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Ensifentrine (RPL554)

Top-Line Data from 3 Day Phase 2 Clinical Trial in COPD Patients Added-on to LAMA/LABA

January 14, 2019

Ensifentrine (RPL554)

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3 Day Phase 2 Clinical Pharmacology Study in 79 Patients with Moderate to Severe COPD

Trial Description	Phase 2 randomized, double blind, placebo controlled, cross over study to assess the effect of nebulized RPL554 in patients with moderate to severe COPD added on to the LAMA/LABA (tiotropium/olodaterol) Stiolto®/Spiolto® with and without ICS*
Patient Population	79 moderate-to-severe COPD patients diagnosed >12 months previously, reversible to albuterol and ipratropium, males and females, age 40-80, lung function 30-70% predicted
Locations	3 centres in the US and UK
Ensifentrine (RPL554) Dosage	3-Day, three arm cross-over design, twice daily dosing with RPL554 1.5 mg, 6 mg or placebo

* ICS= inhaled CorticoSteroid

Ensifentrine (RPL554) Provides Additional Bronchodilation on Top of Dual and Triple Therapy

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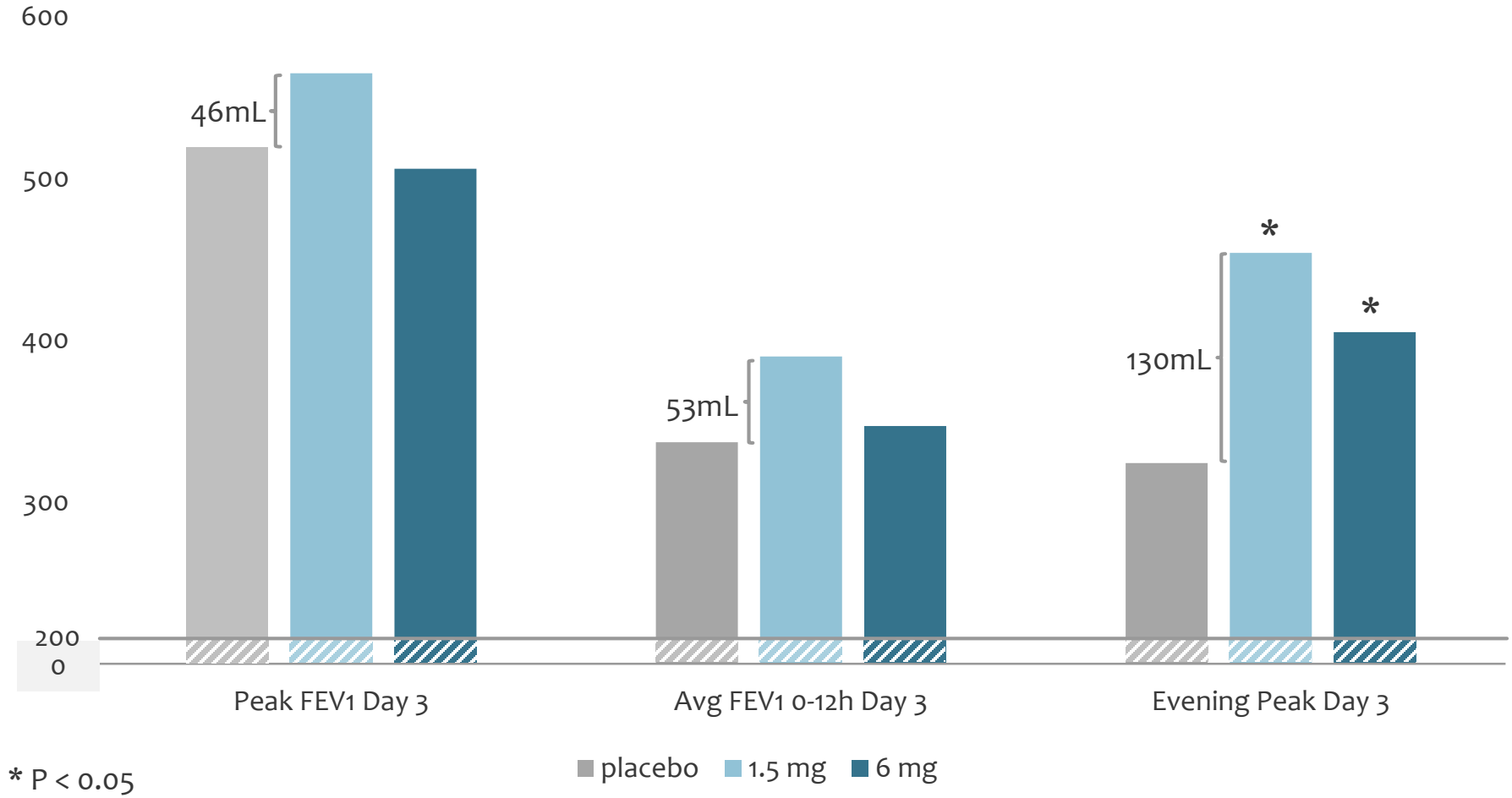
Lung Function Assessments FEV_1 (mL) Change from Baseline

