RPL554 (dual PDE3/4 enzyme inhibitor): Baseline airway reversibility impacts immediate bronchodilation, in contrast to progressive symptom improvement

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Introduction

- RPL554 (ensifentrine) is a first-in-class, inhaled dual phosphodiesterase (PDE) 3/4 inhibitor in development for the maintenance therapy of chronic obstructive pulmonary disease (COPD) and asthma.
- Ensifentrine has demonstrated bronchodilator, bronchoprotective and anti-inflammatory effects.
- In a four-week, placebo-controlled, dose-ranging study, ensifentrine improved lung function and reduced symptoms in patients with COPD.[1] This poster reports post-hoc analyses of this study, with patients subgrouped by baseline reversibility.

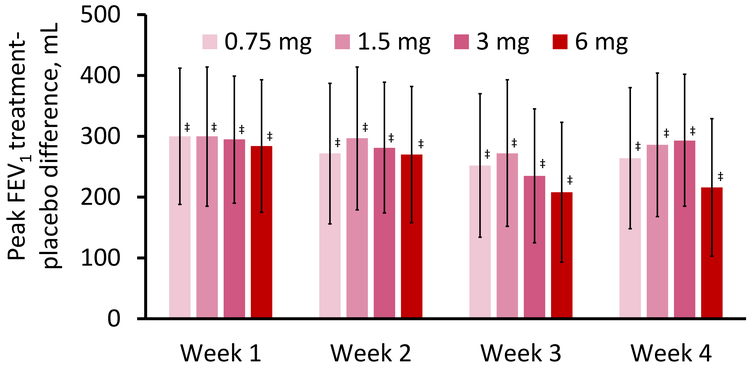
Methods

- Patients were:
  - male or female,
  - between 40 and 75 years of age,
  - with a diagnosis of COPD (post-albuterol FEV_1 40–80% predicted, FEV_1/FVC ≤0.7).
- Eligible patients were randomized to ensifentrine 0.75, 1.5, 3 or 6 mg or placebo twice daily for four weeks.
- FEV_1 was assessed at baseline, on Day 1, and after 1, 2, 3 and 4 weeks.
- Symptoms (Evaluating Respiratory Symptoms; E-RS™:COPD) were recorded by patients in daily diaries, with weekly averages calculated.
- Reversible patients had a pre- to post-albuterol change in FEV_1 at screening of ≥200 mL and ≥12%; non-reversible patients had a change of <200 mL or <12%.

Results

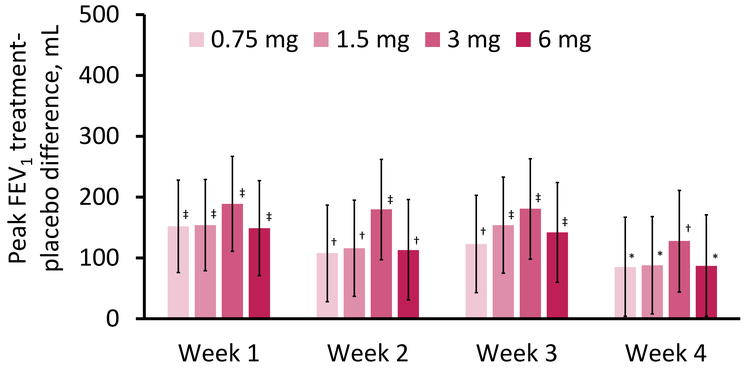
- A total of 403 patients were recruited (mean age 63.2 years, mean reversibility 11.7%):
  - Reversible subgroup: 133 (33%) patients
  - Non-reversible subgroup: 270 (67%) patients
- Baseline characteristics were similar in the two subgroups:
  - Mean post-albuterol FEV_1 % predicted:
    - Reversible subgroup: 56.4% (mean in the individual treatment groups 54.6 to 58.1%)
    - Non-reversible subgroup: 55.5% (54.4 to 56.7%).
  - Mean Medical Research Council dyspnea scale score:
    - Reversible subgroup: 2.61 (2.52 to 2.68)
    - Non-reversible subgroup: 2.59 (2.41 to 2.81).

