Zacks Small-Cap Research

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Pulmatrix Inc (PULM-NASDAQ)

PULM: Pulmatrix Broadens Its Pulmonary Portfolio With Addition of In-Licensed Janssen Compound for COPD

Based on our 10-year DCF model that uses a 15% discount rate, our current valuation of PULM is $182 million. We believe the shares are fairly valued at $7.50. Our assumptions and financial model will be updated based on relevant news.

Current Price (08/03/17)	$1.97
Valuation	**$7.50**

OUTLOOK

Lexington, MA-based Pulmatrix is an emerging specialty pharmaceutical company focused on the development and commercialization of drugs delivered by inhalation for the treatment of unmet needs in severe respiratory diseases. Leveraging the company's novel iSPERSE™ inhaled dry powder technology, the Pulmatrix pipeline is focused on clinical stage development of PUR1800 as a novel anti-inflammatory for treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD), PUR1900 for cystic fibrosis (CF) and severe asthma and PUR0200 for COPD. Pulmatrix has built a formidable IP portfolio which covers the platform technology and product pipeline into the 2030s.

SUMMARY DATA

52-Week High	**$5.10**
52-Week Low	**$0.55**
One-Year Return (%)	**-3.43**
Beta	**1.85**
Average Daily Volume (sh)	**143,810**
Shares Outstanding (mil)	**19**
Market Capitalization ($mil)	**$38**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**23**
Insider Ownership (%)	**37**
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 2017 Estimate	**-1.4**
P/E using 2018 Estimate	**-1.8**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**Small-Blend**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	$0 A	$0 A	$0 A	$0 A	$0 A
2017	$0 A	$0 E	$0 E	$0 E	$0 E
2018					$0 E
2019					$0 E

Price/Sales Ratio (Industry = 2.5x)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	-$0.38 A	-$0.62 A	-$0.21 A	-0.87A	-$1.88 A
2017	-$0.21 A	-$0.30 E	-$0.40 E	-0.50 E	-$1.40 E
2018					-$1.20 E
2019					-$1.10 E

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WHAT'S NEW

PULM: Pulmatrix Broadens Its Pulmonary Portfolio With Addition of In-Licensed Janssen Compound for COPD

On June 13, 2017, Pulmatrix announced the addition of a portfolio of novel inhaled narrow spectrum kinase inhibitor (NSKI) anti-inflammatories (PUR1800 and PUR5700) from RespiVert, a wholly owned subsidiary of Janssen Biotech, Inc. Terms of the licensing agreement remain undisclosed. The addition of PUR1800 and PUR5700 will expand the company's pulmonary franchise to include treatments for COPD, IPF and asthma.

Background Indication: COPD

Respiratory diseases affect roughly 300 million people globally and COPD was the 3rd leading cause of death in the U.S. in 2014[1]. The incidence of COPD is higher in people who smoke and in places where people are exposed to noxious respiratory particles in the atmosphere. The direct and indirect healthcare costs in COPD are primarily related to treating exacerbations which reach $50 billion annually in the US alone[1]. Further, the costs to treat an individual patient rise dramatically with the increasing frequency of exacerbations that accompany COPD progression. Since hospital re-admissions for COPD exacerbations are common and cost intensive, healthcare strategies focus on optimal therapeutic strategies to prevent and/or limit the severity of exacerbations.

Hallmarks of COPD include airway obstruction and inflammation. Inflammation in COPD is generally steroid resistant due to the activation of multiple inflammatory pathways, many of which are driven by infection with viruses or bacteria. The inflammatory response may increase the frequency and/or intensity of exacerbations which may play a role in COPD progression. Further, individuals with a propensity for frequent exacerbations are more prone to a rapid decline in respiratory function.

As per the 2017 GOLD guidelines, COPD treatment commences with LAMA therapy (in group C) and treatment is escalated to ICS plus LABA therapy as necessary. Similarly, initiating therapy on both bronchodilators for symptom control before adding an ICS is recommended by the available data. Since the pathophysiology of COPD is complex, there is a pressing need for the development of new therapies for COPD particularly, as no existing treatment has shown reduction in disease progression.

GOLD also offers clear guidelines for managing disease to prevent or reduce the severity of acute exacerbations of COPD (AECOPD). The 2017 GOLD guidelines outline treatment algorithms for the treatment of AECOPD at the time of an exacerbation with the goal of limiting losses in lung function and managing patients back to a stable state. AECOPD treatment commences with increased dose and / or frequency of short acting bronchodilators (*e.g.* SABA and/or SAMA) followed by use of oral corticosteroids in events that are considered moderate or severe. Antibiotics are used if there is evidence of bacterial infection.

Despite well defined diagnosis and treatment guidelines, there is significant unmet need in COPD indicated by morbidity/mortality data and cost to the healthcare system. Specifically, while oral steroids represent the current standard of care for treating inflammation associated with AECOPD, oral steroids are effective in only a fraction of AECOPD (*i.e*. eosinophilic) with limited

efficacy in treating AECOPD caused by viral and bacterial infection. Therefore, there is a significant unmet need for non-steroidal approaches to managing inflammation in COPD patients.

Narrow Spectrum Kinase Inhibitors

Structural and inflammatory cells are activated in COPD lungs via many different kinases. One hypothesis for the lower suppression of inflammation in COPD is reduced levels of a histone deacetylase enzyme[2] (HDAC2). The reduction in HDAC2 is postulated to result from the activation of phosphoinositide-3-kinase δ[3]. The development of kinase blockers along multiple signal transduction pathways is a promising approach for potential new anti-inflammatory treatments.

Studies have shown kinase inhibitors to be useful in the treatment of inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel diseases. With inflammatory disease being a significant problem in the lung, kinase inhibitors are also being investigated as a potential new drug class for COPD[4] which target the chronic inflammatory process[5,6]. Kinase inhibitors have not yet been approved for clinical use in asthma and COPD and have not yet reached Phase 3 studies.

Since kinases are found in many different types of cells in the body, it poses a limitation to administering kinase inhibitors orally due to concerns with systemic side effects. There have been considerable challenges in developing the kinase inhibitors as most inhibitors target the TP-binding site instead of the catalytic site which is well conserved between them. This implies that the kinase inhibitors are often poorly selective and have an impact on other off-target sites which increases the risk of adverse events. Therefore, a work around to this challenge is to develop narrow spectrum kinase inhibitors that are inhaled rather than orally administered to the lungs. This should result in a large reduction in systemic exposure, while delivering an effective amount of the drug to the primary site of inflammation.

In order to achieve this targeted goal, the ideal candidate drug will have high potency and low oral bioavailability. In addition, inhaled delivery provides the opportunity to enhance kinase inhibition in the lung while reducing unwanted systemic effects of systemic kinase inhibition.

Many different kinases have been found to be activated in COPD: p38 MAP kinases, JAK kinases, Src kinases and Syk kinases. Previous studies have shown that NSKIs restore steroid sensitivity through inhibition of p38 MAP kinases (p38MAPK). They also prevent viruses and bacteria from stimulating p38MAPK to drive inflammation and mucus hypersecretion, which directly lead to exacerbations in COPD patients and block growth factor mediated activation of primary lung fibroblasts.

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[1] http://www.cdc.gov/nchs/hus/

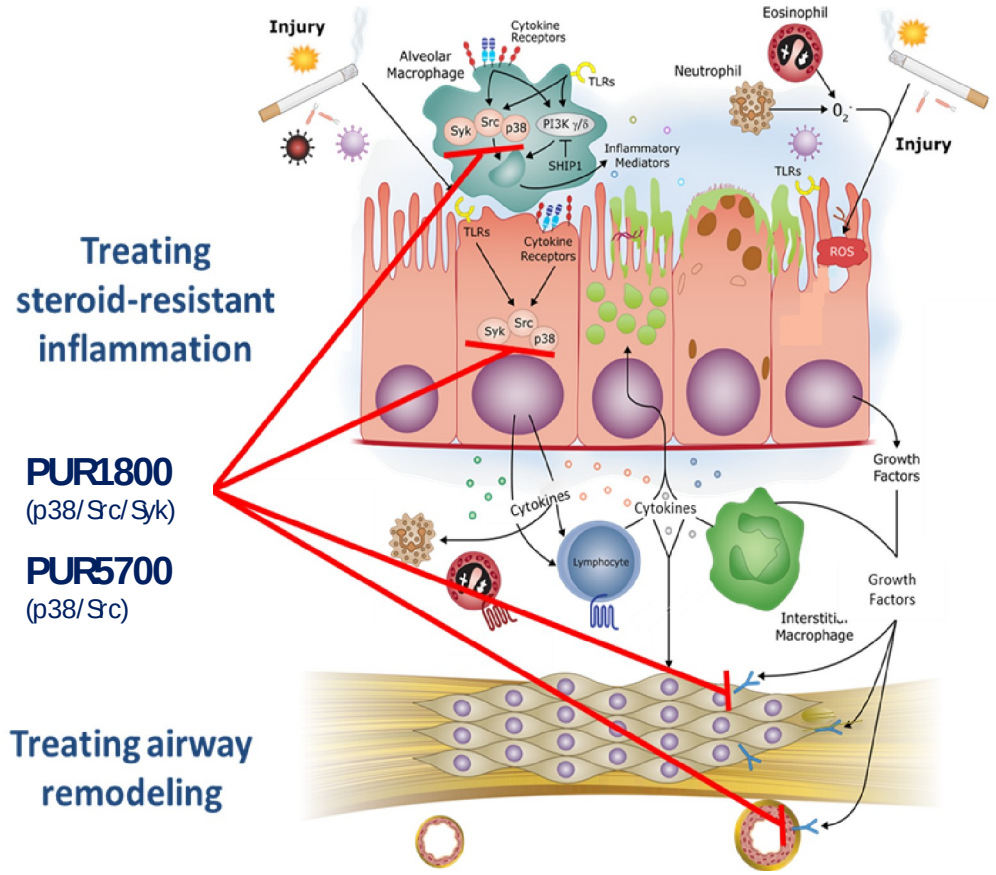
[2] Clinicoecon Outcomes Res. 2013; 5: 235–245.

[3] Clin Chest Med. 2014 Mar;35(1):219-39

[4] J Med Chem. 2016 Mar 10;59(5):1727-46

[5] Arch Bronconeumol. 2015 Aug;51(8):403-16

[6] J Pharmacol Exp Ther. 2007 Apr;321(1):1-8



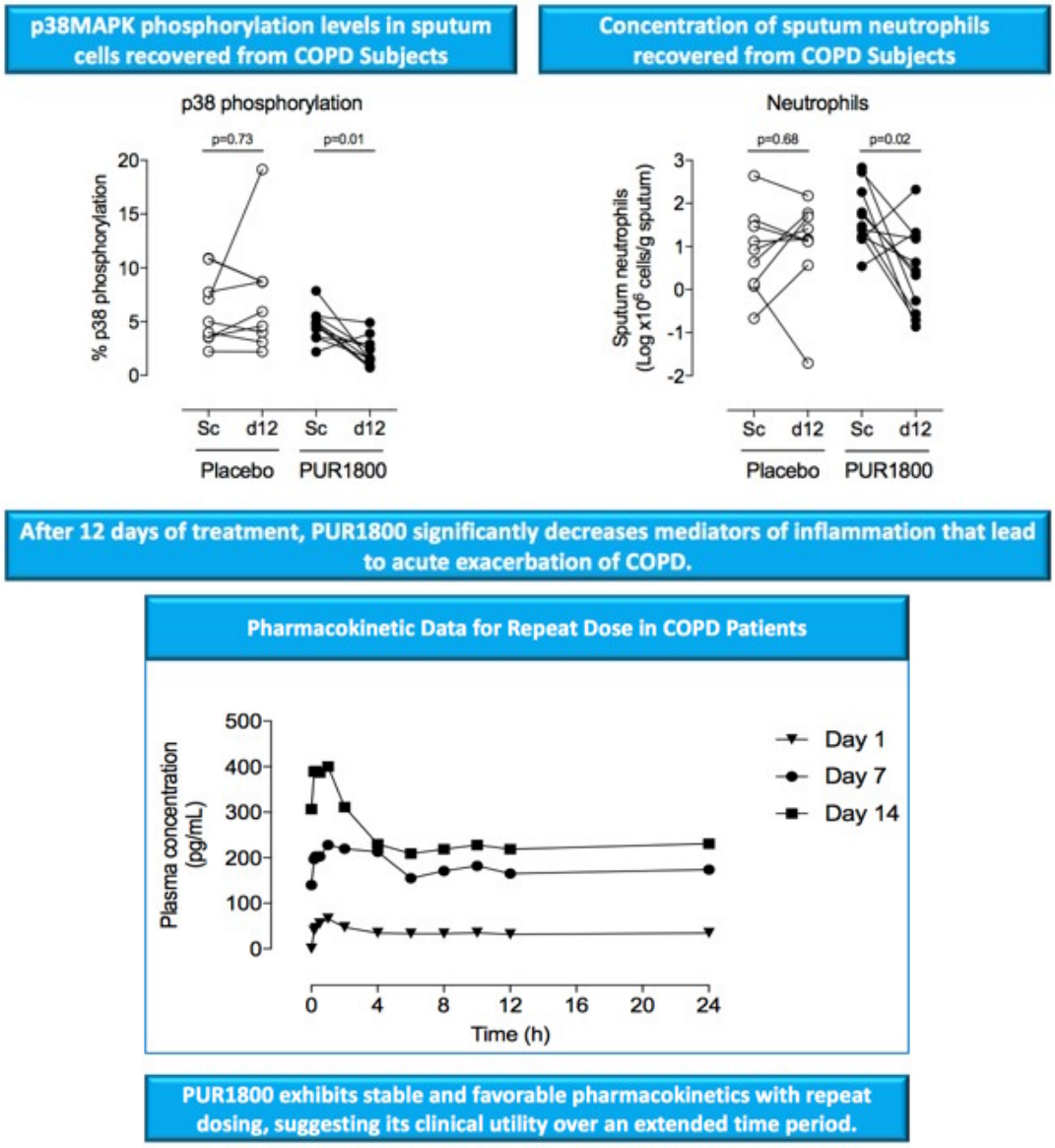
(Source: www.pulmatrix.com)

PUR1800 Program: Inhaled NSKI for AECOPD

PUR1800 inhibits steroid resistant inflammatory processes induced by a variety of stimuli including cytokines, pathogens and free radical stressors such as cigarette smoke. PUR1800 would be the first known triple kinase inhibitor. Unlike oral steroids, PUR1800 impacts P38, Src and Syk kinase and is hypothesized to provide anti-inflammatory effect in eosinophilic, bacterial and viral induced AECOPD.

Clinical Development

Study #1: A double-blind placebo controlled study was conducted to investigate the safety and tolerability of single and repeat inhaled doses of PUR1800 in healthy subjects and subjects with moderate to severe COPD (GOLD II/III). Systemic PK exposure and the effects of repeat inhaled doses of PUR1800 on markers of inflammation in sputum from COPD subjects were also evaluated in healthy and COPD subjects. Seventy-eight subjects (38 healthy and 40 with COPD) were recruited at a single investigator site in the UK. PUR1800 was delivered via a DPI at doses of 100µg and 500µg for 14 days. PK was measured on Days 1, 7 and 14.



