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Efficacy and safety of revefenacin for nebulization in patients with chronic obstructive pulmonary disease taking concomitant ICS/LABA or LABA: subgroup analysis from phase III trials

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Abstract

Background: Combinations of a long-acting muscarinic receptor antagonist (LAMA), long-acting β-agonist (LABA), and inhaled corticosteroid (ICS) are used for patients with persistent chronic obstructive pulmonary disease (COPD) exacerbations on bronchodilator monotherapy. In this prespecified subgroup analysis, we assessed the efficacy and safety of the LAMA revefenacin in patients with COPD taking concomitant LABA, including ICS/LABA (LABA subgroup).

Methods: Efficacy data were obtained from two 12-week, replicate, placebo-controlled trials and safety data were pooled from the 12-week and a 52-week tiotropium-controlled trial. Patients received revefenacin 175 µg or placebo in the 12-week or tiotropium 18 µg in the 52-week studies. The efficacy endpoint was least squares (LS) mean change from baseline in trough forced expiratory volume in 1 second (FEV_1). Clinical health outcomes were assessed using the St. George's Respiratory Questionnaire (SGRQ).

Results: Revefenacin produced similar improvements from baseline in trough FEV_1 in the non-LABA and LABA subgroups [placebo-adjusted LS mean change (95% confidence interval) in day 85 trough FEV_1, 150.9 (110.3–191.6) ml and 139.2 (82.9–195.5) ml; $p < 0.0001$ *versus* placebo]. Similar improvements were observed in SGRQ scores in the non-LABA and LABA subgroups [–3.3 (–5.4 to –1.2) and –3.4 (–6.3 to –0.6)]. Improvements in lung function and health outcomes were observed regardless of airflow obstruction severity. Revefenacin was well tolerated with more adverse events reported in the LABA than the non-LABA subgroup.

Conclusions: Once daily revefenacin for nebulization can be an effective and well-tolerated treatment for patients who require concomitant use of LABA with or without ICS.

ClinicalTrials.gov identifiers: NCT02512510, NCT02459080, NCT02518139

The reviews of this paper are available via the supplemental material section.

Keywords: long-acting muscarinic receptor antagonist, nebulization, triple therapy

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide with three million deaths in 2015, a 12% increase from 1990.[1] Global disease burden is expected to increase further because of continued exposure to COPD risk factors (e.g. smoking and ambient particulate matter) and an aging population.[2] Treatment with inhaled bronchodilators remains the foundation of pharmacologic management of symptoms in patients with COPD. Long-acting muscarinic antagonists (LAMA) and long-acting β-agonists (LABA) monotherapy, or a combination of LAMA/LABA for more severe symptoms, is

recommended as the first-line treatment in patients with COPD.[3] Stepping up to a LAMA/LABA combination or LABA/inhaled corticosteroid (ICS) combination therapy is recommended in patients who continue to have exacerbations while on long-acting bronchodilator monotherapy.[3] Escalation to triple therapy consisting of LAMA/LABA/ICS is recommended in patients with further exacerbations and continuing symptoms.[3]

Revefenacin inhalation solution is a once daily, lung-selective LAMA administered using a standard jet nebulizer,[4–6] which is of particular interest to patients with COPD who prefer nebulized therapies or are unable to use handheld dry powder inhalers (DPIs) or pressurized metered-dose inhalers (pMDIs). Studies have shown that a substantial proportion of patients do not use their DPIs and pMDIs appropriately with up to 92% of patients with COPD or asthma having at least one critical error in the device's use.[7] The possible reasons for improper use of inhalation devices include cognitive dysfunction, lack of hand-breath coordination, inability to hold breath, or generating insufficient inspiratory flow or capacity.[8–10] Soft mist inhalers, which use liquid formulations similar to those used for nebulizers, may provide an alternative. However, like DPIs and pMDIs, they require a special breathing technique to deliver the appropriate amount of medication.[9] Therefore, long-acting bronchodilators delivered through nebulization are an important treatment option for COPD symptom management.

Efficacy and safety of revefenacin for nebulization was demonstrated in two randomized, placebo-controlled, phase III trials.[11] Revefenacin treatment significantly improved lung function [trough forced expiratory volume in 1 second (FEV_1) and overall treatment effect FEV_1] compared with placebo in two replicate 12-week studies.[11] Long-term safety of revefenacin in clinical trials was demonstrated in a 52 week, randomized, tiotropium-controlled, phase III safety and tolerability trial.[12] Revefenacin was well tolerated during the phase III trials and had a safety profile that supports its long-term use in patients with COPD.[11,12]

Many patients with COPD require combination bronchodilator therapy for symptom management, and because more than 40% of patients in the phase III trials of revefenacin were taking concomitant LABA-containing therapy, we performed a prespecified subgroup analysis in this patient population to evaluate the efficacy and safety of revefenacin in combination with LABA-containing bronchodilators. The subgroup data were obtained from the two replicate 12-week and one 52-week randomized controlled trials of revefenacin in patients with moderate to very severe COPD. Here, we report the efficacy and safety results from this subgroup analysis.

