# A 28-day, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Nebulized Revefenacin in Patients With Chronic Obstructive Pulmonary Disease

**BACKGROUND:**

- Long-acting bronchodilators are an important part of therapy for patients with COPD. Monotherapy with a long-acting muscarinic antagonist (LAMA) is considered first-line in some patients. Revefenacin is a new once daily nebulizer LAMA therapy approved for maintenance treatment of COPD.
- Sometimes, other dosage forms (metered-dose and dry powder inhalers) are not easy to use, especially in older patients or those with cognitive impairment. These factors may cause inaccurate dosing, and poor adherence leading to undesirable clinical outcomes.

**OBJECTIVE**

- To evaluate the safety, efficacy, and tolerability of revefenacin in patients with COPD.

**METHODS**

- **Design**: randomized, double-blind, placebo-controlled, multiple-dose, parallel-group study conducted at 41 US centers within a 4 month period in 2014. 70 participants were assigned to each of 5 treatment groups:
    - **Group 1**: placebo
    - **Group 2**: 44 mcg revefenacin
    - **Group 3**: 88 mcg revefenacin
    - **Group 4**: 175 mcg revefenacin
    - **Group 5**: 350 mcg revefenacin
- **Exclusion**: patients who had a >12% change or >200 mL increase in $FEV_1$ after placebo inhalation.
    - LABA or LAMA use was not allowed during the study
    - Patients using LABA/ICS therapy → ICS monotherapy was allowed (LABA component discontinued)
    - SABA therapy was allowed except 6 hours before the initial spirometry assessment at each study visit
- **Inclusion**: men and women ages 40 to 75 with moderate to severe COPD, current or former smoker (>10 pack-years), with a post-ipratropium bromide $FEV_1$:FVC <0.7, $FEV_1$ 30-80% that of the predicted normal value after withholding short-acting bronchodilators for at least 6 hours and long-acting bronchodilators for at least 14 days. Regardless of change in $FEV_1$ after bronchodilator inhalation using a PARI LC Sprint nebulizer, patients were included in the study.
- **Randomization**: patients were randomized according to responsiveness to ipratropium (responsive or non-responsive).
- **Primary outcome**: $FEV_1$ change in baseline from day 1 to day 29 (last dose on day 28)
    - $FEV_1$: measured 45 and 15 minutes before a dose, and 0 to 6 hours after the dose. Baseline measurement day 1, then another on day 15, 16, and 28.
    - Primary outcome analyzed using repeated measures model. This incorporated treatment group, smoking status, responsiveness to ipratropium or albuterol, age, and sex as fixed class terms and a continuous covariate for baseline $FEV_1$. Results are reported as LS mean on 95% confidence intervals.
- **Secondary outcome:** change in weighted mean baseline $FEV_1$ over 0 to 6 hours, 0 to 12 hours, and 0 to 24 hours, time to a 100mL increase in $FEV_1$ from day 1 baseline, change in PEF and puffs per day of albuterol rescue medication (puffs per day and % of rescue-free days)
    - Peak expiratory flow rate (PEF): measure each morning and evening until post-treatment follow-up visit
    - Safety and tolerability: AEs, clinical lab findings, vitals, physical exams, ECG readings
- Power 80% with alpha level of 5% to detect a 120mL difference in trough $FEV_1$ → need 70 patients in each
- Data handling method was intent to treat

**RESULTS**

| **Primary Outcomes** | Placebo | Revefenacin | | | |
|---|---|---|---|---|---|
| | | 44 mcg | 88 mcg | 175 mcg | 350 mcg |
| D28 trough $FEV_1$ change from baseline (mL) | | | | | |
| N | 55 | 60 | 64 | 59 | 63 |

