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Improvements in health status with revefenacin, a once-daily, nebulized, long-acting muscarinic antagonist for chronic obstructive pulmonary disease

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Abbreviations:

COPD, chronic obstructive pulmonary disease; **SGRQ**, St. George's Respiratory Questionnaire; **CAT**, COPD Assessment Test; **CCQ**, Clinical COPD Questionnaire; **PRO**, patient-reported outcome; **LABA**, long-acting beta-agonists; **OR**, odds ratio; **SD**, standard deviation; **BMI**, body mass index; **CI**, confidence interval; **FEV_1**, forced expiratory volume in 1 second; **FVC**, forced vital capacity; **ICS**, inhaled corticosteroid; **mMRC**, modified Medical Research Council dyspnea scale; **LS**, least square; **SE**, standard error.

Abstract (max 250 words)

Background: Replicate 12-week phase 3 trials (0126 and 0127) of once-daily nebulized revefenacin 175 µg vs placebo demonstrated significant bronchodilation and improvements in health status in patients with moderate to very severe chronic obstructive pulmonary disease (COPD). This post hoc analysis evaluated improvement in patient-reported outcomes (PROs), including the St. George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), and Clinical COPD Questionnaire (CCQ) in both women and men.

Methods: Participants were pooled from the two 12-week studies (411 [51%] women and 401 [49%] men). Changes in PROs were assessed overall and separately in men and women.

Results: Revefenacin improved SGRQ and CAT total scores from baseline in both studies; improvement in CCQ total score reached significance only in 0126. In pooled data, a greater proportion of patients achieved clinically meaningful response in SGRQ score (≥4-unit decrease from baseline) with revefenacin vs placebo (odds ratio, 1.5; 95% confidence interval, 1.1–2.1; *P* = 0.012). Clinically meaningful responses were also seen in CAT (≥2-unit decrease from baseline) and CCQ (≥0.4-unit decrease from baseline) scores with revefenacin vs placebo. When stratified by sex, improvements from baseline in SGRQ, CAT, and CCQ scores following revefenacin vs placebo reached statistical significance only in women.

Conclusions: Maintenance treatment with revefenacin improved health status in patients with moderate to very severe COPD; however, the effect was more pronounced for women than men.

ClinicalTrials.gov: NCT02459080; NCT02512510

Keywords: Clinical COPD Questionnaire; COPD; COPD Assessment Test; Patient-reported outcomes; revefenacin; St. George's Respiratory Questionnaire

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by high symptom burden, particularly among women, who often have more severe symptoms, earlier disease onset, and worse health-related quality of life (HRQoL) than men [1-4]. Further, treatment options for COPD have shown mixed outcomes based on sex. Female patients treated with indacaterol/glycopyrronium achieved higher rates of minimal clinically important difference (MCID) in St. George's Respiratory Questionnaire (SGRQ) total scores vs males, whereas treatment with tiotropium showed no sex-based biases in patient-reported outcomes (PROs) [2, 4]. Revefenacin inhalation solution (Yupelri®) is a once-daily, nebulized, long-acting muscarinic antagonist approved in the US for the maintenance treatment of patients with COPD. Replicate 12-week pivotal phase 3 trials and a 52-week phase 3 trial showed that once-daily nebulized revefenacin was well tolerated and demonstrated statistically significant improvements in bronchodilation and health status in patients with moderate to very severe COPD at a dose of 175 µg vs placebo [5, 6]. This analysis evaluated whether revefenacin vs placebo improved PROs in patients from the 12-week replicate studies. Subgroup analyses in women and men were conducted to evaluate improvements in PROs by sex.

Materials and Methods

This was a post hoc subgroup analysis of two replicate, randomized, double-blind, 12-week phase 3 trials (Study 0126 [ClinicalTrials.gov: NCT02459080] and Study 0127 [ClinicalTrials.gov: NCT02512510]). The trials were performed in accordance with the

principles stated in the Declaration of Helsinki. Study design and patient criteria were described previously [5].

Participants received once-daily revefenacin 175 µg via a standard jet nebulizer (PARI LC Sprint® [Starnberg, Germany]) or placebo. PROs included SGRQ, COPD Assessment Test (CAT), and Clinical COPD Questionnaire (CCQ). Clinically meaningful improvements were defined as decreases of ≥4-units in SGRQ [7], ≥2-units in CAT [8], and ≥0.4-units in CCQ [9] scores from baseline.