Methods

Study design and conduct

Efficacy data for the subgroup of patients taking concomitant LABA, including ICS/LABA combination (LABA subgroup) were obtained from two 12-week trials, and the safety data were pooled from the two 12-week and one 52-week studies. The study design for all three studies was described previously.[11,12] In brief, the 12-week studies 0126 (ClinicalTrials.gov identifier: NCT02459080) and 0127 (ClinicalTrials.gov identifier: NCT02512510) were replicate, 12-week, randomized, double-blind, placebo-controlled, multiple-dose, parallel-group, phase III studies. The 52-week study 0218 (ClinicalTrials.gov identifier: NCT02518139) was a randomized, active-controlled (tiotropium), parallel-group, phase III safety study.

Studies were conducted according to the principles of the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guideline for good clinical practice,[13] and the code of ethics of the World Medical Association's Declaration of Helsinki;[14] written informed consent was obtained from all patients. The protocols were approved by an institutional review board (Quorum Review IRB, 1501 Fourth Avenue, Suite 800, Seattle, WA 98101, USA).

Patients and treatments

Inclusion and exclusion criteria for the three studies have been described previously.[11,12] For the 12- and 52-week studies, we enrolled patients aged at least 40 years with moderate to very severe COPD, a smoking history of at least 10 pack-years, a postipratropium FEV_1/forced vital capacity ratio <0.7, and a postipratropium FEV_1 $<80\%$ of predicted normal and >700 ml at screening. Patients with a substantially increased risk for cardiovascular events, such as myocardial infarction within the past 6 months, unstable or

life-threatening cardiac arrhythmia, or New York Heart Association Class IV heart failure were excluded from the study.

In studies 0126 and 0127, patients were randomized (1:1:1) in a double-blind manner to receive revefenacin 175 µg, revefenacin 88 µg, or placebo administered once daily *via* PARI LC® Sprint jet nebulizer (Pari Respiratory Equipment, Inc.) for 12 weeks. In study 0128, patients received revefenacin 175 µg, revefenacin 88 µg, or tiotropium 18 µg for 52 weeks. Revefenacin inhalation solutions were administered similar to the 12-week studies, and the open-label tiotropium was administered *via* oral inhalation using the HandiHaler® device (Boehringer Ingelheim). Because 175 µg is the US Food and Drug Administration approved dose,[15] safety and efficacy results for revefenacin 175 µg, the clinically relevant dose, are reported here. Efficacy results for revefenacin 88 µg are included as part of the supplemental information.

In the 12-week studies, up to 40% of patients were permitted concomitant use of LABA (LABA cap, controlled through stratification during randomization) with or without ICS. In the 52-week study, all patients were permitted concomitant use of LABA or ICS/LABA, and patients who started LABA-containing medication after enrolling to treat a COPD exacerbation were allowed to remain in the study. The dose of these agents was required to be stable for at least 30 days before screening and throughout the studies. The choice of LABA-containing products was not restricted, whereas the ICS component was restricted to ⩽1000 µg/day fluticasone propionate or equivalent. ICS/LABA or LABA was administered immediately before revefenacin to standardize the drug administration procedure, and spirometry measured the combined effect of LABA-containing drug and revefenacin.

Assessments and endpoints

Effect on bronchodilation was assessed as the change from baseline in trough FEV_1 at days 15, 29, 57, and 85 in pooled studies 0126 and 0127. Trough was defined as the mean of the 15- and 45-min predose assessments on days 29, 57, and 85. Change in trough FEV_1 from baseline was also analyzed based on airflow obstruction in patients with FEV_1 ⩾50% predicted (mild to moderate airflow obstruction) and patients with FEV_1 <50% predicted (severe to very severe obstruction) in the non-LABA and LABA subgroups.

Clinical health outcomes were assessed using the St. George's Respiratory Questionnaire (SGRQ).[16] Change from baseline in SGRQ total score (1-month recall period) on days 29, 57, and 85 was assessed for the 12-week studies. A decrease of ⩾4 units from baseline in SGRQ total score is considered the minimal clinically important difference. Change in SGRQ total score was also analyzed based on airflow obstruction.

The pooled incidence of adverse events (AEs) from studies 0126, 0127, and 0128 are reported and include treatment-emergent AEs, moderate or severe AEs, antimuscarinic AEs, and adverse cardiovascular events.

