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Efficacy and Safety of Revefenacin Versus Glycopyrronium in Indian Chronic Obstructive Pulmonary Disease (COPD) Patients: A Randomized, Active-Controlled, Phase III Trial

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) affects 50-55 million individuals in India. Long-acting muscarinic antagonists (LAMAs) are a cornerstone of maintenance pharmacotherapy according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations. Revefenacin, a once-daily nebulized LAMA approved by the US FDA in 2018, lacks clinical evidence in Indian patients. This phase III study evaluated the efficacy and safety of revefenacin 175 mcg versus glycopyrronium 25 mcg in patients with moderate-to-very-severe COPD.

Methods

This prospective, randomized, open-label, active-controlled, multicenter phase III trial enrolled participants aged ⩾40 years with moderate-to-very-severe COPD (post-bronchodilator FEV_1/FVC <0.70; FEV_1 <80% predicted) and a smoking history of ⩾10 pack-years across 10 sites in India (Clinical Trials Registry-India: CTRI/2025/06/089258). Participants were randomized 1:1 to receive revefenacin 175 mcg once daily (n=121) or glycopyrronium 25 mcg twice daily (n=121) for 12 weeks. The primary endpoint was the change from baseline (CFB) in trough FEV_1 at week 12. Secondary endpoints included peak FEV_1 and FVC on day 1, trough FEV_1 at week 4, trough FVC at weeks four and 12, and the St. George's Respiratory Questionnaire (SGRQ) responder rate at week 12. Safety was assessed based on adverse events (AEs), vital signs, ECG findings, and laboratory parameters. Analysis of covariance (ANCOVA) was used, with comparability defined as p⩾0.05.

Results

Of the 242 randomized participants, 233 (96.3%) completed the study. Baseline characteristics were well balanced (mean age, 56.4 years; moderate COPD, 61.2%; severe COPD, 36.8%). The mean CFB in trough FEV_1 at week 12 was 256.3±232.32 mL for revefenacin and 251.8±265.14 mL for glycopyrronium (per-protocol population); the least squares (LS) mean difference was 4.5 mL (95% CI, -58.21 to 67.16; p=0.89). Secondary endpoints showed no significant between-group differences in peak FEV_1 (p=0.87), peak FVC (p=0.30), trough FEV_1 at week 4 (p=0.37), trough FVC at week 4 (p=0.81) and 12 (p=0.98), or SGRQ responder rate (87.2% vs. 84.8%; OR, 1.21; p=0.69). No deaths or serious AEs occurred. AE incidence was 11.57% with revefenacin and 12.40% with glycopyrronium. All events were mild to moderate, with no discontinuations due to AEs.

Conclusion

Revefenacin 175 mcg once daily demonstrated comparable efficacy and safety to glycopyrronium 25 mcg twice daily in Indian patients with COPD, supporting its use as a once-daily nebulized LAMA for COPD management in India.

Categories: Therapeutics, Pharmacology, Pulmonology
Keywords: chronic obstructive pulmonary disease, glycopyrronium, india, long-acting muscarinic antagonist, nebulized bronchodilator, revefenacin

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to abnormalities in the airways and/or alveoli, usually caused by significant exposure to noxious particles or gases [1]. It is the third leading cause of death worldwide and accounts for approximately 6% of all deaths globally [2]. The global prevalence of COPD is estimated to be approximately 9%-10% among individuals aged 40 years and above [3]. India has one of the highest burdens of COPD in the world, with an estimated 50-55 million affected individuals, and chronic respiratory diseases, predominantly COPD, account for more than 10% of total deaths in the country [4,5]. Tobacco smoking, biomass fuel exposure, indoor and outdoor air pollution, and occupational hazards are considered significant context-specific risk factors in India [4,6].