(Source: *ClinicalTrials.gov NCT01970618*)

Results: PUR1800 was found to be well tolerated in heathy subjects and in those with moderate to severe COPD. The drug demonstrated low, dose proportional systemic exposure. PUR1800 demonstrated target engagement after dosing COPD subjects with 500µg for 14 days. COPD subjects dosed with 500µg had a reduction in phosphorylated p38 (p-p38) levels in sputum cells (p=0.01) and had a reduction in sputum neutrophil numbers on Day 12 compared to baseline (p=0.02). Total sputum cell (p=0.02) & sputum macrophage (p=0.04) numbers also decreased (data not shown). Subjects dosed with 100µg had a trend towards a reduction in p38 phosphorylation (p = 0.084). COPD subjects dosed with 100µg also demonstrated statistically significant changes in MMP12 (p=0.001), IL-13 (p=0.02), MCP1 (p=0.03) and MDA (p=0.04) in sputum supernatant (data not shown). No difference between PUR1800 and placebo treated patients was observed on spirometry or plethysmography measures. No deaths or serious adverse events (SAEs) were reported.

PUR1800 Therapeutic Development

The initial trial showed that PUR1800 can reduce the inflammatory burden in COPD patients completed using a lactose blend dry powder of the molecule in PUR1800. PUR1800 is being reformulated using the iSPERSE technology and is targeted for a 14-day Phase IIA study in COPD patients with similar end points to the trial completed by Janssen/Respivert that is anticipated in 2H 2018. Demonstration of target engagement and measure of anti-inflammatory biomarkers will be the primary readouts in the study along with safety and tolerability.

Based on the results from this Phase IIA trial, Pulmatrix plans to move directly into a Phase IIB Proof-of-Concept trial in COPD patients. This subsequent trial could address the impact of PUR1800 as a possible treatment of acute exacerbations of COPD (AECOPD) as well as inform the potential of the agent to prevent exacerbations of COPD. Subsequent trials could also address the impact of this treatment when used acutely at the time of an AECOPD in conjunction with the standard of care to determine if this treatment will be effective across all AECOPD phenotypes. As part of future development consideration, PUR1800 could also be evaluated in a prevention of exacerbation paradigm in longer term trials.

p38 MAP kinase inhibitors in development

These molecules have mainly focused on p38 inhibition. Mereo Biopharma, a clinical stage, UK-based, biopharmaceutical company is developing Acumapimod, an orally active compound for AECOPD as a first line of therapy. Previous studies undertaken by Novartis showed that acumapimod demonstrated a statistically significant reduction of the inflammatory marker TNFα and a clinically meaningful increase in forced expiratory volume in one second (FEV1), a clinically relevant endpoint in the treatment of COPD. In studies to date, acumapimod has been shown to be safe and well tolerated in the target patient population. Top-line data from a double-blind, placebo-controlled Phase 2 dose-ranging study of acumapimod is expected in the second half of 2017.

Glaxo Smith Kline's GW856553, or losmapimod, was tested in a 12-week randomized double-blind study in COPD patients. An oral dose of losmapimod, 7.5mg b.i.d., was compared with an inhaled corticosteroid (ICS)-LABA dry powder (Advair ®) or placebo. The primary endpoint, sputum neutrophils, was not reduced by either active treatment. However, plasma fibrinogen was modestly, but statistically reduced in the losmapimod arm. However, in January 2016, GSK pulled the plug on another Phase 3 trial with losmapimod for acute myocardial infarction (heart attack) after disappointing trial results.

Pfizer's once daily oral agent PH-797804 was tested in a 6-week dose-ranging study in COPD patients. Each of several doses resulted in improvements of trough FEV1 that were statistically significant and around 75 ml better than placebo. There were also meaningful improvements in dyspnea index, a modest decrease in the use of rescue medication and reductions in high sensitivity C-reactive protein. However, levels of clara cell secretory protein CC16, IL-6, surfactant protein-D and fibrinogen were unchanged. Although some nausea and headaches were seen, other adverse events were not a problem. Pfizer subsequently discontinued this program.

The above candidates are all oral inhibitors as compared to PULM's inhaled drug candidate, and in most cases development is focused on the long term chronic use of these compounds to prevent exacerbations. PUR1800 is different in terms of the triple kinase inhibition profile and

since inhaled pharmacologic therapy is the cornerstone of COPD treatment, these patients may especially benefit from the use of Pulmatrix's drug candidate

IPF

Indication: Idiopathic Pulmonary Fibrosis (IPF) is a progressive and fatal disease (the cause of which is unknown) that scars the lungs thereby causing an irreversible loss of the ability of the lung tissue to transport oxygen.

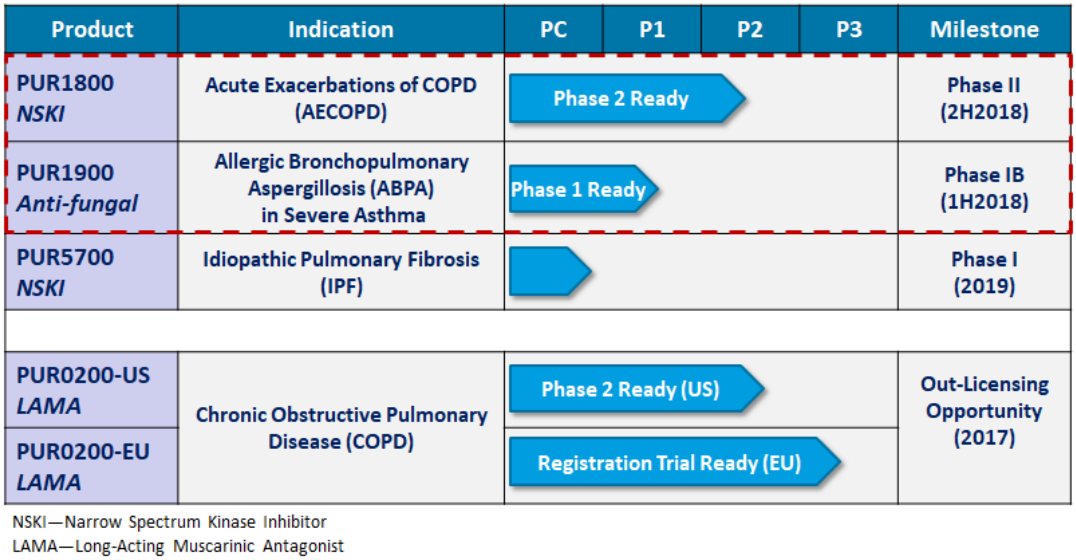
Current Treatment Options: Two recently approved drugs, Ofev (nintedanib) and Esbriet (pirfenidone) offer therapeutic options for IPF patients in the U.S. Both Ofev and Esbriet are oral therapies and commonly cause gastrointestinal side effects that could be severe depending on the patient. Pharmaceutical giants such as Bristol-Myers Squibb (BMY) and Biogen (BIIB) are developing oral and injectable therapies for IPF that are in Phase 2 clinical trials.

Market Potential: IPF kills about 40,000 people in the U.S. annually. It is estimated that over 200,000 people in the U.S. and EU suffer from IPF[7, 8], which represents a viable commercial market and offers the potential for orphan drug status. Given the underserved market, the potential for the currently marketed products is expected to be in the billions of dollars annually. With the limitations of the currently approved oral therapies, innovative inhalation approaches to IPF treatment such as that offered with Pulmatrix's iSPERSE technology could have the opportunity to capture significant share of the market.

PUR5700, an inhaled NSKI is in preclinical development. While PUR5700 could also have therapeutic potential in COPD and severe Asthma, preclinical data demonstrate the potential of PUR5700 as a novel anti-inflammatory for IPF. The premise of inhalation as a better route of delivery for IPF drugs has been established in preclinical studies. Pulmatrix has evaluated use of iSPERSE in IPF and Respivert also did early pre-clinical work to evaluate PUR5700 in IPF as well. Pulmatrix is confident in these leading indicators and intends to evaluate PUR5700 in iSPERSE in appropriate preclinical models of IPF as a first step in the next 12 months.

[7] https://pharmastore.informa.com/wp-content/uploads/2016/10/idiopathicpulmonaryfibrosis_12770_10-2016.pdf
[8] European Respiratory Review 2012 21: 355-361

Pulmatrix Pipeline and Development Timeline



NSKI—Narrow Spectrum Kinase Inhibitor
LAMA—Long-Acting Muscarinic Antagonist

(Source: www.pulmatrix.com)

Management seems to be taking a disciplined approach to developing the respiratory portfolio with a number of potential catalysts over the next 12-15 months. The clear priority is advancing both PUR1900 and PUR1800 into the clinic with clinical milestones in 2018.

Pulmatrix's most advanced product PUR0200 is a Spiriva® HandiHaler® branded alternative for the US and substitutable product in the EU. Following favorable guidance from two European regulatory authorities, Pulmatrix is actively engaged in out-licensing future clinical development and commercialization.

Pulmatrix also acquired PUR5700 from RespiVert (Janssen) and, while it is a pre-clinical pipeline program, it is promising given its potential in markets of asthma, COPD and IPF that are valued at over $25 billion in the aggregate. We expect Pulmatrix's focus will initially be with bringing PUR1900 and PUR1800 to market with the iSPERSE technology, with PUR5700 likely on the back-burner for now as an early stage partnering opportunity.

PUR1900 will begin Phase IB in Q1 2018. Oral Itraconazole has been studied in severe asthmatics with ABPA and demonstrated efficacy. The planned Phase IB study will be an important milestone as the company hopes to demonstrate a favorable safety, tolerability and PK profile for PUR1900, the iSPERSE reformulation of Itraconazole, in comparison to the oral form of the drug.

PUR1800 is being developed as a novel anti-inflammatory for treatment of AECOPD. In the PUR1800 Phase 2A study, the company intends to bridge the encouraging results from the Phase 1B studies run by Janssen showing effectiveness, signals of anti-inflammatory benefit, safety and tolerability. If all goes well the company is targeting a Phase 2A study in 2H 2018 with completion targeted around the end of the year. If a PUR1800 Phase 2A study confirms earlier findings and continues to demonstrate positive results, it could lead into a Phase IIB proof-of-concept trial for exacerbations in COPD patients which would be very positive for PULM.

We estimate an approximate 18 month timeline for completion of the Phase IIB follow on trial. Based on statistics and studies[9], a Phase 2 trial in the respiratory space costs on average approximately $12 million. Since the terms of the licensing agreement remain undisclosed, we model Pulmatrix to bear the development costs and think any proceeds from potential future revenue of PUR1800, are subject to tiered royalty payments (undisclosed) to RespiVert.

Valuation

With the new assets added to the portfolio, what is Pulmatrix worth today? PULM is addressing the COPD market that has a patient population of about 65 million worldwide. At least a third of these patients experience acute exacerbations once annually . Further, since COPD patients are susceptible to many insults that can rapidly snowball into an acute deterioration in lung function, this chronic disease is complex and requires aggressive and prompt intervention. Although the company's candidates are in the pulmonary space, particularly COPD, PUR0200 is a branded generic of a once-daily long-acting muscarinic antagonist (LAMA) that is a bronchodilator and PUR1800 is an NSKI that addresses inflammation in COPD. We think this unique opportunity might enable Pulmatrix to positively impact the lives of more patients globally while generating attractive returns for investors. Together the two programs position Pulmatix for sustainable long-term growth in respiratory therapeutics.

PUR1800 and PUR 1900 are in mid-stage development. We expect operating expenses to remain elevated during the coming years as a result of ongoing R&D and regulatory activities for the PUR 1800 and PUR 1900 product candidates. We expect that Pulmatrix will need sufficient capital for conducting PUR1800 Phase 2 studies as well as for initial business development. The Phase 2 trial may need to be completed before PUR1800 becomes an asset that can be partnered.

We use a Discounted Cash Flow (DCF) analysis and revised our financial model following the addition of the new assets. We have not included PUR5700 in our current valuation as this program is at a very early stage in development. Our model and assumptions will be updated based on progress in its development plan and could prompt a revision to our forecast, particularly as it relates to our out-years. We derive the total equity value of PULM to be approximately $182 million with a target price of $7.50/share, implying an upside to the current trading price.

[9] Clin Trials. 2016 Apr;13(2):117-26.

SNAPSHOT



- Pulmatrix (NASDAQ:PULM) is a Lexington, MA based clinical stage biopharmaceutical company developing innovative inhaled products to address unmet medical needs in serious pulmonary diseases. The firm has developed an engineered novel dry powder delivery platform, which is designed to improve drug delivery to the lungs and reduce systemic side effects for pulmonary medications.

- The firm's product candidates utilize their proprietary iSPERSE™ (inhaled Small Particles Easily Respirable and Emitted) technology resulting in formulations that are small, dense and easily dispersible. The iSPERSE technology allows efficient pulmonary administration of large therapeutic doses, which presents a highly compelling opportunity to effectively treat many pulmonary diseases.

- Pulmatrix's most advanced product PUR0200 is a branded generic once daily long acting muscarinic antagonist (LAMA) bronchodilator in clinical development for chronic obstructive pulmonary disease (COPD). The product is following the expedited pharmacokinetic (PK) bioequivalence (BE) path for European Union (EU) approval. The firm is also pursuing a 505(b)(2) path for US approval.

- Pulmatrix's pipeline is focused on developing treatments for respiratory diseases: PUR1900, an inhaled anti-fungal for patients with cystic fibrosis (CF) and severe asthma, and additional product opportunities for pulmonary disease facilitated by the iSPERSE technology.

- Pulmatrix recently added a portfolio of novel inhaled narrow spectrum kinase inhibitor anti-inflammatories (PUR1800 and PUR5700) from RespiVert, a wholly owned subsidiary of Janssen Biotech, Inc. PUR1800 is being developed as a novel anti-inflammatory for treatment of AECOPD. PUR5700 is a pre-clinical pipeline program and is promising given its potential in markets of asthma, COPD and IPF.

- The company was founded by Dr. Robert Langer (MIT) and Dr. David Edwards (Harvard), both of whom have a history of biotech successes including developing the AIR inhaled technology which was acquired by Alkermes and later was the basis of the Civitas acquisition by Acorda Therapeutics.

- The Pulmatrix management team is lean but agile with significant expertise in the early development of inhaled therapeutics. CSO (Chief Scientific Officer) Dave Hava and CEO (Chief Executive Officer) Robert Clarke both hold doctoral degrees and trained at Harvard, lending strong scientific leadership to the company. CBO (Chief Business Officer), Ted Raad has 20 years of life science experience leading commercial and business development functions. CFO,

Bill Duke has more than 20 years of experience in finance leadership roles, with the majority at life sciences companies including Valeritas and Genzyme.

- The board of directors, similarly steeped in life sciences expertise, provide strategic guidance, expertise, important networks and invaluable experience beyond that of the internal leadership team.

- We have dug into the professional background of Pulmatrix s team. Of the 23 employees, Pulmatrix has four people on the senior management team and sixteen employees (or ~70%) in research. Dr. Clarke has extensive experience in novel drug research and development, particularly in the area of pulmonary drug delivery and the role of particles and infection in the lung. Dr. Hava has been involved in the early stage development of the iSPERSE dry powder delivery platform. The management team is solid and Pulmatrix has expanded its internal expertise team with extensive experience in biotechnology and pharmaceuticals to pursue the development of their therapeutic platform. Specifically, Mr. Iwicki, who chairs Pulmatrix's Board, has more than 25 years of experience managing all stages of drug development and was instrumental in the success of a number of drugs, including Prilosec, Diovan, Zelnorm, Lunesta, and Latuda. He was with Civitas Pharmaceuticals in 2014 and while at Sepracor, he marketed six products that generated over $1.2 billion in annual sales. Mr. Michael Higgins, who serves on the Board and chairs Pulmatrix's Audit Committee, has overseen the advancement and commercialization of a wide range of biopharmaceuticals and has successfully transformed companies from development to commercial stage while growing and diversifying Pulmatrix s development pipeline.