Statistical analyses

Efficacy analyses for the subgroup of patients taking concomitant LABA (with or without ICS) *versus* those not taking LABA were predefined in the study protocol. Selected analyses were conducted using the subgroup analysis sets. For the pooled data analysis from the 12-week studies, a repeated statement of subject identification nested within the study instead of a random statement to ensure convergence was used. Nominal *p* values are reported for all comparisons. *p*-value indicates the statistical significance of testing the null hypothesis that there is no difference from baseline in trough FEV_1 within each dose and treatment.

Results

Study population

Patient demographics and baseline characteristics for pooled studies 0126 and 0127, and study 0128 are summarized in Table 1. Demographics were consistent between the non-LABA and LABA subgroups across all studies, except that more patients were currently smoking in the non-LABA subgroup in the 12- and 52-week studies. In the combined 12-weeks studies, the LABA subgroup included 300 (36.9%) patients [revefenacin, 153 (51.0%); placebo, 147 (49.0%)] and the majority of these patients [290 (96.7%); revefenacin, 148 (96.7%); placebo, 142 (96.6%)] were taking a combination of ICS and LABA. In the 52-week study, 335 (50.0%) patients were taking concurrent LABA-containing product [revefenacin, 158 (47.2%); tiotropium, 177 (52.8%)] and the majority [318 (94.9%); revefenacin, 146 (92.4%); tiotropium,

Table 1. Key demographic and baseline clinical characteristics from pooled studies 0126 and 0127 and study 0128.

Characteristic	Pooled studies 0126 and 0127				Study 0128			
	Non-LABA		LABA		Non-LABA		LABA	
	Placebo (*n* = 270)	REV 175 µg (*n* = 242)	Placebo (*n* = 147)	REV 175 µg (*n* = 153)	TIO 18 µg (*n* = 174)	REV 175 µg (*n* = 161)	TIO 18 µg (*n* = 177)	REV 175 µg (*n* = 158)
Age, mean (SD), y	63.2 (8.8)	63.1 (8.9)	65.3 (9.2)	65.2 (8.7)	63.3 (9.5)	63.8 (8.5)	66.6 (8.0)	65.3 (8.7)
Sex (male), *n* (%)	135 (50.0)	112 (46.3)	71 (48.3)	83 (54.2)	93 (53.4)	95 (59.0)	118 (66.7)	93 (58.9)
Race (white), *n* (%)	247 (91.5)	212 (87.6)	132 (89.8)	138 (90.2)	160 (92.0)	148 (91.9)	166 (93.8)	146 (92.4)
BMI, mean (SD), kg/m^2	29.3 (6.8)	29.1 (7.2)	29.4 (6.7)	29.5 (6.9)	29.0 (6.4)	28.4 (6.5)	28.7 (6.3)	29.7 (6.6)
Current smoker, *n* (%)	142 (52.6)	133 (55.0)	56 (38.1)	57 (37.3)	97 (55.7)	90 (55.9)	67 (37.9)	50 (31.6)
Concurrent ICS use, *n* (%)	25 (9.3)	25 (10.3)	146 (99.3)	149 (97.4)	14 (8.0)	12 (7.5)	173 (97.7)	153 (96.8)
Concurrent LABA or ICS/LABA use, *n* (%)	0	0	147 (100)	153 (100)	0	0	177 (100)	158 (100)
Concurrent ICS/LABA use, *n* (%)	0	0	142 (96.6)	148 (96.7)	0	0	172 (97.2)	146 (92.4)
FEV_1, mean (SD), L	1.4 (0.5)	1.3 (0.4)	1.2 (0.4)	1.2 (0.4)	1.4 (0.5)	1.4 (0.5)	1.2 (0.5)	1.3 (0.4)
Patients with mMRC ⩾2, *n* (%)	140 (51.9)	103 (42.6)	77 (52.4)	81 (52.9)	86 (49.4)	78 (48.4)	94 (53.1)	92 (58.2)
Patients with CAT ⩾10, *n* (%)	243 (90.0)	208 (86.0)	133 (90.5)	138 (90.2)	157 (90.2)	148 (91.9)	162 (91.5)	140 (88.6)
Patients with ⩾1 exacerbation in prior year, *n* (%)	56 (20.7)	44 (18.2)	38 (25.8)	43 (28.1)	30 (17.2)	25 (15.5)	50 (28.2)	52 (32.9)
SGRQ Total Score, mean (SD)	48.9 (17.3)	46.9 (18.2)	50.8 (17.2)	49.2 (18.2)	50.4 (17.7)	49.3 (15.9)	49.5 (14.6)	52.0 (17.7)

BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; mMRC, modified Medical Research Council dyspnea scale; REV, revefenacin; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; TIO, tiotropium; y, years.