Pharmacological management of COPD aims to reduce symptoms, improve exercise tolerance and health status, and reduce the frequency and severity of exacerbations [1]. The current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend long-acting bronchodilators, including long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs), as the foundation of maintenance therapy in patients across all symptom and risk categories [7]. LAMAs competitively inhibit muscarinic M3 receptors on airway smooth muscle, with kinetic selectivity for prolonged M3 receptor occupancy, to prevent acetylcholine-induced bronchoconstriction, thereby decreasing airway resistance and dynamic hyperinflation and improving lung function [8,9].

Long-acting bronchodilators (e.g., LABAs or LAMAs) are often delivered via handheld devices, such as a dry powder inhaler (DPI) or a metered-dose inhaler (MDI). However, some patients with COPD (e.g., older adults and those with cognitive or physical limitations or suboptimal peak inspiratory flow rates (PIFRs)) find it difficult to use such devices, resulting in inaccurate dosing, poor adherence, and potentially poor clinical outcomes [10,11]. For these patients, nebulized drug delivery, which is easier to use and provides similar efficacy to handheld inhalers, can be an alternative treatment option [10,12].

Nebulized LAMAs, such as glycopyrronium, have consistently demonstrated efficacy in improving trough forced expiratory volume in 1 second (FEV_1) and health outcomes in patients with moderate-to-very-severe COPD [13]. Glycopyrronium is available in DPI and MDI formulations and as an inhalation solution for nebulization, used once or twice daily depending on the formulation [13,14]. It has demonstrated utility as a maintenance bronchodilator and, in nebulized form, for the management of acute exacerbations of obstructive airway disease in hospitalized patients in India [13-15]. However, twice-daily dosing regimens may affect long-term treatment adherence, especially among older adults, those with comorbid conditions, and those on complex multidrug regimens [16].

Revefenacin is a lung-selective, once-daily nebulized LAMA that was approved by the United States Food and Drug Administration (US FDA) in November 2018 for the maintenance treatment of COPD [17]. It exhibits kinetic selectivity for the M3 over the M2 muscarinic receptor, which translates into a prolonged bronchodilatory effect that supports once-daily dosing [18]. Clinical studies have demonstrated significant and sustained improvements in trough FEV_1 over 24 hours when revefenacin is delivered using a standard jet nebulizer [19,20].

The phase III clinical trials (Studies 0126 and 0127) demonstrated that revefenacin 175 mcg once daily produced statistically significant and clinically meaningful improvements in trough FEV_1 at 12 weeks compared with placebo, with a well-characterized safety profile consistent with the LAMA drug class [20]. Long-term safety data from the 52-week, randomized, active-controlled phase III trial of revefenacin (Study 0128), involving 1,055 patients with moderate-to-very-severe COPD, further established the tolerability of revefenacin 175 mcg once daily, with adverse event (AE) rates comparable to those with tiotropium and a safety profile supporting its use across diverse COPD populations [21,22]. Post hoc analyses have shown consistent improvements in lung function with revefenacin in patients with markers of more severe COPD [23]. In patients with suboptimal PIFR and severe airflow limitation, nebulized revefenacin produced greater improvements in trough FEV_1 than tiotropium delivered via DPI [12].

Although adequate international clinical evidence supports revefenacin, clinical evaluation in the Indian population is lacking. Given India's unique epidemiological context, characterized by a substantial burden of biomass fuel-related COPD, an earlier age of disease onset, distinct comorbidity profiles, and healthcare infrastructure considerations, local clinical evidence is needed before broader adoption in the country [4,5,24]. The once-daily dosing advantage of revefenacin is particularly relevant in the Indian context, where adherence to inhaled therapy is frequently suboptimal because of treatment complexity and socioeconomic factors [25,26].

The present phase III multicenter study, sponsored by Zydus Healthcare Limited, India, evaluated revefenacin inhalation solution to generate clinical evidence. To our knowledge, this is the first clinical trial of revefenacin conducted in India, providing India-specific evidence for a once-daily nebulized LAMA in patients with moderate-to-very-severe COPD. This study aimed to evaluate the efficacy and safety of revefenacin inhalation solution 175 mcg once daily compared with glycopyrronium inhalation solution 25 mcg twice daily in Indian patients with moderate-to-very-severe COPD over 12 weeks of treatment.