- Pulmatrix has built a formidable IP portfolio which covers the platform technology and product pipeline into the 2030s.

INTRODUCTION

PULM: Breathe Easy!

Company Description

Lexington, MA-based Pulmatrix is an emerging specialty pharmaceutical company focused on the development and commercialization of drugs delivered by inhalation for the treatment of unmet needs in severe respiratory diseases. Leveraging the company's novel iSPERSE™ inhaled dry powder technology, the Pulmatrix pipeline is focused on clinical stage development of PUR0200 for chronic obstructive pulmonary disease (COPD) and PUR1900 for cystic fibrosis (CF) and severe asthma. The company is also exploring other programs where iSPERSE™ inhaled dry powder can provide efficacy or safety advantages to currently available therapies.

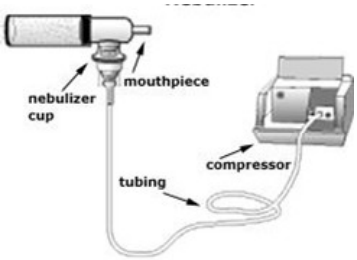
Pulmatrix has completed two clinical trials with PUR0200, a once daily bronchodilator, in support of European Union approval based on pharmacokinetic bioequivalence (PK BE) and US approval via 505(b)(2) regulations. Pulmatrix most recently completed a pilot PK BE trial in Europe. The company is progressing the program towards partnership and a pivotal PK BE clinical trial to support EU registration as a first target.

For patients with CF and severe asthma, Pulmatrix is developing an inhaled itraconazole formulation to effectively treat fungal infections. Pulmatrix is advancing the program towards a Phase I/IB trial which will include safety/tolerability and PK assessment of itraconazole in the blood and lung sputum of patients. The company expects to complete this trial in 1H 2018 and report data shortly thereafter.

iSPERSE: A Leap Forward in Inhalation Drug Delivery

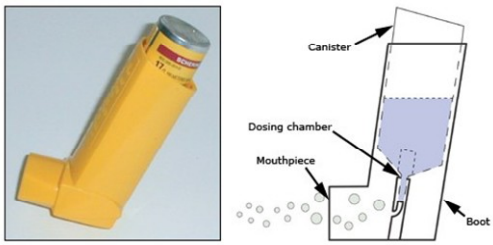
Traditionally, orally inhaled drugs have been delivered to the lung in liquid or dry powder formulations. While these approaches have been used successfully for pulmonary drug delivery, they have a number of limitations associated with patient use, drug compatibility, dose ranging, and delivery efficiency.

Nebulizer



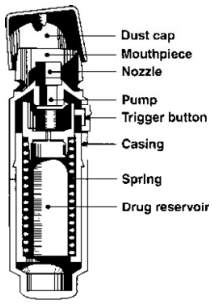
(Source: clevelandclinic.org)

pMDI



(Source: donaldmahler.com)

Soft mist Inhaler



(Source:advances-in-medicine.net)

Liquid inhaled drug products include nebulizers, pressurized metered dose inhalers (pMDIs), and soft mist inhalers. Nebulizers are low efficiency, require routine maintenance, and can be cumbersome in terms of dosing duration and portability. pMDIs and soft mist inhalers are dose limited and require coordinated actions of the patient to effectively deliver the drug.

The majority of inhaled dry powder products that have made it to market are lactose blend dry powders, which rely on a lactose carrier to deliver micronized drug into the airways. These dry powder inhalers (DPI) are limited to potent small molecule drugs that require small lung doses for efficacy. Lactose blends have limited delivery efficiency, are flow rate dependent, and can cause significant side effects based on high throat deposition (i.e. much of the drug deposited in the throat instead of the lungs). Figure 1A illustrates the limitations of lactose blend DPIs, which principally derives from the poor dissociation of the drug from the lactose carrier particles.

The Pulmatrix iSPERSE technology overcomes the limitations of traditional lactose-based DPIs. iSPERSE formulations contain no carrier and the particles are highly dispersible requiring very little inhalation energy for aerosolization. The combination of these factors translate to very high delivery efficiency and consistent delivery across a range of patient inspiratory flow rates. Figure 1B shows the improved delivery characteristics of iSPERSE formulations where in the absence of carrier particles, respirable iSPERSE particles are highly dispersible and readily deagglomerate (disperse or break up) resulting in a high fraction of drug delivered to the lungs.

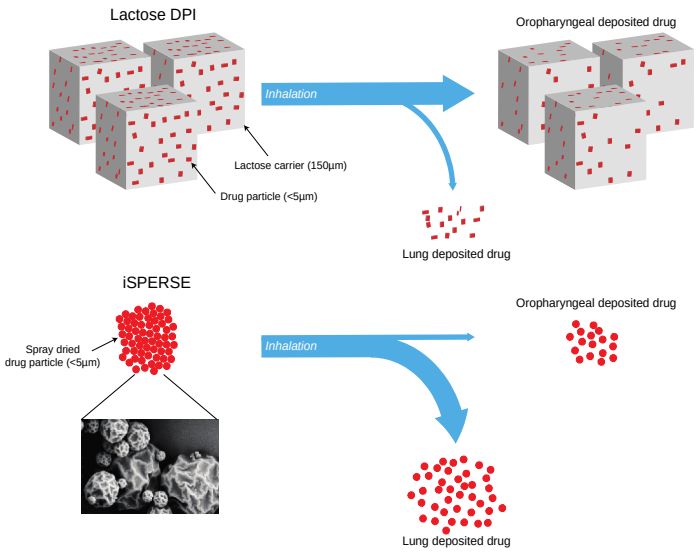


Figure 1A. Lactose-based DPIs are comprised of micronized crystalline drug particles (red) blended with lactose carrier to reduce cohesive forces between drug particles and enhance the dispersion of micronized drug. During inhalation, a small fraction of the drug dissociates from the lactose carrier and is inhaled. In contrast, iSPERSE particles are created by spray drying, a process that incorporates the drug into a dry, respirable particles that are readily dispersible and result in a high fraction of inhaled drug.
(Source: ondrugdelivery.com/publications/66/Pulmatrix.pdf)

These advantages in inhaled delivery support much higher dose thresholds than lactose blend DPIs; iSPERSE can deliver tens of milligrams of drug in a single inhalation versus microgram drug quantities for lactose blends. The particles, which are made by spray drying, can have a wide range of drug loading, with <1% to 85% of the individual particles being comprised of drug. The manufacturing process for iSPERSE also resolves issues of drug chemistry and solid state allowing for formulation of virtually any drug class ranging from highly insoluble small molecules to peptides, proteins, nucleic acids and even antibodies. The technology can also be modulated for site of delivery in the lung allowing considerations of both local and systemic therapeutic targets.

iSPERSE is manufactured via spray drying, a process where the drug is dissolved in a solution with excipients and forced through a jet nozzle to form droplets, which are then quickly dried and collected. Manipulating process conditions allows for the optimization of powder properties and performance, including aerosolization behavior and dispersibility, which potentially allows for reduction of the API dose while maintaining the amount delivered to the target site. Because the drug is formulated directly into the dried particle in a size that can be inhaled into the lungs, there is no need for additional blending or carrier particles resulting in highly efficient delivery to the lungs and an expanded range of drug classes and doses to consider (Figure 2).

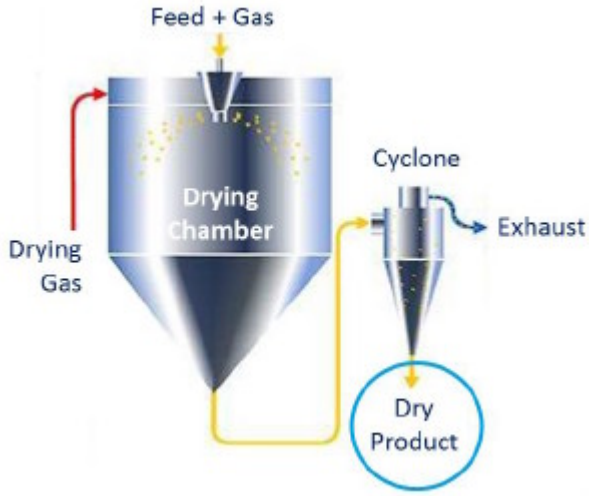


Figure 2. iSPERSE Technology
(Source: www.niro.com)

iSPERSE: A Next Generation in Inhalation Engineering

iSPERSE is not the first engineered approach to dry powder inhalation drug delivery, but is a further progression in the field. Several other particle engineering approaches have been developed in the past to overcome the limitation of lactose blend DPIs and expand the potential classes of drugs that can be stably formulated and delivered to the lung. These technologies, many of which emerged in the late 1990's and are either in late stage clinical development or have been successfully used in approved products, include Nektar PulmoSphere ™ Technology, the Acorda Therapeutics ARCUS® technology, and the Aradigm AerX® Drug Delivery System.

iSPERSE provides the same formulation and delivery advantages of these earlier technologies but in a differentiated intellectual property estate built around the density profile of the formulations. The earlier engineered dry powder technologies were built around the concept of low density, high diameter porous particles resembling microscopic whiffle balls or crumpled pieces of paper. The low density profile allowed these large, porous particles to have high aerodynamic efficiency and deliver higher drug loads than lactose blends. In contrast, the iSPERSE technology has a small particle diameter and a high density profile yet shares the same aerodynamic efficiency as the large porous particle technologies. The hallmark description of the iSPERSE technology, small, dense, and dispersible, differentiates the platform from other engineered approaches providing a robust and new intellectual property estate.

In summary, the iSPERSE technology offers several advantages over other commercially available DPIs:

- iSPERSE powders are small, dense, and dispersible providing superior delivery efficiency to the airways.

- iSPERSE dry powders have small geometric size along with good dispersibility across a wide range of flow rates. For pediatric patients or those with impaired lung function, the flow rate independence provides for reliable dose delivery.

- iSPERSE dry powders are comprised of simple and safe excipients including salts. The use of the specific salts in Pulmatrix's proprietary formulations enable efficient drug delivery achieving the delivery of high drug payloads per powder volume (up to 60-80%), enabling both large molecule (e.g., proteins, peptides) and low potency drug formulations.

- iSPERSE dry powders are made using a scalable, one-step spray drying process with high and consistent yields.

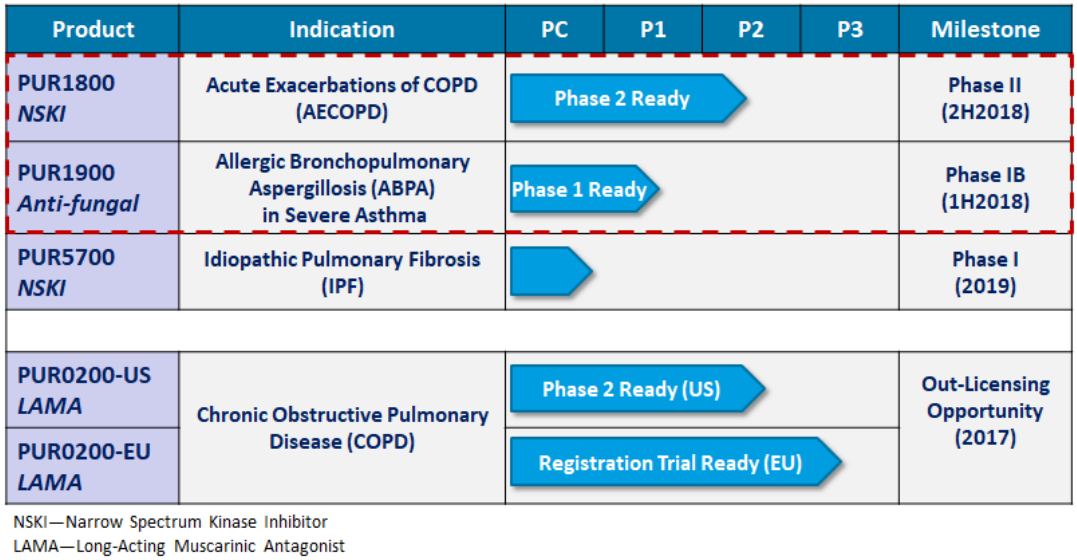
- The iSPERSE dry powders can be used along with commercially available passive capsule, reservoir, or blister-based DPI devices.

- iSPERSE offers flexible and robust formulation capabilities and manufacturing. Small and large molecule drugs as well as drug combinations (including double/triple drug combinations or higher) can be formulated and manufactured. The iSPERSE platform is suited for creating branded as well as branded generic products.

- The compositions, technology and uses related to the iSPERSE technology are protected by 64 patents.

PIPELINE PRODUCTS

Pulmatrix is building a robust pipeline around the iSPERSE platform. PUR1800 is being developed as a novel anti-inflammatory for treatment of AECOPD. PUR1900 is an orphan designated inhaled anti-fungal designed to treat pulmonary fungal infections in CF and asthmatic patients. PUR0200, a lead clinical stage once-daily bronchodilator for COPD, is under development via the Guideline on the Investigation of Bioequivalence in the European Union and the 505(b)(2) path in the U.S.



(Source: www.pulmatrix.com)

PUR0200 Program: Once Daily Inhaled LAMA Bronchodilator for COPD

Indication Background: COPD

COPD is associated with an abnormal inflammatory response of the lungs to dust, smoke, noxious particles or gases. It is a chronic condition that is accompanied by symptoms such as chronic cough, excess production of mucus in the lungs, breathlessness, reduced exercise capacity and characterized by destruction of the airways and limited airflow in the lungs. COPD is comprised of emphysema and chronic bronchitis and is considered a progressive disease. While COPD is not curable and is a major cause of serious long-term disability, treatment ameliorates symptoms and may slow progression of the disease[10]. Management of COPD focuses on reducing symptoms and reducing the risk of exacerbations of disease, and consequentially the progression of disease. Pharmacological treatments focus on the use of inhaled bronchodilators and inhaled corticosteroids as monotherapies and in combination depending on the severity of disease and risk of exacerbation. Two classes of bronchodilators, long-acting β-agonists (LABA) and long-acting muscarinic antagonists (LAMA), are the predominant first line therapies for the management of stable COPD. Although COPD has low diagnosis rates, there are efforts being made to increase awareness among patients and physicians.

[10] H.J. Thibaut et al. / Biochemical Pharmacology 83 (2012) 185 192

LAMA Market Potential: About 24 million people suffer from COPD, of which in an estimated 12 million people the disease remains undiagnosed[11]. COPD was the fourth leading cause of death in Europe and the rest of the world in 2011. The WHO estimates that COPD will be the third leading cause of death by 2020. According to IMS Health, global sales of LAMA monotherapies for COPD were close to $5 billion in 2014, including $1.5 billion outside of the U.S. As per GBI Research, the global COPD therapeutics market is expected to grow to more than $15 billion by 2020 as physician and patient awareness grow and contribute to additional diagnoses.

