivers iNO mostly to the well-ventilated areas of the lungs. This targeted delivery provides for distinct advantages, particularly as it relates to the optimization of treatment (and, specifically, to the mitigation of related side effects) of patients with certain lung diseases in which both respiratory function is impaired and blood flow is constricted.

Treatment with systemic pulmonary vasodilators can cause 'ventilation-perfusion mismatch' in patients with these diseases, a potentially serious complication resulting in abnormal oxygen desaturation of the blood (i.e. hypoxemia). INOpulse avoids this ventilation-perfusion (V/Q) mismatch through targeted delivery made possible by its novel

[1] www.accessdata.fda.gov. INOmax FDA label, Indications for Use

pulsed action (synchronized with a patient's breathing rate) and the rapid inactivation of inhaled nitric oxide upon contact with hemoglobin. INOpulse's ability to safely, effectively and significantly improve vasodilation/ventilation balance, increase blood vessel volume, decrease pulmonary arterial pressure (PAP) and increase exercise capacity in patients with highly debilitating and progressive pulmonary diseases has been demonstrated in randomized controlled clinical trials.

BLPH is pursuing three specific PH-related (potential orphan) chronic indications; PH associated with interstitial lung disease (PH-ILD) which includes PH associated with idiopathic pulmonary fibrosis (PH-IPF), PH associated with chronic obstructive pulmonary disease (PH-COPD) and PH associated with Sarcoidosis (PH-Sarc). As each of these are associated with impairment to both lung function and pulmonary vasculature and characterized by high unmet therapeutic needs and severe limitation to quality of life, they offer highly attractive commercial opportunities for BLPH and INOpulse.

While results of a Phase 3 study evaluating INOpulse in the treatment of pulmonary arterial hypertension, or PAH, (a specific subgroup of PH, the underlying causes of which have key differences than those of the PH-associated diseases that BLPH is now pursuing) was discontinued (in August 2018) due to a determination that the primary endpoint would not be met, it did provide valuable clinical (such as clinically and statistically significant improvement in NT-ProBNP, a marker of right ventricle dysfunction) and safety data, helping to reinforce the opportunity for INOpulse in diseases more likely to benefit from targeted iNO administration (such as PH-ILD, PH-COPD and PH-Sarc).

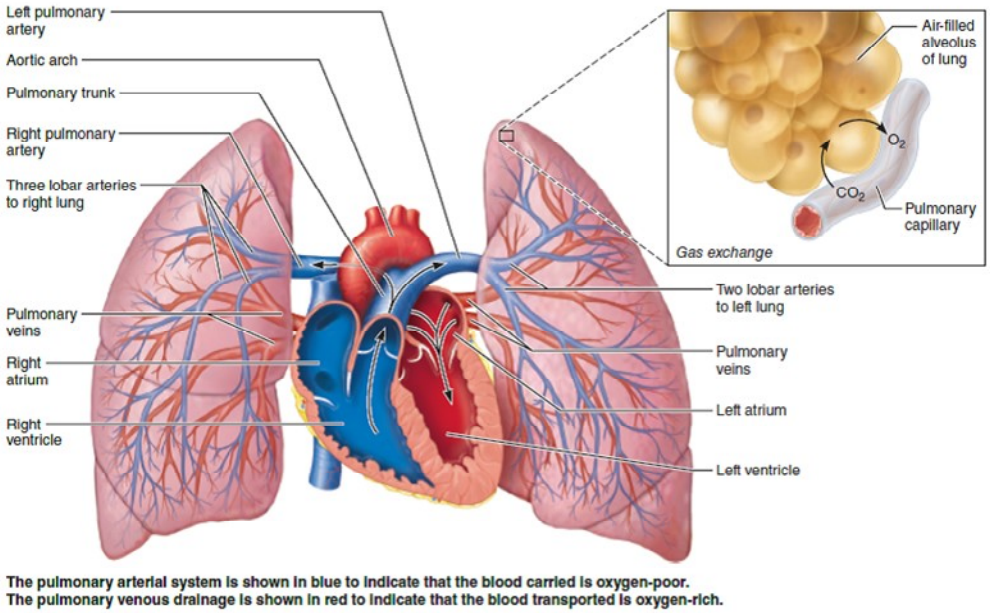
Earlier this year BLPH announced positive topline data from a Phase 2 portion (i.e. 'Cohort 1') of an ongoing Phase 2/3 study of INOpulse in PH-ILD. This includes a statistically significant improvement in multiple clinically meaningful activity parameters, which is particularly encouraging as the proposed Phase 3 (pivotal) study is expected to use the same measures as its primary endpoint. On August 1st BLPH announced that Cohort 2 (higher dose group) of the Phase 2 portion completed enrollment, results of which are anticipated later this year and which will inform on the optimal dose to be used in the Phase 3 study. If all goes well the Phase 3 study could begin early next year.

Meanwhile, BLPH also expects to build on statistically significant Phase 2a results in PH-COPD, which were announced in September 2017. Design of a Phase 2b (n=90) study was recently reviewed and finalized by FDA. The goal of this study, which will assess multiple endpoints including activity monitoring and oxygen saturation, is to inform design, including specifics around patient population and clinical endpoints, of a subsequent Phase 3 (pivotal?) study. BLPH anticipates commencement in 2020.

And finally, the PH-Sarc program currently consists of an ongoing Phase 2a dose-escalation study which will use right heart catheterization to assess the safety and hemodynamic effect of INOpulse. The study commenced in Q1 and could have topline results later this year.

BACKGROUND

The pulmonary arteries are responsible for delivering deoxygenated blood from the heart to the lungs. The main pulmonary artery originates at the base of the right ventricle of the heart, where it is known as the pulmonary trunk. From the right ventricle, a large chamber in the heart which pushes the blood through the pulmonary arteries and into the lungs, the pulmonary trunk branches off to left and right pulmonary arteries which lead to the left and right lungs, respectively. The left and right pulmonary arteries then each branch into lobar arteries which segment further and finally culminate at the pulmonary capillaries, which are enveloped by alveoli. It is there that gas exchange takes place with carbon dioxide moving from the (deoxygenated) blood across the pulmonary capillaries into the alveoli and oxygen moving from the alveoli across the capillaries and into the blood. From there the oxygenated blood exits the lungs through pulmonary veins into the left atrium/ventricle of the heart where it is then pumped through the rest of the body.

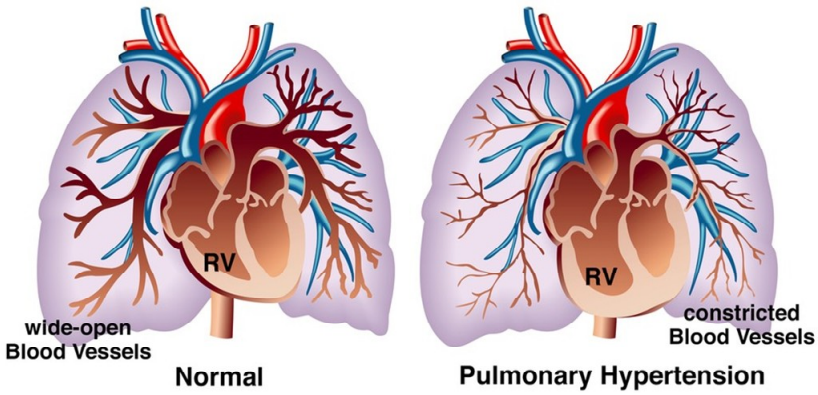


The pulmonary arterial system is shown in blue to indicate that the blood carried is oxygen-poor. The pulmonary venous drainage is shown in red to indicate that the blood transported is oxygen-rich.

Source: chugg.com

Pulmonary hypertension describes high blood pressure in the lungs which can be accompanied by a variety of symptoms including dyspnea (shortness of breath), chest pain, fatigue, fainting and a racing heartbeat (among others). PH is defined by a mean pulmonary arterial pressure $\geq$ 25mmHg (as compared to normal 8 to 20mmHg) at rest during right heart catheterization or 30mmHg during exercise. It is a progressive disease with no known cure and a one-year mortality rate of approximately 10% -15%.

The increase in blood pressure associated with PH is the result of changes in the endothelial cells that line the pulmonary arteries, causing the blood vessels to become thickened or narrowed and inhibiting or altogether blocking the flow of blood from the heart to the lungs. Constriction of the pulmonary arteries causes an increase in blood pressure, making it more difficult for the heart to pump blood (as quantified by pulmonary vascular resistance, or PVR) and putting strain on the right ventricle which can lead to right ventricle failure and, in some cases, death.

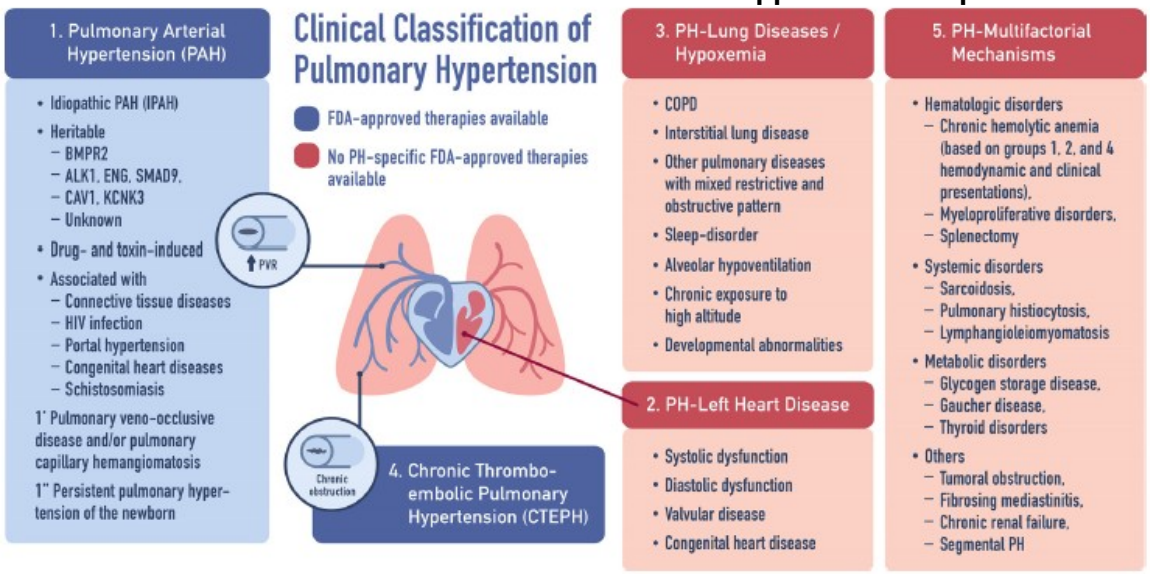


Source: Mirna Analytics LLC

To better understand the underlying cause(s) of these changes, which can be varied and, in some cases, unknown, the World Health Organization (WHO) has classified PH into five groups based on the mechanism (i.e. cause) of the disease. These groups (which also includes sub-groups of Group 1) define the cause of PH as related to; Group 1: Pulmonary Artery Disease, Group 2: Left heart disease, Group 3: Chronic lung disease or hypoxia, Group 4: Chronic thromboembolic PH and Group 5: Due to unclear multifactorial mechanisms.

There are no currently available FDA-approved therapies to treat the underlying causes of PH related to Groups 2, 3 and 5. Bellerophon hopes to capitalize on this unmet need and is focusing their development efforts of INOpulse on indications in PH-ILD (Group 3), PH-COPD (Group 3) and PH-Sarcoidosis (Group 5).

WHO PH Classification and Status of Approved Therapies[2]



The pathogenesis of PH is not yet fully understood although is believed that endothelial dysfunction results in a change (i.e. increase or decrease) in the production of endothelium-derived vasoactive mediators including the vasodilators nitric oxide and prostacyclin and the vasoconstrictors Endothelin-1 and thromboxane (Budhiraja et al).

The severity, or functional significance of PH is determined by measuring exercise capacity. The more severe the disease, the greater the limitations it places on an individual. Functional classification, based on guidelines from WHO and the New York Heart Association (table below[3]) has been shown to be a strong predictor of mortality.[4] Echocardiography (which measures pulmonary artery systolic pressure) is initially used to diagnose PH while right ventricular function (during heart catheterization) is required in order to make a definitive diagnosis.

Functional Assessment of PH

A. NYHA Functional Classification

Class 1:	No symptoms with ordinary physical activity
Class 2:	Symptoms with ordinary activity. Slight limitation of activity
Class 3:	Symptoms with less than ordinary activity. Marked limitation of activity
Class 4:	Symptoms with any activity, or even at rest

B. WHO Functional-Assessment Classification

Class I:	PH, but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
Class II:	PH resulting in slight limitation of physical activity; patient comfortable at rest; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class III:	PH resulting in marked limitation of physical activity; patient comfortable at rest; less-than-ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class IV:	PH with inability to carry out any physical activity without symptoms; patient manifests signs of right heart failure; dyspnea or fatigue may be present even at rest; discomfort increased by any physical activity

PH: pulmonary hypertension; NYHA: New York Heart Association; WHO: World Health Organization.
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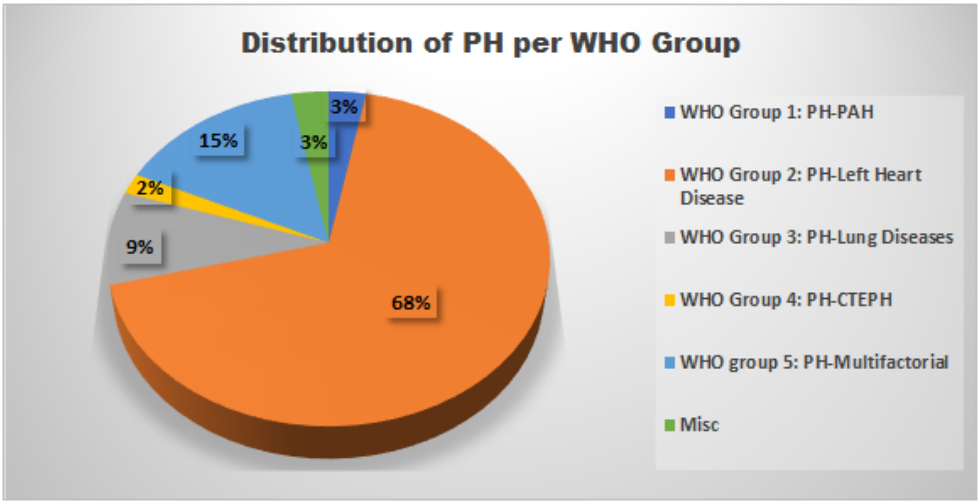
[2] Hensley et al. Am J Physiol Lung Cell Mol Physiol 314: L769–L781, 2018 as adapted from Simonneau et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 62, Suppl: D34–D41, 2013.
[3] Bream H., Hobbs R. Pulmonary Hypertension: An Update. Aug 19, 2008. US Pharmacist
[4] McLaughlin VV et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004 Jul;126(1 Suppl):78S-92S.

PH is a life-threatening disease, the prognosis of which is particularly dire if not effectively managed. There are currently no FDA-approved treatments for PH associated with lung disease (such as PH-ILD, PH-COPD and PH-Sarcoidosis). As PH is not curable, treatment is aimed at addressing the symptoms, slowing its progression, mitigating the effects of the underlying cause and improving quality of life.

PH-PAH (WHO Group 1) is a distinct disorder from other forms of PH. With PAH, the causes of narrowing of the pulmonary vasculature and other symptoms of PH can include other medical conditions such as congenital heart disease, drugs or toxins, heritable disease or may not be known (idiopathic). Narrowing and stiffening of the pulmonary arteries as a result of PAH causes an increase in pulmonary vascular resistance and a decrease in cardiac output. This puts stress on the right ventricle of the heart which can ultimately lead to heart failure.



Source: phassociation.org. Strange G, et al. Heart. 2012;98(24):1805-11.

Treatment of PAH is based on therapy that is directed at the PH itself with the goal of dilating the pulmonary vasculature and reducing pulmonary vasculature resistance. PH-specific therapy is typically used for patients with WHO functional class II, III and IV (reference table above) and widely accepted as appropriate for patients with WHO PH classification Group 1 (i.e. PH-PAH). For patients with WHO PH Groups 3 (PH-Lung Diseases), 4 (PH-Left Heart Disease) and 5 (PH-multifactorial), PH-specific therapy should only considered on a case-by-case basis due to the potential for therapy-related complications. PH-specific therapy is not recommended for WHO PH Group 2 (PH-CTEPH). Objective goals of PH treatment (which are often utilized as endpoints in clinical studies) include improvement in WHO Functional Class, exercise capacity (typically measured by 6MWD and cardiopulmonary exercise and treadmill tests), hemodynamics and survival.