Materials And Methods

Study design

This was a prospective, randomized, open-label, parallel-group, active-controlled, multicenter Phase III clinical trial (Protocol No. 24-03) conducted at 10 investigational sites across India. The study was

conducted between July and December 2025.

Study setting and location

The study was conducted in the outpatient pulmonology and respiratory medicine departments of tertiary-care teaching hospitals and multispecialty hospitals in nine cities across seven Indian states: Rohtak (Haryana), Jaipur (Rajasthan), Bhubaneswar (Odisha), Belagavi (Karnataka), Prayagraj and Kanpur (Uttar Pradesh), Ahmedabad and Gandhinagar (Gujarat), and Tirupati (Andhra Pradesh). A tenth site in Vadodara (Gujarat) was initiated but did not randomize any participants.

Trial registration

The trial was registered with the Clinical Trials Registry-India (CTRI) before the enrollment of the first participant (registration number CTRI/2025/06/089258).

Ethical considerations

The study protocol, informed consent document, and participant diary card were approved by the Drug Controller General of India (DCGI), Central Drugs Standard Control Organization (CDSCO), and the institutional ethics committee (IEC) at each participating site before any study procedure was undertaken at that site [27]. The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines, the CDSCO GCP guidelines, the Indian Council of Medical Research (ICMR) National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, and the New Drugs and Clinical Trials Rules, 2019 [27-31]. Written informed consent was obtained from every participant before any study-related procedure [28,29,31].

Study population, sampling technique, and eligibility criteria

Inclusion criteria were: (i) adults of either sex aged ⩾40 years; (ii) a clinically confirmed diagnosis of moderate-to-very-severe COPD for at least six months prior to screening, as defined by GOLD guidelines; (iii) spirometric eligibility requiring a post-bronchodilator FEV_1/FVC ratio <0.7 and a post-bronchodilator FEV_1 <80% of the predicted normal value; (iv) a smoking history of ⩾10 pack-years (current smokers or former smokers who had quit >6 months prior to screening); (v) the ability to self-administer the study medication; (vi) understanding of the study requirements and provision of written informed consent; and (vii) sufficient literacy to complete the diary card [7,20,29,31,32].

Exclusion criteria were: (i) previous treatment with revefenacin and/or glycopyrronium inhalation solution; (ii) a current diagnosis of asthma; (iii) alpha-1 antitrypsin deficiency; (iv) other active or chronic respiratory disorders; (v) an acute COPD exacerbation requiring antibiotics, oral/systemic corticosteroids, or hospitalization; (vi) a history of pulmonary hypertension, respiratory failure, cor pulmonale, or right ventricular failure, or previous surgical treatment of the lungs; (vii) supplemental oxygen therapy exceeding 15 hours per day; (viii) participation in or plans to participate in the active phase of a supervised pulmonary rehabilitation program during the trial (participation in a maintenance program was permitted); (ix) use of medications with the potential to interact with revefenacin, glycopyrronium, salbutamol, or ipratropium bromide, or medications with the potential to affect or confound COPD status; (x) a history of adverse reactions or hypersensitivity to any of the following inhaled drugs or drugs belonging to similar classes: short- or LABAs, anticholinergic agents, corticosteroids, or sympathomimetic amines; (xi) clinically significant, uncontrolled systemic diseases, such as cardiovascular, renal, neurological, psychiatric, endocrine, immunological, or hematological disorders, or malignancy; (xii) hepatic dysfunction (serum transaminases ⩾3 times the upper limit of normal) or renal dysfunction (serum creatinine ⩾2.5 mg/dL) at screening; (xiii) ongoing alcohol and/or drug abuse; (xiv) pregnancy or lactation; and (xv) participation in another clinical trial within the preceding three months.