Analyses were performed using the intent-to-treat analysis set. Day 85 least squares mean (LSM) changes from baseline in PROs and LSM treatment differences between revefenacin 175 µg and placebo were estimated using a mixed model for repeated measures (MMRM) including fixed-effect class terms for treatment group, smoking status, reversibility status, concomitant long-acting beta-agonist (LABA) use at baseline, sex, and age at baseline. Odds ratio (OR) estimates and differences between revefenacin 175 µg and placebo in least squares proportion of responders across PROs were compared using a repeated-measures logistic regression model with similar covariates as the MMRM (Appendix, Supplementary Methods).

Results

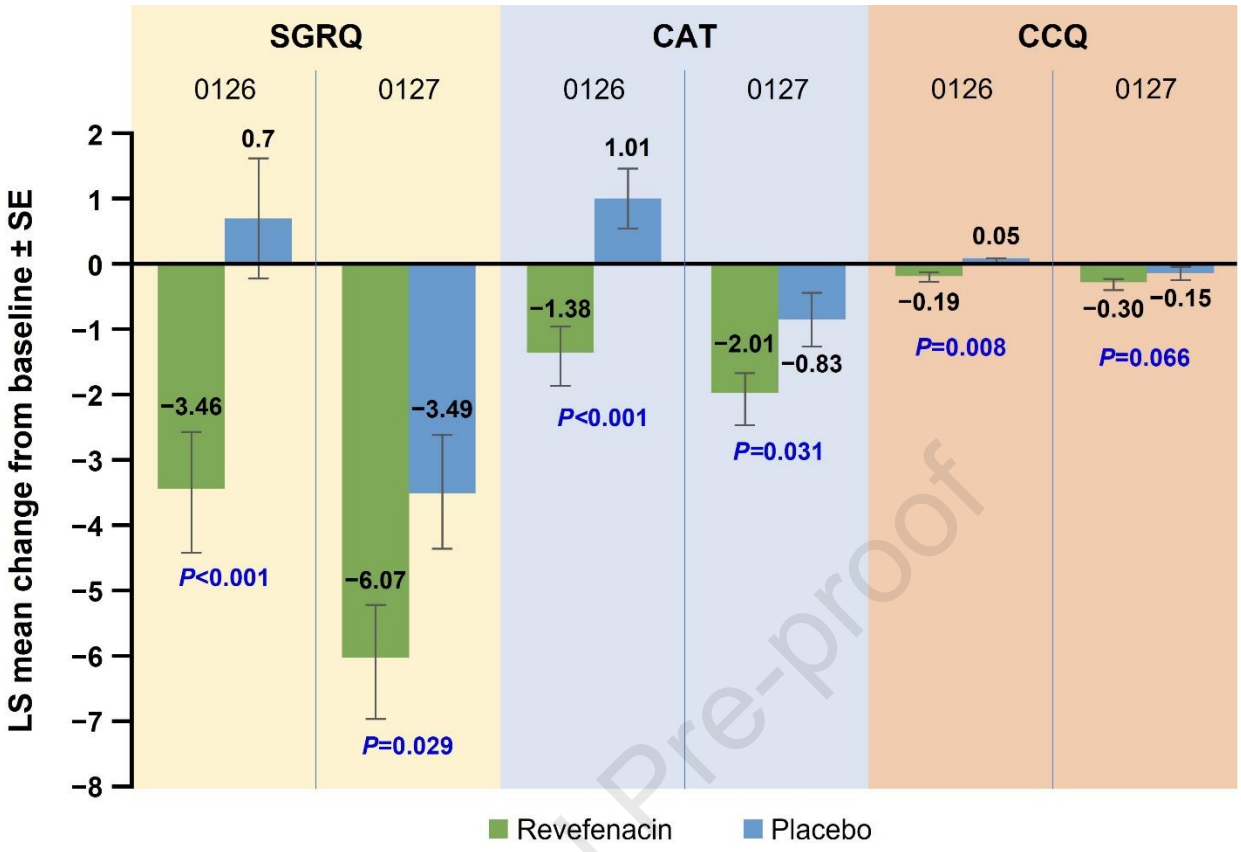
Patient demographics and baseline characteristics were described previously [5]. The post hoc subgroup analysis included 411 (51%) women and 401 (49%) men (Appendix, **Table S1**). For women vs men, the mean (standard deviation) age was 63 (9) vs 64 (9) years, baseline body mass index was 29.5 (7.5) vs 29.0 (6.3) kg/m^2, 51% vs 45% were

current smokers, and 36% vs 38% were concurrent LABA or inhaled corticosteroid + LABA users.