PH-specific therapy, which is aimed at reducing pulmonary arterial pressure and relieving strain on the right ventricle, includes the use of vasodilators to open blood vessels. A variety of vasodilators are commonly used including prostacyclin pathway agonists, endothelin receptor antagonists, nitric oxide and, in some cases, calcium channel blockers. These were all designed to treat PH-PAH (WHO Group 1) and despite not being FDA-approved to treat PH-lung diseases (WHO Group 3), are often used to do so given the lack of other options. The choice of which particular vasodilator(s) to use may be based on a variety of factors including the severity and underlying cause of PH (i.e. WHO Group), right ventricular function, hemodynamics and other variables

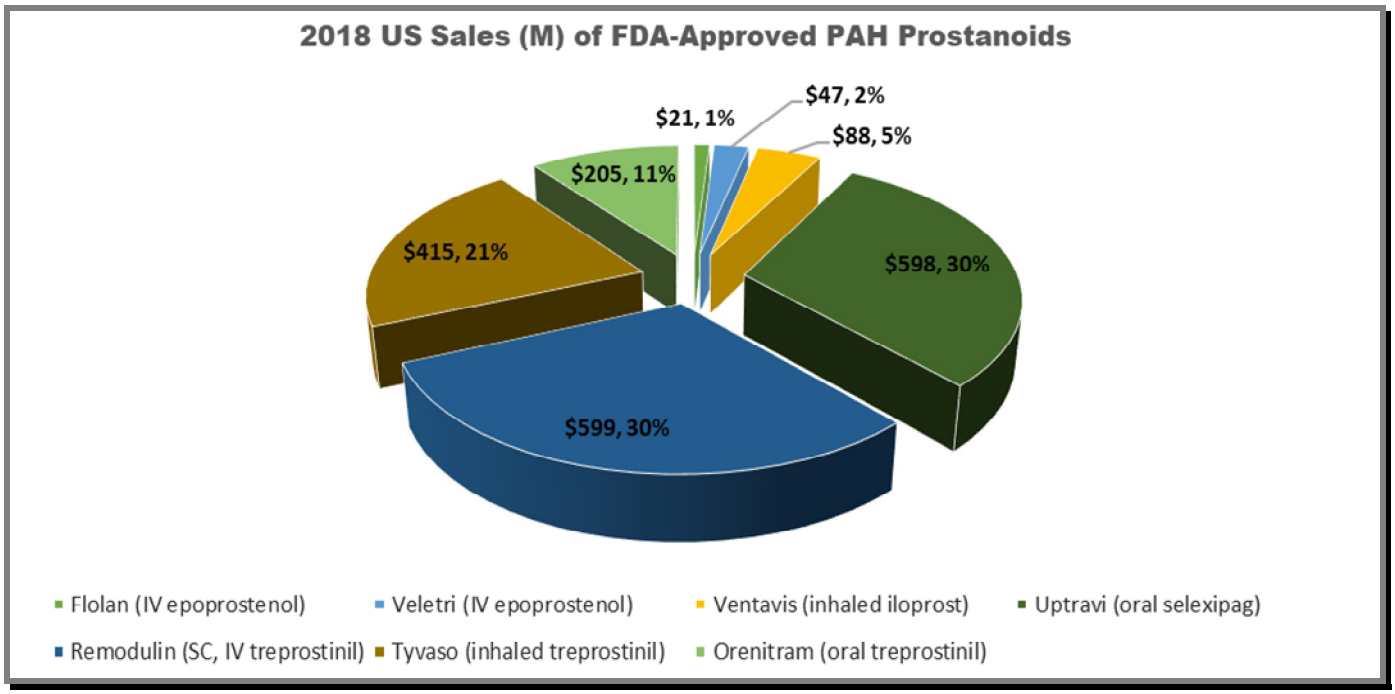
PH is associated with decreased levels of prostacyclin, a prostaglandin released by endothelial cells which helps prevent the formation of blood clots and promotes vasodilation through smooth muscle relaxation. **Prostacyclin pathway agonists (i.e. prostanoids)** that are FDA approved for the treatment of PAH (WHO Group 1) include epoprostenol (Flolan, Veletri), iloprost (Ventavis), selexipag (Uptravi) and treprostinil (Remodulin).

Epoprostenol is delivered via continuous intravenous flow, treprostinil is administered either continuously via subcutaneously or intravenous flow, orally (Orenitram) or via inhalation (Tyvaso), selexipag is taken orally and iloprost is inhaled. The most commonly reported side effects of prostacyclin pathway agonists are nausea, vomiting, diarrhea, headache, hypotension, flushing, dizziness, jaw pain and musculoskeletal pain.[5]

[5] Kingman M. et al. Management of prostacyclin side effects in adult patients with pulmonary arterial hypertension. Pulm Circ. 2017 Sep; 7(3): 598–608.

Inhaled prostanoids, which are generally accepted as having a more favorable safety and tolerability profile as compared to the intravenously delivered options, are often employed as first-line prostanoids in patients that fail PAH background therapy. They are typically prescribed as add-ons to oral therapy and used in an out-patient setting. As continuous flow infusion presents additional risks associated with constant drug exposure and those related to thrombosis, pump (and/or user-error related) malfunction, rebound hypoxemia (if pump fails) and infection, it is often reserved for patients that fail first line vasodilators, including inhaled iloprost and inhaled treprostinil.

FDA approved prostanoids for the treatment of PAH generated $1.973B of sales in the U.S. in 2018. Uptravi (oral selexipag) and Remodulin (SC, IV treprostinil) lead the market, each generating nearly $600M in revenue and, combined, account for 60% of total U.S. sales. Meanwhile, inhaled prostanoids (i.e. those with similar route of administration as INOpulse) generated a combined $503M in sales, accounting for 26% of total U.S. sales of the drug class.



Endothelin-1 (ET-1) is produced by endothelial cells and acts as a potent vasoconstrictor. **Endothelin receptor antagonists** facilitate smooth muscle relaxation by inhibition of ET-1 receptors (ET-A) resulting in decreased vasoconstriction. Dual endothelin receptor antagonists bind at ET-A as well as ET-B, which is believed to be associated with both vasoconstriction and vasodilation of vascular smooth muscle. Bosentan (Tracleer) and macitentan (Opsumit) are orally administered dual endothelin receptor antagonists while ambrisentan (Letairis) is an orally administered ET-A receptor agonist. All three are FDA-approved for the treatment of PAH (WHO Group 1). Drawbacks of endothelin receptor antagonists include risk of hepatoxicity, liver failure and peripheral edema.

PDE5 inhibitors stop the degradation of cGMP-specific phosphodiesterase type 5 (PDE5), thereby enhancing the vasodilatory effects of nitric oxide. PDE5 inhibitors have been shown to have a favorable effect on increasing exercise capacity and decreasing PAP in PAH clinical studies. Sildenafil (Revatio) and tadalafil (Adcirca) are the only PDE5 inhibitors approved by the FDA for the treatment of PAH (they are also FDA-approved for the treatment of erectile dysfunction under the brands Viagra and Cialis, respectively). Side effects include headache, gastrointestinal dysfunction, flushing, respiratory infection and joint pain.

Other drawbacks of prostanoids and lack of FDA-approved options for WHO Groups 2-5
While the seven prostanoids that we discussed above are FDA-approved for the treatment of PH-PAH (WHO Group 1), none are approved for the treatment of PH associated with lung diseases, such as PH-ILD, PH-COPD and PH-Sarcoidosis. Side effects, treatment-associated risks and insufficient efficacy (see table below) mean that prostanoids' risk-benefit profile may disqualify their use in the treatment of PH associated with lung diseases. This has also prevented them from gaining regulatory approval for these conditions.

Lack of Evidence Supporting Effectiveness of PAH Therapies in Lung Disease-PH

Drug class	WHO PH Classification (strength of evidence)†				
	Group 1	*Group 2*	*Group 3*	*Group 4*	*Group 5*
ERAs	Beneficial (strong)	Harmful (weak)	Neutral (weak)	Neutral (moderate)	Unknown
PDE5 inhibitors	Beneficial (strong)	Beneficial (weak)	Harmful (weak)	Beneficial (weak)	Unknown
Prostacyclin analogs	Beneficial (strong)	Harmful (moderate)	Neutral (weak)	Beneficial (weak)	Unknown

†Strong: multiple randomized clinical trials agree; Moderate: one clinical trial completed or multiple trials conflict; Weak: only small or nonrandomized trials available; Unknown: not enough data to determine benefit.
ERA: Endothelin receptor antagonist; PDE5: Phosphodiesterase type 5; PH: Pulmonary hypertension.
Source: Duarte J et al. Pharmacologic Treatments for Pulmonary Hypertension. Medscape

In addition to the noted risk of adverse side effects, many of these vasodilators suffer from other drawbacks as well, including oxygen desaturation. Oral, subcutaneous and intravenously delivered prostanoids such as epoprostenol, treprostinil and selexipag are susceptible to the risk of non-selective pulmonary and systemic vasodilation, particularly if used in patients with PH associated with lung diseases (i.e., WHO Groups 2 – 5).

In fact, clinical studies of patients with respiratory failure associated with COPD have shown that the non-selective pulmonary and systemic vasodilatation resulting from treatment with intravenous prostanoids is associated with significant reductions in arterial oxygenation.[6] Oxygen desaturation, as we discuss in detail below, can result in adverse events such as hypoxemia and 'ventilation-perfusion mismatch'.

And while inhaled administration of prostanoids, such as Ventavis and Tyvaso, has been hypothesized to mitigate the risk of systemic vasodilation as a result of a more targeted delivery (to the lungs), clinical data is somewhat mixed in that regard. While earlier studies appear to support the relative advantage of inhaled versus oral and parenteral administration as it relates to risk of oxygen desaturation, some more recent studies have not. This includes a randomized, double blind, crossover study in 16 patients with PH-COPD which found that inhaled iloprost (as compared to placebo) failed to improve 6MWD and resulted in significant impairment of arterial oxygenation at rest. The investigators concluded that, "Improvement of the exercise capacity after iloprost inhalation in patients with COPD-associated mild to moderate PH is very unlikely."[7]

It is also important to note that Ventavis and Tyvaso are aerosolized versions of liquid drugs, not gases. So, while the administration is similar to that of (the gas) nitric oxide, their ability to reach and disperse throughout the well-ventilated areas of the lungs is not necessarily the same (iNO may also be less likely to induce systemic vasodilation as a result of deactivation when coming into contact with hemoglobin). Moreover, the aerosolization of inhaled prostanoids makes them a less efficient mode of delivery as compared to infused administration which can limit their effectiveness.[8]

And in addition to having many of the same risks of IV, SC and oral prostanoids, inhaling aerosolized versions of the drug comes with other potential drawbacks as well such as less precise drug dosing due to variability in breathing patterns, intolerance to the inhaled drug (potentially resulting in coughing, wheezing and bronchospasms), syncope (loss of consciousness believed to be associated with lack of drug exposure while sleeping) and errors in operating the inhalation device (i.e. nebulizer). Intolerance can be a particularly significant issue of inhaled prostanoids when used to treat PH associated with lung diseases. In a (n=22) study evaluating iloprost in the treatment of children with PH-PF (pulmonary fibrosis), one-third of participants dropped out due to airway-related intolerance to the inhaled drug.[9] And finally, the significant dosing regimen (of up to nine times per day, with each dose taking up to 10 minutes to administer) and requisite daily cleaning and maintenance of the nebulizer makes inhaled prostanoids less convenient for long-term use.

[6] Barnett C., De Marco T. Pulmonary Hypertension Due to Lung Disease in Murray and Nadel's Textbook of Respiratory Medicine (Sixth Edition), 2016
[7] Boeck L, et al. Acute Effects of Aerosolized Iloprost in COPD Related Pulmonary Hypertension - A Randomized Controlled Crossover Trial. PLoS One. 2012; 7(12): e52248.
[8] Duke J. Pulmonary Hypertension: What are prostanoids and their therapeutic counterparts? Anesthesia Secrets (Fourth Edition), 2011
[9] Ivy DD, et al. Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol 2008;51(2):161-169.

Insurers largely classify non-FDA approved use of medications as investigational and non-reimbursable. This appears to be the case (based on our cursory research of various private payors' and pharmacy benefit managers' related reimbursement policies) with use of prostanoids for the treatment of PH associated with lung diseases. For example, Anthem (BCBS) and BlueCross BlueShield of North Carolina specifically state that the use prostacyclins for the treatment of WHO Groups 2, 3, 4 and 5 is not approved (or similar language).[10] This means that providers that use these drugs for off-label indications such as PH-ILD, PH-COPD and PH-Sarcoidosis do so at the risk of insurers denying reimbursement. And, given the exorbitant cost of prostanoids, which can reach or even exceed $200k per patient per year, the financial risk is significant.

Nitric Oxide and INOpulse

Nitric oxide is an endogenously synthesized gas known as an endothelium-derived relaxing factor. It is produced by nitric oxide synthases (enzymes) and is responsible for a variety of functions in the human body including in the regulation of vascular flow. Nitric oxide produced by endothelial cells (i.e. cells that line the inside of blood vessels) plays a key role in maintaining vasorelaxation of vascular muscle cells and in dilation of blood vessels. In addition to vasorelaxation, nitric oxide also has anticoagulatory (i.e. antiplatelet and antithrombotic) and anti-inflammatory effects in the vasculature. Synthesis of endothelial nitric oxide through biochemical or physical stimuli results in dilation of blood vessels while impaired production or availability of nitric oxide in the endothelium leads to vasoconstriction.[11]

Inhaled nitric oxide is absorbed by and relaxes the smooth muscles surrounding the arteries, resulting in dilation of blood vessels and reduction in blood pressure, pulmonary vascular resistance and strain on the right ventricle. Inhaled nitric oxide has an extremely short half-life of just ~3 to 4 seconds which requires nearly constant administration for use as a vasodilator. It is commonly used in the hospital setting for the acute treatment of neonates with persistent pulmonary hypertension and the acute treatment of adults with pulmonary hypertension (e.g. following cardiac surgery). It is also commonly used for long-term acute pulmonary vasoreactivity testing (i.e. to identify patients which may respond well to long-term calcium channel blockers).

The benefits of inhaled nitric oxide as compared to other PH therapies includes a very rapid onset, easy and efficient inhalation and the fact that, unlike many other medications, it confines its vasodilator effects only to the aerated airspaces of the lungs. This highly targeted action is possible as iNO is efficiently inhaled and quickly inactivated when coming into contact with hemoglobin (forming methemoglobin) in the vascular lumen. This minimizes any systemic effects on pulmonary circulation. These are important characteristics as it means iNO provides almost immediate improvement in perfusion and blood oxygenation and does so without the potential systemic risks or complications associated with (less targeted) oral and intravenously delivered medications. In addition, iNO's pharmacokinetic and established safety profile means that it is well-suited to be used in combination with other vasodilators (combining more than one vasodilator is common in the treatment of PH, particularly when patients fail to sufficiently respond to monotherapy).

There are potential drawbacks of iNO, however, including risk of methemoglobinemia and nitrogen dioxide toxicity (the latter, particularly when iNO is used with oxygen). As noted, when coming into contact with hemoglobin, iNO oxidizes to methemoglobin, a form of hemoglobin that cannot bind oxygen. While low levels of methemoglobin are constantly present in the body, elevated levels reduce the oxygen carrying capacity of the blood which can result in symptoms such as shortness of breath, rapid heart rate and, in extreme cases, hypoxia and even death.

The formation of excess nitrogen dioxide is another risk of iNO therapy. Nitrogen dioxide (NO_2) is formed when nitric oxide is mixed with oxygen. Excessive amounts of NO_2 are dangerous and can cause damage to the airways and potentially lead to serious complications including edema and bronchoconstriction.

Risk of methemoglobinemia and nitrogen dioxide toxicity, has largely limited inhaled nitric oxide therapy to acute, short-term use. INOpulse mitigates the risk of methemoglobinemia through its pulsed action, administering the gas in relatively small volumes (using only ~5% as much as continuous flow delivery) of short bursts timed with a patient's breath. Meanwhile its triple-lumen nasal cannula reduces risk of nitrogen dioxide toxicity by enabling precise dosing of nitric oxide and minimizing infiltration of oxygen.