N=79



* P < 0.05

Ensifentrine (RPL554) Provides Sustained Additional Bronchodilation Over 12 Hours

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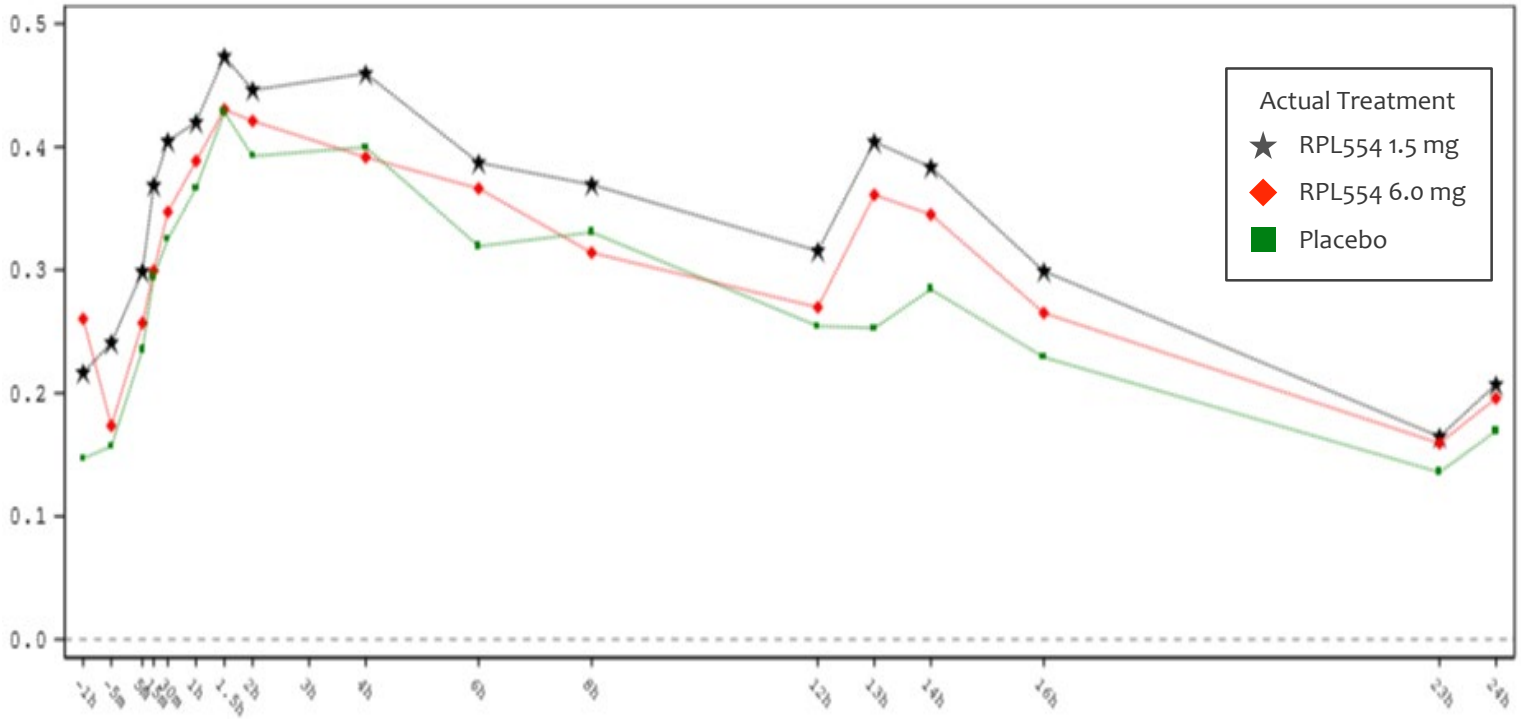
Day 3 Lung Function Profile FEV_1 (L) over Time by Treatment

N=79



* P < 0.05

Ensifentrine (RPL554) Produces Substantial Reduction in Air-Trapping in Patients Treated with Dual and Triple Therapy

