

## Novel Inhaled Therapies to treat Respiratory Diseases focusing on COPD, Asthma, Cystic Fibrosis and Idiopathic Pulmonary Fibrosis



**Dr. Robert Clarke, Ph.D.**  
CEO  
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(NASDAQ: PULM)

**CEOCFO: Dr. Clarke, would you please tell us about Pulmatrix?**

**Dr. Clarke:** Pulmatrix is a clinical stage small pharmaceutical company focused on the respiratory disease area. We are developing novel inhaled therapies to treat respiratory diseases. Specifically, we look at COPD, asthma, cystic fibrosis, and idiopathic pulmonary fibrosis, all of which are major diseases of the lung.

**CEOCFO: You have a proprietary technology called iSPERSE. Can you tell us about that?**

**Dr. Clarke:** iSPERSE is our engineered dry powder technology that we developed in-house. A number of the key scientists here at Pulmatrix, myself included, all have backgrounds in pulmonary drug delivery. Personally, I am a biomedical engineer and a pulmonary physiologist. As part of our own work in our laboratories, we discovered the iSPERSE platform. The term iSPERSE captures the dispersibility of the platform technology. What differentiates it from traditional inhaled approaches is that the particles fly very easily. Our particles can easily get into the patients' airways, provide efficient drug delivery to the lungs and at the same time allow us to deliver higher doses than traditional technologies. iSPERSE is IP protected via a patent portfolio that is wholly owned by the company. iSPERSE is the basis of all of our current pipeline products.

**CEOCFO: Are you the first ones venturing into this platform?**

**Dr. Clarke:** There are engineered technologies that pre-date iSPERSE and have been the basis of inhaled product candidates. The engineered approach provides advantages over traditional technologies like lactose-blend dry powders based on delivery and aerodynamic traits. Two approved products on the market today are based on engineered platforms – one is Novartis Pharmaceuticals' tobramycin Podhaler and the other is MannKind's AFREZZA® inhaled insulin. Pearl Therapeutics, which is owned by AZ, recently received approval of its LABA/LAMA dual bronchodilator that is an engineered metered dose inhaler containing suspended Nektar particles. Acorda Therapeutics is in later stage clinical development for an inhaled L-Dopamine for Parkinson's disease based on their ARCUS low-density dry powder technology. What is different about iSPERSE from the other engineered technologies is the particle density profile. Although we have a higher particle density than all the other engineered platforms, we discovered that we get the same benefits as these other technologies and achieve high delivery efficiency to the airways, flow rate independence, and higher dosing capabilities. We are part of the continuum of seeking improved approaches for delivery by inhalation that dates back to antiquity with inhaled smoke and vapors.

Over the past seventy years, since the invention of the meter dose inhaler, there has been a great emphasis on the idea of developing better engineering approaches to get higher delivery efficiency in the airways. We look at ourselves as a

next-generation approach to solving that problem. We have created a number of proprietary opportunities for the company and are looking to treat patients directly via inhalation at the site of the disease within the airways.

**CEOCFO: *Where are you in the development process?***

**Dr. Clarke:** Our most advanced program, PUR0200, is a once daily bronchodilator that has been tested in COPD patients. COPD is a disease that can develop after a life of smoking cigarettes. It affects tens of millions of patients worldwide and the number is growing as other countries emerge into more industrialized economies. We have generated efficacy data demonstrating the advantages of our version of this bronchodilator. With a dose that uses more than 80% less of the active drug compared to the current lactose-blend dry powder standard of care, we see the same benefit in terms of bronchodilation in COPD patients. For European approval, we are following a specific regulatory path that exists only in the EU that allows us to seek approval based on pharmacokinetic bioequivalence. This means that, if we can show the blood levels match the currently marketed product, we can register our product as a bioequivalent. We just completed another trial targeting the pharmacokinetic bioequivalence with our previously disclosed pharma partner who has an option on the EU rights to the program. The next stage for the EU would be to move towards a pivotal bioequivalence trial and product registration. The US path is a 505(b)2 path, so it is an expedited development path but not bioequivalence. Pulmatrix retains the rights for the US program but remains open to partnering those rights.

**“With our iSPERSE technology, we are seeking to improve currently approved respiratory drugs based on our enhanced delivery efficiency and, with respect to oral medications given for lung diseases, improve the drug profile by inhalation delivery directly to the lungs.”- Dr. Robert Clarke, Ph.D.**

One of the other programs we are working on is PUR1900, an inhaled antifungal focused on treating fungal infection in the airways of patients. This includes a number of affected patients ranging from cystic fibrosis patients to severe asthmatics. Patients get a fungal infection by inhaling fungal spores that then take residence in the airways. Because these patients have compromised lungs, they cannot clear out these fungi and fungal infections can take root. It can manifest itself in a couple of ways. One is it can cause an acute bronchitis and it will look much like a bacterial pneumonia but it is specific to a fungal infection. The other is that over time, if the fungus is resident in the airways, it actually causes an allergic sensitization that results in inflammation in the airways that later worsens to systemic inflammation. We want to treat both of these conditions. The current standard of care is to take high doses of oral antifungals for up to six months. The limitation of this approach is that you have to take a lot of the antifungal orally to get drug into the bloodstream and all the way into the lung tissue to treat the fungal infection. You can imagine the chances for low efficiency in that process. Because you have to take a long regimen of high-doses orally, there are unwanted side effects. We believe we can correct both of those issues. By delivering directly via inhalation, the antifungals are administered topically to where the infection is in the patient’s airway and we believe we will get much higher local concentrations of the anti-fungal to treat the fungal infection in the lung. At the same time, the vast majority of the drug will remain in the lung and delivery via inhalation will avoid it getting into the blood, thus improving the systemic side-effect profile of the oral drugs. We believe we can improve the overall lung levels while reducing the overall systemic levels, which will be a dual benefit to patients. We are moving the PUR1900 program through preclinical testing with a goal of moving next into a Phase IB healthy normal/patient clinical trial.

