Clinical milestones of a candidate COPD treatment

Dual inhibition of intracellular enzymes

Chronic obstructive pulmonary disease (COPD) is a major public health problem. According to the research programme, Global Burden of Disease, COPD is the third leading cause of death in the world. Yet it remains underdiagnosed in many geographies.

COPD is characterised by progressive airflow obstruction that is largely irreversible, and includes pathological changes such as airway remodeling and parenchymal destruction often involving neutrophilic airway inflammation which gives rise to the symptoms of cough, mucus secretion and difficulty breathing.[1,2] These manifestations of the disease, particularly the debilitating persistent breathlessness, have a devastating impact on a person's ability to perform basic daily activities such as getting out of bed, showering, eating and walking.

In this article we describe Verona Pharma's strategy to develop a candidate drug therapy for COPD, ensifentrine, which targets the enzymes phosphodiesterase (PDE) 3 and 4 in a single compound. Ensifentrine is currently in Phase 2b clinical testing and clinical results to date suggest potential benefits from its novel mechanism of action when compared with available treatments.

The goal of any pharmacological therapy is to improve patients' quality of life by treating symptoms, reducing the frequency and severity of exacerbations (often an escalation of symptoms), and to improve a patient's ability to function.[3] The current standard of care maintenance therapies for COPD are listed in Figure 1. Treatments with these mechanisms are often combined in patients who remain uncontrolled on one or two therapies. In the US alone, more than 800,000 patients are still symptomatic even after receiving the maximal available therapies. These include LAMA/LABA combinations or LAMA/LABA/ICS combinations.

Unfortunately, a substantial number of patients remain functionally impaired and symptomatic despite the available pharmacological therapies. For example, over 60% of patients with severe and very severe COPD failed to achieve a clinically meaningful improvement in lung function after maintenance use of combined LABA, LAMA and ICS treatment.[4] In addition, it has been reported that 65% of patients on dual LAMA/LABA therapies do not achieve a meaningful improvement in dyspnea.[5] These reports and others indicate the very large unmet need for alternative classes of therapies for patients with COPD that can bring meaningful improvements in lung function and symptoms such as breathlessness.

Figure 1. Standard of Care Maintenance Therapy in COPD

Effect (Route)	Mechanism	COPD Target
Bronchodilator (inhaled)	Short-acting β-agonist (SABA)	Airway smooth muscle
	Long-acting β-agonist (SABA)	
	Short-acting muscarinic antagonist (SAMA)	
	Long-acting muscarinic antagonist (LAMA)	
Anti-inflammatory (inhaled)	Corticosteriod (ICS)	Predominantly eosinophilic inflammation
Anti-inflammatory (oral)	Phosphodiesterase 4 inhibitor	Neutrophilic and eosinophilic inflammation

New pharmacological targets for COPD

Phosphodiesterase (PDE) 3 and 4 are ubiquitous intracellular enzymes known to play key roles in important cellular functions related to airways disease, such as smooth muscle relaxation, mucociliary dysfunction, airway re-modeling and inflammatory mediator release.[6]

The anti-inflammatory effects from PDE4 inhibitors in COPD are well characterised and are distinct from the corticosteroid effects.[7,8] These include effects on neutrophil recruitment and inflammatory mediator release among others. Clinically, a reduction in exacerbation risk in patients with severe chronic bronchitis has been demonstrated with the oral PDE4 inhibitor, roflumilast (Daliresp). Studies with selective inhibitors of PDE4 have not shown consistent or meaningful bronchodilation.[9,10] Oral PDE4 therapy has been associated with unfavourable gastrointestinal side effects such as nausea, emesis, diarrhoea, abdominal pain, loss of appetite, and weight loss.[11] The bronchodilator and bronchoprotective effects of PDE3 inhibitors have been known for over 30 years, and this has been demonstrated in patients with asthma [12,13] and healthy volunteers [14] dosed intravenously, orally and via the inhaled route. The clinical utility of older generations of PDE3 inhibitors for the treatment of respiratory conditions has been limited by a narrow therapeutic index with systemically delivered agents and short duration of action.[14]

However inhibition of both PDE3 and PDE4 may optimise the bronchodilatory and anti-inflammatory properties beneficial for the treatment of obstructive and inflammatory conditions such as COPD.