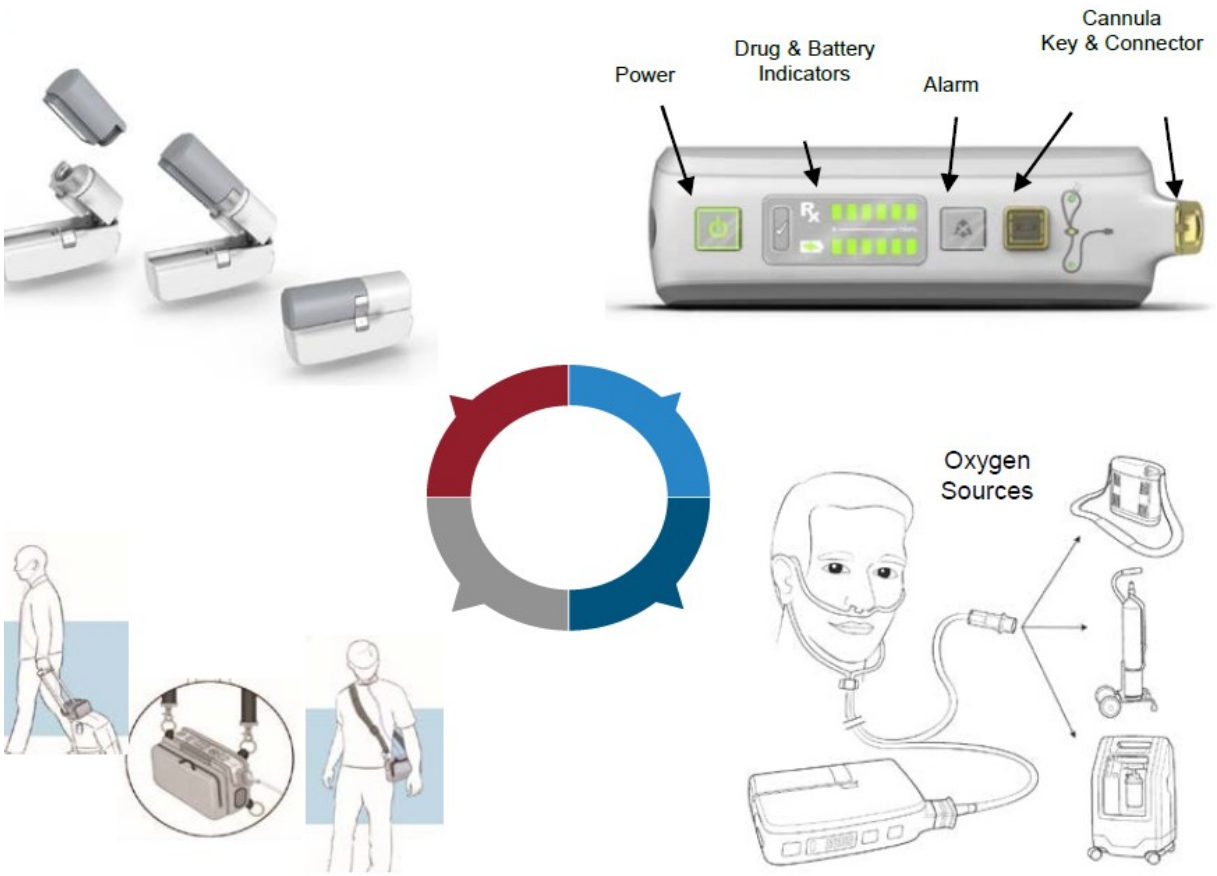
[10] Anthem, Prostacyclin Infusion and Inhalation Therapy, Clinical Criteria published 4/8/19. BlueCross BlueShield of North Carolina, Pulmonary Hypertension, Drug Management, Corporate Medical Policy published 3/2019.

[11] Jin R., Loscalzo J. Vascular nitric oxide: formation and function . J Blood Med. 2010; 1: 147–162.

INOpulse, the company's flagship product development program, is a relatively small and portable iNO (weighing ~2.5 lbs) delivery device that is intended to be used in the ambulatory setting (including in the patient's home) and designed for continuous use in the treatment of chronic lung diseases associated with PH. It was designed for ease of patient use with a simple interface and quick and easy drug cartridge replacement. INOpulse delivers a set hourly dose of nitric oxide with brief, controlled pulses synchronized with the beginning of a patient's breath and can be combined with external oxygen therapy (via the same triple-lumen cannula). The triple-lumen nasal cannula consists of a thin, plastic tube that is divided into three channels. The prongs 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. The device is also compatible with existing long-term oxygen therapy systems.

This novel pulsed method of action, which has been designed to automatically adjust to a patient's breathing pattern (seamlessly compensating for a change in a patient's activity level), optimizes the delivery of iNO to only the well-ventilated (i.e. relatively healthy and viable) areas of the lungs. The pulsed delivery also consumes relatively minimal amounts of iNO which both mitigates risk of toxicity and reduces cost of operation. By contrast, current iNO delivery systems administer the gas under a continuous flow (using significantly higher volumes of iNO) and are relatively very bulky, rendering them only appropriate for the hospital setting and restricting use to mostly acute conditions.

INOpulse System: designed for easy, portable, convenient and safe use



Source: Bellerophon

Bellerophon licenses the underlying INOpulse technology, which is protected by over 100 issued and pending patents, from Ikaria, Inc (a subsidiary of Mallinckrodt plc), the company's former parent which markets the continuous flow inhaled nitric oxide product, INOmax. In addition to the existing and pending intellectual property protection, successful regulatory approval for the orphan designated condition PH-IPF/PH-ILD could provide marketing exclusivity for the indication for seven years in the U.S. and ten years in Europe.

Per terms of the licensing agreement, BLPH has exclusive rights to the technology for 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, PH-CTEPH, PH-sarcoidosis, PH associated with pulmonary edema from high altitude sickness and PH-PF (the latter which includes idiopathic

interstitial pneumonias, chronic hypersensitivity pneumonitis, occupational and environmental lung disease).[12] BLPH will pay Ikaria a 5% royalty on any net sales related to PH-CTEPH, PH-sarcoidosis or PH associated with pulmonary edema from high altitude sickness, a 3% royalty on any net sales related to PAH and a 1% royalty on any net sales related to PH-PF.

Ikaria's INOmax, which has a current annual revenue run-rate of more than $600M, is used by hospitals for (the FDA-approved indication of) the treatment of term and near-term (> 34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

While the devices are similar, there are some important differences between the two products; INOmax delivers a continuous flow of iNO while INOpulse delivers it via pulsed action based on a patient's breathing pattern, INOmax uses significantly more iNO than INOpulse (which also relates to the difference in delivery), INOmax is used exclusively in the hospital while INOpulse is being developed for home use (i.e. outpatient therapy), INOpulse is portable and lightweight while INOmax is not, and INOmax is indicted for the short-term (14 days) treatment of neonates while INOpulse has been developed for long-term treatment of adult patients with chronic PH-related diseases.

INOpulse Intellectual Property Protection

Patent	Status	Expiration	Description
Method of NO administration	US/EU: Issued Other Territories: Issued/Pending	Jan 2027	Covers consistent delivery of prescribed dose independent of respiratory rate
Breath Skipping & Pulse Volume Variation	US: Issued	Sept 2025	Covers skipping breaths or modifying pulse volume to ensure consistent dose independent of respiratory rate
Method of Administering High Concentration NO	US/EU: Pending Other Territories: Pending	Mar 2033	Limits delivery rate of high concentration iNO to prevent safety concerns
Optimized Pulse Shape	US: Pending	Oct 2035	Covers key parameters of pulse shape
INOpulse Design	US: Issued	Apr 2028	Covers design of the INOpulse device
Tip Purge	US: Issued EU/Other Territories: Pending	Apr 2033	Covers the use tip purge to ensure purity of iNO within the cannula
Triple-Lumen Cannula	US/ EU: Issued Other Territories: Pending	Dec 2033	Covers accurate dose delivery and reduced NO_2 formation
Index valve	US/EU: Issued Other Territories: Issued/Pending	May 2029	Ensures other cartridges cannot be used with INOpulse

- Orphan Drug designation for PH-IPF/PH-ILD would provide **potential exclusivity for 7 years (US) and 10 years (EU)**
- Multiple provisional patent applications filed from 2017-2019 that can extend patent coverage into 2039

Source: Bellerophon Investor Presentation

The ability of INOpulse to target delivery of iNO to the well-ventilated areas of the lungs is a critical point in fully understanding the advantages of the device as compared to most other PH-related therapies, especially and specifically in the context of pulmonary hypertension associated with underlying lung diseases such as ILD, COPD and Sarcoidosis. As these diseases are characterized by both irreversibly compromised lung function and PH-related pathogenesis optimal therapy requires the ability to both improve oxygenation (i.e. effectively address compromised lung function) and reduce pulmonary arterial pressure (i.e. effectively address PH). INOpulse's targeted iNO delivery was designed to do just that through what BLPH refers to as a **'dual mechanism of action'** (i.e. increased oxygenation and reduction in PAP by targeting vasodilation of only the well-ventilated / functioning areas of the lungs).

These diseases damage the lungs in such a way that they impair their ability to deliver oxygen from the alveoli and across the capillaries into the bloodstream. This results in increased pulmonary shunting, or the amount of deoxygenated blood that moves from the left to the right side of the heart without participating in gas exchange. The body compensates for this by inducing hypoxic vasoconstriction, narrowing the pulmonary arteries to reduce pulmonary shunt and directing blood to better oxygenated (i.e. healthier and better functioning) areas of the lungs.

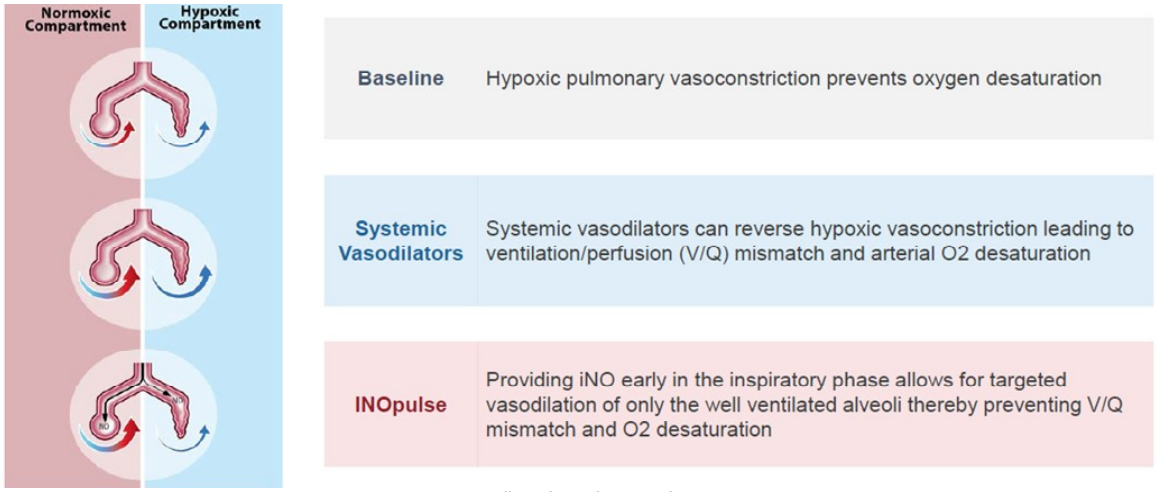
[12] Bellerrophon SEC filings

But **when oral and injected vasodilators are used to treat diseases such as PH-ILD, they can result in systemic vasodilation**, indiscriminately opening up the pulmonary arteries including in areas where lung function and their ability to deliver oxygen to the bloodstream is impaired (essentially undoing the body's hypoxic vasoconstriction mechanism of diverting blood to healthier regions of the lungs). This results in too much blood flow relative to the body's ability to oxygenate it. This 'ventilation-perfusion (V/Q) mismatch' causes oxygen desaturation and hypoxemia and in serious cases can lead to hypoxia (in which the body is of deprived of oxygen). V/Q mismatch is the leading cause of hypoxemia, the symptoms of which can include a change in the color of the skin, rapid heart rate, confusion and shortness of breath (among others).

So, while these systemic vasodilators are effective at reducing PAP and PVR (i.e. at addressing PH), V/Q mismatch means that they may not as-effectively improve oxygenation (i.e. address impaired lung function). Conversely, INOpulse's targeted delivery of nitric oxide to only well-ventilated (i.e. healthy and functioning) areas of the lungs means it provides the dual mechanisms of vasodilation (reduction in PAP) and increased oxygenation (by matching vasodilation to ventilation).

The ability of INOpulse to deliver iNO to the well-ventilated areas of the lungs, to provide targeted vasodilation and improve hemodynamics including reducing pulmonary arterial pressure and pulmonary vascular resistance has been evaluated and validated in several clinical trials (discussed in detail later).

INOpulse's Targeted iNO Delivery to Healthy Areas of the Lungs Reduces Risk of V/Q Mismatch



Source: Bellerephon Therapeutics

iNO Ability to Match Vasodilation with Ventilation Already Established by INOmax

While pulsed delivery (timing administration with a patient's inhalation) is believed to provide additional substantive advantages to continuous flow, potentially including deeper and more complete coverage of the lungs (in addition to requiring significantly less NO and reducing risk of toxicity), the ability of iNO to balance vasodilation and ventilation (and mitigate risk of systemic vasodilation) has already been established in clinical trials of INOmax.

Per the 'mechanism of action' section on INOmax's FDA label; "Nitric oxide relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature. INOmax appears to increase the partial pressure of arterial oxygen (PaO2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios."[13]

Phase 3 PAH Study: Stopped for Futility but Trends Favor INOpulse and Confirms Safety Profile

The FDA has granted orphan drug designation to nitric oxide/INOpulse for the treatment of PAH, a rare disease estimated to afflict approximately 5 of every 1 million adults. PAH, a subgroup of PH classified under WHO Group 1, is a disease of the blood vessels of the lungs that is associated with a host of underlying causes including idiopathic (i.e. unknown cause), drugs or toxins, other disease such as HIV and congenital heart disease (among others), persistent pulmonary hypertension of the newborn (the indication for which INOmax is approved) and pulmonary capillary disorders.

[13] accessdata.fda.gov. INOmax Full Prescribing Information. Reference ID: 3831195

A Phase 3 study evaluating INOpulse in the treatment of pulmonary arterial hypertension was discontinued in August 2018 due to a determination that the primary endpoint would not be met. The study, which commenced in 2016, was stopped after a pre-specified interim analysis of the first ~50% of patients at 16 weeks of follow-up found that improvement on the primary endpoint (6MWD) was not sufficient to continue the study.

The "INOvation-1" Phase 3, placebo controlled, double-blind, randomized clinical study was designed to determine the safety, tolerability, and efficacy of INOpulse versus placebo in symptomatic subjects with pulmonary arterial hypertension (PAH). Enrollment inclusion criteria included symptomatic of PAH and undergoing approved PAH monotherapy or combination therapy and long-term oxygen therapy (LTOT). Among the exclusion criteria were any subjects with WHO Groups 2, 3, 4 or 5 (which would have included anyone with PH-ILD, PH-COPD and PH-Sarc).

In addition to the (sole) primary endpoint of six-minute walk distance, secondary measures included time to clinical worsening (TTCW) and change in WHO functional class. In addition, several hemodynamic and other outcome measures (including a quality of life questionnaire were assessed). The INOpulse arm underwent iNO dose of 15mcg/kg of ideal body weight (IBW) per hour during a two-week run-in period followed by 16 weeks of iNO at 75/mcg/kg IBW/hr. All patients (in the treatment and placebo arms) continued to receive PAH standard of care (such as oral vasodilators and LTOT).

Based on a pre-specified interim analysis by the study's Data Monitoring Committee of the first 75 patients to complete the 16 weeks of treatment, it was recommended that the study be halted due to futility. While there were no safety concerns, INOpulse treatment was well-tolerated and there was evidence of clinically meaningful improvement on several of the outcome measures, the decision to stop the study was made based on insufficient improvement among INOpulse patients as compared to those that received placebo in the 6MWD primary endpoint (which measures how far a patient can walk in six minutes).

Specifically, INOpulse patients experienced a clinically meaningful improvement in pulmonary vascular resistance (18%), cardiac output (0.7 L/min) and NT Pro-BNP (a marker of right ventricle dysfunction). Moreover, 6MWD improved among those INOpulse patients which were on less background PAH therapy and more placebo patients deteriorated on 6MWD as compared to those on INOpulse. More specifically, INOpulse patients on PAH monotherapy had an average 23-meter improvement in 6MWD and those that were not on prostanoid therapy (such as selexipag, treprostinil, etc) exhibited a 17-meter improvement.