172 (97.2%)] were taking an ICS/LABA combination.

Patients in the LABA subgroup generally had a more severe disease than the non-LABA subgroup. Baseline mean [standard deviation (SD)] FEV_1 was numerically lower in the LABA subgroup [revefenacin, 1.2 (0.4) l; placebo, 1.2 (0.4) l] than the non-LABA subgroup [revefenacin, 1.3 (0.4) l; placebo, 1.4 (0.5) l] in the pooled 12-week studies and in 52-week study [LABA: revefenacin, 1.3 (0.4) l; tiotropium, 1.2 (0.5) l and non-LABA: revefenacin, 1.4 (0.5) l; tiotropium, 1.4 (0.5) l]. More patients in the LABA subgroup had a score of at least two on the modified Medical Research Council dyspnea scale than in the non-LABA subgroup across all studies [pooled 0126 and 0127, 158 (52.7%) *versus* 243 (47.5%); 0128, 186 (55.5%) *versus* 164 (49.0%)]. A higher percentage of patients in the LABA subgroup [studies 0126 and 0127, 81 (27.0%); study 0128, 102 (30.4%)] had experienced at least one COPD exacerbation in the year before the study initiation than the non-LABA subgroup [studies 0126 and 0127, 100 (19.5%); study 0128, 55 (16.4%)].

Table 2. Summary of change from baseline in day 85 trough FEV_1 and SGRQ total scores.

	ITT				$FEV_1 \geq 50\%$ predicted				$FEV_1 < 50\%$ predicted			
	Non-LABA		LABA		Non-LABA		LABA		Non-LABA		LABA	
	Placebo	REV 175 µg	Placebo	REV 175 µg	Placebo	REV 175 µg	Placebo	REV 175 µg	Placebo	REV 175 µg	Placebo	REV 175 µg
Change from baseline in trough FEV_1												
Evaluable patients	207	192	89	118	156	137	53	55	51	55	36	63
LS mean (SE), ml	−33.3 (14.7)	117.7 (15.0)	−27.4 (21.9)	111.8 (19.7)	−55.0 (17.6)	114.9 (18.5)	−31.9 (29.8)	76.1 (29.0)	9.1 (26.4)	106.8 (25.3)	−13.5 (30.7)	167.4 (24.5)
LS mean difference (SE), ml		150.9 (20.7)		139.2 (28.7)		169.8 (25.2)		107.9 (40.9)		97.7 (36.3)		180.8 (38.5)
95% CI for mean difference, ml		110.3 to 191.6		82.9 to 195.5		120.4 to 219.2		27.6 to 188.3		26.4 to 169.1		105.0 to 256.7
Nominal *p**		<0.0001		<0.0001		<0.0001		0.008		0.007		<0.0001
Change from baseline in total SGRQ score												
Evaluable patients	191	170	85	118	143	120	48	56	48	50	37	62
LS mean (SE)	−0.4 (0.8)	−3.8 (0.8)	−1.5 (1.1)	−5.0 (1.0)	−1.6 (0.9)	−3.8 (0.9)	−1.9 (1.5)	−5.0 (1.4)	2.2 (1.5)	−3.9 (1.5)	−1.0 (1.7)	−5.3 (1.4)
LS mean difference (SE)		−3.3 (1.1)		−3.4 (1.4)		−2.2 (1.2)		−3.1 (2.0)		−6.1 (2.1)		−4.2 (2.2)
95% CI for mean difference		−5.4 to −1.2		−6.3 to −0.6		−4.6 to 0.2		−6.9 to 0.8		−10.3 to −2.0		−8.5 to 0.1
Nominal *p**		0.002		0.018		0.078		0.115		0.004		0.054

*Nominal *p* values for comparison with placebo.
CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ITT, intention-to-treat; LABA, long-acting β-agonist; LS, least squares; REV, revefenacin; SE, standard error; SGRQ, St. George's Respiratory Questionnaire.

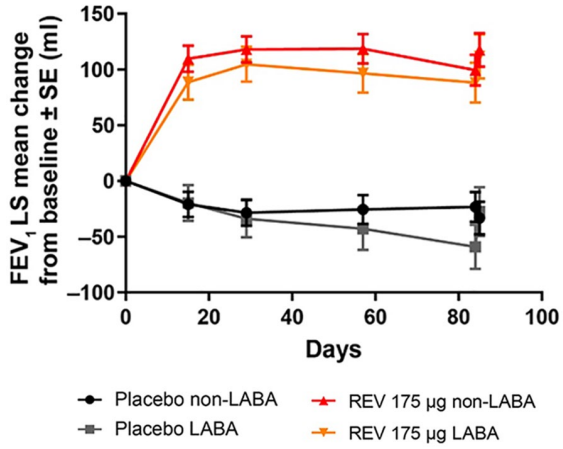

Figure 1. Sustained improvement in trough FEV_1 over 12 weeks.
FEV_1, forced expiratory volume in 1 second; LABA, long-acting β-agonist; LS, least squares; REV, revefenacin; SE, standard error.