Patients with COPD attending the outpatient departments of the participating sites were recruited for the study. A non-probability consecutive sampling technique was used: patients presenting during the enrollment period were screened for eligibility, and all those who met all inclusion criteria, none of the exclusion criteria, and provided written informed consent were enrolled, with competitive recruitment across sites until the target sample size was reached. Enrolled participants were then allocated to treatment by randomization, as described under randomization and blinding.

Treatments

Eligible participants were randomized in a 1:1 ratio to one of two treatment arms for 12 weeks. The test treatment comprised revefenacin inhalation solution 175 mcg/3 mL (Batch No. TR5006; Zydus Healthcare Limited, India), administered by oral inhalation once daily, preferably in the morning, via a standard jet nebulizer with a mouthpiece. The reference treatment comprised glycopyrronium inhalation solution 25 mcg/2 mL (Batch No. EC50053; Axa Parenterals Ltd., India), administered by inhalation twice daily (25 mcg in the morning and 25 mcg in the evening) via a nebulizer, yielding a total daily dose of 50 mcg. Salbutamol MDI (100 mcg/puff) was provided as rescue medication for all participants. Participants were permitted to remain on stable doses of LABAs or inhaled corticosteroid (ICS)/LABA combinations, provided the ICS component was equivalent to fluticasone propionate ⩽1000 mcg/day.

Randomization and blinding

Randomization was performed using a centrally generated randomization plan in a 1:1 ratio. Each eligible

participant was assigned a unique randomization number at the baseline visit (visit 2, day 0). Due to differences in the physical characteristics of the investigational product (respules) of the test and reference treatments, blinding was not feasible; therefore, the study was conducted as an open-label investigation. The randomization schedule was prepared, and randomization numbers were provided to each investigator. Each eligible participant received the next available randomization number in sequence, and the numbers assigned to participants who discontinued were not reassigned.

Study visits and assessments

The total study duration was up to 16 weeks, comprising a screening period of up to 30 days (visit 1), followed by a 12-week treatment period with in-clinic visits on day 0 (visit 2), at week 4 (±3 days; visit 3), and at week 12 (±3 days; visit 4), and a telephone follow-up seven to 14 days after visit 4.

At screening, assessments included demographic data, medical and smoking history, vital signs, clinical examination, 12-lead electrocardiogram (ECG), spirometry (FEV_1 and FVC before and after bronchodilator administration), a urine pregnancy test (in females of childbearing potential), chest radiography (if not performed within the preceding 12 months), and hematological and biochemical laboratory investigations. Spirometry was performed at baseline (visit 2), week 4 (visit 3), and week 12 (visit 4), before and approximately two hours after the morning dose of the allocated study drug. Trough FEV_1 and FVC were defined as pre-dose spirometric values obtained approximately 24 (±2) hours after the last administered dose at visits 3 and 4. The St. George's Respiratory Questionnaire (SGRQ) was administered at baseline (visit 2) and at the end of treatment (visit 4) [33].

Endpoints

The primary efficacy endpoint was the change from baseline (CFB) in trough FEV_1 (mL) at the end of the 12-week treatment period. Secondary efficacy endpoints included: (i) CFB in peak FEV_1 during the two-hour post-dose period on the first day of dosing (visit 2); (ii) CFB in peak FVC during the two-hour post-dose period on the first day of dosing (visit 2); (iii) CFB in trough FEV_1 at week 4; (iv) CFB in trough FVC at weeks 4 and 12; and (v) the proportion of SGRQ responders (defined as a decrease of ⩾4 units from baseline in the SGRQ total score) at week 12. Safety endpoints included AEs, serious adverse events (SAEs), and COPD exacerbations reported during the study [34].