Phase 3 PAH Study (INOvation-1) Efficacy Results (August 2018)

	iNO	Placebo	
PVR (dynes*sec*cm^{-5})	-75	+111	• Placebo corrected change of 186 (18% change) • Placebo corrected change for: • PDE5s: 192; ERAs: 245; Prostanoids: 291
Cardiac Output (L/min)	+0.5	-0.2	• Placebo corrected change of 0.7 (correlates to Cardiac Index change of 0.4) • Placebo corrected change for (Cardiac Index): • PDE5s: 0.39; ERAs: 0.30; Prostanoids: 0.32
NT-ProBNP (pmol/L)	-48	+20	• Placebo corrected change of 68 • Placebo corrected change for: • Selexipag: 15; Inhaled Treprostinil: 22
6MWD			
• mono PAH therapy	+41	+18	• Placebo corrected change of 23
• excluding prostanoids	+25	+8	• Placebo corrected change of 17
			• Placebo corrected change for: • Selexipag: 12; Macitentin: 22; Oral Treprostinil: 10-26

Unlike approved PAH therapies, INOpulse was evaluated on multiple background therapies that include prostanoid

Source: Bellerophon Investor Presentation / SEC 8-K filing

Our take: While disappointing that INOpulse therapy failed to show a statistically significant improvement on 6MWD, we think that there are some substantively positive take-aways from the results. These include;

- Safety and tolerability of iNO/INOpulse therapy continues to largely be a non-issue, confirming findings of earlier studies. Studies to-date have established iNO/iNOpulse as associated with a relatively consistent and low-risk safety profile even when used for extended periods (including up to 4 years in Ph2 PAH study) and in combination with other vasodilators, including (relatively high-risk) parenterally administered prostanoids. The significance of this should not be underestimated as safety concerns have hindered FDA approval of systemic vasodilators for the same indications BLPH is now pursuing (PH-COPD, PH-ILD, PH-Sarc). Moreover, regulators may assign a higher safety hurdle for both ambulatory (as opposed to hospital) use and long-term/chronic use, so establishment of 'sufficient safety' is a major milestone in our opinion
- Efficacy signal present (table above)
    - Clinically meaningful improvement in PVR, cardiac output and NT Pro-BNP
    - 6MWD improved among those INOpulse patients which were on less background PAH therapy and more placebo patients deteriorated on 6MWD as compared to those on INOpulse
- If not for prostanoid and other PAH background therapies, INOpulse therapy might have shown to be significantly more potent (as compared to placebo)
- The underlying cause of PAH is vascular disease itself, which may not lend itself to fully benefitting from INOpulses's dual mechanism of action (targeting both ventilation and perfusion), which may be more well suited to conditions with both pulmonary and vascular disease pathologies. Moreover, while there are numerous vasodilatory therapies approved for the treatment of PAH, there are none for the conditions that BLPH is now focused on

Focus is now on PH-COPD, PH-ILD and PH-Sarc: Clinical Data Is Promising

The PAH program has been mothballed and BLPH's full focus is now on PH-COPD, PH-ILD and PH-Sarcoidosis, diseases for which there are no FDA approved therapies and which are associated with underlying lung diseases. These conditions are characterized by constriction of the pulmonary arteries and significant compromised lung function which, as explained earlier, makes them highly susceptible to adverse risks associated with systemic vasodilation. In fact, "there is limited evidence to suggest that PH-specific vasodilators such as phosphodiesterase-type 5 (PDE-5) inhibitors, endothelin receptor antagonists (ERA), and prostanoids have a role in the treatment of patients with CLD [chronic lung diseases, including PH-COPD, PH-ILD and PH-sarcoidosis]. On the contrary, they may nonselectively dilate the vessels in hypoventilated areas of the lung and worsen hypoxemia".[14]

Clinical progress has been encouraging and includes promising results of several Phase 2 studies in PH-COPD and in PH-ILD studies (including Cohort 1 of the Ph2 portion of an ongoing Ph2/3 PH-ILD study which read out earlier this year). Earlier this year BLPH announced that FDA agreed with their proposal to amend their Ph2b PH-ILD study to a Phase 2/3 trial, with the Phase 3 portion expected to serve as a pivotal registrational trial. A PH-Sarc program is also progressing with design of a Phase 2 dose-escalation study now finalized and enrolment expected to commence later this year.

Mid-to-Late Stage Clinical Trials Ongoing in PH-ILD, PH-COPD and PH-Sarc

PH-ILD	PH-COPD	PH-Sarc
Successful Phase 2a study in PH-IPF completed in May 2017 Positive results for Phase 2/3 study in Cohort 1; Cohort 2 ongoing Pivotal Phase 3 cohort to initiate in 1Q2020 with FDA agreement on primary endpoint	Successful Phase 2 study completed in September 2017 Phase 2b study design finalized in agreement w/ FDA	Phase 2 study initiated in 1Q2019

Source: Bellerophon June 2019 Presentation

PH-IPF Program

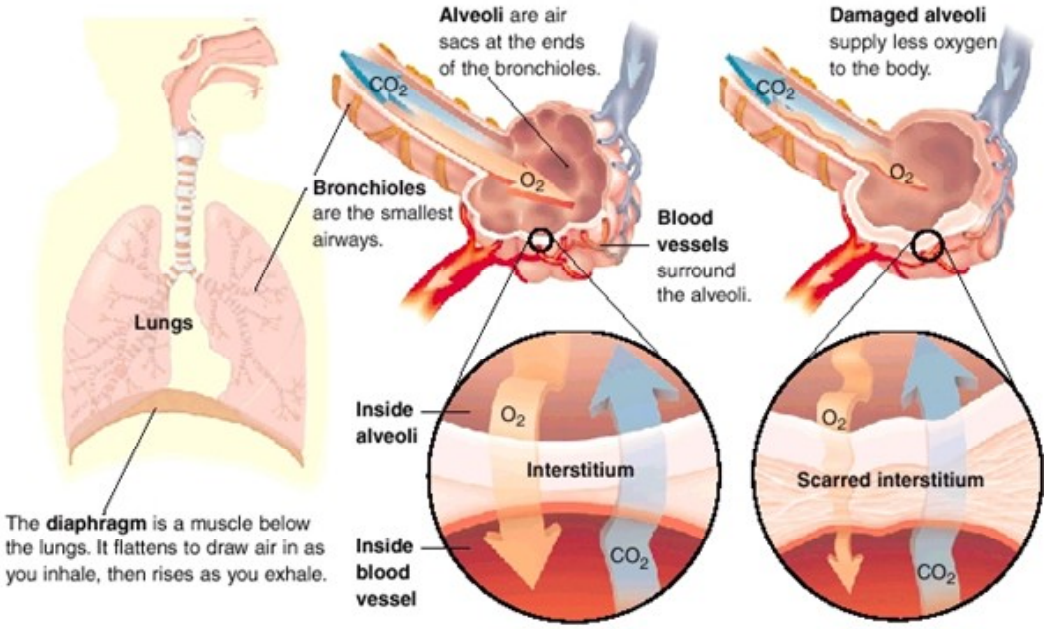
Interstitial lung disease (ILD) is a broad category of relatively rare disorders encompassing more than 200 lung diseases characterized by scarring, or fibrosis, and inflammation of the interstitium area of the lungs. The interstitium is a matrix of collagen that surrounds alveoli. In healthy lungs, oxygen moves from the alveoli through the interstitium and into the blood while carbon dioxide passes from the bloodstream through the interstitium and

[14] Zangiabadi et al. Pulmonary Hypertension and Right Heart Dysfunction in Chronic Lung Disease BioMed Research International Volume 2014, Article ID 739674

into the alveoli. However, in people with interstitial lung disease, fibrosis, increased amounts of connective tissue and inflammation impede the gas exchange process.

While the potential causes of ILD are vast, they can be generalized into one of four broad categories:
- associated with other diseases
- associated with exposure to certain substances (such as toxins or adverse reaction to medication)
- associated with genetic diseases
- idiopathic, or unknown cause (idiopathic pulmonary fibrosis)

Interstitial Lung Disease



Source: geisinger.org

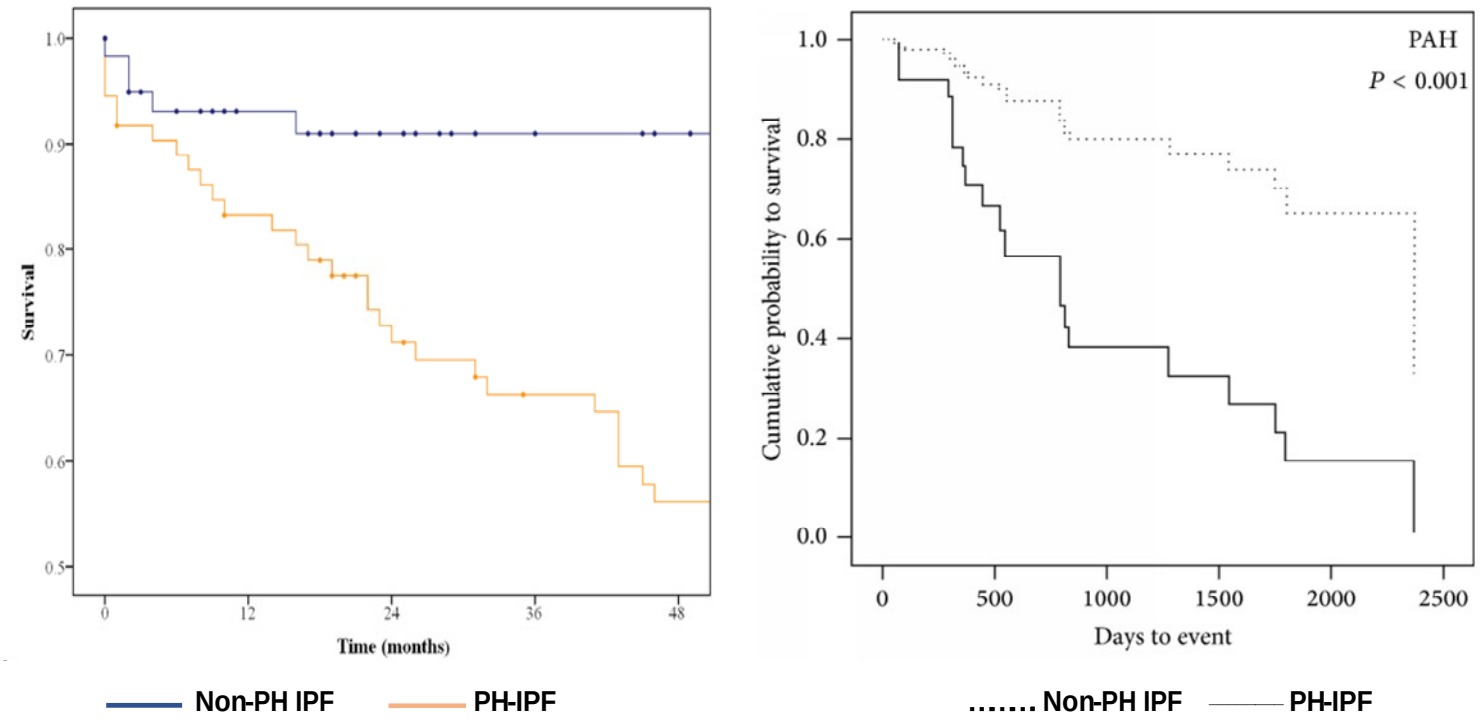
Idiopathic pulmonary fibrosis, or disease related to an unknown cause, represents the most common form of ILD. IPF is classified as an orphan disease by the FDA (i.e. disease that afflicts 200k or fewer people in the U.S.). While prevalence rates of ILD and IPF are not known, general estimates are that approximately 75 of every 100k U.S. adults have ILD and ~70% of these have IPF. That equates to U.S. ILD and IPF prevalence of approximately 160k and 110k, respectively.[15,16] It is further estimated that up to one-third of IPF cases also have PH, implying U.S. prevalence of PH-IPF is ~35k – 40k.[17]

IPF is a progressive and irreversible disease characterized by difficulty breathing, coughing, lung crackles and worsening pulmonary function tests as well as deterioration in quality of life. Symptoms typically worsen over time. Median survival after diagnosis with IPF is two to three years and studies indicate that mortality of the disease is increasing. Respiratory failure due to progression of the disease is the most common cause of death.[18]

PH and right heart failure are very severe complications of IPF and contribute significantly to morbidity and mortality in of the disease. The **presence of PH in IPF has not only been shown to significantly increase mortality but has also been implicated as the leading predictor of death**. Different studies have shown that PH is associated with decreased survival when measured over both one-year and five-year periods (with five-year survival plummeting from 62% with non-PH IPF to just 17% with PH-IPF). Moreover, lung transplant does not improve survival of PH-IPF. The presence of PH in IPF is also associated with a significant decrease in exercise capacity (as measured by 6MWD) and ventilatory efficiency.[17,19]

[15] Thoracic.org, Interstitial Lung Disease.
[16] Nalsnyk, L. et al. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. European Respiratory Review 2012 21: 355-361
[17] Lettieri CJ et al. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest. 2006; 129:746-752
[18] Agrawal A. et al. Cardiac manifestations of idiopathic pulmonary fibrosis. Intractable & Rare Diseases Research. 2016; 5(2):70-75.
[19] Gläser S. et al. Pulmonary Hypertension in Patients with Idiopathic Pulmonary Fibrosis – The Predictive Value of Exercise Capacity and Gas Exchange Efficiency. PLOS ONE 8(6): e65643. https://doi.org/10.1371/journal.pone.0065643

Separate RCTs Show Presence of PH is a Significant and Independent Predictor of Mortality of PH-IPF



Sources: Gläser S. et al. (L) and Lettieri CJ et al (R)

Aside from lung transplantation **there are no known treatments that effectively address the underlying cause of IPF**. As such, treatment of IPF focuses on addressing symptoms of fibrosis and inflammation. Corticosteroids are often used to address inflammation, which may precede fibrosis in many instances, while two prescription drugs are approved in the U.S. to slow the progression of fibrosis.

Pirfenidone (Esbriet) and nintedanib (Ofev) have orphan drug designation and are approved by FDA for the treatment of IPF (although not specifically for PH-IPF). Combined**, these two products generated nearly $1.8B in U.S. sales in 2018** related to their respective IPF indications. Pirfenidone was approved by FDA in 2014 (after failing to gain approval in 2010) while nintedanib received U.S. regulatory approval in 2015. Both are orally administered antifibrotics that slow lung fibrosis by inhibiting the production of growth factors. Clinical studies have shown these may be effective in improving progression-free survival, reducing progression of IPF and slowing the decline in lung function. Aside from gastrointestinal side effects, pirfenidone was found to be generally safe and tolerable. Nintedanib is similarly associated with some gastrointestinal side effects and in addition, approximately 10% of patients in pivotal studies had adverse cardiovascular events (although rarely fatal).

A combination of prednisone (glucocorticoid used for inflammation), azathioprine (an immunosuppressive typically used to treat autoimmune diseases) and N-Acetylcysteine (which promotes the breakdown of mucus in the lungs) was also studied in a randomized placebo controlled trial for the treatment of IPF although results were not positive. The combination treatment was associated with an increased risk of death and hospitalizations.

INOpulse PH-IPF Market Opportunity

Approximately 75 of every 100k U.S. adults are believed to have ILD and ~70% of these are IPF. That equates to U.S. ILD and IPF prevalence of approximately 160k and 110k, respectively. It is further estimated that up to one-third of IPF cases also have PH, implying U.S. prevalence of PH-IPF is ~35k – 40k.

We view INOpulse's initial target market as those patients with moderate-to-severe disease and on LTOT, which we estimate represents approximately two-thirds of all PH-IPF patients. This means BLPH's total U.S. opportunity in this indication represents a population of about 25k people. If we assume INOpulse therapy will be priced at a level

similar to that of Esbriet and Ofev, monthly per-patient (retail) cost of which averages approximately $7,700 (or about $92k per year), this equates to an annual revenue opportunity for BLPH in PH-IPF of $2.3B[20]

Proof-of-Concept of INOpulse in Treatment of PH-IPF Established in Small (n=4) Phase 2a Pilot Study
The ability of INOpulse therapy to provide targeted delivery of iNO to well-ventilated areas of the lungs and improve hemodynamics and exercise capacity of patients with PH-IPF was established in a small Phase 2a pilot study.

