Ensifentrine (RPL554) is an investigational, first-in-class, inhaled dual inhibitor of PDE 3 and 4 that combines unique bronchodilator and anti-inflammatory actions in a single compound. In previous trials, nebulised ensifentrine delivered clinically meaningful and significant improvements in FEV1 and COPD symptoms. This abstract reports on the efficacy and safety of ensifentrine delivered twice daily over 7 days via dry powder inhaler (DPI) in patients with moderate to severe COPD (NCT04027439). This was a randomized, double-blind, placebo-controlled complete block cross-over study. Patients demonstrated post-bronchodilator (4 puffs of albuterol) FEV1 ≥40% and ≤80% predicted and ≥150 mL increase from pre-bronchodilator FEV1.

Patients were washed out of bronchodilator therapies for 7-10 days prior to randomization to receive one of four ensifentrine dose levels (150µg, 500µg, 1500µg, or 3000µg) or placebo via DPI twice daily over 7 days. Serial spirometry, ECG and vital signs were recorded at days 1 and 7. The primary endpoint was improvement in peak FEV1 on Day 7 compared to placebo. Secondary objectives included evaluation of safety, tolerability, bronchodilator profile, and pharmacokinetic profile. Thirty-five patients were randomized and 28 completed the study. Mean age was 59.4 years, 65% were female and 79.4% were current smokers. Peak FEV1 corrected for placebo showed statistically significant and dose-dependent improvements over baseline of 102mL, 175mL, 180mL and 260mL for the 150µg, 500µg, 1500µg and 3000µg ensifentrine doses, respectively (p<0.0001 for all doses). Statistically significant improvements (p<0.05) in average FEV1 over 12 hours were observed with all ensifentrine doses vs placebo: 36mL, 90mL, 80mL and 147mL for the 150µg, 500µg, 1500µg and 3000µg doses, respectively. A 12-hour duration of effect was observed. This was further supported by improvements in morning trough FEV1 on Day 7 of 98mL, 87mL and 97mL with the top 3 doses (p<0.001). Ensifentrine was well tolerated at all doses. The frequency of reported adverse events was similar between treatment groups and placebo. There was no effect on mean heart rate, no meaningful effect on blood pressure and no PDE4 inhibitor like adverse events. This study demonstrates that ensifentrine administered by DPI over one week provides clinically meaningful, statistically significant and dose-dependent bronchodilation. Both the primary (peak FEV1) and secondary lung function endpoints were met for ensifentrine vs placebo. Ensifentrine administered by DPI was well tolerated and shows a safety profile comparable to that observed in prior studies with nebulized ensifentrine.

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