Spiriva HandiHaler, co-promoted by Boehringer Ingelheim and Pfizer, is the best selling LAMA monotherapy for COPD and generated close to €3.0 billion worldwide in 2016[12] with no generic competition. Spiriva has shared the bulk of the COPD market with GlaxoSmithKline's (GSK) Advair/Seretide (salmeterol and fluticasone), a LABA, for years, but sales of Advair/Seretide have recently slumped due to payer pressure, generic threats and launch of Breo, GSK's new once-daily COPD/asthma (LABA) therapy. Currently, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines state that patients with COPD who have frequent symptoms and/or at high risk for exacerbations need to be treated using LAMA as monotherapy since they have well-established safety and efficacy profiles. Despite the arrival of new combination therapeutics, market research suggests that LAMAs as monotherapy are here to stay. Spiriva HandiHaler is expected to retain the majority of share of the LAMA market and has U.S. patent protection until 2027.

Current Treatment: Treatment of COPD relies on the use of bronchodilators such as long-acting muscarinic antagonists (LAMAs) as they reduce bronchial obstruction, airflow limitation, hyperinflation, and improve exercise performance. Most guidelines state that inhaled bronchodilators are the primary medication for all stages of COPD. LAMAs appear to be more effective than long-acting β-agonists (LABAs) if COPD exacerbations need to be treated[13]. LAMAs such as tiotropium, glycopyrronium and umeclidinium cause bronchodilation and are used once daily. Globally, tiotropium is the most frequently used LAMA[14].

Tiotropium bromide is available in two dosage formats both marketed by Boehringer Ingelheim: The Spiriva HandiHaler lactose blend dry powder inhaler (18 μg tiotropium) and the Spiriva Respimat softmist inhaler (5 μg tiotropium). Spiriva HandiHaler is typically prescribed about three to one over the Respimat. Spiriva capsules contain 18 μg tiotropium blended with lactose monohydrate. Spiriva HandiHaler's labeling reads that it "…is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema and for reducing COPD exacerbations…". Spiriva HandiHaler has side effects including sore throat, cough, dry mouth, infections in the respiratory tract and sinuses.

In August 2016, TEVA launched Braltus (tiotropium bromide) in Europe. Braltus uses the new Zonda inhaler to deliver the same dose of tiotropium as Spiriva HandiHaler for patients with COPD. Zonda is a breath-actuated, capsule-based inhaler and Braltus (dry powder formulation) is bioequivalent to Spiriva. Both inhalers are similar in style and technique and have shown similar benefits in improving lung function and relieving symptoms in COPD patients. Braltus provides the same 10 microgram delivered dose of tiotropium as the Spiriva HandiHaler. The Braltus Zonda is not licensed for children and adolescents.

Pulmatrix's Drug Candidate: PUR0200 is a once-daily, inhalable iSPERSE reformulation of tiotropium bromide for COPD patients. PUR0200 is under development as a substitutable

[11] https://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=77
[12] http://annualreport.boehringer-ingelheim.com/fileadmin/pdf/bi_annual_report_2016_en_gesamt.pdf
[13] Long-acting bronchodilators in COPD: where are we now and where are we going? Mario Cazzola, Clive Page, Breathe 2014 10: 110-120
[14] Spina, Domenico. "Pharmacology of novel treatments for COPD: are fixed dose combination LABA/LAMA synergistic?." *European Clinical Respiratory Journal* [Online], 2 (2015):

product for Spiriva HandiHaler in the European Union (EU) and as a branded alternative to Spiriva HandiHaler in the U.S.

EU Development

For EU development, Pulmatrix is following the 2010 European Medicines Agency (EMA) guidelines on PK BE for orally inhaled drugs. In general, there are considerable challenges in replicating a fixed-dose therapy and the associated delivery device. An effective and easy-to-use delivery device is crucial for COPD patients to ensure that the appropriate dose of medicine is delivered to the lungs. EMA's regulatory guidance states that demonstrating single dose PK BE to the reference product is sufficient for product registration. This reduces development timelines and complexity allowing Pulmatrix to leverage the established safety and efficacy studies conducted for the branded drug that has already received approval. As part of ongoing development, Pulmatrix is seeking scientific advice regarding the PK BE guidance from EU regulatory agencies to assist in finalizing plans for an upcoming pivotal PK BE study.

Pulmatrix uses a commercially available capsule based inhaler offered by an Italian manufacturer, Plastiape. The RS01 inhaler (Figure 3; below) is a simple, easy to use device that is familiar to patients and physicians with similar directions-for-use to Spiriva HandiHaler. This device has been used in PULM's clinical trials thus far.

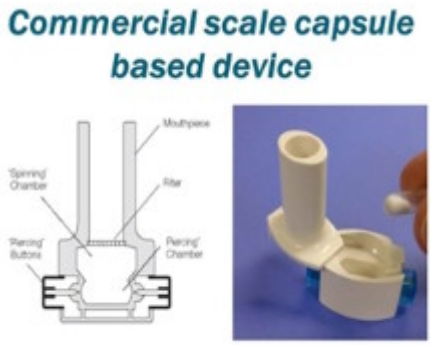


Figure 3.
(Source: www.pulmatrix.com)

US Development

In the U.S., there is no FDA guidance regarding the requirements for the development of a generic tiotropium product. Pulmatrix is building a strategy focused 505(b)(2) development plan and will seek FDA guidance via a pre-IND meeting in mid-2017. The pre-clinical and clinical studies described in more detail below provide supportive data for the U.S. development path. As part of the 505(b)(2) pathway and the conduct of longer duration clinical studies, Pulmatrix plans to evaluate differentiating factors between PUR0200 and Spiriva HandiHaler such as the potential for lower efficacious doses and a differentiated device.

PUR0200 Pre-Clinical Development

Spiriva HandiHaler is a lactose blend dry powder inhaler. As described above, one of the hallmark advantages of iSPERSE over lactose blend formulations is increased delivery efficiency and the avoidance of drug deposition in the throat. Figure 4 (below) captures that specific advantage for PUR0200 formulation compared to Spiriva HandiHaler. In the in vitro study shown, the mass of tiotropium bromide retained in the device and capsule of the drug product or depositing in the throat of a cascade impactor was compared between PUR0200 (blue lines) and Spiriva HandiHaler (red lines). Spiriva HandiHaler (18 µg dose) is highly inefficient, with a high

percentage of the drug left behind in the capsule and device or depositing in the throat resulting in only a small fine particle fraction (FPF) that would actually reach the lungs. In contrast, in the PUR0200 drug product (6 µg dose) the drug losses associated with device and capsule retention and impaction in the throat are significantly reduced, resulting in a high FPF. Due to these differences, PUR0200 may achieve similar lung deposition, exposure and lung function improvements as Spiriva HandiHaler at much lower nominal doses.

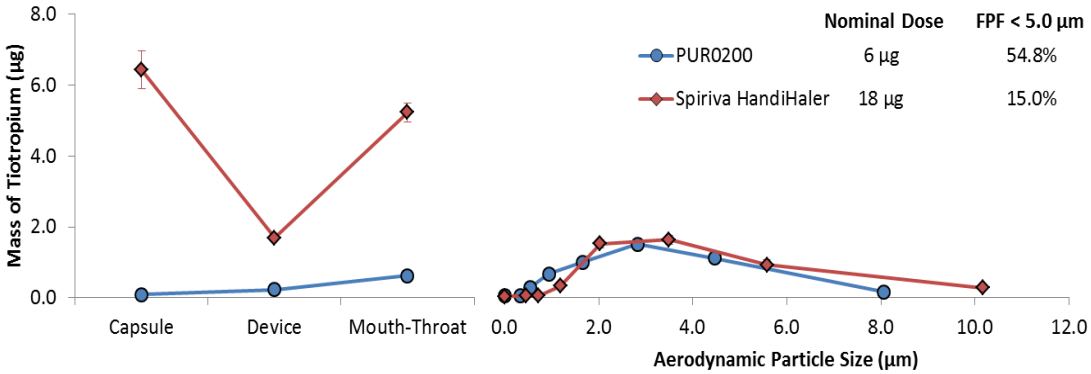


Figure 4. In vitro comparison of PUR0200 and Spiriva HandiHaler. Aerosol characteristics of PUR0200 and Spiriva HH were measured by cascade impaction using analytical next generation impactor (NGI) assays.0
(Source: ERS Poster Presentation, 2015)

PUR0200 Clinical Development

PUR0200 Trials for PK BE: Pulmatrix has completed two Phase 1 clinical trials of PUR0200 in support of PUR0200 bioequivalence to Spiriva HandiHaler. Bioequivalence is achieved when the plasma concentrations (C_{max} and AUC_{0-t}) of the drug after administration of the test formulation (PUR0200) are equivalent to the plasma concentrations after administration of the reference product (Spiriva HandiHaler). The completed clinical trials focused on identifying the necessary PUR0200 strength and aerosol properties to define a formulation that will achieve bioequivalence in a pivotal PK study.

In December 2013, Pulmatrix completed a two-part Phase 1b dose ranging clinical trial involving moderate-to-severe COPD patients to assess the safety and tolerability of PUR0200 along with the PD and PK in a single dose study. A second Phase I trial evaluating the single dose PK profile and safety and tolerability of five (5) PUR0200 formulations that varied in strength and aerosol particle size was completed in May 2016 in healthy normal volunteers.

- ***Study #1:***

A two-part Phase 1b study was designed to determine the PK, PD and safety and tolerability of PUR0200 compared to Spiriva HandiHaler 18 µg in COPD patients. In the first part of the study, subjects were randomized to receive placebo or PUR0200 at one of 4 dose levels. The goal of the Part 1 study was to evaluate safety and tolerability of PUR0200 and compare the PK of PUR0200 to historical data to select dose levels to be tested in Part 2 of the study. Data from Part 1 of the study supported the selection of 3, 6, or 9 µg of PUR0200 for Part 2.

Part 2 of the study was a randomized, placebo-controlled, dose-ranging, five period cross-over study to test the PK and PD of PUR0200 and Spiriva HandiHaler. In the study, 38 subjects received placebo, three different dose levels (3, 6, or 9 µg) of PUR0200 or Spiriva HandiHaler 18 µg in each of the five study periods. Each study period was separated by a seven-day washout

period. PK and Forced Expiratory Volume in 1 second (FEV1, a measure of lung function) were evaluated over the 24 hour period after dosing.

From a safety and tolerability perspective, PUR0200 was well tolerated with mild adverse events reported in both parts of the study.

Following inhalation of PUR0200, absorption of tiotropium was rapid with maximal plasma concentrations achieved 5 minutes after dosing followed by reduced plasma concentrations over the following 24 h (Figure 5). Maximal plasma concentrations (C_{max}) was similar between PUR0200 3 µg and Spiriva HandiHaler 18 µg, whereas PUR0200 9 µg resulted in a 4.5 times higher lung dose of tiotropium than Spiriva HandiHaler 18 µg. These data demonstrate the improved delivery efficiency of tiotropium to the airways from PUR0200 versus the lactose blend Spiriva HandiHaler. This PK data also demonstrates dose stacking of tiotropium from the PUR0200 formulations demonstrating that the improved dosing efficiency to the lungs is maintained at higher doses.

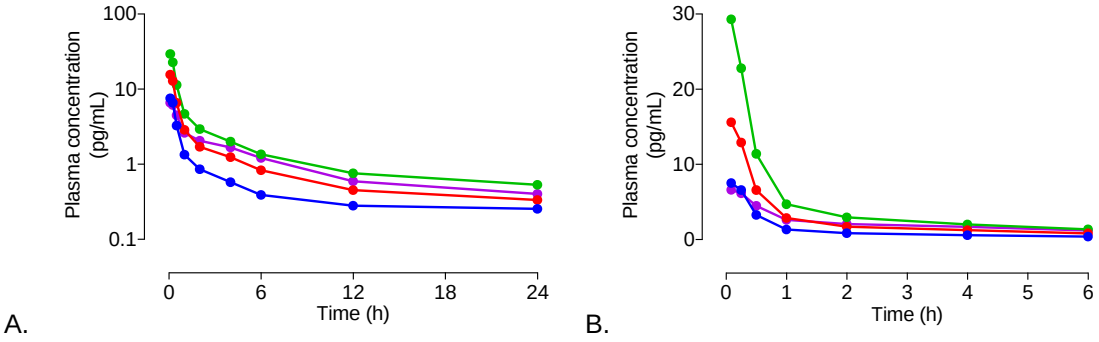


Figure 5. Tiotropium Plasma Concentrations in Part 2 of the Phase 1 Study. A. Log-linear plot of plasma concentrations over 24h and B. Linear-linear plot of plasma concentrations over 6h. ● - PUR0200 3 µg; ● - PUR0200 6 µg; ● - PUR0200 9 µg; ● - Spiriva HH
(Source: Singh D, Ferguson GT, Bolitschek J, et al. Tiotropium + olodaterol fixed-dose combination shows clinically meaningful improvements in quality of life versus placebo. Poster PA2958 presented at the European Respiratory Society International Congress, Amsterdam, Netherlands, September 2015.)

In pharmacodynamic assessments serial spirometry was performed over a 24 h period after dosing and pulmonary function improvement was measured by the forced expiratory volume over one second (FEV_1), a standard measure of airway bronchodilation. PUR0200 resulted in a statistically significant increase in FEV_1 at all PUR0200 doses compared to placebo (Figure 6). Relative to placebo, PUR0200 increased trough FEV_1 by 151, 218 or 198 mL for the 3, 6, and 9 µg doses respectively. A similar improvement in trough FEV_1 was observed after dosing with Spiriva HandiHaler (169 mL). The low dose of PUR0200 (blue; 3 µg) resulted in a similar lung function improvement over time and across a number of pulmonary function parameters, whereas the 6 µg and 9 µg doses exhibited a slightly greater numerical improvement in FEV_1. The relatively flat dose response curve of PUR0200 is similar to that of other muscarinic antagonists and data generated during the development of Spiriva HandiHaler.