The study used two separate doses (30/mcg/kg IBW/hr and 75/mcg/kg IBW/hr) of iNOpulse in combination with oxygen in the treatment of PH-IPF and assessed both acute and chronic pulsed iNO therapy in the treatment of PA-IPF. Two patients received low dose and the other two the high dose. All patients received 20-minute (acute) iNO administration while two patients (one from each dose cohort) also underwent iNO therapy for four weeks (i.e. chronic therapy). Vessel volume and change in regional blood flow were assessed by low dose CT scans. **Results, announced in May 2017** and presented at the American Thoracic Society International Conference, showed

- Acute results: INOpulse therapy resulted in a 15.3% (significant, p<0.001) increase in blood vessel volume during acute inhalation, the study's primary endpoint. In addition, INOpulse demonstrated the ability to provide targeted vasodilation to the well-ventilated areas of the lungs as supported by a demonstrated significant association between ventilation and vasodilation (and no signs of oxygen desaturation). Also, INOpulse therapy resulted in a consistent benefit in hemodynamics as demonstrated by a 14% (i.e. clinically meaningful) reduction in systolic pulmonary arterial pressure. iNO 30 (i.e. 30/mcg/kg IBW/hr) was chosen as the dose to proceed with in subsequent studies as iNO 75 showed potential signs of rebound pulmonary hypertension upon treatment discontinuation.
- Chronic results: chronic outcomes focused on change in exercise capacity as assessed by 6MWD, Distance Saturation Product (DSP, which is the product of the distance walked and the lowest oxygen saturation during the 6MWT) and Integral Distance Saturation Product (IDSP, the product of the distance walked and the integral average of the oxygen saturation during the 6MWT). Results showed an average increase in 6MWD of 75 meters as well as an increase of approximately 80m% of the composite endpoints of 6MWD and oxygen saturation (DP and IDSP)

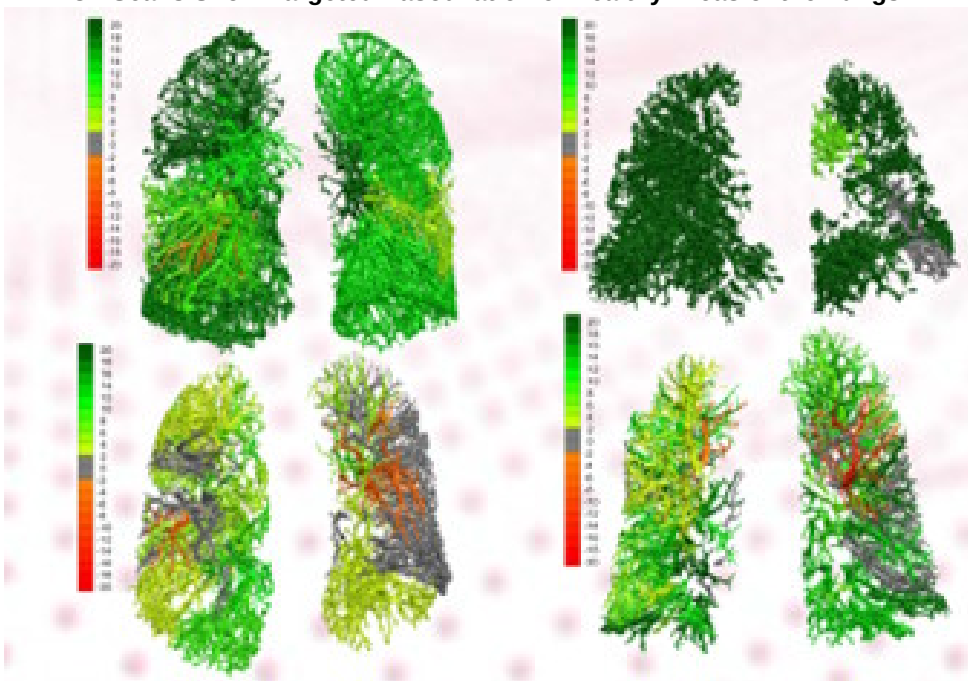
Positive PH-IPF (n=4) Pilot Study Results

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	71	67	66	75
Gender	Female	Female	Male	Male
iNO Dose (µg/kg IBW/hr)	75	75	30	30
TLC (% predicted)	76	57	59	73
Acute Change Blood Vessel Volume (%)	14.0 ± 4.7	34.2 ± 7.6	2.8 ± 3.0	10.1 ± 3.4
Acute Change sPAP (%)	-9.3	-9.7	-14.3	-23.3
Chronic Change 6MWD (meter)	99	-	50	-
Chronic Change DSP* (meter%)	81.1	-	75.1	-
Chronic Change IDSP** (meter%)	82.9	-	82.8	-

Source: Bellerophon, Hajian et al. ATS May 2017 Poster Presentation

[20] Evaluate Pharma, Federal Supply Schedule

CT Scans Show Targeted Vasodilation of Healthy Areas of the Lungs



Source: Bellerophon, Hajian et al. ATS May 2017 Poster Presentation

Phase 2/3 Study: positive Ph2 data announced in May, Ph3 to serve as pivotal U.S. registration study
In January of this year BLPH announced positive initial results from a Phase 2b clinical trial of INOpulse in the treatment of PH-ILD. The company leveraged those compelling results, which we discuss below, to successfully petition FDA on the choice of the primary endpoint and modify the study from a Phase 2b to a Phase 2/3, with the Phase 3 portion expected to serve as a pivotal registrational trial. BLPH announced in early April that FDA concurred.

Results from Cohort 1 (of the Phase 2b portion) were announced in January. The randomized, double-blind, placebo-controlled study (iNO-PF) is evaluating the safety and effectiveness of INOpulse in the treatment of patients with PH associated with ILD and on LTOT. Enrollment was initially intended to be 80 patients among three cohorts and across three doses (iNO 30 n=40, iNO 45 n=20 and iNO 75 n=20). However, the update from Ph2b to Ph2/3 modified the design of the Ph2 portion to two cohorts across two doses (iNO 30 = 40, iNO 45 = 40), which will determine the dose to use in the (newly created) Ph3 portion, which is expected to enroll approximately 300 patients. The updated design allows for a seamless transition (without requiring a end-of-Phase 2 meeting with FDA) from Ph2 to P3 (pivotal) studies. The Ph2 portion also includes an open label ('part 2') dose-escalation treatment period.

Primary endpoints had initially been the change from baseline in multiple parameters including; activity monitoring, right and left ventricular function, (several) oxygen de/saturation measures, 6MWD, QoL (as measured by patient reported outcomes), pulmonary hemodynamics and NT-ProBNP, among others. BLPH announced in April that FDA agreed to their proposal to use 'improvement in moderate to vigorous physical activity (MVPA) as measured by a medical wrist-worn continuous activity monitor' (known as actigraphy) as the primary endpoint in the Phase 3 study. BLPH's proposal to use MVPA as the primary endpoint was motivated by results of Cohort 1 which showed INOpulse patients experienced a statistically significant improvement (of 34%) in MVPA versus patients on placebo.

Importantly, FDA's decision to accept MVPA as the primary endpoint also confirms that this is considered a clinically meaningful measure (a classification that can be critical in attracting clinician interest and adoption and can also have reimbursement-related significance). This is also supported by numerous clinical studies that have demonstrated that physical activity is associated with a host of clinically meaningful outcomes and is an independent predictor of survival and death, including in patients with various cardiopulmonary diseases. MVPA/actigraphy has also been used as a primary or secondary endpoint in a number of late-stage (drug and device) clinical trials for pulmonary and cardiovascular conditions including as the primary endpoint in Novartis'

ongoing Ph3 study of Entresto (in chronic heart failure) and Actelion's Ph4 (post-marketing) study of selexipeg in PAH, among others.

Cohort 1 (n=41: iNO=23, placebo=18), was intended to be randomized 1:1 and evaluated iNO 30 dose. A one-week run-in period was followed by eight weeks of treatment. Patients then transfer to open label therapy at iNO 30 x 8 weeks, iNO 45 x 8 weeks, iNO 75 x 8 weeks which is followed by long-term open label therapy. Results, announced in January and (additional data in) May 2019, are discussed below.

Cohort 2 (n=40) is randomized 2:1 and evaluates iNO 45 dose. A one-week run-in period is followed by 16 weeks of treatment. Patients then transfer to open label therapy at iNO 45 x 8 weeks, iNO 75 x 8 weeks which is followed by long-term open label therapy. BLPH announced on August 1st that Cohort 2 completed enrollment. The Ph2 study is **expected to complete later this year.**

Cohort 3/Phase 3 (n=~300): The optimal dose to be used in Phase 3 will be determined by results of Cohort 1 and Cohort 2. BLPH anticipates Ph3 to begin in 1H 2020 and while the study size has not yet been determined, the company estimates total enrollment of around 300 patients (150/arm) and a completion timeline of 18 to 24 months.

Phase 2 Cohort 1 Results: significant improvement in MVPA, clean safety profile
Results of Cohort 1 (i.e. 8 weeks treatment at iNO 30) were initially announced in January and additional data released in May, which were presented at the American Thoracic Society International Conference. Highlights included statistically significant improvements versus placebo in MVPA and overall activity (illustrated in graph below with distinct treatment vs placebo separation beginning ~week 4) and clinically meaningful improvement in NT-ProBNP as well as oxygen saturation. In summary, INOpulse demonstrated targeted delivery of NO, resulting in oxygen saturation during exercise and significant improvement in key activity measures. iNO therapy was well tolerated, incidence of serious adverse events were low (and similar in both groups) and all SAEs were unrelated to iNO.

Specifically;

- MVPA (primary endpoint): iNO patients saw a statistically significant 34% improvement vs placebo and
    - 23% of iNO patients has clinically meaningful improvement in MVPA vs 0% on placebo ['clinically meaningful' increase is defined as >15% increase in MVPA from baseline]
    - 39% of iNO patients has clinically significant decline in MVPA vs 71% on placebo ['clinically meaningful' decrease is defined as >15% decrease in MVPA from baseline]
- Portion of awake time spent in MVPA improved by a statistically significant 38%
- Overall activity improved by a statistically significant 12%
- Calorie expenditure improved by a statistically significant 12%

Data from the open label portion showed that patients continued benefit from iNO treatment and those that transitioned from placebo to iNO experienced a change from deterioration to improvement in both MVPA and overall activity.

- Placebo patients had an average weekly decrease of three minutes per day of MVPA during blinded treatment, which reversed to an average weekly increase of one minute per day during open-label
- Placebo patients had an average weekly decrease of 22 counts/minute in overall activity during blinded treatment, which reversed to an average weekly increase of 15 counts/minute during open-label
- iNO patients remained stable for both MVPA and overall activity during blinded treatment, both of which improved during open-label, with an average weekly increase of 1 minute/week in MVPA and 15 counts/minute in overall activity

Our take: the Cohort 1 results are highly encouraging, particularly achievement of statistical significance on improvement in MVPA versus placebo, which will serve as the primary endpoint in the Phase 3 study. The clean safety profile, while not a surprise given the lack of INOpulse-associated SAEs in prior clinical trials, is equally encouraging. We will be eagerly awaiting results of Cohort 2 and curious to see if the increased treatment period (to 16 weeks) and dose (to iNO 45) results in further separation on the efficacy measures and/or any adverse change in safety. While we would view meeting statistical significance in MVPA in Cohort 2 as a highly positive event, the combination of statistical significance on MVPA and strong evidence of dose response could be particularly compelling as it relates to providing insight into the potential utility of INOpulse in PH-IPF.

Cohort 1 Results: Significant Improvement in Primary Endpoint, Clinically Meaningful O^2 Measures

	iNO 30	Placebo	Placebo Corrected Change	
Moderate vigorous physical activity (MVPA) (minutes/day)	+8.1%	-26.1%	+34.2%	• Statistically significant improvement as compared to placebo (p=0.04) • Primary endpoint for pivotal Phase 3 cohort
Overall Activity (counts/min)	+0.0%	-11.9%	+11.9%	• Statistically significant improvement as compared to placebo (p=0.05)
SpO2 Nadir	+0.3%	-1.4%	+1.7%	• Higher nadir for iNO=better saturatic
Oxygen Desaturation (Percent Improvement)	+9.3%	-10.5%	+19.8%	• Reduced desaturation for iNO=bette saturation

Source: Bellerophon. Nathan et al. Pulmonary Vasc Res Inst Wrld Cngrs Poster Presentation Feb 2019

Cohort 1 Results: Significant Improvement in Key Activity Measures Bodes Well for Ph3 Study

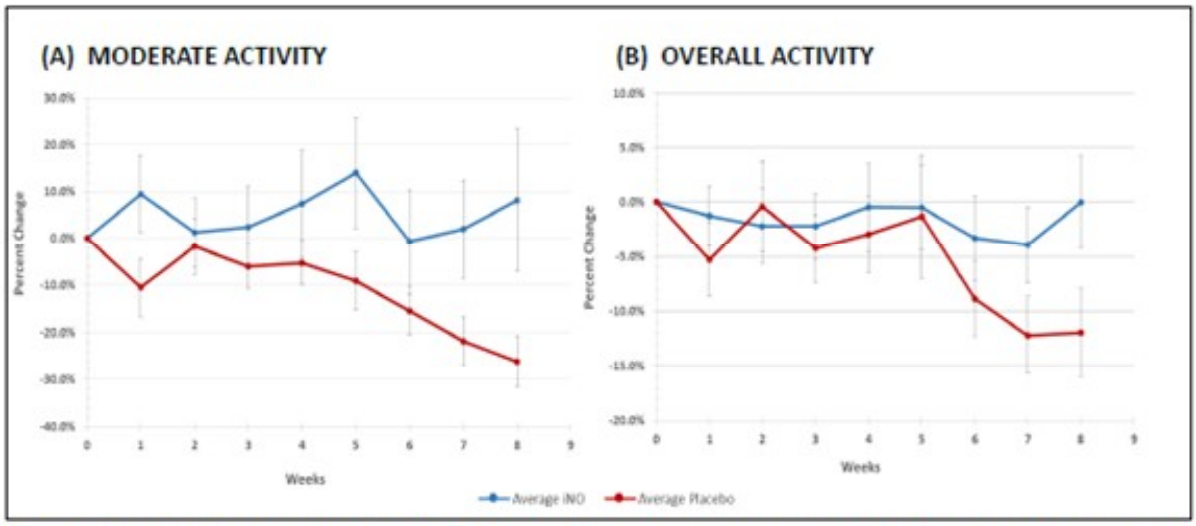


Figure 2: Weekly Assessment of Activity Parameters in (A) moderate activity and (B) overall activity where error bars represent standard errors. In both cases there is clear separation between iNO (—●—) and placebo (—●—) after 4 weeks that reaches statistical significance at week 8.