Our research shows that dual PDE3/PDE4 inhibition has the potential to have a therapeutic profile distinct from existing classes of bronchodilator and anti-inflammatory treatments. In particular, development of PDE3/4 targeting therapies delivered directly to the lung via the inhaled route may further optimise the therapeutic utility

in patients with COPD, asthma and cystic fibrosis. It is not just the combined bronchodilatory and anti-inflammatory effects that makes dual inhibition of PDE3 and PDE4 appealing in a new therapeutic. Several pre-clinical reports have shown that dual inhibition of PDE3 and PDE4 have also produced enhanced or synergistic effects on contraction of airway smooth muscle and suppression of inflammatory mediator release compared to either inhibition of PDE3 or PDE4 alone.[6, 15, 16, 17]

Ensifentrine was invented by Sir David Jack, a former head of research and development at Glaxo who pioneered many leading respiratory drugs including Ventolin, Serevent and Flixotide. Ensifentrine was designed to inhibit both PDE3 and PDE4 and be delivered via the inhaled route to maximise its therapeutic index, thus reducing the likelihood of experiencing common gastrointestinal and other adverse reactions observed with oral PDE3 and PDE4 inhibitors. Preclinically, ensifentrine has produced potent and long-lasting bronchodilatory and bronchoprotective effects, improvements in mucociliary dysfunction and anti-inflammatory effects in preclinical models.[18, 19] Ensifentrine has also shown a synergistic effect on relaxation of contracted isolated human bronchi when combined with muscarinic antagonists such as glycopyrronium. [20, 21]

Furthermore, the drug has demonstrated submicromolar functional and mechanistic potency in cellular assays evaluating effects linked to inhibition of PDE4, including inhibition of pro-inflammatory mediator release, and cellular proliferation (indicating downstream elevation of cyclic adenosine monophosphate resulting from inhibition of PDE4).[18] In addition, the doses of ensifentrine that produced bronchoprotective effects *in vivo* also inhibited antigen-induced inflammatory cell infiltration into the lungs and nose of allergic animals. The anti-inflammatory effect of ensifentrine was confirmed clinically in a study dosed over six days in healthy volunteers following lipopolysaccharide-challenge, a standard model of COPD-like inflammation.[22]

Mechanism of action

Ensifentrine is currently in Phase 2b development as a nebulised maintenance treatment for moderate to severe/very severe COPD patients. The nebulised formulation will also provide an alternative method of administration to individuals with difficulty activating handheld inhaler devices and patients with limited inspiratory flow.[23] The drug has been well tolerated in 13 completed studies with 623 subjects treated to date. These studies have included healthy volunteers and patients with asthma, allergic rhinitis, cystic fibrosis and COPD.

In asthmatic patients, ensifentrine has demonstrated bronchodilation comparable to a therapeutic dose of nebulised albuterol. In addition, fewer systemic effects were observed with ensifentrine dosed up to 24 mg compared to salbutamol. Salbutamol showed classic adrenergic side effects, including tremor, tachycardia, palpitations, and hypokalaemia.[24]

In five completed Phase 2 studies in patients with moderate to severe COPD, twice daily nebulised ensifentrine has shown substantial bronchodilation when used alone or as an add-on treatment to other classes of bronchodilators commonly used in COPD. Also, it has shown meaningful reductions in residual volume either alone or added onto standard beta-agonist and muscarinic antagonist therapies over one to three days of treatment.[25]

In a Phase 2b study in over 400 patients with COPD, ensifentrine dosed up to six mg twice daily over four weeks produced statistically significant and meaningful improvements in both lung function and troublesome symptoms associated with COPD including dyspnea, cough and sputum at all doses.[26] It was observed that the improvements in symptoms were progressive from week one through week four and unrelated to the rapid improvements in lung function, suggesting an anti-inflammatory contribution.[27] In this large study, ensifentrine was well tolerated over all of the doses studied, with a safety profile similar to placebo. Holter monitoring did not show any evidence of arrhythmogenic effects. No evidence was seen of treatment-related gastrointestinal disturbance, including nausea and vomiting.

Another recent study showed that twice daily ensifentrine (1.5 mg and 6 mg) demonstrated additional bronchodilation in patients receiving maximum bronchodilator treatment with the LAMA/LABA Stiolto Respimat, including approximately 28% of patients on triple therapy. Incremental improvements in residual lung volumes were also observed with benefits on lung function and lung volumes observed over the daytime and nighttime dosing periods.

Discussion

Clinical results from ensifentrine to date highlight the important potential benefits of this novel, dual PDE3/4 inhibitor for the treatment of COPD. These include the novel and complementary mechanism of action compared to current classes of treatments, the meaningful improvement in symptoms and the potential to provide a therapeutic benefit to patients who are uncontrolled on currently available standard of care. In the US alone, more than 800,000 patients remain symptomatic despite receiving maximum current therapy. These patients are in urgent need of new alternatives to help them breathe.

A second Phase 2b clinical study in patients with symptomatic COPD added-on to tiotropium is underway and expected to be completed around the end of 2019. The study is intended to inform on dose selection for the upcoming Phase 3 programme that Verona Pharma plans to initiate in 2020.

Verona Pharma is currently conducting clinical studies to evaluate a dry powder inhaler ("DPI") formulation as well as a metered-dose inhaler ("MDI") formulation of ensifentrine for the maintenance treatment of COPD as part of a comprehensive clinical programme intended to fully demonstrate the clinical utility of ensifentrine in improving the standard of care for COPD.

This article was written by Tara Rheault, PhD, MPH, Vice President, R&D and Global Project Management at Verona Pharma Plc and Margot MacDonald-Berko, MS, Director of Medical Science, also at Verona.

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