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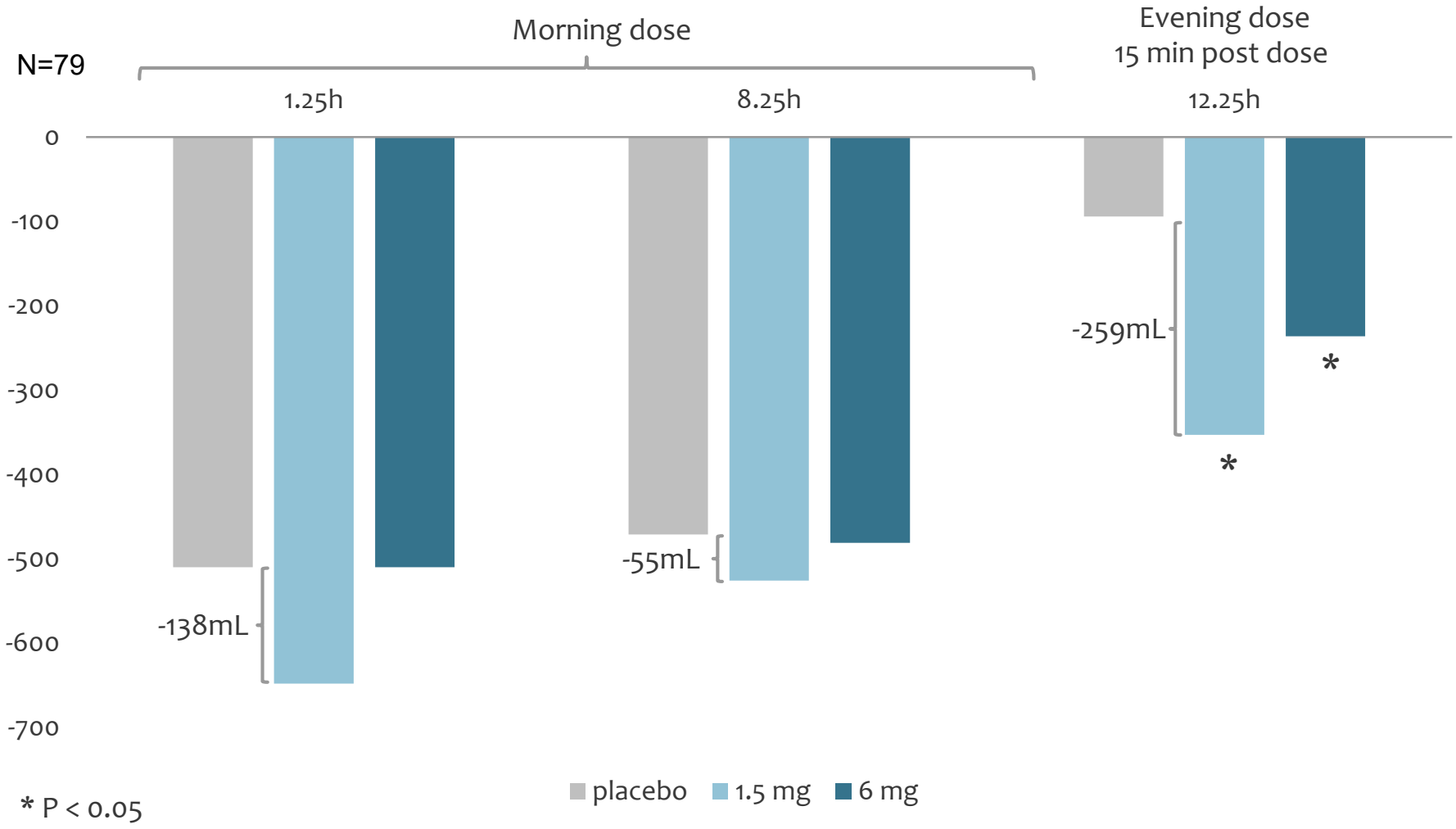
Residual Volume (mL) by Plethysmography on Day 3



* P < 0.05

Ensifentrine (RPL554) Improves Lung Function over 24h in Patients Treated with Dual or Triple Therapy

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FEV1 Endpoints

- Primary endpoint of peak FEV_1 after morning dose on day 3 was not met with statistical significance, although the 1.5 mg morning dose improved peak FEV_1 by ~ 50 mL, compared to placebo
  - 1.5 mg produced consistent improvements in lung function of ~ 50 mL over 12 hours following morning dose on day 3. These improvements were not statistically significant when adjusted for multiple doses
- Importantly, peak FEV_1 after evening dose on day 3 showed substantial improvement with both doses: 1.5 mg (130 mL improvement, $p<0.001$) and 6.0 mg (81 mL improvement, $p=0.002$)

Additional Endpoints

- Reductions in residual volume compared to placebo were observed at all time points on day 3 with the 1.5 mg dose
  - Statistically significant reductions in residual volume post evening dose on day 3: 1.5 mg (-259 mL, $p=0.002$) and 6.0 mg (-142 mL, $p=0.036$)
- 6.0 mg dose did not show additional improvement over 1.5 mg dose
- Ensifentrine was well tolerated at both doses

This 3 Day Study Provides Further Clarity for Future Development of ensifentrine (RPL554)

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- RPL554, a first-in-class drug, was shown to further improve lung function in patients believed to be on maximal bronchodilator therapy with dual and triple agents
  - Twice daily dosing with RPL554 provided a sustained improvement in FEV1 for 24h period
  - Substantial effect after the evening dose on FEV1 and RV* was statistically significant; a reduction in RV may lead to improvement in dyspnea and other COPD symptoms
- This study provides clarity on the further ensifentrine clinical development program
  - Dose selection: lower doses may be effective, providing larger therapeutic window, lower COGS, etc
  - Patients and background treatment: later development program can include symptomatic patients on dual and triple therapy, potentially a very significant commercial opportunity
- Ensifentrine continues to be well tolerated, also when combined with dual and triple COPD treatments

* RV=Residual Volume