Source: Bellerophon. Nathan et al. Pulmonary Vasc Res Inst Wrld Cngrs Poster Presentation Feb 2019

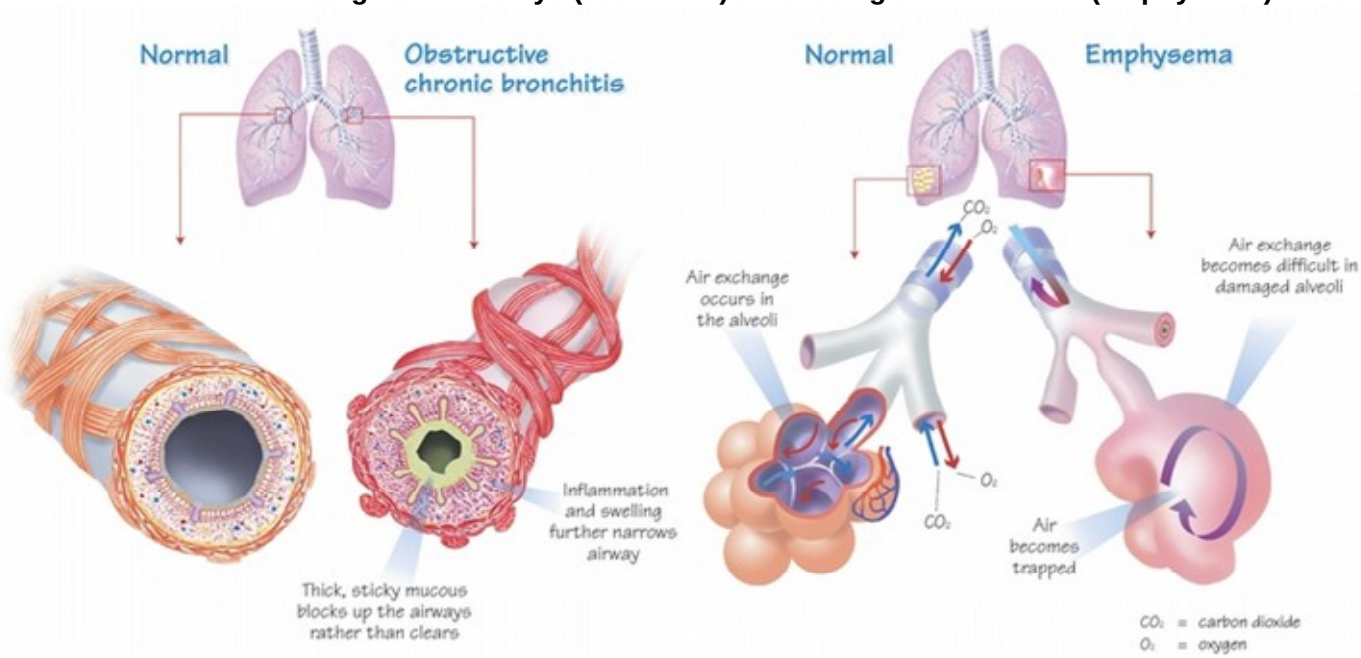
PH-COPD Program

Chronic obstructive pulmonary disease (COPD) is a progressive, uncurable disease that is characterized by difficulty breathing due to impeded air flow. Smoking is the leading cause of COPD although it has also been associated with urban air pollution and genetics. COPD includes damage to the air sacs in the lungs (emphysema) and a narrowing of the airways (bronchitis). Cigarette smoke, toxins or other chronically inhaled airborne irritants can breakdown and damage sensitive tissue of the bronchioles (small airways leading to the alveoli) and alveoli (where gas exchange takes place between the lungs and bloodstream). Loss of elasticity and injury to the walls of the alveoli inhibit gas exchange. Meanwhile, inflammation and mucus production from the body's immune response cause narrowing of the airways, making breathing (particularly exhaling) more difficult.

Lung damage and impeded breathing as a result of COPD compromise the pulmonary system's ability to oxygenate blood. Symptoms of COPD, which include dyspnea, coughing and difficulty exercising or performing daily activities (such as walking up the stairs), typically worsen over time. Hypoxemia is a common complication associated with severe COPD necessitating the use of long-term oxygen therapy. The frequency of hypoxemia is significantly

greater in patients with PH-COPD than with non-PH COPD.[21] This is likely explained by the fact that hypoxemia is also associated with vascular remodeling, which is the major cause of PH in COPD.[22]

COPD: Narrowing of the airways (bronchitis) and damage to the alveoli (emphysema)



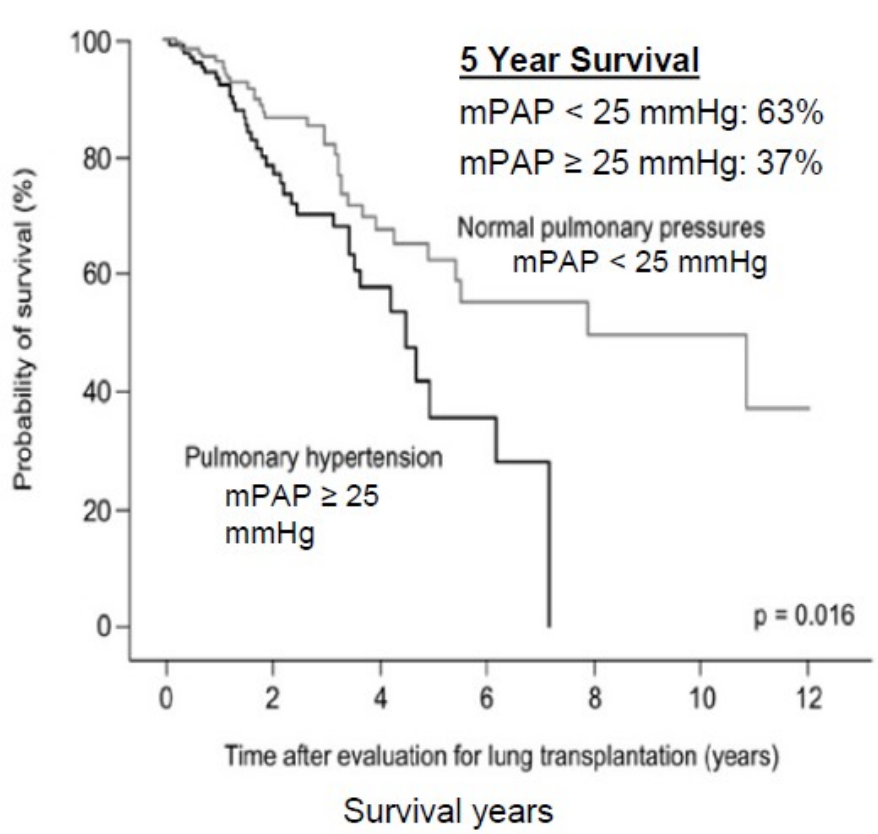
Source: Living Well with COPD

COPD treatment focuses on symptom management and delaying (inevitable) progression of the disease. Therapy is largely aimed at reducing the incidence of acute exacerbations (such as shortness of breath), easing dyspnea, improving survival, increasing exercise tolerance and improving quality of life. Common treatments include LTOT, short and long-acting inhaled bronchodilators (β2 agonists and anticholinergics), corticosteroids and, in some cases, antibiotics.

COPD has an average five-year life expectancy of 40% to 70%, depending on the severity, while severe COPD is associated with two-year life expectancy of only 50%. **Prognosis and average life expectancy deteriorate further with the presence of PH**, which worsens gas exchange and dyspnea.[23] PH has been shown to be an independent predictor of the number of exacerbations and length of hospital stay in patients with COPD. It has also been shown to be an independent predictor of exercise capacity as measured by 6MWD.[24] Elevated pulmonary arterial pressure associated with PH is also a predictor of death independent of COPD-associated airflow limitation (with large studies showing five-year survival of 37% with mean PAP > 25mmHg and 0% with mean PAP > 50mmHg).[25,26] This association is supported by other studies as well which includes a finding that **severe PH in patients with COPD reduces median survival by approximately 40 months**.[27]

[21] Gologanu, D. et al. Prevalence and Characteristics of Pulmonary Hypertension Associated with COPD - A Pilot Study in Patients Referred to a Pulmonary Rehabilitation Program Clinic. MAEDICA – a Journal of Clinical Medicine 2013; 8(3): 243-248
[22] Jyothula S1, Safdar Z. Update on pulmonary hypertension complicating chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2009;4:351-63. Epub 2009 Sep 24.
[23] Cavaillès A. et al. Comorbidities of COPD. European Respiratory Review 2013 22: 454-475
[24] M. W. Sims, D. J. Margolis, A. R. Localio, R. A. Panettieri, S. M. Kawut, and J. D. Christie, "Impact of pulmonary artery pressure on exercise function in severe COPD," Chest, vol. 136, no. 2, pp. 412–419, 2009.
[25] Higham MA, et al. Utility of echocardiography in assessment of pulmonary hypertension secondary to COPD. Eur Respir J 2001; 17: 350–355
[26] Andersen KH. Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. J Heart Lung Transplant. 2012 Apr;31(4):373-80
[27] Chaouat A, Bugnet AS, Kadaoui N, et al. 2005. Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 172:189–94

PH an Independent Predictor of Death in PH-COPD



Source: BLPH and Andersen KH. J Heart Lung Transplant. 2012 Apr;31(4):373-80

INOpulse PH-COPD Market Opportunity

There are no currently approved treatments for COPD, which is the third leading cause of mortality in the U.S. and results in about 120k deaths in this country each year. An estimated ~24M Americans (~50% of which have been diagnosed) are believed to have the disease, approximately 40% of which are moderate to severe cases. While prevalence of PH associated with COPD is not known with certainty, various studies have indicated that it falls somewhere between 10% to 30% of patients (we use the midpoint for our calculations) with moderate to severe COPD.[28] While the majority of these patients are likely to be on LTOT, for our calculations we use a more conservative 50% LTOT-experience assumption. This implies that BLPH's U.S. target population in PH-COPD is approximately 480k people.

INOpulse Clinical Data in PH-COPD

Clinical data supporting the use of pulsed iNO in COPD go as far back as 2003 and as recently as the positive results of a Ph2a study in PH-COPD, which completed in 2017. BLPH is now preparing to commence a Ph2b study in PH-COPD, the design of which was finalized earlier this year.

Initial RCT supporting use of iNO for long-term treatment of COPD: published in April 2003 in the journal Thorax, this n=40 study was the first RCT to demonstrate that pulsed iNO can be safely and effectively used for the long-term treatment of severe COPD (while this was the first study to demonstrate safety and effectiveness of pulsed iNO in this indication, INOpulse was not the device that was used for delivery). Acute testing was also performed. Pulsed iNO was used to reduce ventilation-perfusion mismatch and toxic reaction of NO and oxygen. Patients were randomized to either LTOT or pulsed iNO plus LTOT over a three-month treatment period.

Results showed that patients treated with iNO plus LTOT experienced a significant decrease in mean pulmonary artery pressure ($p<0.001$) and pulmonary vascular resistance ($p<0.001$) without a decrease in arterial oxygenation. In addition, cardiac output increased ($p=0.025$) while systemic hemodynamics and left heart function

[28] Elwing J., Panos R. Pulmonary hypertension associated with COPD. International Journal of COPD 2008:3(1) 55–70

remained unchanged. No increase in toxic reaction products of nitric oxide was observed.[29]

Phase 2 n=159 Study in PH-COPD
BLPH sought to confirm the results of the n=40 study in a (n=159) Phase 2 dose-ranging RCT using INOpulse in the acute treatment of PH-COPD. Doses ranged from iNO 3 to iNO 75.

Endpoints
- Primary: Change in pulmonary arterial pressure (PASP) from baseline to end of day 1
- Secondary: Occurrence of decrease ≥ 5mm Hg of partial pressure of oxygen in arterial blood (PaO2) from baseline to end of Day 1

The study included two parts
- Part A, n=80, split evenly into 4 groups (n=20 each): 3mcg/kg, 10 mcg/kg, 15 mcg/kg or placebo (non-pulsed nitrogen at the same 3mcg/kg, 10mcg/kg and 15mcg/kg settings)
- Part B, n=60, split into 3 groups (n=20 each): 30mcg/kg, 75mcg/kg or placebo (i.e. non-pulsed oxygen at the same settings)

While results, which were announced in 2014, showed that the primary endpoint, a significant reduction in pulmonary arterial pressure versus placebo, was not met for any of the doses tested, there were some positive findings. The study identified an iNO dose range that demonstrated reduction in PAP versus baseline that was similar to the acute effects of pulsed iNO in the n=40 study (described above). For context, acute testing in that n=40 study showed that pulsed iNO plus oxygen therapy resulted in a decline of PAP from 27.6 mmHg to 23.1 mmHg ($p<0.001$) (table below). Additionally, none of the doses tested in this n=159 study had adverse effects related to hypoxemia as compared to placebo. As such, results were meaningful as they helped confirm a dose range that has been shown to result in significant reduction in PAP and without hypoxemia.

Acute Test Results of Pulsed iNO + Oxygen (from n=40 third-party study)

Table 2 Haemodynamic values on acute test

	Oxygen alone			Oxygen + NO		
	Baseline	Acute test	p value	Baseline	Acute test	p value
PAPm (mm Hg)	24.6 (5.7)	21.6 (6.2)	0.0001	27.6 (4.4)	23.1 (5.3)	<0.0001
PVR (dyne.s^{-1}.cm^{-5})	259 (101.7)	180.2 (75.1)	0.0001	276.9 (96.6)	193.5 (78.7)	0.0001
PVRI (dyne.s^{-1}.cm^{-5}.m^{-2})	519.7 (209.5)	375.6 (162.2)	0.0001	569.7 (208.1)	394.6 (150.3)	0.0001
CO (l/min)	5.5 (1.3)	6.1 (1.8)	<0.01	5.6 (1.3)	6.2 (1.4)	<0.01
CI (l/min/m^2)	2.7 (0.5)	2.9 (0.5)	<0.01	2.7 (0.6)	3.0 (0.6)	<0.01
PCWP (mm Hg)	9.6 (2.9)	9.8 (2.6)	0.6798	10.4 (3.3)	10.2 (3.1)	0.5488

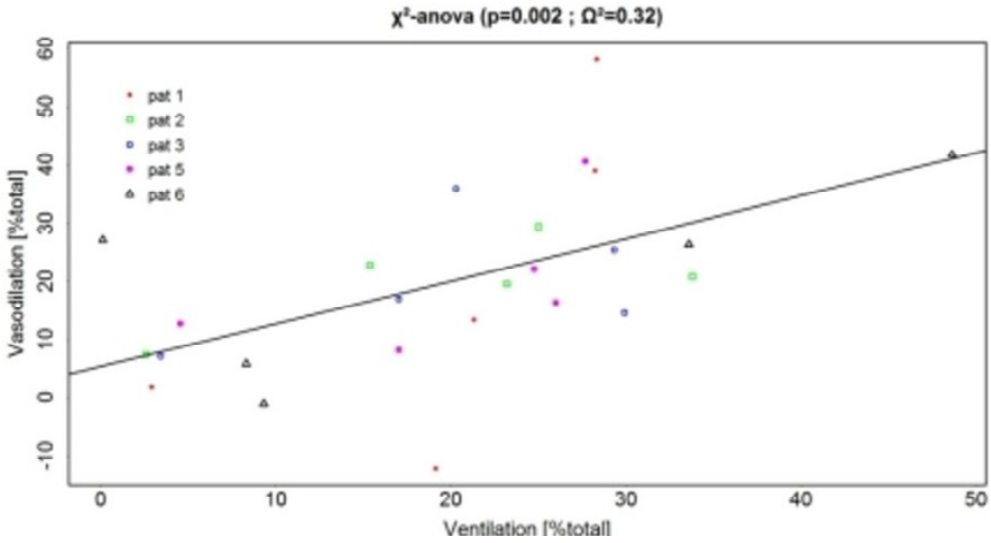
Values are mean (SD); n=40.
PAPm=mean pulmonary artery pressure; PVR=pulmonary vascular resistance; PVRI=pulmonary vascular resistance index; CO=cardiac output; CI=cardiac index; PCWP=pulmonary capillary wedge pressure.

Source: Vonbank K. et al. Thorax 2003;58:289–293

Phase 2 n=6 Study in PH-COPD
INOpulse was evaluated as an acute treatment (20min pulsed iNO (30 mcg/kg IBW/hr) in six patients with PH-COPD and on LTOT. Outcome measures were blood vessel volume, oxygen saturation and blood pressure. Results, presented at the European Respiratory Society International Congress in September 2015 and subsequently published in the International Journal of COPD (July 2016), showed that INOpulse was associated with a 7% average increase in blood vessel volume (with some areas showing blood vessel volume increasing by more than 20%), preserved oxygen saturation and vasodilation was highly correlated with ventilation (p=0.002).

[29] Vonbank K. et al. Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. Thorax. 2003 Apr; 58(4): 289–293.

Ph2 (n=6) PH-COPD Study: Vasodilation highly correlated with ventilation



Source: Hajian B. et al. European Respiratory Journal 2015

Phase 2a n=10 Study in PH-COPD
This study was designed as a follow-up to the n=6 study in order to investigate the acute effect of iNO on targeted vasodilation and the chronic (4-weeks) effect of iNO on changes in exercise tolerance and hemodynamic. iNO 30 dose was used.

Results, announced in 2017:[30]

- Acute iNO treatment was associated with a statistically significant increase (average 4.2%) in blood vessel volume versus baseline (p=0.03) and a statistically significant correlation in Ventilation-Vasodilation (p=0.01), indicating targeted delivery to the well-ventilated alveoli.
- Chronic iNO treatment was associated with statistically significant and clinically meaningful increases in 6MWD at both two and four weeks (+50.7m; p=0.04), as compared to baseline. In addition, the study demonstrated a statistically significant and clinically meaningful decrease of 19.9% in systolic pulmonary arterial pressure (sPAP) at four weeks (p=0.02), as compared to baseline. The therapy was well tolerated with no related safety concerns.

Our take: While the small size and lack of comparator means caution is warranted in drawing any concrete conclusions as to the effect of iNO on exercise tolerance and hemodynamics in patients with PH-COPD, results are nonetheless encouraging as it relates to the safety of iNO 30 dose as well as providing more potential evidence as to the utility of iNO in this indication. As PH-COPD is associated with significant and progressive deterioration of exercise capacity, which is as independent predictor of worsening prognosis, replication of these results in larger RCTs (such as the anticipated Ph2b study, below) could provide substantive insight into the potential commercial opportunity of INOpulse in the treatment of PH-COPD.