| | | | | | |
|---|---|---|---|---|---|
| LS mean (SE) | -32.4 (25.36) | 19.4 (24.98) | 155.0 (24.61) | 134.2 (25.07) | 138.2 (24.38) |
| LS mean difference from placebo (95% CI) | NA | 51.8 (-17.3, 121) | 187.4 (118.8, 256.1) | 166.6 (97.3, 236) | 170.6 (101.9, 239.3) |
| D1 weighted mean $FEV_{1(0\text{-}6h)}$ (mL) | | | | | |
| N | 69 | 66 | 68 | 70 | 70 |
| LS mean (SE) | 33.3 (15.93) | 145.1 (16.57) | 193.8 (16.42) | 180.0 (16.06) | 214.9 (15.98) |
| LS mean difference from placebo (95% CI) | NA | 111.7 (67.6, 155.9) | 160.5 (116.4, 204.5) | 146.7 (103.2, 190.2) | 181.5 (138.1, 225) |
| D28 weighted mean $FEV_{1(0\text{-}12h)}$ (mL) | | | | | |
| N | 55 | 63 | 63 | 59 | 64 |
| LS mean (SE) | -32.8 (27.03) | 34.3 (26.13) | 129.8 (26.10) | 123.4 (26.88) | 143.1 (25.42) |
| LS mean difference from placebo (95% CI) | NA | 67.1 (-4.9, 139.2) | 162.6 (90.5, 234.7) | 156.2 (83, 229.4) | 176.0 (104.3, 247.7) |
| D28 weighted mean $FEV_{1(0\text{-}24h)}$ (mL) | | | | | |
| N | 54 | 59 | 63 | 59 | 62 |
| LS mean (SE) | -78.1 (25.46) | 3.4 (25.21) | 87.0 (24.50) | 84.1 (24.97) | 96.3 (24.13) |
| LS mean difference from placebo (95% CI) | NA | 81.5 (12.8, 150.2) | 165.1 (97.2, 233) | 162.1 (93.4, 230.8) | 174.3 (106.5, 242.2) |

- $FEV_1$ 0 – 6: statistically significant change in baseline for all doses of revefenacin compared to placebo ($p < 0.001$)
- $FEV_1$ 0 – 12: statistically significant change in baseline for 88mcg, 175mcg, and 350mcg of revefenacin compared to placebo ($p < 0.001$)
- $FEV_1$ 0 – 24: statistically significant change in baseline for all doses of revefenacin compared to placebo.

| **Secondary Outcomes** | Placebo | Revefenacin | | | | P - value |
|---|---|---|---|---|---|---|
| | | 44 mcg | 88 mcg | 175 mcg | 350 mcg | |
| Time to 100mL increase in $FEV_1$ from day 1 baseline | | | | | | |
| Median time in minutes (95% CI) | NA | - | 30 (30,60) | 30 (30,60) | 30 (15,30) | - |
| LS mean difference in PEF from placebo (AM, PM) (Figure 5a and 5b) | | | | | | |
| L/min | NA | - | - | 27, 29 | 27, 29 | - |
| Puffs per day of rescue medication (Figure 4a) | | | | | | |
| N | 3 | - | Decreased by 1 puff per day | Decreased by 1 puff per day | Decreased by 1 puff per day | < 0.005 |
| % of rescue inhaler-free days (average increase in days per week) (Figure 4b) | | | | | | |
| N | 5NA | - | - | >14% (1) | >14% (1) | < 0.05 |

- Side effects: most common were headache, shortness of breath, and cough
  - Dry mouth experienced by 2 subjects (1 in 88mcg group, 1 in 350mcg → both were mild)
  - Patients wore Holter monitors, results were unremarkable throughout study
  - Table 4 lists treatment-emergent AEs, no statistical comparisons are made
- Drop-outs:
  - 91% completed placebo (64/70), 2 discontinued due to AE, 1 deviated from protocol, 1 was lost to follow-up, 2 withdrew
  - 96% completed 44mcg revefenacin (65/68), 1 had an AE, 1 deviated from protocol, 1 withdrew
  - 96% completed 88mcg revefenacin (68/71), 1 had AE, 1 deviated from protocol, 1 withdrew
  - 90% completed 175mcg revefenacin (64/71), 5 had AE, physician withdrew, 1 withdrew
  - 91% completed 350mcg revefenacin (67/74), 5 had AE, 1 withdrew, 1 other (investigator removed due to non-treatment QTc >500)