Control of confounding and bias

Randomization was used to balance known and unknown prognostic factors between the two treatment arms. Baseline outcome value, age category (40-59 years or ⩾60 years), sex, and smoking status (current smoker or former smoker) were identified a priori as potential confounders of lung function response and were included as covariates or fixed effects in all efficacy models. Medications with the potential to interact with the study drugs or affect COPD status were not permitted; background LABA or ICS/LABA therapy was allowed only at stable doses, and participants taking such therapy took their morning dose after pre-dose spirometry. Spirometry was performed in the morning at standardized times relative to dosing (trough measurements approximately 24 ± 2 hours after the previous dose and post-dose measurements approximately 2 hours ± 15 minutes after dosing), and laboratory investigations were performed predominantly at a central laboratory. Because the open-label design could not exclude performance and detection bias, an objective spirometric measure was chosen as the primary endpoint.

Statistical methods

The sample size for the primary endpoint was calculated assuming a meaningful difference between groups of 100 mL, a standard deviation (SD) of 227, and 90% power with a two-sided significance level of 5%. The calculation was based on a two-sided, two-sample comparison of means, using n per arm=$2(Z1\text{-}\alpha/2+Z1\text{-}\beta)^2\sigma^2/\delta^2$, where $Z1\text{-}\alpha/2=1.96$, $Z1\text{-}\beta=1.2816$ (90% power), $\sigma=227$ mL, and $\delta=100$ mL, which gave 108.3 participants per arm. Rounding up, a minimum of 218 evaluable participants (109 per arm) was required. Accounting for a 10% dropout rate and a 1:1 treatment allocation, 242 participants (121 per arm) were enrolled in the study.

Three analysis populations were defined: the Safety Population (all randomized participants who received at least one dose of the study drug), the modified intent-to-treat (mITT) population (all randomized participants who completed at least one post-randomization efficacy visit), and the per-protocol (PP) population (all randomized participants who completed all scheduled post-randomization visits without major protocol deviations). The PP population served as the primary analysis population, and mITT results were presented for consistency.

The primary endpoint (CFB in trough FEV_1 at week 12) was analyzed using analysis of covariance (ANCOVA), with smoking status, age category (<60 or ⩾60 years), sex, and treatment as independent fixed effects and baseline FEV_1 as a covariate. An identical ANCOVA model was applied to continuous secondary endpoints, while the SGRQ responder endpoint was analyzed using logistic regression, with baseline SGRQ total score as an additional covariate. Comparability between treatments for the primary endpoint was declared if the p-value was ⩾0.05 (i.e., no statistically significant difference at the 5% significance level). Treatment differences were presented as least squares (LS) means with 95% confidence intervals (CIs) and associated p-values. Continuous demographic and baseline variables were summarized using the mean, SD, median, minimum, and maximum, while categorical variables were summarized using frequencies and percentages. In each ANCOVA, the treatment effect was tested using the F-test (numerator degrees of freedom (df)=1; denominator df=223 in the PP population), and in the logistic regression model, it was

tested using the Wald chi-square (χ^2) test (df=1). These test statistics were reported alongside the p-values in the tables. All tests were two-sided, with α=0.05. No adjustment for multiplicity was made because no confirmatory secondary hypotheses were specified. Safety data (AEs, SAEs, COPD exacerbations, vital signs, ECG, and laboratory parameters) were summarized descriptively by treatment arm in the safety population, without formal hypothesis testing. AEs and medical history were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 28.0, and concomitant medications were coded using the WHO Drug Dictionary (March 2025). Missing data were not imputed; efficacy analyses used observed data on a visit-wise basis. All statistical analyses were performed using SAS® version 9.4 (PROC MIXED for ANCOVA; SAS Institute Inc., Cary, NC, USA).

Results

Patient disposition and baseline characteristics

A total of 256 participants were screened, and 243 participants met the study eligibility criteria. Among these, 242 participants were randomized (121 per treatment arm) to the revefenacin and glycopyrronium treatment groups. Nine participants (3.72%) discontinued the study (revefenacin: 4 (3.31%); glycopyrronium: 5 (4.13%)) due to loss to follow-up (n=4), withdrawal of consent (n=3), or investigator discretion (n=2). Overall, 233 participants (96.28%) completed the 12-week treatment period. The safety population comprised 242 participants, the mITT population 238 (98.35%), and the PP population 229 (94.63%). Figure *1* presents the CONSORT-style participant disposition flow.