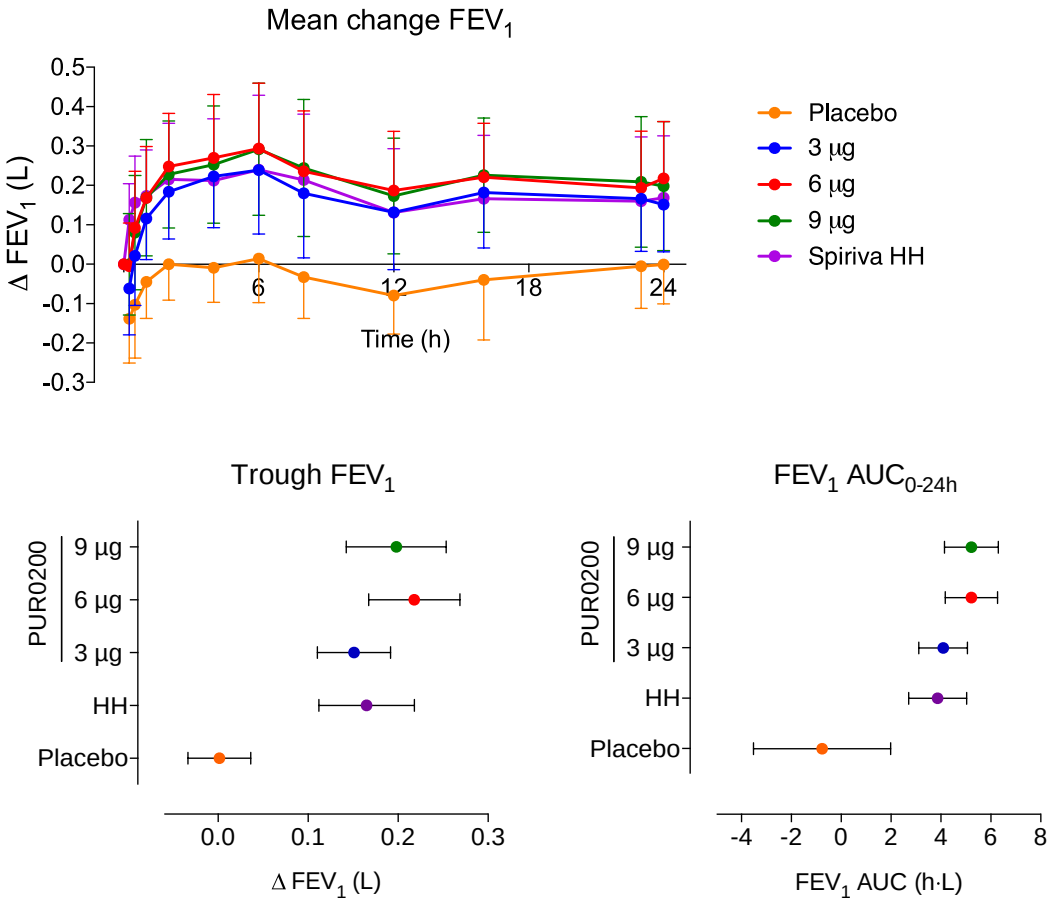


Figure 6. An increase in the mean absolute FEV_1 was apparent within 30 minutes post-dose following inhalation of PUR0200 3, 6 and 9 µg. Statistically significant increases from baseline in trough FEV1 were observed with all doses of PUR0200 (151mL, 218mL and 198mL for 3, 6 and 9 µg, respectively) and 18 µg tiotropium (169mL). All doses of PUR0200 resulted in improvement of lung function [time-adjusted FEV_1 ($AUC_{0\text{-}24h}$)] compared to placebo.
(Source: Singh D, Ferguson GT, Bolitschek J, et al. Tiotropium + olodaterol fixed-dose combination shows clinically meaningful improvements in quality of life versus placebo. Poster PA2958 presented at the European Respiratory Society International Congress, Amsterdam, Netherlands, September 2015)

Conclusions: PUR0200 was safe, well tolerated and improved pulmonary function compared to placebo. Administration of PUR0200 resulted in increase in plasma drug levels that was proportional to the delivered dose. ***Further, inhalation of 3µg PUR0200 (PUR0200 dose that is 80% less than Spiriva HandiHaler) resulted in similar PK and PD as 18µg Spiriva.*** This study resulted in an understanding of the formulation parameters and *in vitro* performance criteria required to achieve a PK match to the reference product in subsequent studies.

- ***Study #2:*** A second clinical trial completed in March 2016 to further study the PK profile of PUR0200 compared to Spiriva HandiHaler towards a PK BE approval in the EU. Bioavailability is a measure of the rate and extent to which the active ingredient (tiotropium) is absorbed and becomes available in blood.

  In this PK study, 42 subjects were randomized to receive a single dose of one of five PUR0200 formulations or two administrations of Spiriva HandiHaler in a 7-period crossover design. The

goal of the study was to assess the PK, safety and tolerability of PUR0200 and its bioavailability relative to Spiriva HandiHaler. The five unique PUR0200 formulations varied in aerosol properties and strength. Of the 42 enrolled subjects, 41 completed all dosing periods.

There were no serious adverse events and the safety profile of PUR0200 was comparable to that of Spiriva HandiHaler.

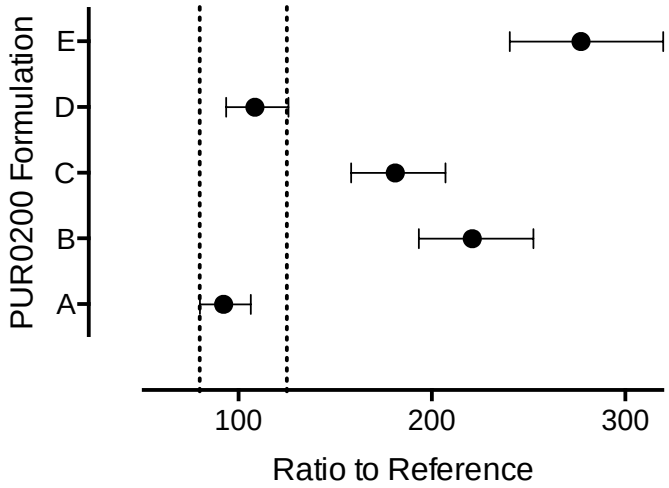


Figure 7. Pharmacokinetic evaluation of the C_{max} of 5 different formulations of PUR0200 compared to Spiriva HandiHaler.
(Source: www.pulmatrix.com)

Results: PUR0200 kinetics were similar for all doses and formulations tested. Plasma PK measures were comparable between selected PUR0200 formulations and Spiriva HandiHaler, with the PK of two PUR0200 formulations aligning with the PK of Spiriva HandiHaler. The C_{max} (Figure 7) and AUC (plasma levels over time; not shown) following dosing with each of 5 PUR0200 formulations (A-E) were compared to Spiriva HandiHaler. The geometric mean ratio to reference is shown as the PUR0200 C_{max} relative to the Spiriva HandiHaler C_{max}. Bioequivalence criteria are achieved when the geometric mean ratio and the 90% CI intervals fall between 80 and 125%(dashed lines). In this study, two PUR0200 formulations (A and D) nearly achieved bioequivalence to the C_{max} of Spiriva HandiHaler.

Conclusions: The trial defined key criteria – dose and aerosol particle size – for demonstrating PK BE and identified the target product profile of a bioequivalent PUR0200 formulation.

Inhaler devices have been a significant part of COPD therapy as they contribute to providing differentiation and patent protection. Further, the inhaler device itself seems to be influential in the decision making process while prescribing treatment for COPD patients. The patient's ability in using the inhaler device to obtain an adequate inspiratory flow has been a major factor influencing treatment adherence and consequently patient outcomes. Boehringer Ingelheim filed a petition with the FDA in 2012 requesting the FDA to apply specific standards to any product that cites Spiriva HandiHaler or any product containing the active ingredient, tiotropium bromide as the Reference Listed Drug (RLD). Further, Boehringer Ingelheim has requested the FDA to approve such products only if it has undergone extensive clinical studies that fully addresses all safety and efficacy issues and demonstrates the efficacy and safety of the product for all indications without extrapolation of the conclusions from one indication to another[15]. Since the

[15]https://www.pharmamedtechbi.com/~/media/Supporting%20Documents/The%20Pink%20Sheet%20DAILY/2012/November/Boehringer_Ingelheim_Citizen_Petition.pdf

FDA reviews the products for clinical endpoints to ensure equivalent delivery of drug to the lung site as well as the PK endpoint in determining bioequivalence of orally inhaled products in ANDA applications, Pulmatrix will need to demonstrate BE of PUR0200 in *in vitro*, PK, and clinical studies when submitting such an application.

Recently the first generic copy of Advair was developed by Mylan as well as Hikma and its partner Vectura. The FDA has delayed the approval which implies a significant delay for these companies. If the clinical trial is unable to demonstrate bioequivalency or if there are technical issues relating to the manufacturing design of the inhaler device, PULM will be forced to return to the drawing board.

PUR1800 Program: Inhaled NSKI for AECOPD

PUR1800 inhibits steroid resistant inflammatory processes induced by a variety of stimuli including cytokines, pathogens and free radical stressors such as cigarette smoke. PUR1800 would be the first known triple kinase inhibitor. Unlike oral steroids, PUR1800 impacts P38, Src and Syk kinase and is hypothesized to provide anti-inflammatory effect in eosinophilic, bacterial and viral induced AECOPD.

Clinical Development

Study #1: A double-blind placebo controlled study was conducted to investigate the safety and tolerability of single and repeat inhaled doses of PUR1800 in healthy subjects and subjects with moderate to severe COPD (GOLD II/III). Systemic PK exposure and the effects of repeat inhaled doses of PUR1800 on markers of inflammation in sputum from COPD subjects were also evaluated in healthy and COPD subjects. Seventy-eight subjects (38 healthy and 40 with COPD) were recruited at a single investigator site in the UK. PUR1800 was delivered via a DPI at doses of 100µg and 500µg for 14 days. PK was measured on Days 1, 7 and 14.

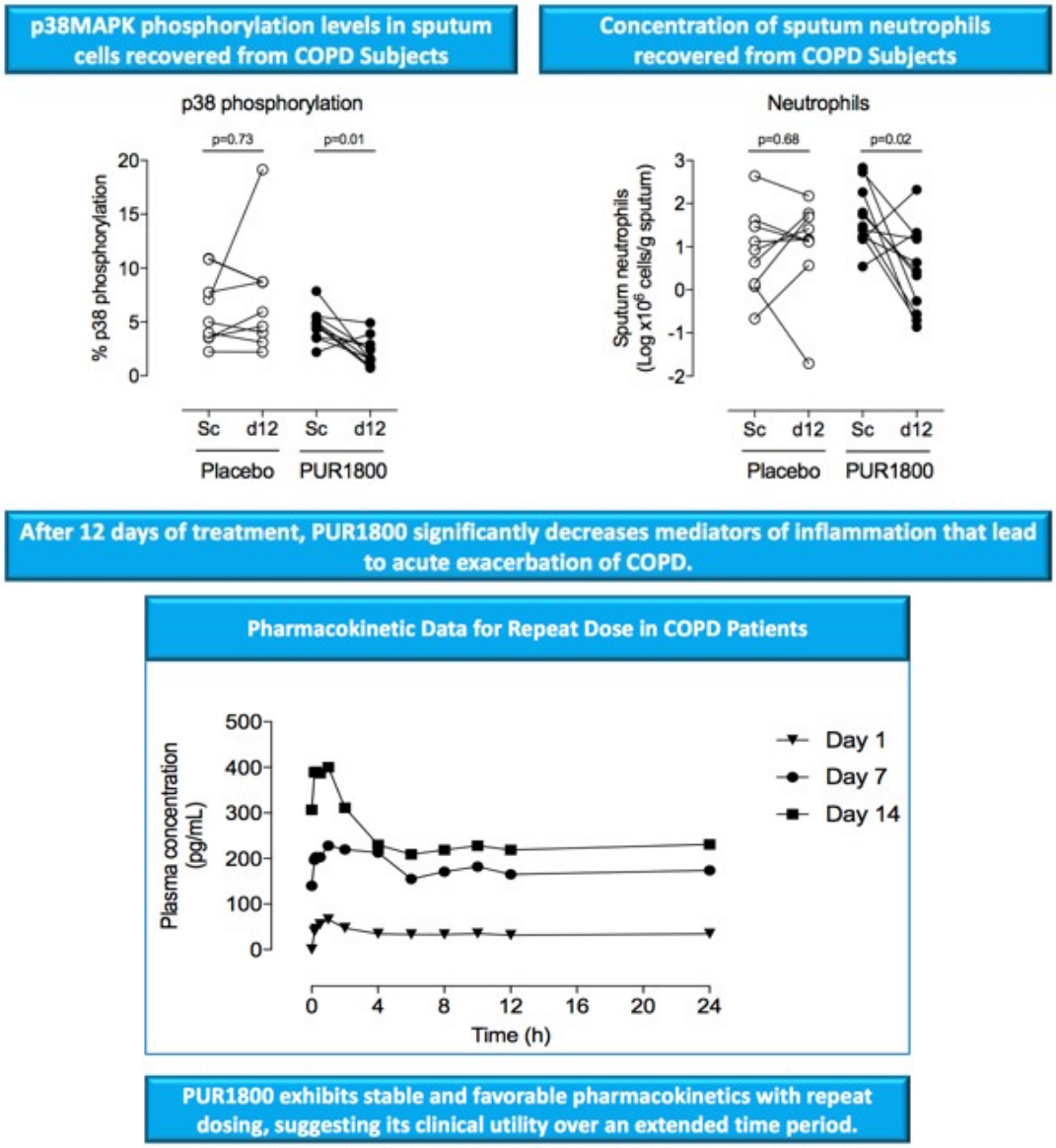


Figure 8. PUR1800 decreases markers of inflammation in patients with moderate-to-severe COPD (top); PK data for PUR1800 (bottom)
(Source: *ClinicalTrials.gov NCT01970618*)

Results: PUR1800 was found to be well tolerated in heathy subjects and in those with moderate to severe COPD. The drug demonstrated low, dose proportional systemic exposure. PUR1800 demonstrated target engagement after dosing COPD subjects with 500µg for 14 days. COPD subjects dosed with 500µg had a reduction in phosphorylated p38 (p-p38) levels in sputum cells (p=0.01) and had a reduction in sputum neutrophil numbers on Day 12 compared to baseline (p=0.02) (Figure 8). Total sputum cell (p=0.02) & sputum macrophage (p=0.04) numbers also decreased (data not shown). Subjects dosed with 100µg had a trend towards a reduction in p38 phosphorylation (p = 0.084). COPD subjects dosed with 100µg also demonstrated statistically significant changes in MMP12 (p=0.001), IL-13 (p=0.02), MCP1 (p=0.03) and MDA (p=0.04) in

sputum supernatant (data not shown). No difference between PUR1800 and placebo treated patients was observed on spirometry or plethysmography measures. No deaths or serious adverse events (SAEs) were reported.

PUR1800 Therapeutic Development

The initial trial showed that PUR1800 can reduce the inflammatory burden in COPD patients completed using a lactose blend dry powder of the molecule in PUR1800. PUR1800 is being reformulated using the iSPERSE technology and is targeted for a 14-day Phase IIA study in COPD patients with similar end points to the trial completed by Janssen/Respivert that is anticipated in 2H 2018. Demonstration of target engagement and measure of anti-inflammatory biomarkers will be the primary readouts in the study along with safety and tolerability.

Based on the results from this Phase IIA trial, Pulmatrix plans to move directly into a Phase IIB Proof-of-Concept trial in COPD patients. This subsequent trial could address the impact of PUR1800 as a possible treatment of acute exacerbations of COPD (AECOPD) as well as inform the potential of the agent to prevent exacerbations of COPD. Subsequent trials could also address the impact of this treatment when used acutely at the time of an AECOPD in conjunction with the standard of care to determine if this treatment will be effective across all AECOPD phenotypes. As part of future development consideration, PUR1800 could also be evaluated in a prevention of exacerbation paradigm in longer term trials.

p38 MAP kinase inhibitors in development

These molecules have mainly focused on p38 inhibition. Mereo Biopharma, a clinical stage, UK-based, biopharmaceutical company is developing Acumapimod, an orally active compound for AECOPD as a first line of therapy. Previous studies undertaken by Novartis showed that acumapimod demonstrated a statistically significant reduction of the inflammatory marker TNFα and a clinically meaningful increase in forced expiratory volume in one second (FEV1), a clinically relevant endpoint in the treatment of COPD. In studies to date, acumapimod has been shown to be safe and well tolerated in the target patient population. Top-line data from a double-blind, placebo-controlled Phase 2 dose-ranging study of acumapimod is expected in the second half of 2017.

Glaxo Smith Kline's GW856553, or losmapimod, was tested in a 12-week randomized double-blind study in COPD patients. An oral dose of losmapimod, 7.5mg b.i.d., was compared with an inhaled corticosteroid (ICS)-LABA dry powder (Advair ®) or placebo. The primary endpoint, sputum neutrophils, was not reduced by either active treatment. However, plasma fibrinogen was modestly, but statistically reduced in the losmapimod arm. However, in January 2016, GSK pulled the plug on another Phase 3 trial with losmapimod for acute myocardial infarction (heart attack) after disappointing trial results.