The third focus for the company is PUR1500 and this is an early-stage preclinical program for idiopathic pulmonary fibrosis, a fatal lung disease. The prevailing approach that we are hoping to propagate is an improvement on the current standard of care for IPF. The two approved drugs for IPF are oral medications with limitations in bioavailability and side effects. The obvious next step is considering inhaling drugs to treat IPF since it is also an airway disease. That is where we come in with the iSPERSE technology. We are working on several programs using different molecules that have different targets in terms of treating IPF. Our goal is to generate a preclinical data set that will allow us to identify a lead program that we can move into the clinic.

**CEOCFO: *Is your platform the drugs themselves, the delivery, or a combination?***

**Dr. Clarke:** It is a combination of both. The company’s focus is the iSPERSE technology, which we invented. With our iSPERSE technology, we are seeking to improve currently approved respiratory drugs based on our enhanced delivery efficiency and, with respect to oral medications given for lung diseases, improve the drug profile by inhalation delivery directly to the lungs. We went down the path of purposefully selecting drugs we believe meet patient needs but also have great market potential, which obviously matters to investors. Since the drugs are already approved in some form, this approach takes a degree of risk out and provides access to more efficient regulatory paths like 505(b)2. As the company

advances these early programs and matures the iSPERSE technology, we will consider future programs with novel drug candidates.

**CEOFCO: *Are these drugs all antifungal types?***

**Dr. Clarke:** No, although we certainly could consider a novel antifungal molecule following up our PUR1900 program. We can consider essentially any drug class with iSPERSE and that opens up the entire array of target indications. We believe we can formulate small molecules, combinations of small molecules, all the way up to peptides and proteins, even whole antibodies. Each of our current lead pipeline candidates is a small molecule. Our pipeline includes an antifungal, a bronchodilator for COPD and undisclosed targets for IPF.

**CEOFCO: *Regarding cystic fibrosis, what made you decide to look at an antifungal drug for this?***

**Dr. Clarke:** We began by looking at the landscape of treatments that cystic fibrosis patients need. For CF, the Holy Grail is eventually to have a gene editing approach that could cure the disease but that is years away. In the near-term, patients still have a number of niche infections that they develop and broader infections that are a real problem. We started by looking at the prospects of an inhaled antibiotic but felt it was a crowded space. There were quite a few inhaled antibiotics in development and there was one approved dry powder product, tobramycin Podhaler, for treatment of the most prevalent bacterial infection that CF patients get, *Pseudomonas aeruginosa*. When we looked at the idea of an inhaled antifungal, we realized there is a need. Patients want a therapy that is more effective and easier to use. From discussions with CF patients that have a history of fungal infections, the common feedback is that they never want to have another one and that treatment is a debilitating process. Part of this is because doctors have problems identifying when a patient has a fungal infection. Patients often have their fungal infections misdiagnosed as bacterial infections. Following a month of treatment on antibiotics with no improvement, they will switch to a treatment for fungal infection – a high dose oral antifungal therapy. Aside from the side effects, the patients may not actually get a therapeutic dose to the lung to get rid of the fungal infection from the oral dose and that can result in a recurrence of the fungal infection. The vicious cycle is a challenge to the patient. What we have heard from CF physicians as part of our primary research is that this is a growing and not a waning concern. We know that the Cystic Fibrosis Foundation considers this a concern for patients and wants to learn more about the diagnosis and treatment paradigm for fungal infections in patients. In parallel with the foundation's efforts, we are looking to bring an inhaled treatment forward for patients.

Outside cystic fibrosis, the same logic applies in immunocompromised patients or severe asthmatics who are at risk for fungal infection. Therefore, an inhaled antifungal could have benefit to a significant number of at risk patients.

**CEOFCO: *Do you have the funding that you need or are you looking to raise funds or partnerships?***

**Dr. Clarke:** We are not currently raising money. We believe that we raised enough money last year to take us into mid-2017. Regarding partnerships, with PUR0200, we have a R&D collaboration with a pharma company that has an option to negotiate the EU rights to the program.

**CEOFCO: *What is the main takeaway about Pulmatrix?***

**Dr. Clarke:** We are a patient centric company. There is such a large unmet need and we have this applicable technology to bring better products forward for patients. We have elected to work in rare diseases that include CF and IPF because we think it is something that a company our size can dig into and take through development.

Our iSPERSE technology can also improve treatment in diseases with larger patient populations like COPD and asthma. Given the size of the required clinical trials and costs involved in moving products to commercialization for these diseases, this is where the typical biotech partner model could be advantageous for us. We enable the idea and bring it to proof of concept but a pharma partner can provide the capital resources and infrastructure to help bring that idea to reality for the patient.

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Interview conducted by: Lynn Fosse, Senior Editor, CEOFCO Magazine



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