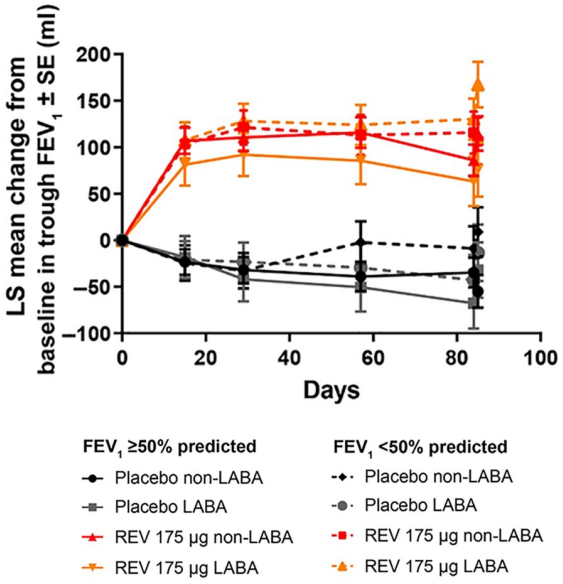

Figure 2. Changes from baseline in trough FEV_1 according to the airflow obstruction.
FEV_1, forced expiratory volume in 1 second; LABA, long-acting β-agonist; LS, least squares; REV, revefenacin; SE, standard error.

Efficacy outcomes

Overall, treatment with 175-µg revefenacin produced significantly greater improvements from baseline in trough FEV_1 than placebo regardless of concomitant ICS/LABA or LABA use (nominal $p < 0.0001$; Table 2). Similar improvements in trough FEV_1 were observed for the non-LABA [least squares (LS) mean difference from placebo in day 85 trough FEV_1, 150.9 ml; 95% confidence interval (CI), 110.3–191.6 ml] and LABA subgroups (LS mean difference, 139.2 ml; 95% CI, 82.9–195.5 ml; Table 2). A clinically significant improvement of an approximately 100 ml increase in trough FEV_1 was sustained for 12 weeks with revefenacin in both subgroups (Figure 1).

Sustained improvements in trough FEV_1 from baseline were observed with revefenacin for 12 weeks among patients with airflow obstruction ranging from moderate to very severe regardless of the ICS/LABA use (Figure 2). Revefenacin produced a placebo-adjusted LS mean difference from baseline in day 85 trough FEV_1 of 169.8 (95% CI, 120.4–219.2) ml in the non-LABA and 107.9 (95% CI, 27.6–188.3) ml in LABA subgroups among patients with FEV_1 ⩾50% predicted (Table 2). In patients with more severe airflow obstruction (FEV_1 <50% predicted), the placebo-adjusted LS mean difference in trough FEV_1 on day 85 was 97.7 (95% CI, 26.4–169.1) ml in the non-LABA subgroup and 180.8 (95% CI, 105.0–256.7) ml in the LABA subgroup (Table 2).

Improvements from baseline in trough FEV_1 were also observed with an 88 µg dose of revefenacin in the overall population and patients with moderate to very severe airflow obstruction regardless of ICS/LABA use (Supplementary Figure 1).

Health outcomes assessments

Revefenacin treatment produced substantial improvements in SGRQ total score compared with placebo for 12 weeks in the non-LABA and LABA subgroups (Figure 3). Significantly greater improvements than placebo in the day 85 SGRQ total score were observed for 175-µg revefenacin with LS mean difference from placebo of –3.3 (95% CI, –5.4 to –1.2; nominal *p*, 0.002 *versus* placebo) in the non-LABA subgroup and –3.4 (95% CI, –6.3 to –0.6; nominal *p*, 0.018 *versus* placebo) in the LABA subgroup (Table 2). Improvement in total scores with revefenacin approached a clinical significance of ⩾4-unit change from baseline in both subgroups (Figure 3). A total of 79 patients (46.5%) in the non-LABA subgroup and 56 patients (47.5%) in the LABA subgroup had ⩾4-unit change from baseline in the total SGRQ scores.