Pfizer's once daily oral agent PH-797804 was tested in a 6-week dose-ranging study in COPD patients. Each of several doses resulted in improvements of trough FEV1 that were statistically significant and around 75 ml better than placebo. There were also meaningful improvements in dyspnea index, a modest decrease in the use of rescue medication and reductions in high sensitivity C-reactive protein. However, levels of clara cell secretory protein CC16, IL-6, surfactant protein-D and fibrinogen were unchanged. Although some nausea and headaches

were seen, other adverse events were not a problem. Pfizer subsequently discontinued this program.

The above candidates are all oral inhibitors as compared to PULM's inhaled drug candidate, and in most cases development is focused on the long term chronic use of these compounds to prevent exacerbations. PUR1800 is different in terms of the triple kinase inhibition profile and since inhaled pharmacologic therapy is the cornerstone of COPD treatment, these patients may especially benefit from the use of Pulmatrix's drug candidate

PUR1900 Program: Inhaled Itraconazole to Treat ABPA in CF and Asthma

Indication Background: Pulmonary Fungal Infections

The majority of inhaled anti-infective therapies have focused on the treatment of bacterial infections in the lungs. However, CF and severe asthmatic patients often suffer from fungal infections in the lungs that impact pulmonary function and quality of life. Pulmonary fungal infections caused by the spore-forming mold *Aspergillus fumigatus* result in chronic pulmonary infection in patients with CF and in patients with severe asthma. *Aspergillus* infection is also associated with allergic bronchopulmonary aspergillosis (ABPA), an allergic response resulting from hypersensitivity to fungal antigens. ABPA is characterized by a local and systemic eosinophilic and IgE inflammatory response and acute exacerbations that lead to worsening of disease. In addition to patients with CF and severe asthma, *Aspergillus* infections cause fatal infections in immunocompromised patients.

Market Potential: The total addressable market size for the treatment of pulmonary fungal infections includes multiple patient populations. It is estimated that nearly 50% of adult patients with CF experience pulmonary fungal infections as do high number of severe asthmatics. According to the Cystic Fibrosis Foundation Patient Registry, more than 30,000 people are living with CF in the U.S. and greater than 70,000 globally. Approximately 1,000 new cases of CF are diagnosed each year. In both cases, patients experiencing chronic bronchitis and/or allergic reactions have diminished lung function, inflammation and poor long term outcomes. Over the last twenty years, there has been an increase in the number of diagnosed ABPA cases due to the heightened physician awareness and the wide spread availability of serologic assays. The prevalence of ABPA is about 1-2% in all asthma patients and 2-15% in all CF patients.

In addition to treating fungal infections for patients with lung disease like severe asthma or CF, the same product could also be developed to prevent fungal infections in people with compromised immune systems, further widening the potential addressable patient population. The sum of asthmatic patient population (more than 193 million), specifically those with chronic aspergillosis and ABPA, exceeds 5 million patients worldwide as estimated by Denning et al[16].

Current Treatment Options: ABPA is treated with oral steroids and antifungal drugs to reduce inflammation and eradicate infection, respectively. Current oral dosing regimens can be up to six months of therapy or longer with these agents.

Oral corticosteroids are the mainstay for treatment of ABPA targeted at reducing local (and at times systemic) inflammation associated with hypersensitivity to fungal antigens. Unfortunately, steroid therapy manages the immunological response to the fungus, but does not directly act to eradicate the fungus and the source of the hypersensitivity from the lungs. In addition, the potential long term use of steroid is associated with a number of adverse side effects which physicians would prefer to avoid.

[1616] Denning D, Pleuvry A, Cole D (2013) Global burden of ABPA in adults with asthma and its complication chronic pulmonary aspergillosis in adults. Med Mycol 51: 361–370.

Anti-fungal therapy is typically initiated after oral corticosteroids fail to adequately control the disease. Oral azoles are the commonly first line anti-fungal therapy to treat patients with ABPA, with about 80% of patients with ABPA and/or *Aspergillus* bronchitis, are treated with oral azoles. It is estimated that approximately five million of the ~193 million people with asthma throughout the world also suffer from ABPA[17].

Itraconazole is one of the first-line azole therapies that acts to inhibit fungal growth through the inhibition of fungal cell wall biosynthesis. Specifically, itraconazole acts to block ergosterol synthesis resulting in formation of toxic sterols that disrupt the fungal wall synthesis and replication (Figure 9). In addition to its anti-fungal activity, itraconazole has anti-allergic and anti-inflammatory action. Itraconazole is available commercially as Sporanox (Janssen Pharmaceuticals) in both a capsule and oral solution forms.

Itraconazole Inhibits Fungal Cell Wall Synthesis

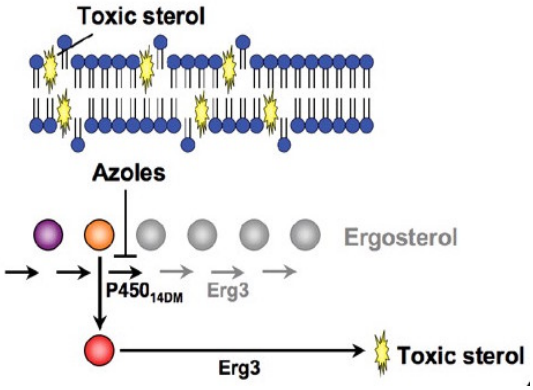


Figure 9. Itraconazole acts to block ergosterol synthesis.
(Source: Pulmatrix IR Presentation – Sept 2016)

Itraconazole in CF

The utility of oral itraconazole in the treatment of ABPA in patients with CF is limited by poor PK, inconsistent exposure in the lungs at the site of infection and a challenging safety profile for long-term use. In general, well controlled randomized clinical trials of oral azole therapy in CF ABPA patients is lacking, yet a number of case reports support the successful use of azoles in reducing the long-term need of oral steroids in managing ABPA and in improving clinical outcomes[18].

The broader efficacy of oral itraconazole is also limited by poor PK and variability in the achieved plasma concentrations of itraconazole. Oral bioavailability of itraconazole in healthy volunteers is 55%, which may be further reduced in patients with poor digestive function, such as those with CF. Itraconazole pharmacokinetics (PK) following oral dosing have been evaluated in CF patients. An exploratory PK study in 12 CF patients >16 years old and 5 CF patients <16 years old examined plasma concentrations of itraconazole over 14 days of dosing [19]. Steady-state concentrations were achieved after 8 days of dosing with high inter-subject variability. None of the young patients and only 50% of the older patients achieved steady-state itraconazole trough

[17] Isabel Rodriguez-Goncera, Rob Nivenb, David W. Denninga, Successful long-term terbinafine therapy in an asthmatic patient with Aspergillus sensitization and bronchiectasis, Medical Mycology Case Reports (2017), 16:31–33
[18] Denning, D.W., et al., Adjunctive therapy of allergic bronchopulmonary aspergillosis with itraconazole. Chest, 1991. 100(3): p. 813-9, Moreira, A.S., et al., Antifungal treatment in allergic bronchopulmonary aspergillosis with and without cystic fibrosis: a systematic review. Clin Exp Allergy, 2014. 44(10): p. 1210-27, Nepomuceno, I.B., S. Esrig, and R.B. Moss, Allergic bronchopulmonary aspergillosis in cystic fibrosis: role of atopy and response to itraconazole. Chest, 1999. 115(2): p. 364-70.
[19] Conway SP et al, "Pharmacokinetics and safety of itraconazole in patients with cystic fibrosis". J Antimicrob Chemother, 2004, Vol 53(5), pp 841-847.

concentrations greater than 250 ng/mL, which is a target trough concentration required to get sufficient itraconazole lung levels to treat infection[20].

In a second study of 11 CF patients aged 5 to 15 received oral itraconazole for 15 days and itraconazole levels in plasma and sputum were determined. The concentrations of itraconazole in plasma and sputum for 10 patients 4 h after dosing are shown in Figure 10. The plasma levels of itraconazole were variable across patients, yet in most cases achieved levels above the therapeutic target threshold. In contrast, only 2 of the 10 patients achieved a sputum concentration of itraconazole that exceeded 250 ng/mL. Given that the drug level in the lung is the primary driver of efficacy, it is not surprising that efficacy of oral itraconazole is questionable in CF patients where therapeutic efficacy is inconsistently achieved[21].

In addition to its poor lung penetration, high plasma concentrations of azoles are associated with significant risks of drug-drug interactions due to itraconazole is metabolism in the liver by CYP3A4. Due to this, itraconazole is contraindicated for a large number of drugs due to potential severe drug-drug interactions including the Vertex gene modifying drugs Kalydeco and Orkambi. Current use of oral azoles including itraconazole in CF patients is frequently associated with unfavorable side-effects, including nausea, vomiting, toxicity, and reversible visual disturbances due to the high systemic bioavailability required to achieve therapeutic levels in the lungs.

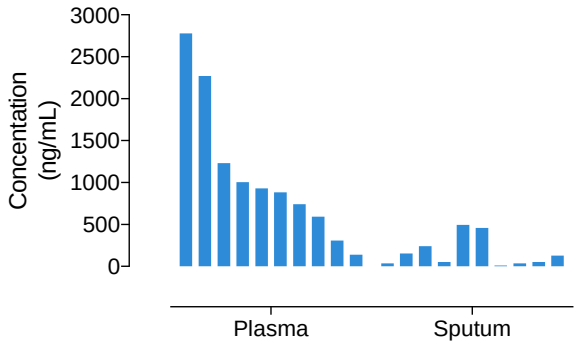


Figure 10. Itraconazole levels in CF patients (n=10) measured in plasma and lung sputum following oral dosing.
(Source: http://aac.asm.org/content/45/6/1937.full.pdf)

Itraconazole in Severe Asthma

Oral itraconazole is a first line anti-fungal therapy to treat ABPA in severe asthmatics that are poorly controlled or treated with oral steroids. The poor PK profile and risk of side effects and drug-drug interactions associated with high plasma concentrations of azoles is a challenge in the long-term management of the disease.

Two randomized, placebo controlled studies have been completed that assessed the anti-inflammatory effect and clinical response to oral itraconazole in asthmatics with ABPA[2223]. These studies both describe a benefit of oral itraconazole therapy versus placebo in the treatment of severe asthmatics with ABPA. Stevens *et al*. performed a 16-week double blind, placebo controlled randomized study in 55 asthmatics with ABPA, with a 16-week open label extension in which all patients received oral itraconazole. The primary endpoint was the clinical response to

[20] Boogaerts, M.A., et al., Antifungal prophylaxis with itraconazole in prolonged neutropenia: correlation with plasma levels. Mycoses, 1989. 32 Suppl 1: p. 103-8
[21] Aaron SD et al, "Treatment of Aspergillus fumigatus in patients with cystic fibrosis: a randomized, placebo-controlled pilot study". PLoS One, 2012, Vol 7(4),
[22] Stevens DA, Schwartz HJ, Lee JY, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med 2000; 342:756–62.
[23] Wark PA et al, "Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial". J Allergy Clin Immunol, 2003, Vol 111(5), pp 952-957.

therapy, defined as a combination of decreasing corticosteroid use and decrease in systemic IgE, with either an improvement in lung function or exercise tolerance. The study found a significant improvement in clinical response in the itraconazole group compared to placebo (13/28 versus 5/27; *p*=0.04), with more than 70% of patients reducing oral corticosteroid dose by 50% or more. Notably, 12 of 33 patients who did not respond in the double-blind portion of the study had a clinical response in the open label extension. In a complementary study, Wark *et al*. studied the impact of oral itraconazole on pulmonary inflammation by assessing sputum eosinophilia and sputum levels of eosinophil cationic protein (ECP) in 29 stable patients with ABPA. Itraconazole therapy was associated with a significant drop in sputum eosinophils over the first month of therapy (35% reduction versus placebo; *p<0.01*) that was maintained over 16 weeks. Similar effects were seen with ECP. Serum levels of IgE and *Aspergillus*-specific IgG were also reduced by treatment.

Pulmatrix's Drug Candidate: PUR1900

PUR1900, a dry powder formulation of itraconazole using the iSPERSE platform technology, is being developed as the first known inhaled antifungal medication for CF and severe asthma that will provide a superior product profile to current oral therapy (Figure 8).

Attribute	Oral delivery	Inhaled delivery
Total dose	> 400 mg daily	< 40 mg daily
Lung to plasma exposure ratio	Low	High
Bioavailability	55% - itraconazole > 95% - voriconazole	> 60% directly to site of infection
Lung exposure	Variable; affected by diet	Consistently high
Side effects	Systemically and orally driven • Gastrointestinal • Phototoxicity (Voriconazole) • Drug-drug interactions	Locally driven

Figure 11.
(Source: http://ondrugdelivery.com/publications/66/Pulmatrix.pdf)

The anticipated product profile of PUR1900 should provide significant advantages over the current oral version of the drug. Oral dosing requires much higher plasma concentrations for achieving therapeutic levels of drug in the lungs. PUR1900 may reverse this profile by delivering high lung concentrations while limiting systemic exposure as demonstrated in Figure 12.

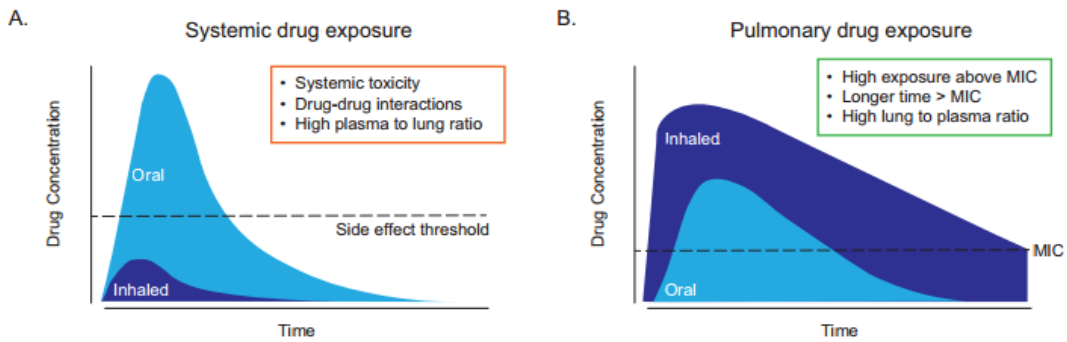


Figure 12.
(Source: http://ondrugdelivery.com/publications/66/Pulmatrix.pdf)

Preclinical Evaluation of PUR1900:

In vitro studies of PUR1900 have demonstrated that the formulation will likely preferentially deposit in the lung at the site of fungal infection. Figure 13 shows the particle size distribution of PUR1900 development formulations with mass median aerosol diameters (MMAD) of ~3 µm and more than 50% of the nominal dose reaching the lungs. Importantly, the aerosol target range is similar for *Aspergillus* conidia and PUR1900, which allows itraconazole to be delivered to the same sites in the lung where fungal spores also deposit upon inhalation. PUR1900 also enables the delivery of high doses of itraconazole (>5 mg) to the lungs, greater than the levels achievable with oral dosing suggesting a much higher local level of anti-fungal exposure.

