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. 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 FEV1 40–80% predicted, FVC ≤ 0.7).
- Eligible patients were randomized to ensifentrine 0.75, 1.5, 3 or 6 mg or placebo twice daily for four weeks.
- FEV1 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 FEV1 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 FEV1 % 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).

- All ensifentrine doses significantly increased peak FEV1 0–3 h vs placebo in both subgroups, with consistent efficacy from Week 1 onwards.
- The improvement in peak FEV1 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.

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

Dave Singh1, Brian T. Maurer,2 Fernando Martinez,3 Thomas Bengtsson4
1. Medicines Evaluation Unit, University of Manchester, Manchester University NHS Foundation Trust, Manchester, UK; 2. Verona Pharma, plc, New York, USA; 3. Weill Cornell Medical College, New York, USA; 4. StatMind AB, Lund, Sweden