MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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# ENSIFENTRINE (RPL 554) FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

## EXECUTIVE SUMMARY

Chronic obstructive pulmonary disease (COPD) is a progressive and life-threatening respiratory disease without a cure. Early diagnosis and treatment, including smoking cessation support, are needed to slow the progression of symptoms and reduce flare-ups.

Ensifentrine (RPL554) is a first-in-class dual inhibitor of phosphodiesterase 3 (PDE3) and phosphodiesterase 4 (PDE4) enzymes that has the potential to act as both a bronchodilator and an anti-inflammatory in COPD. It was developed by Verona Pharma, United Kingdom. The phase 2b study of ensifentrine in mild-to-moderate COPD has been completed and demonstrated improvements in both lung function and COPD symptoms, including breathlessness.[5] In September 2020, phase 3 ENHANCE (Ensifentrine as a Novel inHAled Nebulized COPD thErapy) trials were initiated to evaluate the efficacy and safety of nebulised ensifentrine in patients with moderate to severe COPD and the interim results for these trials are expected around the end of 2022. Verona Pharma intends to file a New Drug Application (NDA) with the U.S. Food & Drug Administration (FDA) in the first half of 2023.[6]

In conclusion, ensifentrine treatment was well tolerated and it has the potential to improve lung function and symptoms in COPD patients. However, the results of the phase III study are important to gain more evidence on the effectiveness and safety of ensifentrine in moderate-to-severe COPD patients.

*Keywords: RPL554, ensifentrine, chronic obstructive pulmonary disease, COPD*

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive and life-threatening respiratory disease without a cure. It causes persistent and progressive respiratory symptoms, including difficulty in breathing, cough and/or phlegm production. Environmental exposure to tobacco smoke, indoor air pollution, occupational dust, fumes, and chemicals are important risk factors for COPD. Early diagnosis and treatment, including smoking cessation support, are needed to slow the progression of symptoms and reduce flare-ups.

According to the World Health Organization (WHO), COPD is the third leading cause of death worldwide, causing 3.23 million deaths in 2019. Almost 90% of these deaths occurred in low- and middle-income countries.[1] The mortality burden of COPD is

expected to rise to 8.6% by 2030.[2] Global sales of drugs used for chronic maintenance therapy of COPD were $13.6 billion in 2019. About 1.2 million United States COPD patients on dual/triple inhaled therapy [long-acting beta-agonist (LABA)/long-acting muscarinic antagonist (LAMA) plus inhaled corticosteroid (ICS)] remain uncontrolled, experiencing symptoms that impaired quality of life (QoL).[3]

In the Asia-Pacific region, the prevalence of COPD was estimated as 6.2% and one-fifth were experiencing severe or very severe COPD. The WHO estimated that COPD prevalence will increase threefold in Asia, compared with the rest of the world by 2020.[2] In Malaysia, respiratory disease ranks as the most common cause of medical consultation and the fourth leading cause of hospital admission. Approximately 448,000 cases were reported in 2010, with an estimated burden of Malaysian ringgit (MYR) 2.8 billion. Chronic obstructive pulmonary disease is commonly associated with cigarette smoking and it is more common in men (4.7%) than women and increases with age.[4]

The current standard of care for COPD is at least one or two bronchodilators, sometimes supplemented by an anti-inflammatory ICS, however, two-thirds of patients on the maximum triple therapy for the condition remain symptomatic. Ensifentrine was developed by Verona Pharma, which has a novel mechanism of action and combines bronchodilator and anti-inflammatory properties to treat COPD patients. Ensifentrine differs from existing treatment and has a good safety profile.

## THE TECHNOLOGY

Ensifentrine (RPL554) is a first-in-class dual inhibitor of phosphodiesterase 3 (PDE3) and phosphodiesterase 4 (PDE4) enzymes that has the potential to act as both a bronchodilator and an anti-inflammatory in COPD. Phosphodiesterase is an enzyme involved in the pathogenesis of chronic inflammatory diseases and degenerative diseases e.g. asthma, COPD, psoriatic arthritis, atopic dermatitis and dementia of Alzheimer. Ensifentrine is designed to maximise its effectiveness with high selectivity for PDE3 and PDE4, and direct delivery to the lungs by inhalation which can maximise pulmonary exposure to ensifentrine while minimising systemic distribution and potential adverse events. Ensifentrine is given using a dry powder inhaler (DPI) or pressurised metered-dose inhaler (pMDI) and the dose depends on the symptoms experienced.[5]

In phase 2 studies in patients with moderate-to-severe COPD, nebulised ensifentrine, has demonstrated significant improvements in both lung function and COPD symptoms, including breathlessness. The positive results from a phase 2 study of the DPI formulation of ensifentrine was reported in August 2019. Positive data with a single dose of pMDI formulation of ensifentrine in a Phase 2 trial were reported in March 2020 and with multiple doses in February 2021.[5]

In September 2020, phase 3 ENHANCE (Ensifentrine as a Novel inHAled Nebulized COPD thErapy) trials were initiated to evaluate the efficacy and safety of nebulised ensifentrine in patients with moderate-to-severe COPD. The phase 3 ENHANCE program consists of two double-blind, placebo-controlled studies (ENHANCE-1 and ENHANCE-2) evaluating nebulised ensifentrine for the maintenance treatment of COPD. The 48-week subset of the ENHANCE-1 trial completed enrollment of approximately 400 subjects in December 2021, which was first reported in January

2022. Enrolment in the 24-week subset of ENHANCE-1 is expected to complete in the second quarter of 2022. Data for both subsets of ENHANCE-1 are expected around the end of 2022. Verona Pharma intends to file a New Drug Application (NDA) with the U.S. Food & Drug Administration (FDA) in the first half of 2023.[6]

## PATIENT GROUP AND INDICATION

Ensifentrine (RPL554) has potential to be an effective bronchodilator and anti-inflammatory in COPD patients.