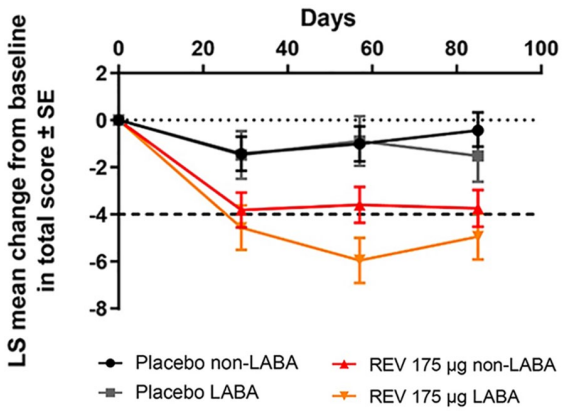

Figure 3. Change from baseline in total SGRQ scores.
LABA, long-acting β-agonist; LS, least squares; REV, revefenacin; SE, standard error; SGRQ, St. George's Respiratory Questionnaire.

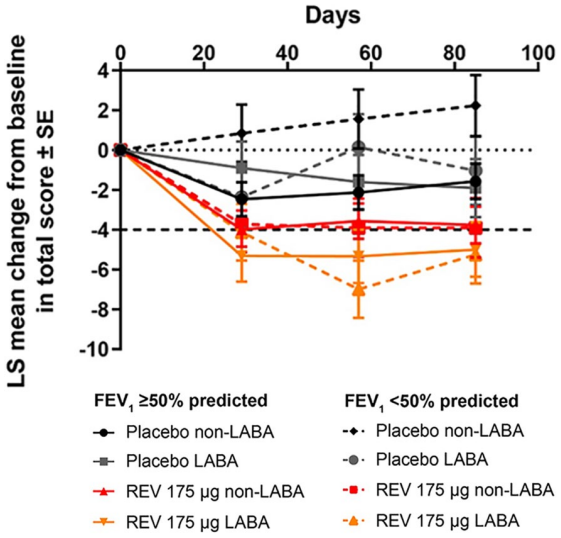

Figure 4. Changes from baseline in total SGRQ score according to the airflow obstruction.
FEV_1, forced expiratory volume in 1 second; LABA, long-acting β-agonist; LS, least squares; REV, revefenacin; SE, standard error; SGRQ, St. George's Respiratory Questionnaire.

Numerically higher improvements were observed in the total SGRQ score with revefenacin than placebo among patients with FEV_1 ⩾50% predicted and those with FEV_1 <50% predicted in the non-LABA and LABA subgroups (Figure 4). In patients with FEV_1 ⩾50% predicted, the LS mean difference from placebo in the change from baseline in day 85 total score was –2.2 (95% CI, –4.7 to 0.2) in the non-LABA and –2.9 (95% CI, –6.7 to 1.0) in LABA subgroups. In patients with severe to very severe airflow obstruction, the LS mean difference in day 85 total score was –5.9 (95% CI, –10.1 to –1.8) in the non-LABA subgroup and –4.0 (95% CI, –8.3 to 0.3) in the LABA subgroup. Among patients with FEV_1 ⩾50% predicted, 58 patients (48.3%) in the non-LABA subgroup and 25 (44.6%) in the LABA subgroup had ⩾4-unit change from baseline in the total SGRQ score; 21 patients (42.0%) in the non-LABA subgroup and 31 (50.0%) in the LABA subgroup among patients with FEV_1 <50% predicted had a similar change in total SGRQ score.

Improvements in SGRQ total scores were also observed with an 88 µg dose of revefenacin in the overall population and patients with moderate to very severe airflow obstruction in both the non-LABA and LABA subgroups (Supplementary Figure 2).

Safety outcomes

The pooled overall incidence of treatment-emergent AEs was higher in the LABA subgroup (50.2%) than the non-LABA subgroup (37.5%) for all treatments in the 12- and 52-week studies (combined data from studies 0126, 0127, and 0128; Table 3). Exacerbation of COPD was the most commonly reported treatment-emergent AE, and the incidence was higher in the LABA subgroup (25.0%) than the non-LABA subgroup (11.8%).

Incidence of moderate or serious AEs was also higher in the LABA subgroup (46.7%) than in the non-LABA subgroup (34.1%) for all treatments with COPD exacerbations as the most common moderate or severe AE (Table 3). Antimuscarinic-related AEs were reported more frequently in the LABA-subgroup (2.5%) than the non-LABA subgroup (1.4%). Dry mouth (non-LABA, 1.0%; LABA, 1.1%) and constipation (non-LABA, 0.6%; LABA, 1.2%) were the most frequently reported antimuscarinic-related AEs with one patient reporting dysuria in the LABA subgroup.

Treatment-emergent adverse cardiovascular events were reported in 34 (4.0%) patients in the non-LABA and 29 (4.5%) in LABA subgroups. More patients in the LABA subgroup (n=86; 13.3%) permanently discontinued treatment because of an AE than in the non-LABA subgroup (n=90; 10.5%). Four deaths were reported in the non-LABA subgroup and five in the LABA

Table 3. Pooled summary of AEs in patients from studies 0126, 0127, and 0128.