Large Ph2b RCT in PH-COPD: design confirmed w/ FDA, anticipated to commence in 2020
BLPH hopes to confirm results of the n=10 Ph2a study in a larger Ph2b study. The randomized, double-blind, placebo-controlled study, the design of which the company announced has been reviewed and finalized by FDA, will include 90 patients with PH-COPD. The goal of this study is to inform design, including specifics around patient population and clinical endpoints, of a subsequent Phase 3 study. Endpoints of this Ph2b study include activity monitoring, right ventricular function, oxygen saturation, time to clinical worsening, time to clinical improvement as well as composite endpoints. BLPH anticipates commencement in 2020.

PH-Sarcoidosis Program
Sarcoidosis is a disease in which inflammatory cells, called granulomas, form and accumulate in the lungs, skin or lymphatic tissue (and less commonly effect the eyes, liver, heart and other organs). While the underlying cause of the disease is not known, it has been postulated that it could be associated with immune reactions to infection or toxins.

[30] Bellerophon Sept 5, 2017 Press Release

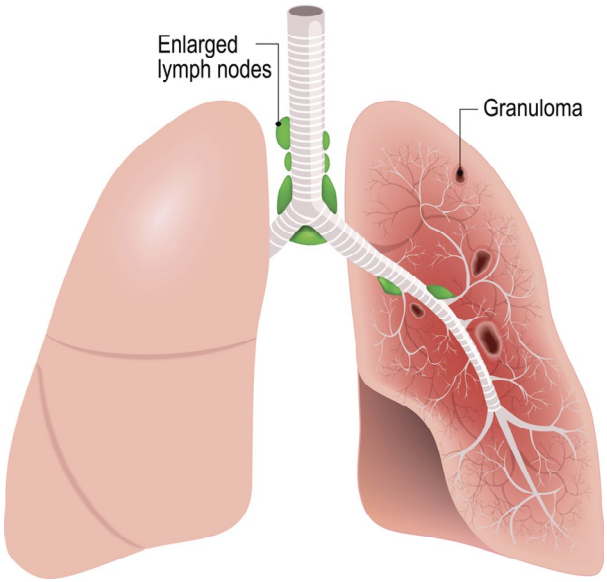
Sarcoidosis of the lung, known as pulmonary sarcoidosis, can cause in inflammation and fibrosis and result in thickening and stiffening of the lung tissue, making it difficult to breath. Symptoms can include coughing, wheezing, dyspnea and chest pain. In about 90% (or more) of all sarcoidosis cases the lungs are affected to some degree and ~50% of people afflicted experience permanent lung dysfunction.

In the majority of cases the disease is mild enough where treatment is either unnecessary or symptoms can be managed with only non-steroidal anti-inflammatories (NSAIDs). In more severe and chronic cases of pulmonary sarcoidosis, glucocorticoids (such as prednisone), antimetabolites (such as azathioprine) and monoclonal anti-tumor necrosis factor antibodies may be prescribed. There are no approved therapies to treat PH-sarcoidosis. The presence of PH in sarcoidosis is an independent predictor of worse outcomes including death.[31]

INOpulse PH-Sarc Market Opportunity
U.S. prevalence of sarcoidosis is estimated at approximately 40 cases per 100k population, which implies that about 84k adults in the U.S. have the disease at any given time. Prevalence of PH in sarcoidosis is less clear, although estimates suggest that between 5% and 20% of all sarcoidosis patients and up to 74% of patients awaiting lung transplant also have PH (i.e. PH-sarcoidosis).[32]

This implies that BLPH's U.S. target population in PH-Sarc is approximately 15k people. If we assume that pricing of INOpulse therapy is similar to that of our calculated per-patient treatment of PH-IPF (i.e. ~$92k per year), then PH-Sarcoidosis represents a potential total market opportunity of approximately $1.4B

Pulmonary Sarcoidosis



Source: lungandsleepspecialists.com

Proof-of-Concept of iNO in Treatment of PH-sarcoidosis
Vasoresponsiveness of sarcoidosis-associated pulmonary hypertension, a manuscript of a study published in Chest in September 2001 provides support for the potential utility of iNO in the treatment of PH-sarcoidosis. The observational study (which was not sponsored by Bellerophon and did not use INOpulse as the iNO delivery method) evaluated the effects (hemodynamic and exercise capacity) of three vasodilators in eight patients with sarcoidosis-associated PH. A 'favorable' response was defined as ≥ 20% decrease in PVR.

Patients underwent short-term treatment with iNO, IV epoprostenol, and/or oral calcium-channel blockers. Five patients received long-term treatment with iNO (with one patient also receiving epoprostenol) and underwent follow-up hemodynamic and/or 6-min walk testing. Two patients received long-term treatment with calcium-channel blockers.

[31] Gerke A. Morbidity and Mortality in Sarcoidosis. Curr Opin Pulm Med. 2014 September ; 20(5): 472–478.
[32] Huitema MP, et al. Pulmonary hypertension complicating pulmonary sarcoidosis. Neth Heart J (2016) 24:390–399

Results showed:

- A favorable short-term response in seven of eight patients receiving iNO, four of six patients receiving epoprostenol, and two of five patients receiving calcium-channel blockers.
    - with iNO, PVR decreased 31 +/- 5% (p = 0.006) and mPAP decreased 18 +/- 4% (p = 0.003
    - with epoprostenol, PVR decreased 25 +/- 6% (p = 0.016) and mPAP decreased 6 +/- 2% (p = not significant)
    - with calcium-channel blockers, decreased systemic vascular resistance was the only significant response
- 6MWD improved in all five patients receiving long-term treatment with iNO
- Follow-up hemodynamic responses in three (of the five) iNO patients showed preserved vasoresponsiveness. These three patients subsequently died, as did the two patients receiving calcium-channel blockers. The two remaining patients continue to receive iNO.

Phase 2 (n=16) Study in PH-Sarc initiated in Q1 2019

In Q1 2019 BLPH initiated a Phase 2 (n=16) open label, acute dose-escalation (iNO 30 - iNO 125) study designed at verifying the hemodynamic effects (via right heart catheterization) of INOpulse in patients with PH-sarcoidosis or PH-PF and on LTOT. Per clinicaltrials.gov, the study (NCT03727451) is segmented into two treatment groups for PH-sarc and PH-PF, with eight patients per group. Primary endpoints include change in mean PAP, PCWP, cardiac output and PVR. Secondaries are safety/tolerability oriented and included SAEs, pulmonary rebound, distance saturation product (DSP), dyspnea and QoL. A long-term open label extension study follows.

ANALYSIS, ASSUMPTIONS, OUTLOOK, VALUATION and FINANCIAL MODEL

PAH Setback May Have a Silver Lining: the failed Ph3 PAH Study (stopped in August 2018 due to futility), while disappointing, may eventually prove to just be a short-term setback and one with a silver lining. And it was far from a complete failure given clinically meaningful improvement in hemodynamics. In addition, the lack of efficacy on 6MWD in PAH may have been confounded by prostanoid and other PAH background therapy - which is approved for use in PAH but not in PH-IPF, PH-COPD or PH-sarcoidosis. Safety and tolerability were also non-issues in this study (largely confirming results of previous studies) - the significance of which should not be underestimated given that safety concerns have hindered FDA approval of systemic vasodilators for the same indications that BLPH is now pursuing. Moreover, given that the underlying cause of PAH is vascular disease itself, it may not lend itself to fully benefitting from INOpulses's dual mechanism of action (targeting both ventilation and perfusion), which may be more well suited to conditions with both pulmonary and vascular disease pathologies. And finally, while there are numerous vasodilatory therapies approved for the treatment of PAH, there are none for the conditions that BLPH is now focused on.

Significant Unmet Need for Safe and Effective PH-Lung Disease Therapy: the presence of PH and certain symptoms of PH, including diminished exercise capacity, has been shown to be an independent predictor of adverse outcomes, including death, in patients with lung diseases such as the ones BLPH is pursuing. Lack of FDA-approved therapies and off-label use of systemic vasodilators (which may risk doing more harm than good) means that there is a significant unmet need for safer and more effective treatment of these diseases. As such, significant market demand should materialize if BLPH can continue to demonstrate sufficient effectiveness and safety of chronic use of INOpulse in these indications (and obtain regulatory approval).

Lack of Direct competition: while iNO is not currently approved for chronic conditions or for ambulatory use, Beyond Air's (Nasdaq: XAIR) AirNOvent cylinder-free nitric oxide system is in late-stage development for the in-hospital treatment of PH (the company's pipeline status webpage indicates that they may also pursue at-home treatment of PH at a later time), an FDA filing for which they anticipate will happen later this year. The system (which generates NO from air, thereby eliminating the need for NO cylinders) is also in earlier stage development for the treatment of bronchiolitis and for ambulatory use in the treatment of nontuberculous mycobacteria. Meanwhile, Praxair's[33] Noxivent nitric oxide (recently approved by FDA under ANDA citing Inomax Gas for Inhalation as the reference listed drug) and NOxBOXi delivery system (which cited INOmax System as its predicate for FDA 510(k) clearance) are approved for the same indications as INOmax (i.e. the in-hospital treatment of term

[33] Interestingly, In October 2018 Praxair merged with The Linde Group, which had previously owned the legacy INOmax technology before selling it (in 2007) to INO Therapeutics (which combined it with their Ikaria Inc division). Ikaria was acquired by Mallinckrodt in 2015.

and late pre-term neonates with hypoxic respiratory failure). As INOpulse is being developed specifically for ambulatory use and for different indications, we do not view AirNOvent or Praxair's products as near-term competitive threats.

FDA Pathway: INOpulse is designated a drug-device combination product with primary oversight by the agency's Division of Cardiovascular and Renal Products in the Center for Drug Evaluation and Research with consultation from the Division of Pulmonary, Allergy, and Rheumatology Products. While BLPH has not disclosed specifically the anticipated FDA pathway, we anticipate the drug portion will follow either an Abbreviated New Drug Application (ANDA) or 505(b)(2) route – and leverage either Mallinckrodt's NDA for Inomax or its referenced safety data – along with INOpulse's indication-specific clinical data. The device portion should be relatively straightforward given that it is an extension of INOmax. We do anticipate, however, that ambulatory use will require some type of patient user study – although do not expect that to be a significant hurdle or to consume significant resources.

Reimbursement: given that INOpulse is a novel product we do not anticipate that dedicated reimbursement (public or private) will be in place upon commercialization. However, the dire prognosis of these diseases, exorbitant cost (and wanting efficacy) of current treatment options and lack of FDA-indicated therapies means insurers should have sufficient motivation to cover INOpulse treatment. However, while we think that there is a reasonably good chance that reimbursement will materialize, we are less certain of just how quickly it will be in place or how widespread shortly following regulatory approval.

Target Market Calculations: our target market calculations are based on two components, estimated size of the affected U.S. population and per-patient iNO drug pricing. As the target market sizes are well documented in population and epidemiological studies, those estimates should prove to be relatively reliable. However, as there are no iNO chronic treatment comparables in the market today, our assumed iNO pricing is based on comparable pricing of vasodilators - which may or may not prove to be reasonably accurate. But we think this is a reasonable methodology given that INOpulse, if and when approved, might be the only indicated first-line treatment for these diseases and would potentially be replacing off-label use of systemic vasodilators.

Commercialization: we use the assumption that BLPH commercializes for any and all FDA-approved indications with an in-house (to-be-hired) sales force (as opposed to, for example, third-party distribution, partnerships, joint-ventures or collaborations). Serious and relatively rare cardio/pulmonary diseases such as those that BLPH is pursuing are typically treated at the specialist levels, which is where we expect BLPH's commercialization efforts to be focused. Pulmonologists are knowledgeable of and most likely to have experience with iNO, LTOT, V/Q mismatch and the drawbacks of systemic vasodilators – which is key to fully appreciating the advantages of INOpulse. It also should help to minimize the cost and time of educating potential customers (and in training customers). Focusing on the largest pulmonary hospitals would allow BLPH to concentrate target customer call-points, which lends itself well to a relatively small and efficient (i.e. inexpensive) sales force.

Modeling Only U.S. Market: while INOpulse received CE Marking in 2016, we assume that, at least initially, BLPH does not enter Europe and focuses all of their commercial efforts on the U.S. As is the case for all of our assumptions, this will be modified if and when warranted.

We use the following per-indication market assumptions (see Market Penetration Forecast, below);

PH-IPF

Current Ph2 Cohort 2 completes and topline data by Q1 2020. Ph3 pivotal (n=300) initiates 1H 2020, completes 1H 2022 and data in Q3 2022. Pre-approval regulatory activities (FDA filing(s), patient user study, etc) follow and FDA approval for ambulatory use of iNO in the treatment of patients with PH-IPF and on LTOT granted in Q2 2023. Commercial launch commences Q3 2023.

U.S. prevalence of this target indication is 35k – 45k people. PH-IPF initial addressable market size equal to approximately $2.3B growing at an annual rate of approximately 2% per year. We model initial (modest) revenue in 2023, increasing to just over 1.25% of the total market opportunity in the first full year on the market for this indication and to almost 17% by 2029.

PH-COPD

Ph2b (n=90) initiates 1H 2020, completes and data in 1H 2021. A Ph3 pivotal study commences Q3 2021, completes 1H 2023 and data Q3 2023. Pre-approval regulatory activities follow and FDA approval for ambulatory use of iNO in the treatment of patients with PH-COPD granted in Q2 2024. Commercial launch commences Q3 2024.

U.S. prevalence of this target indication is ~480k people. PH-COPD initial addressable market size equal to approximately $44B growing at an annual rate of approximately 2% per year. We model initial revenue in 2024, increasing to just over 0.5% of the total market opportunity in 2028 and to 0.71% in 2029.

PH-Sarcoidosis
Current Ph2 (n=16) completes Q4 2019. Initiate a Ph2b study in 1H 2020 which completes with data in 1H 2021. A Ph3 pivotal study commences Q3 2022, completes Q3 2024 and data in Q4 2024. Pre-approval regulatory activities follow and FDA approval for ambulatory use of iNO in the treatment of patients with PH-Sarcoidosis granted in Q3 2025. Commercial launch commences Q4 2025.

U.S. prevalence of this target indication is ~15k people. PH-Sarcoidosis initial addressable market size equal to approximately $1.4B growing at an annual rate of approximately 2% per year. We model initial revenue in 2025, increasing to nearly 1.25% of the total market opportunity in 2026 and to over 6% in 2029.

Total Revenue
We currently model initial total revenue of $5.0M in 2023 and growing to $957M in 2029.

For some context…
We note that given the number of unknowns, particularly the lack of like-kind comparables as a result of the novel nature of INOpulse, that it is difficult to estimate with any degree of reasonable confidence what BLPH's revenue curve may look like. Below we provide what we think is some of the most relevant background on vasodilators that are approved for use in the U.S., although not for the indications that BLPH is pursuing. We provide this mostly for investors to have some insight in order to judge the reasonableness of our revenue forecasts for INOpulse.