Figure 1: Peak FEV_1 0–3 h ensifentrine–placebo differences, reversible subgroup



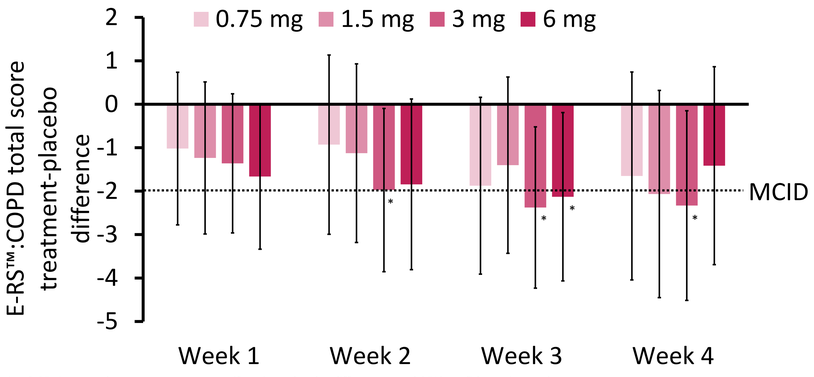
‡p<0.001. Data are least squares mean ensifentrine–placebo differences and 95% confidence intervals.
N= 23, 22, 32, 27 and 29 for ensifentrine 0.75, 1.5, 3 and 6 mg and placebo, respectively.

Figure 2: Peak FEV_1 0–3 h ensifentrine–placebo differences, non-reversible subgroup



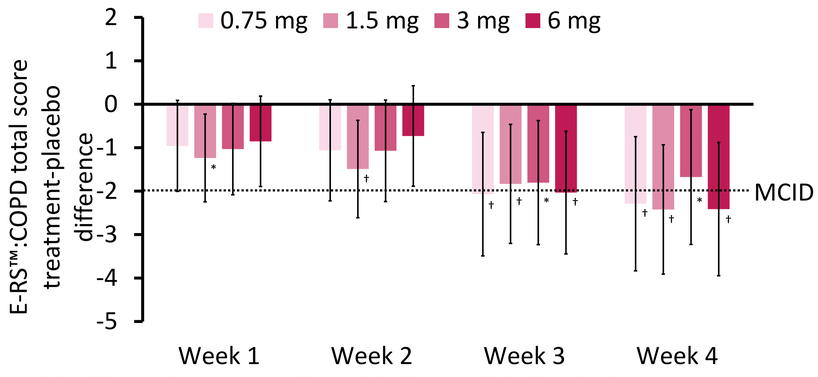
*p<0.05; †p<0.01; ‡p<0.001. Data are least squares mean ensifentrine–placebo differences and 95% confidence intervals.
N= 58, 59, 50, 53 and 50 for ensifentrine 0.75, 1.5, 3 and 6 mg and placebo, respectively.

Figure 3: E-RS™:COPD total score ensifentrine–placebo differences, reversible subgroup



*p<0.05. Data are least squares mean ensifentrine–placebo differences and 95% confidence intervals.
MCID, minimum clinically important difference. N= 23, 22, 32, 27 and 29 for ensifentrine 0.75, 1.5, 3 and 6 mg and placebo, respectively.

Figure 4: E-RS™:COPD total score ensifentrine–placebo differences, non-reversible subgroup



*p<0.05; †p<0.01. Data are least squares mean ensifentrine–placebo differences and 95% confidence intervals.
MCID, minimum clinically important difference. N= 58, 59, 50, 53 and 50 for ensifentrine 0.75, 1.5, 3 and 6 mg and placebo, respectively.

- All ensifentrine doses significantly increased peak FEV_1 0–3 h vs placebo in both subgroups, with consistent efficacy from Week 1 onwards.
  - The improvement in peak FEV_1 was greater in the reversible (Figure 1) than the non-reversible (Figure 2) subgroup.
- Ensifentrine improved COPD symptoms (E-RS™:COPD total score) in both the reversible (Figure 3) and non-reversible (Figure 4) subgroups, with an effect at or near the MCID by Week 4.
  - For this endpoint, there were further improvements from Week 1 to Week 4 in both subgroups.
- Overall, ensifentrine was well tolerated, with all doses having an adverse event profile similar to placebo (33.3 to 44.4% with ensifentrine compared to 39.2% with placebo).

Conclusions

- Ensifentrine was effective in both reversible and non-reversible patients with COPD.
- All ensifentrine doses provided significant improvements in lung function, with a greater effect in the reversible subgroup than the non-reversible subgroup.
- Ensifentrine was highly effective on symptoms in both subgroups, with the effect improving over four weeks.
  - This progressive improvement in symptoms may be due to combined anti-inflammatory effect and bronchodilation leading to greater lung deflation.

Study sponsored by Verona Pharma plc.

1. Maurer et al. Eur Respir J 2018; 52 (Suppl 62): A5894.