AEs in ⩾5% of patients in any group, *n* (%) (MedDRA preferred term)	Non-LABA			LABA		
	Placebo (*n* = 270)	TIO 18 μg (*n* = 176)	REV 175 μg (*n* = 411)	Placebo (*n* = 148)	TIO 18 μg (*n* = 180)	REV 175 μg (*n* = 319)
Any AE	**74 (27.4)**	**92 (52.3)**	**155 (37.7)**	**58 (39.2)**	**106 (58.9)**	**161 (50.5)**
COPD (worsening/exacerbation)	19 (7.0)	39 (22.2)	43 (10.5)	29 (19.6)	61 (33.9)	72 (22.6)
Cough	8 (3.0)	12 (6.8)	24 (5.8)	9 (6.1)	8 (4.4)	18 (5.6)
Dyspnea	15 (5.6)	4 (2.3)	12 (2.9)	8 (5.4)	9 (5.0)	13 (4.1)
Nasopharyngitis	5 (1.9)	8 (4.5)	21 (5.1)	4 (2.7)	9 (5.0)	20 (6.3)
Upper respiratory tract infection	7 (2.6)	8 (4.5)	16 (3.9)	2 (1.4)	16 (8.9)	15 (4.7)
Headache	6 (2.2)	11 (6.3)	12 (2.9)	5 (3.4)	9 (5.0)	17 (5.3)
Urinary tract infection	4 (1.5)	9 (5.1)	11 (2.7)	3 (2.0)	6 (3.3)	4 (1.3)
Hypertension	5 (1.9)	9 (5.1)	7 (1.7)	0	7 (3.9)	8 (2.5)
Pneumonia	1 (0.4)	3 (1.7)	4 (1.0)	1 (0.7)	11 (6.1)	4 (1.3)
Moderate or severe AEs in ⩾5% of patients in any group, *n* (%)						
Any AE	**57 (21.1)**	**95 (54.0)**	**140 (34.1)**	**47 (31.8)**	**115 (63.9)**	**140 (43.9)**
COPD (worsening/exacerbation)	16 (5.9)	36 (20.5)	33 (8.0)	24 (16.2)	57 (31.7)	57 (17.9)
Upper respiratory tract infection	1 (0.4)	1 (0.6)	8 (1.9)	0	12 (6.7)	6 (1.9)
Pneumonia	1 (0.4)	0	3 (0.7)	1 (0.7)	11 (6.1)	2 (0.6)
Patients with antimuscarinic AEs, *n* (%)						
Any AE	**1 (0.4)**	**8 (4.5)**	**3 (0.7)**	**0**	**7 (3.9)**	**9 (2.8)**
Dry mouth	0	6 (3.4)	3 (0.7)	0	4 (2.2)	3 (0.9)
Constipation	1 (0.4)	4 (2.3)	0	0	3 (1.7)	5 (1.6)
Dysuria	0	0	0	0	0	1 (0.3)

AE, adverse event; COPD, chronic obstructive pulmonary disease; LABA, long-acting β-agonist; MedDRA, Medical Dictionary for Regulatory Activities; REV, revefenacin; TIO, tiotropium.

subgroup; deaths were deemed not related to an AE where the cause of death was known.

Numerically fewer treatment-emergent AEs, moderate or severe, and antimuscarinic AEs were reported with revefenacin than tiotropium in both the non-LABA and LABA subgroups (Table 3). Fewer adverse cardiovascular events were reported with revefenacin treatment (non-LABA: $n = 13$, 3.2%; LABA: $n = 15$, 4.7%) than tiotropium (non-LABA: $n = 13$, 7.4%; LABA: $n = 14$, 7.8%) in both the non-LABA and LABA subgroups.

Discussion

Many patients with COPD require a combination of bronchodilator therapy—LAMA/LABA, ICS/LABA, or ICS/LABA/LAMA—for COPD symptom management. Up to 50% of patients with COPD enrolled in the phase III trials of revefenacin were using a LABA-containing medication; therefore, evaluation of efficacy and safety of revefenacin in this subgroup of patients was prespecified in trial protocols. Results of the subgroup analysis provide evidence that revefenacin for nebulization is equally efficacious in improving lung

function and health outcomes among patients taking concomitant LABA-containing medication and those taking revefenacin alone.