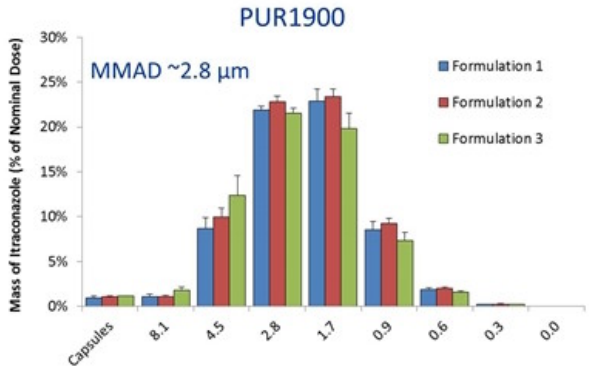


Figure 13.
(Source: www.pulmatrix.com)

In vivo animal testing has corroborated the product profile in terms of higher lung exposure and lower systemic exposure in blood relative to oral dosing. The objective of the study shown in Figure 14A and 14B was to evaluate the PK of itraconazole in dogs following pulmonary delivery and compare the exposure of inhaled drug delivery to oral dosing with Sporanox. The PK of PUR1900 or Sporanox were evaluated in Beagle dogs following inhalation (PUR1900) or oral dosing (Sporanox) at doses of 5□mg/kg over 7 days. Plasma samples were collected over a 24 hour period after a single dose (Day 1) or after multiple doses (Day 7). Lung concentrations of itraconazole were assessed 24h after the last dose.

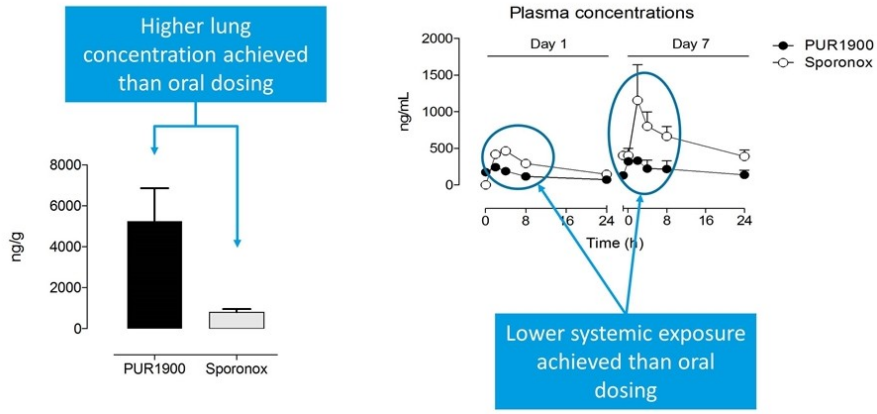


Figure 14A and B
(Source: www.pulmatrix.com)

Results: Aerosol dosing of PUR1900 resulted in similar levels of plasma exposure after both single and repeat dosing, indicating low levels of accumulation systemically following inhalation exposure. Conversely, plasma concentrations of itraconazole after Sporanox dosing were higher than the inhaled formulation after both a single dose and after 7 days of dosing. In addition, significant amounts of systemic accumulation were observed following Sporanox dosing over seven days.

Maximal anti-fungal activity of itraconazole is driven by the duration of drug exposure to the fungus. Analysis of itraconazole concentrations in lung tissue after seven daily aerosol or oral doses showed that lung delivery of PUR1900 resulted in lung concentrations approximately 7-times greater exposure than that achieved with oral dosing (Figure 11A).

Conclusions: Pulmonary delivery of PUR1900 achieves high lung concentrations and low plasma concentrations of itraconazole, reversing the profile achieved with oral dosing. The higher local lung concentrations following inhalation significantly exceed the minimal inhibitory concentration (MIC) of the drug, which is a critical parameter to antifungal activity, while low plasma exposure reduces the risk of side effects and drug-drug interactions.

PUR1900 Clinical Development

In August 2016, the FDA granted orphan drug status to Pulmatrix for PUR1900 for the treatment pulmonary fungal infections in CF patients. Orphan drug status provides for a relatively quick regulatory path to market. In the U.S., an orphan indication is given to the condition that affects less than 200,000 people or has a prevalence rate of less than 5 in 10,000. Pulmatrix may receive R&D tax credits on clinical testing expenses during development, PDUFA fees waiver, access to government grants and seven years of market exclusivity post approval. The FDA also granted the program Qualified Infectious Disease Product (QIDP) status in January 2017. QIDP status provides five additional years of marketing exclusivity for the product post-approval. If PUR1900 is ultimately approved by the FDA, the seven-year period of marketing exclusivity from orphan designation combined with an additional five years of marketing exclusivity provided from the QIDP designation allows for a total of more than a decade (12 years) of potential guaranteed protection from competition.

Pulmatrix management is planning to file a Clinical Trial Application (CTA) in 2H 2017 in the EU to support a Phase 1/1b trial in healthy volunteers and asthmatics in 1H 2018. The goal of the trial is to establish the safety and tolerability of PUR1900 in healthy volunteers and a target patient population, while gaining a greater understanding of the single and repeat dose pharmacology of itraconazole when delivered to the lung. The company anticipates favorable safety and tolerability data as well as PK information from the Phase 1/1b trial in 1H 2018.

Pulmatrix plans to use the Phase 1/1b data to support initiation of a Phase 2 program in patients with ABPA initiating in 2H 2018.

Partnerships: Phase I studies will support the PUR1900 program in both CF and severe asthma, creating partnership opportunities for both indications. Pulmatrix is currently in an active discussion with the Cystic Fibrosis Foundation to support the development of PUR1900. The company is also negotiating U.S., ex-U.S. and worldwide licensing rights to PUR1900 for CF and severe asthma.

IPF

Indication: Idiopathic Pulmonary Fibrosis (IPF) is a progressive and fatal disease (the cause of which is unknown) that scars the lungs thereby causing an irreversible loss of the ability of the lung tissue to transport oxygen.

Current Treatment Options: Two recently approved drugs, Ofev (nintedanib) and Esbriet (pirfenidone) offer therapeutic options for IPF patients in the U.S. Both Ofev and Esbriet are oral therapies and commonly cause gastrointestinal side effects that could be severe depending on the patient. Pharmaceutical giants such as Bristol-Myers Squibb (BMY) and Biogen (BIIB) are developing oral and injectable therapies for IPF that are in Phase 2 clinical trials.

Market Potential: IPF kills about 40,000 people in the U.S. annually. It is estimated that over 200,000 people in the U.S. and EU suffer from IPF[24, 25], which represents a viable commercial market and offers the potential for orphan drug status. Given the underserved market, the potential for the currently marketed products is expected to be in the billions of dollars annually. With the limitations of the currently approved oral therapies, innovative inhalation approaches to IPF treatment such as that offered with Pulmatrix's iSPERSE technology could have the opportunity to capture significant share of the market.

PUR5700, an inhaled NSKI is in preclinical development. While PUR5700 could also have therapeutic potential in COPD and severe Asthma, preclinical data demonstrate the potential of PUR5700 as a novel anti-inflammatory for IPF. The premise of inhalation as a better route of delivery for IPF drugs has been established in preclinical studies. Pulmatrix has evaluated use of iSPERSE in IPF and Respivert also did early pre-clinical work to evaluate PUR5700 in IPF as well. Pulmatrix is confident in these leading indicators and intends to evaluate PUR5700 in iSPERSE in appropriate preclinical models of IPF as a first step in the next 12 months.

[24] https://pharmastore.informa.com/wp-content/uploads/2016/10/idiopathicpulmonaryfibrosis_12770_10-2016.pdf
[25] European Respiratory Review 2012 21: 355-361

COMPETING TECHNOLOGIES

Pulmospheres™ (Novartis AG) and the ARCUS™ (Acorda Therapeutics): were developed as first generation spray dried porous drug particles with low density and small aerodynamic size. These technologies helped overcome several major limitations of lactose blended DPIs, removed the need for lactose blending, allowed delivery of high drug loads and improved delivery efficiency to the lungs. Pulmospheres were the basis for the development of TOBI Podhaler, a dry powder version of tobramycin for treating *Pseudomonas aeruginosa*. In clinical trials, TOBI Podhaler's efficacy was comparable with the inhalation solution, but in portable and more convenient product configuration. Ciprofloxacin DPI (Bayer HealthCare Pharmaceuticals) for treating *P.aeruginosa* and AeroVanc (Savara Inc,) for *methicillin-resistant Staphylococcus aureus* (MRSA) are other dry powders in clinical development for treating pulmonary infections.

Nektar Therapeutics - Pulmosol and PulmoSpheres: The PulmoSphere (tobramycin) capsule formulation contains 28mg of drug per inhalation. PulmoSphere particles are manufactured by incorporating an oil-in-water emulsion and stabilized by the phospholipid distearoylphosphatidylcholine (DSPC). During spray drying, the drug diffuses into the center of the atomized droplet and the excipient forms a shell at the surface, forming a sponge-like morphology. The particles have geometric sizes between 1-5µm.

MannKind Corporation - Technosphere: MannKind Biopharmaceuticals' (MNKD) design comprises of a drug carrier that captures and stabilizes peptides or proteins in small precipitated particles. During the precipitation process, the peptides/proteins are micro-encapsulated and freeze-dried to form a light powder. Clinical studies have demonstrated efficacy, reliability and short-term tolerability of this drug delivery system.

Acorda Therapeutics - AIR/ARCUS technology: Acorda is developing an inhaled L-dopamine formulation for Parkinson's disease based in the ARCUS technology that uses a novel, breath-actuated inhaler. The drug is formulated into large, porous particles that help in effective lung delivery at much lower energies while maintaining aerodynamic size. Natural inhalation delivers a consistent dose.

iSPERSE Versus Competitors: In contrast to Pulmospheres and ARCUS particles, iSPERSE-formulated particles are both geometrically and aerodynamically small and have high density. Drug particles with a diameter greater than 5µm deposit in the oropharynx, and those between 1 and 5µm deposit in the airways and lung surface. iSPERSE formulations contain particles that range from 2-5µm and respirable fine particle fractions are typically greater than 50%. The iSPERSE particles are highly dispersible across a wide range of flow rates (15-60 liters per minute) in spite of their small geometric particle size. Therefore, they should be able to deliver drugs to the lung efficiently with much less effort from the patient. The higher density profile of iSPERSE compared to other engineered particles allows for greater processability during manufacturing and for the powders to be developed in a wide range of inhalation devices including capsule-, reservoir- and blister-based systems.

Potential Systemic Applications: Since iSPERSE also could be targeted for systemic delivery as well via the deep lung, there are many indications to consider for which drugs formulated with iSPERSE technology could help patient outcomes Examples include erectile dysfunction, sleep induction, acute pain (migraine), panic attacks, nausea, heart attacks, Parkinson's disease, diabetes, growth deficiency, osteoporosis, fertility treatment and endometriosis.

INTELLECTUAL PROPERTY

As of May 11, 2017, Pulmatrix had 125 patents and pending patent applications (including provisional applications) related to the iSPERSE technology. The firm solely owns 10 issued U.S. patents and 54 issued foreign patents, with expiration dates ranging from 2025 to 2033. There are approximately 70 additional pending patent applications (including provisional patents) in the U.S., Europe, Asia and other jurisdictions.

FINANCIAL CONDITION

Debt: In June 2015, Pulmatrix received approximately $7 million in the form a secured term loan from Hercules Technology Growth Capital, Inc. The loan is secured by all of PULM's assets, excluding intellectual property and matures on July 1, 2018. As of March 31, 2017, the principal balance outstanding was approximately $5.3 million.

Cash Position: As of March 31, 2017 the firm had cash and cash equivalents of ~$10.5 million. Subsequent to March 31, 2017, Pulmatrix sold ~645k common shares for gross proceeds of approximately $2.2M.

LEADERSHIP TEAM

Robert Clarke, PhD
Chief Executive Officer
Dr. Clarke was promoted to Chief Executive Officer of Pulmatrix in 2012 after serving as the Chief Scientific Officer. Joining Pulmatrix in 2004 as the first PhD level scientist, his role evolved to oversight of Research and Development efforts at Pulmatrix focused on developing the Pulmatrix technologies for treatment of respiratory disease. He has helped raise greater than $60 million in venture capital funding for the company as well as secured more than $10 million in non-dilutive funding to support Pulmatrix R&D programs. Dr Clarke is cited as an inventor on multiple Pulmatrix patents. Previous to Pulmatrix, he worked at Alkermes, Inc. focused mainly on developing inhaled therapeutic products with the AIR® technology platform. Dr. Clarke holds a B.Sc. in Biomedical Engineering from Boston University, has his Ph.D. in Physiology from Johns Hopkins University, and completed his post-doctoral training in Respiratory Biology at Brigham and Women's Hospital and Harvard University. Dr. Clarke has 18 years in industry and over 25 years total experience focused on pulmonary drug delivery and the role of inhaled particles in respiratory biology and medicine leading to co-authorship of over 90 chapters, papers, and abstracts.

David Hava, PhD
Chief Scientific Officer
As CSO, Dr. Hava leads the Research and Development organization in the development of iSPERSE dry powder delivery platform. In addition, Dr. Hava directs and manages the company's therapeutic strategy to identify and prioritize drug targets and drugs that are enabled by the iSPERSE dry powder delivery platform. Dr. Hava joined Pulmatrix in 2006 as one of the first Senior Scientists and has been involved in the early stage research and development programs that identified and characterized several of the key aspects of the Pulmatrix technology. Dr. Hava earned his PhD. in Molecular Biology and Microbiology at Tufts University and completed his post-doctoral training studying immunology and host-pathogen interactions at Harvard Medical School. Dr. Hava has co-authored numerous papers, abstracts and book chapters focused on pulmonary infectious disease, immunology and chronic lung diseases.

William Duke, Jr.
Chief Financial Officer
Mr. Duke previously served as chief financial officer of Valeritas, Inc., a company that manufactures and commercializes an insulin delivery device for adults with Type 2 diabetes. He has more than 20 years of experience in finance leadership roles, with the majority coming at life sciences companies including Valeritas, Genzyme and Haemonetics. Prior to his role as chief financial officer of Valeritas, Mr. Duke held various leadership roles in finance and accounting for public and private companies. Previously, he served as a Senior Director of Finance at Genzyme Corporation and as a Director of Finance/Accounting at Haemonetics Corporation. Mr. Duke holds a Bachelor of Science degree in Accounting from Stonehill College, a Master of Business Administration from Bentley College, and is a Certified Public Accountant.

Ted Raad
Chief Business Officer
Mr. Raad has 20 years of commercial health care and life science leadership experience and most recently served as Chief Commercial Officer at Option Care, where he helped separate the specialty home infusion business unit from Walgreens to create the nation's largest independent home infusion provider. Prior to that, he was a business unit head at Sunovion with overall responsibility for CNS and respiratory products, including assets in asthma and COPD. During his time at Sunovion, Mr. Raad led multiple products through clinical development to commercialization and implemented new strategic alliances in the US and Japan. Earlier in his career he also gained direct launch experience with Sporanox, Janssen's oral itraconazole product to treat fungal infections. Mr. Raad holds a BS in Business Administration from

University of Colorado at Boulder and an MBA from Thunderbird Global School of Global Management.

VALUATION

Pulmatrix has three clinical stage candidates for respiratory indications in its development pipeline – PUR1800 is being developed as a novel anti-inflammatory for treatment of AECOPD, PUR1900 as an anti-fungal treatment for patients with CF and PUR0200 is being developed as a therapeutic (branded generic) for patients suffering from COPD.