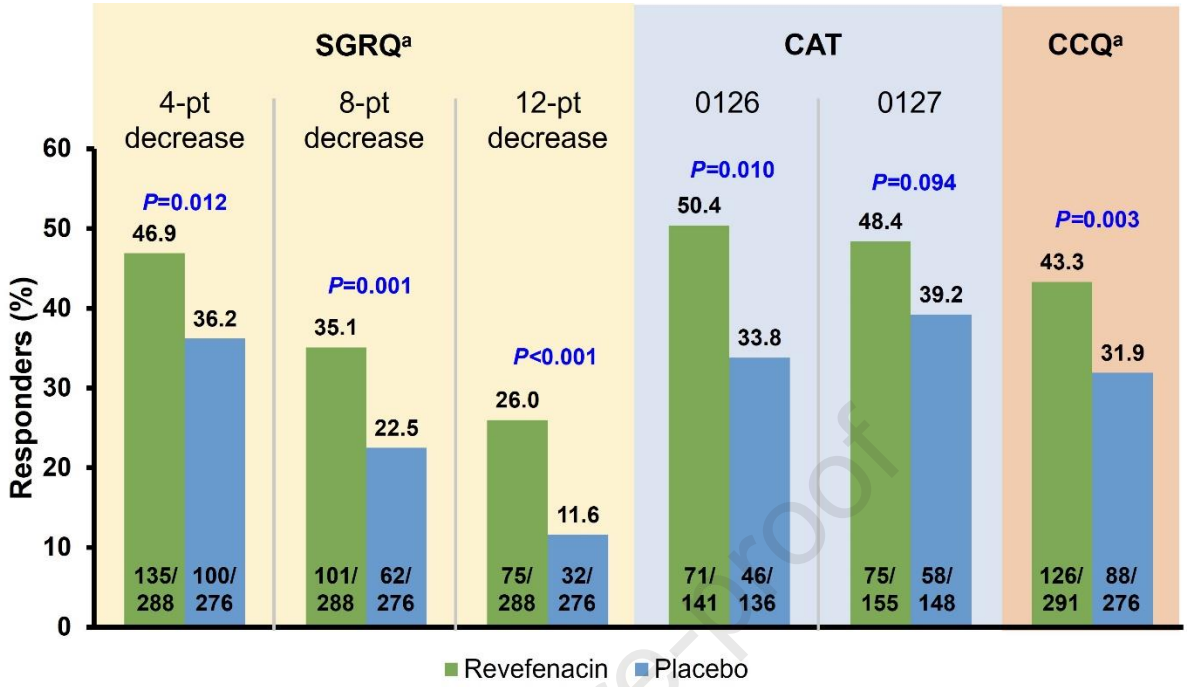
Revefenacin improved SGRQ and CAT total scores from baseline in both studies and CCQ total score in Study 0126; improvement in CCQ did not reach statistical significance in Study 0127, where placebo response was larger than expected (**Figure 1A**). In pooled data, statistically significantly greater percentages of patients achieved clinically meaningful improvements in SGRQ score with revefenacin vs placebo using 4-point (46.9% vs 36.2%; *P* = 0.012), 8-point (35.1% vs 22.5%; *P* = 0.001), and 12-point (26.0% vs 11.6%; *P* = 0.0001) thresholds (**Figure 1B**). Increased rates of clinically meaningful CAT score responses were seen with revefenacin vs placebo in Study 0126 (50.4% vs 33.8%; *P* = 0.010), but the difference did not reach statistical significance in Study 0127 (48.4% vs 39.2%; **Figure 1B**). In pooled data, the percentage of patients with clinically meaningful improvement in CCQ total score was statistically significantly greater with revefenacin vs placebo (43.3% vs 31.9%; *P* = 0.003; **Figure 1B**).

Figure 1. A) SGRQ, CAT, and CCQ total scores for Studies 0126 and 0127 and B) SGRQ, CAT, and CCQ responder analysis

A



B



OR	1.5	1.8	2.5	2.2	1.6	1.7
95% CI	1.1–2.1	1.3–2.7	1.6–3.8	1.2–4.1	0.9–2.9	1.2–2.3

Responders were defined as follows: SGRQ, ≥4-point decrease; CAT, ≥2-point decrease; CCQ, ≥0.4-point decrease.
[a]Denotes pooled study population (Studies 0126 and 0127).
CAT, COPD Assessment Tool; CCQ, Clinical COPD Questionnaire; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LS, least squares; OR, odds ratio; SE, standard error; SGRQ, St. George's Respiratory Questionnaire.