More than 90% of patients taking LABA-containing medication in our trials were taking a combination of ICS/LABA; therefore, after the addition of revefenacin, these patients were effectively using ICS/LABA/LAMA triple therapy. Revefenacin produced similar, nominally significant improvements from baseline in trough FEV_1 than placebo in the LABA and non-LABA subgroups. Even in patients with severe to very severe airflow obstruction (FEV_1 <50% predicted) revefenacin produced significant improvements in trough FEV_1 than placebo in both LABA subgroups. Overall improvement in trough FEV_1 was slightly higher in the non-LABA subgroup than the LABA subgroup, which could be due to a ceiling effect. It is also possible that lower improvements in lung function among patients taking concomitant ICS/LABA were due to the underlying severity of their disease: patients in the LABA subgroup had lower FEV_1 at baseline than the non-LABA subgroup. In addition, more patients in the LABA subgroup had higher dyspnea and more exacerbations than the non-LABA subgroup, requiring additional bronchodilator therapy.

Patients receiving revefenacin treatment reported favorable health outcomes with a greater change from baseline in SGRQ scores than placebo in the non-LABA and LABA subgroups. Placebo-adjusted change from baseline was comparable between the two subgroups. However, the LS mean change from baseline in the LABA subgroup was more pronounced than the non-LABA subgroup, reaching a clinically significant ⩾4-unit change from baseline. It is possible that because the patients in the LABA subgroup had more severe symptoms at baseline, they reported more benefit from additional therapy. Revefenacin improved respiratory health outcomes in the subgroups regardless of the severity of airflow obstruction.

Revefenacin was well tolerated with no additional safety concerns associated with concomitant ICS/LABA use. Incidence of treatment-emergent AEs was numerically higher in the LABA subgroup than the non-LABA subgroup with COPD exacerbation as the most frequently reported AE across all treatments. Higher incidence of COPD exacerbation in the subset of patients taking the triple therapy could be due to the underlying severity of airflow obstruction in these patients. In addition, patients in the LABA subgroup had higher exacerbation rate at baseline than the non-LABA subgroup. Although the number of patients with COPD exacerbations was higher in the LABA subgroup than the non-LABA subgroup, the proportion of patients experiencing exacerbation was similar between patients taking ICS/LABA or LABA in combination with revefenacin and tiotropium. The overall incidence of adverse cardiovascular events was low during the studies, and the addition of revefenacin to ICS/LABA or LABA did not increase the risk for adverse cardiovascular events.

The Global Initiative for Chronic Obstructive Lung Disease strategy document recommends escalation to triple therapy for patients who have recurrent exacerbations or continuing symptoms on LAMA/LABA or ICS/LABA combination therapy.[3] The efficacy of triple therapy has been established in several randomized controlled trials.[17–24] In a systematic review and meta-analysis, Zheng and colleagues reported that the combination of LAMA, LABA, and ICS in patients with advanced COPD demonstrated better lung function and health-related quality of life, and lower rates of moderate or severe exacerbation of COPD than dual therapy or monotherapy.[25] Our results further support the effectiveness of combining LAMA with ICS/LABA. The effect observed with revefenacin for nebulization in our studies is also consistent with those from a subgroup analysis of patients from GOLDEN trials receiving nebulized LAMA glycopyrrolate in addition to ICS/LABA.[26] Similar to our results, nebulized glycopyrrolate was shown to improve lung function and health outcomes in patients with a background of ICS/LABA combination therapy.[26]

We acknowledge that our study has limitations. The majority of patients in the LABA subgroup were taking an ICS/LABA combination; therefore, our results are more applicable to the use of revefenacin as a part of ICS/LABA/LAMA triple therapy instead of LABA/LAMA therapy. This was a subgroup, exploratory analysis and was not powered to show a significant difference between the non-LABA and LABA subgroups. Further studies specifically designed to test the difference in efficacy and safety of revefenacin monotherapy *versus* revefenacin in combination with ICS/LABA, or the real-world data on the use of revefenacin in combination with other therapies would be useful.

Altogether, our results demonstrate that revefenacin for nebulization significantly improved lung function (trough FEV_1) and health outcomes (total SGRQ scores) in patients with moderate to very severe COPD regardless of concomitant ICS/LABA use. Although patients in the LABA subgroup had a more severe disease at baseline, the improvement in trough FEV_1 was similar to that observed in patients taking revefenacin alone (i.e. patients with less severe COPD). Revefenacin was well tolerated with no additional safety concerns in patients taking concomitant ICS/LABA. Patients in the LABA subgroup had a higher incidence of treatment-emergent AEs; however, the safety profile of revefenacin in combination with ICS/LABA was similar to that of the tiotropium/ICS/LABA combination. Altogether, our data demonstrate that revefenacin for nebulization is an effective and safe maintenance treatment option for patients with COPD who require concurrent ICS/LABA or LABA treatment.

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Conflict of interest statement

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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