**STRENGTHS**

- Sufficient design to detect serious ADE with specific attention paid to ADE usually associated with inhaled antimuscarinic agents
- Placebo controlled, double blind
- Proper surrogate markers of disease state chosen ($FEV_1$, PEF, SABA use)
- Appropriate design to make dosing conclusions (excessive doses do not show benefit over lower doses)
- Inclusion criteria mimicked poorly controlled COPD – patients were unable to use LABAs for 14 days before enrollment decisions
- Confounding variable of LABA use was eliminated, it is unethical to disallow any SABA use

- Strong rationale for utility of a nebulized LAMA, but assessing efficacy using surrogate endpoints such as $FEV_1$ and PEF may be difficult in patients that don't even have the ability to use MDI, DPI, or SMI.

**LIMITATIONS**

- Short in length, difficult to conclude clinical efficacy
- Using the standard error of the mean can give a falsely small representation of variability. The standard deviation gives a more appropriate representation of variability.
- LAMA + ICS dual therapy isn't included in any part of the 2018 GOLD COPD Guidelines; we don't know what proportion of patients were maintained on this therapy throughout the study and how that impacted surrogate markers of COPD control
- Didn't classify patients into GOLD status. Patients in the placebo group may have ended up progressing to far worse GOLD statuses after having many maintenance medications being stopped.

**CONCLUSION**

- LAMAs used as early as GOLD Group B treatment (monotherapy or combination with a LABA). Revefenacin could have a market for its use, especially in patients whose physical or comorbid conditions limit the use of DPIs, MDIs, or SMIs. Tiotropium (once daily) is supplied as both a DPI and SMI, glycopyrronium bromide (once or twice daily) comes as a DPI & *nebulizer (BID),* aclidinium bromide (twice daily) comes as a DPI and MDI, and umeclidinium (once daily) comes as a DPI.
- Revefenacin would be the first once daily nebulized LAMA. It has a comparable ability to increase $FEV_1$ to current formulations of a guideline-recommended agent, tiotropium. Revefenacin has long-term storage in a preservative-free solution, and has high lung-to-salivary gland selectivity.
- Interpretation of Results
    - All doses of revefenacin showed a significant benefit over placebo during 24 hour serial spirometry assessments.
    - Largest improvement over placebo in change of trough $FEV_1$ was with revefenacin 88mcg (LS mean 187.4, 95% CI 118.8, 256.1, $p < 0.001$), followed by revefenacin 350mcg (LS mean 170.6, 95% CI 101.9, 239.3, $p < 0.0001$), and revefenacin 175mcg (LS mean 166.6, 95% CI 97.3, 263, $p < 0.0001$)
    - Revefenacin 44mcg was a sub-therapeutic dose.
    - The median time to achieve a 100 mL increase in $FEV_1$ after the first dose was 30 min. for the highest three doses of revefenacin.
    - Revefenacin 175mcg and 350mcg achieved an increase in the LS mean from placebo of 27mL in the morning and 29mL in the evening.
    - The highest 3 doses of revefenacin decreased the average puffs per day of rescue medication by 1 puff/day.
    - The highest 2 doses of revefenacin increased the average inhaler-free days/week by 1 day/week

**FUTURE RESEARCH**

- Clinical efficacy after a greater length of time is the next step
- Head to head trials against tiotropium and/or glycopyrrolate
- Glycopyrrolate nebulized therapy (BID) → how would outcomes compare?
- Combination LABA/revefenacin product against current available combinations (olodaterol/tiotropium once daily, vilanterol/umeclidinium once daily)

Pudi KK, Barnes CN, Moran EJ, et al. A 28-day, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Nebulized Revefenacin in Patients with Chronic Obstructive Pulmonary Disease. Respiratory Research. 2017;18:182.

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