In both men and women, revefenacin produced statistically significant improvements from baseline in CAT scores vs placebo; improvements with revefenacin vs placebo in SGRQ and CCQ scores reached statistical significance only in women (Appendix, **Figure S1**). Percentages of patients with clinically meaningful improvements following treatment with revefenacin vs placebo were observed as follows: SGRQ score, 52.7% vs 36.2% of women (*P* = 0.014) and 40.8% vs 36.3% of men (not statistically significant); CAT score, 51.4% vs 33.3% of women (*P* = 0.006) and 46.9% vs 37.8% of men (not statistically significant); and CCQ score, 49.3% vs 31.9% of women (*P* = 0.002) and 37.1% vs 31.9% of men (not statistically significant; Appendix, **Table S2**).

Discussion

Replicate 3-month studies demonstrated overall HRQoL improvements in patients with moderate to very severe COPD treated with revefenacin, with greater changes from baseline in SGRQ, CAT, and CCQ scores following revefenacin vs placebo. There were greater than expected SGRQ and CAT responses with placebo and no statistically significant difference in CCQ score between revefenacin and placebo in Study 0127. Greater improvements and higher response rates were seen in women vs men following revefenacin vs placebo.

Documented differences in COPD among men and women [3, 4, 10] include greater impairment in health status for women vs men for all SGRQ domains [11] and higher rates of achieving MCID in SGRQ total score for women vs men following indacaterol/glycopyrronium [4]. Similarly, a differential response was observed in our study. However, baseline SGRQ, CAT, and CCQ scores were generally lower in the revefenacin vs placebo group among women, whereas baseline scores were better balanced among men. Further research is needed to ascertain the reasons underlying the different levels of improvement between women and men with revefenacin, although this could be related to sex-based differences in symptom burden often observed among patients with COPD.

This post hoc analysis is limited by the 3-month treatment period, although a 52-week study showed that revefenacin resulted in longer-term improvements in PROs [6]. The study population had stable COPD and excluded patients with recent

hospitalizations or respiratory infections, and the analysis presented was not prespecified.

Conclusions

Maintenance treatment with revefenacin can improve the health status of patients with moderate to very severe COPD; however, the effect may be more pronounced for women than for men.

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Declaration of Interest:

JFD is a consultant and advisory committee member for Theravance Biopharma US, Inc.; Sunovion Pharmaceuticals; and Mylan, a Viatris company.

GTF is a consultant and speaker for and received financial support from Theravance Biopharma US, Inc., and Mylan, a Viatris company.

JAO has served on advisory boards for AstraZeneca, Boehringer Ingelheim, GSK, Mylan Inc., Reckitt Benckiser, Sunovion Pharmaceuticals, and Theravance Biopharma US, Inc.

DAL was a contract employee of Theravance Biopharma US, Inc., at the time of this study.

RFS is an employee of BioMarin Pharmaceuticals, Inc.; has received consulting fees from GSK, Merck, and BreathResearch; and has received salary from Pfizer and from Theravance Biopharma US, where she was employed when these analyses were done.

KJ is an employee of Theravance Biopharma US, Inc.

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Figure Legends

Figure 1. A) SGRQ, CAT, and CCQ total scores for Studies 0126 and 0127 and B) SGRQ, CAT, and CCQ responder analysis.
Responders were defined as follows: SGRQ, ≥4-point decrease; CAT, ≥2-point decrease; CCQ, ≥0.4-point decrease.
[a]Denotes pooled study population (Studies 0126 and 0127).
CAT, COPD Assessment Tool; CCQ, Clinical COPD Questionnaire; CI, confidence interval; COPD, chronic obstructive pulmonary disease; LS, least squares; OR, odds ratio; SE, standard error; SGRQ, St. George's Respiratory Questionnaire.

Highlights

- COPD causes high symptom burden and poor QoL, particularly in women
- Revefenacin improved patient health status in 2 phase 3 COPD trials
- This post hoc analysis assessed PROs for revefenacin vs placebo overall and by sex
- Revefenacin improved several QoL measures vs placebo, particularly among women