- PAH affects approximately 6,500 people in the U.S. Tyvaso (inhaled treprostinil for PAH), which launched in 2009, generated U.S. peak sales of $470M in 2015, representing revenue per patient of more than $107k. Ventavis (inhaled iloprost for PAH), which launched in 2005, generated U.S. sales of $88M in 2018.
- FDA approved prostanoids for the treatment of PAH generated $1.973B of sales in the U.S. in 2018. Uptravi (oral selexipag) and Remodulin (SC, IV treprostinil) lead the market, each generating nearly $600M in revenue and, combined, account for 60% of total U.S. sales. Despite not being approved (or necessarily safe) these prostanoids are sometimes used to treat patients with PH-lung diseases.
- INOmax
    - Persistent pulmonary hypertension of the newborn (the indication for which INOmax is approved) affects about 7,700 babies each year in the U.S. INOmax launched in the U.S. in 2000 and currently generates about $600M in annualized revenue. In addition to the U.S. (including Puerto Rico), INOmax is approved for sale in Canada, Australia and Japan.
    - Mallinckrodt has previously disclosed that approximately 80% of INOmax revenue was generated from off-label use for clinical care applications and the other 20% from the FDA-approved indication (PPHN).
    - In 2005 (i.e. five years after U.S. launch and the first year in which financial data is publicly available) INOmax generated $143M of revenue, ~$29M (i.e. 20%) of which we can estimate was related to PPHN. This is equal to ~$3,800 per individual in the U.S. with PPHN ($29M / 7,700). Recall that INOmax is used for acute indications (as opposed to long-term chronic diseases) and therefore we should expect that average revenue per U.S. individual with PPHN would be significantly less than if used for longer periods. (Note that we are not calculating revenue per treated patient but instead, revenue per incidence of the disease).
        - By comparison, our 2029 (i.e. roughly five years after anticipated initial-indication launch) revenue estimates (PH-IPF $468M, PH-COPD $381M and PH-Sarc $108M) average to ~$6,600 per individual in the U.S. with these respective indications (the characteristics and size of which we have described in this report) – which we think is reasonable (or, arguably conservative) given the chronic nature of these diseases and the long-term indications that BLPH is seeking
        - We acknowledge that this is an unorthodox methodology but, given the number of unknowns (pricing, adoption / placement rates, reimbursement, strength of pivotal data, etc), provide it for context to help gauge the feasibility of our revenue projections

Valuation

We use a 10-year DCF model to value BLPH. Our DCF models only projected U.S. sales of INOpulse for the indications of PH-IPF, PH-COPD and PH-Sarcoidosis. Based on clinical stage, we apply the following risk of regulatory failure rates to each of the programs; IPF 35% (i.e. 65% chance of FDA approval), COPD 50% and Sarcoidosis 65%. These are subject to adjustment based on development progression/success/regression/failure.

Our DCF, which uses a 12% discount rate and 2% terminal growth rate, values BLPH at approximately $3.25/share on a fully diluted basis.

Market Penetration Forecast (000s)

Markets ($000)	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029
INOpulse for PH-ILD	$2,300,000	$2,346,000	$2,392,920	$2,440,778	$2,489,594	$2,539,386	$2,590,174	$2,641,977	$2,694,817	$2,748,713	$2,803,687
INOpulse for PH-COPD	$44,000,000	$44,880,000	$45,777,600	$46,693,152	$47,627,015	$48,579,555	$49,551,146	$50,542,169	$51,553,013	$52,584,073	$53,635,754
INOpulse for PH-Sarc	$1,400,000	$1,428,000	$1,456,560	$1,485,691	$1,515,405	$1,545,713	$1,576,627	$1,608,160	$1,640,323	$1,673,130	$1,706,592

Mrkt penetration	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029
INOpulse for PH-ILD	0.00000%	0.00000%	0.00000%	0.00000%	0.20249%	1.27010%	2.50664%	4.76144%	8.54370%	12.12523%	16.67608%
INOpulse for PH-COPD	0.00000%	0.00000%	0.00000%	0.00000%	0.00000%	0.01818%	0.08967%	0.16796%	0.35754%	0.51668%	0.71024%
INOpulse for PH-Sarc	0.00000%	0.00000%	0.00000%	0.00000%	0.00000%	0.00000%	0.09894%	1.23777%	2.30870%	3.95888%	6.33060%

Revenue ($000)	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029
INOpulse for PH-ILD	$0	$0	$0	$0	$5,041	$32,253	$64,926	$125,796	$230,237	$333,288	$467,545
INOpulse for PH-COPD	$0	$0	$0	$0	$0	$8,833	$44,432	$84,890	$184,321	$271,691	$380,942
INOpulse for PH-Sarc	$0	$0	$0	$0	$0	$0	$1,560	$19,905	$37,870	$66,237	$108,038
Total	**$0**	**$0**	**$0**	**$0**	**$5,041**	**$41,086**	**$110,918**	**$230,591**	**$452,428**	**$671,216**	**$956,525**

Adjusted for Risk of Reg Failure

Revenue ($000)	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	Fail Risk
INOpulse for PH-ILD	$0	$0	$0	$0	$3,277	$20,964	$42,202	$81,768	$149,654	$216,637	$303,904	35%
INOpulse for PH-COPD	$0	$0	$0	$0	$0	$4,416	$22,216	$42,445	$92,161	$135,846	$190,471	50%
INOpulse for PH-Sarc	$0	$0	$0	$0	$0	$0	$546	$6,967	$13,255	$23,183	$37,813	65%
Total	**$0**	**$0**	**$0**	**$0**	**$3,277**	**$25,381**	**$64,964**	**$131,179**	**$255,069**	**$375,666**	**$532,188**	

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FINANCIAL MODEL

Bellerophon Therapeutics, Inc (in millions)

	2018 A	Q1A	Q2E	Q3E	Q4E	2019 E	2020 E	2021 E	2022 E
INOpulse for PH-ILD	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-	-	-
% total sales	-	-	-	-	-	-	-	-	-
INOpulse for PH-COPD	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-	-	-
% total sales	-	-	-	-	-	-	-	-	-
INOpulse for PH-Sarc	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-	-	-
% total sales	-	-	-	-	-	-	-	-	-
Total Revenues	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
YOY Growth	-	-	-	-	-	-	-	-	-
Cost of Revenues	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Margin	-	-	-	-	-	-	-	-	-
R&D	$20.3	$2.3	$2.5	$4.1	$4.9	$13.8	$21.2	$28.7	$32.4
% R&D	-	-	-	-	-	-	-	-	-
SG&A	$7.6	$2.0	$2.1	$2.0	$2.0	$8.1	$8.8	$9.4	$10.1
% SG&A	-	-	-	-	-	-	-	-	-
Operating Income	($27.9)	($4.3)	($4.6)	($6.1)	($6.9)	($22.0)	($30.0)	($38.1)	($42.5)
Operating Margin	-	-	-	-	-	-	-	-	-
Other Income total	$25.3	$1.7	$2.4	($0.3)	($1.2)	$2.6	($3.9)	($6.6)	($11.7)
Pre-Tax Income	($2.6)	($2.6)	($2.2)	($6.4)	($8.1)	($19.3)	($33.9)	($44.7)	($54.2)
Income Tax exp (benefit)	($5.4)	($1.8)	$0.0	$0.0	$0.0	($1.8)	$0.0	$0.0	$0.0
Tax Rate	207.2%	0.0%	0.0%	0.0%	0.0%	9.3%	0.0%	0.0%	0.0%
Net Income	$2.8	($0.8)	($2.2)	($6.4)	($8.1)	($17.5)	($33.9)	($44.7)	($54.2)
YOY Growth	-105.1%	-119.4%	-80.7%	-157.7%	788.2%	-722.1%	93.7%	-31.9%	-21.3%
Net Margin	-	-	-	-	-	-	-	-	-
EPS	$0.04	($0.01)	($0.03)	($0.09)	($0.12)	($0.26)	($0.44)	($0.50)	($0.57)
YOY Growth	-103.1%	-121.5%	-84.0%	-153.9%	640.7%	-694.4%	70.3%	15.2%	12.8%
Diluted Shares O/S	65.0	65.2	68.9	69.0	69.2	68.1	77.4	88.6	95.2

Brian Marckx,

CFA

LEADERSHIP

Management –

Fabian Tenenbaum
Chief Executive Officer
Mr. Tenenbaum serves as our Chief Executive Officer. Previously, Mr. Tenenbaum served as our Chief Financial Officer and Chief Business Officer. Prior to joining Bellerophon, Mr. Tenenbaum served as Chief Financial Officer and Chief Business Officer of Anterios, Inc., a clinical-stage biopharmaceutical company, from 2014 to 2016. Prior to that, Mr. Tenenbaum served as Chief Executive Officer with Syneron Beauty from 2011 to 2014, and Chief Financial Officer and Executive Vice President of Syneron Medical from 2007 to 2011. Prior to Syneron Medical, Mr. Tenenbaum was Vice President Americas for Radiancy, Inc., from 2002 to 2006, and Director, Commercial Operations and Corporate Development at Sunlight Medical, Inc. from 1999 to 2002. Mr. Tenenbaum holds a Bachelor in Medicine (B.Md.) from Ben Gurion University, Israel and an MBA from Columbia Business School.

Hunter Gillies, M.D.
Acting Chief Medical Officer
Hunter Gillies, M.D. joined us as our Acting Chief Medical Office in October 2018. Prior to joining us, Dr. Gillies spent more than 20 years in the pharmaceutical and biotech industry working on early and late phase clinical drug development. Having spent time training in nephrology, he left the NHS in the U.K and joined Pfizer in 1998 where he worked on the PDE5 inhibitor programs supporting the development of sildenafil and back up compounds in both cardiovascular and pulmonary vascular disease indications. In 2010 he joined Gilead Sciences where he led the pulmonary vascular disease program. In 2016 he became an independent consultant to several small biotech start-ups working predominantly in early development across diverse therapeutic areas. Dr. Gillies is trained in internal medicine, exercise physiology and sport medicine.

Peter Fernandes
Chief Regulatory and Safety Officer
Peter Fernandes has been our Chief Regulatory and Safety Officer since May 2015. Prior to joining Bellerophon, Mr. Fernandes was Vice President of Global Regulatory Affairs at Ikaria Inc., from October 2012 to May 2015, and in this capacity also led Bellerophon's regulatory group since its inception in February of 2014. Previously, he led Regulatory Affairs and Quality Assurance for OptiNose, Inc., was Vice President US Drug Regulatory Affairs Respiratory and US DRA Respiratory Franchise Head for Novartis Pharmaceuticals. 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.
Peter 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.

Assaf Korner
Chief Financial Officer
Assaf Korner joined us as our Chief Financial Officer and Principal Financial Officer in January 2018. Prior to joining Bellerophon, Mr. Korner served as the Chief Financial Officer of L&R Distributors, since February 2016. Prior to that, Mr. Korner served as the Chief Financial Officer of Iluminage Beauty, a medical device Joint Venture between Unilever and Syneron Medical, from 2011 through January 2016. Prior to Iluminage, Mr. Korner held several senior finance roles in Syneron Medical from 2005 through 2011. Prior to Syneron Medical, Mr. Korner served as a Senior Auditor at KPMG.
Mr. Korner holds an MBA from Tel-Aviv University, Israel, a Bachelor's degree in Accounting and Economics from Haifa University, Israel and is a Certified Public Accountant.

Parag Shah, Ph.D.
Vice President, Business Operations
Parag Shah, Ph.D. has served as our Vice President, Business Operations since April 2016 with responsibilities for Project Management, Supply Distribution, Pre-Clinical and Business Development activities. Prior to joining Bellerophon, Dr. Shah was Senior Director of Pharmaceutical Science at Ikaria, where he was responsible for leading Pharmaceutical Development and Clinical Supply Management. Previously he 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 received his Bachelor's degree from Carnegie Mellon and his Ph.D. in Chemical Engineering from The University of Texas at Austin.

Martin Dekker
Vice President, Engineering and Manufacturing
Martin Dekker has served as our Vice President, Engineering and Manufacturing since January 2015. Prior to joining us, Mr. Dekker held several positions at Spacelabs Healthcare, a company that develops and manufacturers 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

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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.

Amy Edmonds
Vice President, Clinical Operations and Administration
Amy Edmonds has served as our Vice President of Clinical Operations and Administration since September 2015 with responsibilities for Clinical Operations, Contracts & Outsourcing, Human Resources and Information Technology. Ms. Edmonds has over twenty years of global Clinical Operations and Training experience. Prior to Bellerophon, Ms. Edmonds was responsible for Ikaria's Clinical Operations and Contracts & Outsourcing departments and held several positions of increasing responsibility at Celgene from November 2002 through October 2012. During her time at Celgene, Ms. Edmonds served as Global Clinical Operations Lead for the Americas for multiple therapeutic programs, the Head of North America Monitoring, and the Head of Clinical Operations Training. Ms. Edmonds has also worked in Clinical Operations and Training for Pfizer, Knoll Pharmaceuticals and ICON Clinical Research.
Ms. Edmonds holds a Bachelor's degree from the University of Richmond.

Board of Directors –

Jonathan Peacock
Chairman
Jonathan Peacock serves as the Chairman of our Board of Directors. Previously, Mr. Peacock served as both President and Chief Executive Officer as well as Chairman of our Board of Directors. Prior to joining us, Mr. Peacock served as the Chief Financial Officer of Amgen from August 2010 to January 2014. From 2005 to 2010, he served as Chief Financial and Administrative Officer of Novartis Pharmaceuticals AG, the Pharmaceutical and Biotechnology Division of Novartis AG. Mr. Peacock was also a partner at McKinsey and Co, the strategy consulting firm from 1998 to 2005 and a partner at Price Waterhouse from 1993 to 1998.
Mr. Peacock received an M.A. degree in economics from the University of St. Andrews.

Fabian Tenenbaum
(bio above)

Naseem Amin, M.D.
Director
Naseem Amin has broad industry experience in the Biotech and Medical Device industry and 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.

Matthew M. Bennett
Director
Matthew M. Bennett serves as a Managing Director of New Mountain Capital, LLC (NMC), which he joined in 2007. In addition to working closely with other NMC companies, Mr. Bennett also serves on the board of directors of CIOX Health, Gelest, Cytel and Alteon Health. Mr. Bennett previously served as Chief Executive Officer of CIOX Health and prior to that, was Executive Vice President, Global Medical Operations and Chief Legal Officer for Ikaria, Inc., where he served in additional executive roles as well, including Chief Financial Officer and head of Corporate Development. Prior to joining Ikaria, Mr. Bennett served as Executive Vice President, Chief Administrative Officer, and Chief Business Officer at VIASYS Healthcare, Inc. (NYSE: VAS), where he was responsible for the company's growth and mergers and acquisitions. Prior to VIASYS, Mr. Bennett served as an advisor on mergers and acquisitions, initial public offerings and commercial transactions in the healthcare segment at Morgan, Lewis & Bockius LLP, and as a litigator in the healthcare area at Stradley, Ronon, Stevens & Young. Mr. Bennett holds an A.B. in Political Science from Princeton University and a J.D. from Villanova University School of Law.

Scott P. Bruder, M.D., Ph.D.
Director
Scott Bruder currently leads Bruder Consulting International 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. He is also an adjunct Professor of Biomedical Engineering at Case Western Reserve University, where he previously served as an adjunct faculty member in the Department of Orthopaedic Surgery for thirteen years. Dr Bruder currently serves as the Chairman of the Board of Directors of Amendia, a privately held, leading provider of innovative medical devices used during spinal surgery procedures. Dr Bruder served as the Chief Medical and Scientific Officer of Stryker Corporation from 2012 until 2014, and was the Chief Scientific 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.

Mary Ann Cloyd
Director
Mary Ann Cloyd was a Senior Partner with PricewaterhouseCoopers (PwC) with responsibility for leading PwC's Center for Board Governance at the time of her retirement in 2015. Ms. Cloyd has over 39 years of public accounting experience serving multinational corporate clients in a variety of industries including biotechnology and pharmaceuticals. Ms. Cloyd has served on both PwC's Global and US Boards, where she chaired the Risk Management, Ethics & Compliance Committee and the Partner Admissions Committee on the US Board. On the Global Board, she served on the Risk and Operations Committee and the Clients Committee. Ms. Cloyd is on the Board of Trustees of the PricewaterhouseCoopers Charitable Foundation, Inc. and a past President of the Foundation, and she is Chair of the UCLA Iris Cantor Women's Center Advisory Board. Ms. Cloyd graduated Summa Cum Laude from Baylor University with a Bachelor of Business Administration.

Andre V. Moura
Director
Andre V. Moura is a Director at New Mountain Capital. Prior to joining New Mountain Capital in 2005, Mr. Moura was employed by McKinsey & Company. Mr. Moura also serves on the board of directors of three privately held companies. Mr. Moura received an A.B. in computer science from Harvard College and an M.B.A. from Harvard Business School.

Crispin Teufel
Director
Crispin Teufel has served as the Chief Executive Officer of Lincare Holdings Inc., the leading national provider of respiratory services in the home, since 2017 and as its Chief Financial Officer since 2013. Previously, he served as Finance Director for Linde Engineering in Germany from 2011-2013. Prior to joining Linde, Mr. Teufel held various financial positions at PWC and Arthur Andersen. Mr. Teufel serves on the board of directors of the German-American Chamber of Commerce and served on the IFRS Committee of the Accounting Standards Committee of Germany from 2011-2013. 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.

Dr. Ted Wang
Director
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 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.

HISTORICAL STOCK PRICE



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I, Brian Marckx, CFA, hereby certify that the view expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the recommendations or views expressed in this research report. I believe the information used for the creation of this report has been obtained from sources I considered to be reliable, but I can neither guarantee nor represent the completeness or accuracy of the information herewith. Such information and the opinions expressed are subject to change without notice.

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