With the new assets added to the portfolio, what is Pulmatrix worth today? PULM is addressing the COPD market that has a patient population of about 65 million worldwide. At least a third of these patients experience acute exacerbations once annually. Further, since COPD patients are susceptible to many insults that can rapidly snowball into an acute deterioration in lung function, this chronic disease is complex and requires aggressive and prompt intervention. Although the company's candidates are in the pulmonary space, particularly COPD, PUR0200 is a branded generic of a once-daily long-acting muscarinic antagonist (LAMA) that is a bronchodilator and PUR1800 is an NSKI that addresses inflammation in COPD. We think this unique opportunity might enable Pulmatrix to positively impact the lives of more patients globally while generating attractive returns for investors. Together the two programs position Pulmatix for sustainable long-term growth in respiratory therapeutics.

Based on NPVs: We use a sum-of-the-parts valuation for Pulmatrix by calculating net present value (NPV) of future projected cash flows for PUR1800, PUR1900 and PUR0200. In the company's investor presentation (September 2016) management estimated the product opportunity to be around $8 billion from the worldwide COPD market and ~$250 million from CF market in the U.S. We think this is reasonable given that it is largely corroborated by estimates from ReportsnReports market research which pegged the global COPD drugs market at $5 billion in 2012 with expectations that it reaches $8 billion by 2020 (CAGR of ~6%).

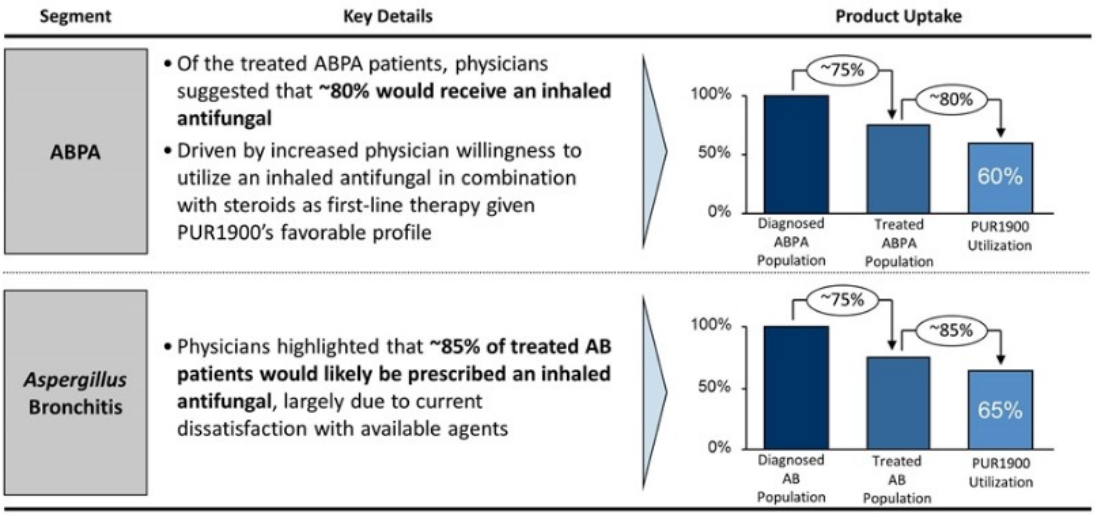
As a reformulation of a drug with established clinical data, PUR1900 has the potential to provide a viable treatment option for pulmonary fungal diseases. In early 2016 a marketing study (sponsored by Pulmatrix) was conducted by ClearView Healthcare Partners with 5 CF KOLs and 25 pulmonologists who treat ~2,000 CF patients (~150 patients treated annually for ABPA and ~100 for aspergillus bronchitis) in the U.S. From the study, management attempted to determine willingness to utilize an inhaled antifungal with steroids as first a first line therapy.

The result of the survey showed a potential favorable utilization environment and high acceptance. Physicians responded favorably to PUR1900's outlined target product profile. The primary research also consisted of 5 interviews with payor experts. Payors were receptive of PUR1900 noting that an inhaled antifungal directly addresses an insufficiency in the current treatment armamentarium which could facilitate a shift towards PUR1900. Increased efficacy and improved patient compliance could be strong drivers of uptake as well as support premium pricing (similar to TOBI Podhaler). Payor research suggests that six months post-approval is a reasonable estimate for when reimbursement could be obtained.

The current treatment for ABPA includes oral azoles. CRESEMBA, an azole antifungal, from Basilea Pharmaceutica International Ltd.and marketed by Astellas Pharma US, Inc. launched in the U.S. in April 2015 and yielded revenue of $22 million in that year. However, these azoles are required in high doses in order to get sufficient quantity of the drug to the lungs which can cause severe side effects including liver toxicity and must be managed and monitored.

PUR1900, an inhaled dry particle technology could satisfy this unmet need for the treatment of ABPA, an indication which has a sparse development pipeline. As per CDC, ABPA affects approximately 5M people worldwide including about15% of patients with CF and 2.5% of those with asthma and tuberculosis. Assuming the median cost for treating APBA with an antifungal is

roughly $3k per patient per month and the average time of treatment is roughly six months[26], we



think that PUR1900 could potentially achieve peak sales of $500 million in ten years' time.

Figure 15.
(Source: www.pulmatrix.com)

Data from the Phase 1b bioequivalence study comparing the bioavailability of PUR0200 with that of Spiriva (which contains the same active ingredient) demonstrated significant bronchodilator activity at all PUR0200 doses. In fact, PUR0200 demonstrated that it matched the maximum plasma concentration of Spiriva at a lower dose while providing the same clinical benefit with considerably lower systemic exposure. Based on successful PK BE studies in COPD, European regulatory authorities allow marketing in that territory. Even though several COPD products are already in the European market, including the recently approved Braltus Zolda, we think the iSPERSE technology offering the potential for lower efficacious doses, has the potential to gain market share in the COPD market segment.

GSK's Anoro (umeclidinium and vilanterol) was the first LAMA/LABA to reach the U.S. market (in 2014) and captured nearly $120 million in sales in its first full year (2015) on the market. Analysts forecast Anoro to generate almost $1 billion in annual revenue by 2020. If PUR0200 is launched around 2020 (assuming approved), we think it has the potential to achieve peak sales of ~$650 million in ten years' time. Meanwhile, Spiriva will lose exclusivity in the U.S. by 2019 which should also help PUR0200 capture additional market share.

[26] R Nové-Josserand et al. Pediatr Pulmonol 52 (2), 190-197. 2016 Oct 07

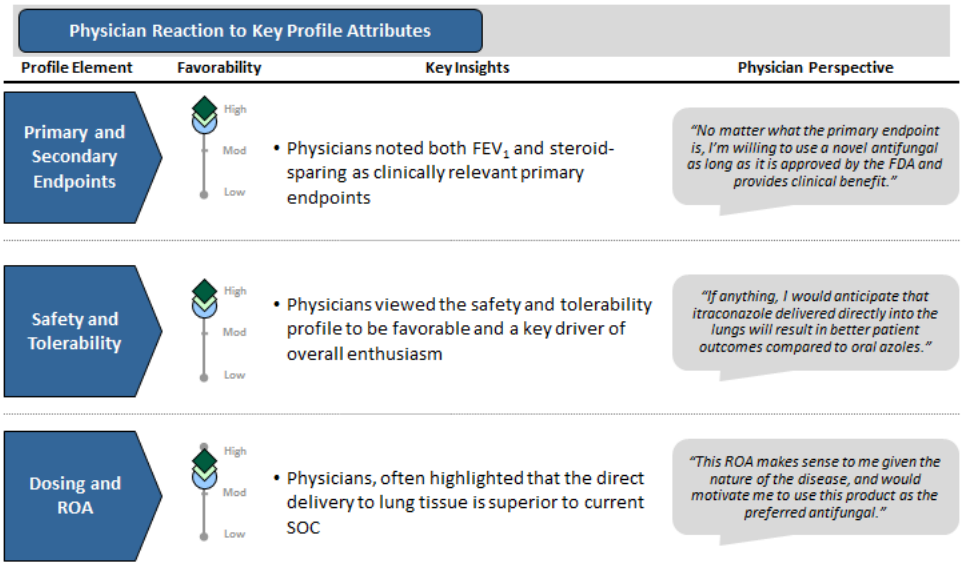


Figure 16.
(Source: www.pulmatrix.com)

PUR1800 and PUR 1900 are in mid-stage development. We expect operating expenses to remain elevated during the coming years as a result of ongoing R&D and regulatory activities for the PUR 1800 and PUR 1900 product candidates. We expect that Pulmatrix will need sufficient capital for conducting PUR1800 Phase 2 studies as well as for initial business development. The Phase 2 trial may need to be completed before PUR1800 becomes an asset that can be partnered.

Pulmarix has addressed the challenges of operational expenses from several angles. The firm's strategy has been to maintain a small management team with the required expertise to carry its business operations. Further, the company decided "not to reinvent the wheel", meaning they improvised on drug delivery technology rather than on the delivery device. Pulmatrix's drug candidates utilize an already existing DPI device for delivering the required dose. Additionally, management has decided not to own any manufacturing facilities to formulate, manufacture, fill or package PUR0200. Currently, the firm works with third party manufacturing agencies to deliver robust, scalable and economical processes for clinical as well as commercial supply of PUR0200. Additionally, Pulmatrix's cost-of-goods may be relatively low given the lower dosing requirements of PUR0200 (~20% of Spiriva in clinical studies) which, combined with (potential) premium pricing (relative to Spiriva) could result in very healthy gross margins. And while Spiriva is supported by significant marketing resources, we think that could actually benefit awareness and eventual uptake of PUR0200 given the potential spillover effects related to all inhaled COPD therapies.

PUR1900 P1 study	$1.20
PUR0200 EU BEQ Study	$4.00
PUR0200 U.S. P2 study	$8.50
OpEx	$10.00
GROSS CAPITAL Required	$23.70
Cash on hand (Mar 31, 2017)	$10.00
NET CAPTIAL Required	**$13.70**

Based on the above factors, we have modeled OpEx to increase from the latter half of 2017 reflecting additional preparations to support commencing clinical trials. Management is of the opinion that the current cash balance of $10 million should provide a working capital runway for the current year by which time the firm hopes to achieve certain milestones. We have estimated the cost of developing PUR1900 and PUR0200 in the table shown above. We believe the company may secure the required funds after presenting data from the trial readouts. We believe there are a number of potential inflection points over the next year which could trigger a partnership deal for PULM.

We use a Discounted Cash Flow (DCF) analysis and revised our financial model following the addition of the new assets. We have not included PUR5700 in our current valuation as this program is at a very early stage in development. Our model and assumptions will be updated based on progress in its development plan and could prompt a revision to our forecast, particularly as it relates to our out-years. Other key variables to our financial modeling include assumption on the probability of trial success and discount rate. Based on historical averages we have assumed a 30% probability of success for PUR0200 and PUR1800 and 10% for PUR1900 given the early stage nature of the program. We derive the total equity value of PULM to be approximately $182 million with a target price of $7.50/share, implying an upside to the current trading price. We believe there are several catalysts that would help investors realize this price in the coming years. Any substantive progress of drug development would increase the likelihood of eventual approval and benefit the target price.

PUR 1800	
Catalyst	**Timing**
Phase 2a Study	2H 2018
Phase 2a Data Readout	end 2018
Phase 2b Study	1H 2019

PUR 1900	
Catalyst	**Timing**
File CTA	2H 2017
Phase 1 Study	1H 2018
Phase 1b Data ReadOut	1H 2018
Phase 2 Study	2H 2018

PUR 0200	
Catalyst	**Timing**
Phase 1 Study	Q1-2016
Phase 1 Data ReadOut	Q2-2016
U.S. clinical study	2H 2017

Based on Comps: We also look at valuation using M&A comps. In 2013, AstraZeneca (AZN) acquired Pearl Therapeutics for $560 million - additionally, the deal called for $450 million in potential development/regulatory and $140 million in sales milestones - aggregating to a potential acquisition cost of up to $1.15 billion. Pearl's PT003, a fixed dose LABA/LAMA combination that is delivered by inhalation using a pMDI, was in late-stage clinical development at the time of acquisition.

In 2014, Acorda Therapeutics acquired privately-held Civitas Therapeutics for $525 million in an all-cash deal. The acquisition also included rights to Civitas' pulmonary delivery technology and a manufacturing facility in Chelsea, MA. Civitas' main asset, CVT-301, an inhalable drug levodopa, which is used as a rescue therapy during OFF episodes in Parkinson's disease, was a Phase 3 trial candidate.

Generally, acquisitions are based on potential commercial synergies and value of the product in the market. In the case of Pulmatrix, all of its candidates are in early clinical stages. Since the outcome of any given clinical development stage is a binary event, the probability of being acquired will increase as the candidates advance towards commercialization resulting in a higher valuation.

Risks

Regulatory Approvals: Pulmatrix's products have yet to undergo extensive clinical trials and be approved by regulatory agencies in the target regions. The evolving regulatory landscape may cause delays that could negatively impact the company's business.

Market Adoption: Since direct head-to-head double-blind comparisons of the different LAMAs are not available, choice of LAMA inhaler depends on patient and clinician preferences. Adoption could be very different from our assumptions primarily driven by reimbursement and market dynamics.

Underlying assumptions for our model could be inexact: We assume a steady growth contribution from Pulmatrix's drug candidates. However, actual product sales could vary significantly from our projections and potentially prove our model as too optimistic. Our assumptions are made using best-guesses based on clinical trial completion, regulatory approval and market penetration of the product.

PROJECTED INCOME STATEMENT

PULMATRIX INC.

PULMATRIX PULM	2016A	Q1A	Q2E	Q3E	Q4E	2017E	2018E	2019E
Revenues	**$0.8**	**$0.0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
Y-o-Y growth	-	-	-	-	-	-	-	-
Research and development	$10.2	$1.7	$2.4	$4.2	$5.3	$13.6	$20.0	$21.6
% R&D	*1216%*	-	-	-	-	-	-	-
General and administrative	$8.0	$1.6	$2.1	$2.3	$2.8	$8.8	$9.7	$10.7
%G&A	*960%*	-	-	-	-	-	-	-
Write-off of intangibles, net of tax provision	$7.5	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Total operating expenses	$25.7	$3.3	$4.5	$6.5	$8.1	$22.4	$29.7	$32.3
Operating Loss	**($24.9)**	**($3.3)**	**($4.5)**	**($6.5)**	**($8.1)**	**($22.4)**	**($29.7)**	**($32.3)**
Operating margin	-	-	-	-	-	-	-	-
Interest expense	($0.88)	($0.19)	($0.23)	($0.23)	($0.23)	($0.88)	($0.88)	$0.00
Impairment of goodwill	($5.03)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Loss on the conversion of convertible notes	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Fair value adjustment of preferred stock warrant liability	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Fair value adjustment of derivative liability	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Other income, net	$0.1	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
EBITDA	**($30.7)**	**($3.5)**	**($4.7)**	**($6.7)**	**($8.3)**	**($23.3)**	**($30.6)**	**($32.3)**
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Benefit from Taxes	$3	$0	$0	$0	$0	$0	$0	$0
Net loss	**($27.8)**	**($3.5)**	**($4.7)**	**($6.7)**	**($8.3)**	**($23.3)**	**($30.6)**	**($32.3)**
Net margin	-	-	-	-	-	-	-	-
EPS	**($1.87)**	**($0.21)**	**($0.3)**	**($0.4)**	**($0.5)**	**($1.4)**	**($1.2)**	**($1.1)**
Shares O/S	14.8	16.8	16.8	17.1	18.0	17.2	25	29

Source: Zacks Investment Research *Anita Dushyanth, PhD*

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HISTORICAL STOCK PRICE



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