## CURRENT PRACTICE

Treatment available for COPD in Malaysia:[7]

- Inhaled short-acting bronchodilators consist of inhaled short-acting β2-agonists (SABAs) and inhaled short-acting anticholinergics (SAACs)
    - Inhaled SABAs e.g. MDI salbutamol 200 µg, fenoterol 200 µg or terbutaline 500 µg PRN or 4 to 6 hourly. They have been shown to improve lung function, dyspnoea and exercise tolerance.
    - Inhaled SAACs e.g. MDI ipratropium bromide 40 µg 6 hourly. Inhaled SAACs act on the muscarinic receptors by blocking their bronchoconstrictor effects and reducing mucus secretions.
- Inhaled long-acting bronchodilators consist of long-acting β2-agonists (LABAs) and long-acting anticholinergics (LAACs). It offers a more sustained relief of symptoms and improvement of lung function and also improves patients' compliance to treatment.
    - Inhaled LABA e.g. salmeterol 50 µg twice daily or formoterol 9 µg twice daily
    - Inhaled LAAC e.g. tiotropium 18 µg once daily
- Inhaled corticosteroids (ICS) e.g. fluticasone 500 µg twice daily and budesonide 400 µg twice daily
- Oral corticosteroids may improve lung function.
- Methylxanthines e.g. oral sustained-release theophylline 125 - 300 mg twice daily
    - Theophylline is a weak bronchodilator, hence offering only a modest improvement in symptoms and exercise tolerance.

## SAFETY AND EFFICACY

Based on retrievable evidence up to 1 April 2022, two randomised controlled trial (RCT) were included in this review.

a. Clinical Impact

A randomised, double-blind, placebo-controlled, 5-arm parallel-group, the dose-ranging study recruited patients with moderate-to-severe COPD. Patients were randomised to open-label tiotropium once daily (QD) plus (+) blinded escalating doses of ensifentrine (0.375 mg, 0.75 mg, 1.5 mg and 3 mg) or placebo twice daily (BID). Effects on lung function, symptoms and quality of life (QoL) were assessed over 4 weeks.[8]

The study demonstrated that nebulised ensifentrine added on to tiotropium was more effective compared with placebo in lung function and QoL over 4 weeks among COPD patients:[8]

- all ensifentrine doses when added to tiotropium showed improvement in peak forced expiratory volume in 1 second (FEV1) from baseline to Week 4, with placebo-corrected differences of:
    - 77.5 mL (95% CI 4.8 to 150.1; p=0.037) for 0.375 mg dose
    - 91.2 mL (95% CI 18.0 to 164.3; p=0.015) for 0.75 mg dose
    - 107.2 mL (95% CI 34.4 to 180.0; p=0.004) for 1.5 mg dose
    - 124.2 mL (95% CI 51.7 to 196.8; p<0.001) for 3 mg dose

  A significant increase in average FEV1 (0 - 12h) was shown in Week 4 with the 3 mg dose (87.3 mL, 95% CI 20.0 to 154.5; p=0.011).
- ensifentrine showed improvements in the St. George's Respiratory Questionnaire-COPD (SGRQ-C) compared with placebo, exceeding the minimal clinically important difference (MCID) of 4 units at Week 4 with the 1.5 and 3 mg arms (both p<0.05).

Another randomised, double-blind, placebo-controlled, parallel-group, dose-ranging phase IIb study recruited patients with COPD, post-bronchodilator FEV1 40 - 80% predicted and FEV1/forced vital capacity ratio ≤0.7. Patients were randomised equally to inhale nebulised ensifentrine 0.75 mg, 1.5 mg, 3 mg or 6 mg or placebo, all twice daily. The study was aimed to investigate the efficacy, in terms of lung function and symptoms, and safety of 4 weeks dosing of a range of ensifentrine doses in patients with COPD who did not receive any concomitant long-acting bronchodilator therapy for COPD.[9]

In this four-week Phase IIb study, all four ensifentrine doses were more effective compared with placebo in improving bronchodilation and symptoms at week 4 among COPD patients:[9]

- for FEV1, all four ensifentrine doses were superior to placebo (p<0.001) with differences between 139 and 200 mL

all four ensifentrine doses showed improvement in symptoms as measured by daily Evaluating Respiratory Symptoms (E-RS™): COPD total score (p<0.05).

## ESTIMATED COST

There was no retrievable data on the cost of ensifentrine. However, the raw cost for ensifentrine ranged from USD380 to USD1,200 for 5 mg to 25 mg.[10]

## OTHER ISSUES

There was no organisational/ethical issue identified.

## POTENTIAL IMPACT

In conclusion, ensifentrine treatment was well tolerated and it has the potential to improve lung function and symptoms in COPD patients. However, the results of the phase III study are important to gain more evidence on the effectiveness and safety of ensifentrine in moderate-to-severe COPD patients.

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