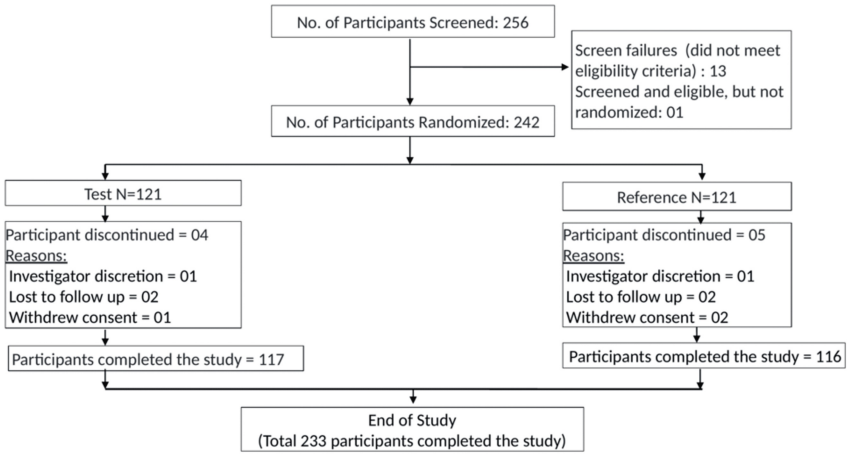


FIGURE 1: Diagrammatic representation of participant disposition

Baseline demographic and clinical characteristics were well balanced between the two treatment arms. All participants were of Asian race and non-Hispanic ethnicity. Baseline trough FEV_1 in the PP population was 1176.6±320.84 mL in the revefenacin arm and 1156.1±323.00 mL in the glycopyrronium arm. Mean treatment compliance was high and comparable between groups (97.45% vs. 96.49%). A summary of the demographic and baseline characteristics of the safety population is presented in Table *1*.

Parameter	Statistic	Revefenacin 175 mcg (n=121)	Glycopyrronium 25 mcg (n=121)
Age (years)	Mean	56.6	56.2
	SD	11.25	10.83
	Minimum	40	41
	Maximum	78	84
Male sex	n	104	96
	%	85.95	79.34
Height (cm)	Mean	166	165.2
	SD	7	7.7
Weight (kg)	Mean	65.2	63.4
	SD	12	10.2
Race: Asian	n	121	121
	%	100	100
Ex-smoker	n	79	79
	%	65.29	65.29
Current smoker	n	42	42
	%	34.71	34.71
Moderate COPD (GOLD 2)	n	74	74
	%	61.16	61.16
Severe COPD (GOLD 3)	n	45	44
	%	37.19	36.36
Very severe COPD (GOLD 4)	n	2	3
	%	1.65	2.48
Treatment compliance (%)	Mean	97.45	96.49
	SD	14.75	16.32

TABLE 1: Summary of demographic and baseline characteristics in the safety population (n=242)

COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease

Primary efficacy endpoint

In the PP analysis population, the mean CFB in trough FEV_1 at week 12 (visit 4) was 256.3±232.32 mL for the revefenacin arm and 251.8±265.14 mL for the glycopyrronium arm. The corresponding ANCOVA-derived LS mean difference was 4.5 mL (95% CI: -58.21 to 67.16; p=0.89), indicating no statistically significant difference between treatments at the 5% significance level. Results from the mITT analysis were consistent with the PP findings (LS mean difference: 18.0 mL; 95% CI: -48.72 to 84.64; p=0.60). A summary of the change in trough FEV_1 (mL) during the study period is presented in Table *2*, and the analysis of the change in trough FEV_1 (mL) from baseline to the end of the 12-week treatment period (visit 4) is presented in Table *3*.

Visit	Statistic	Revefenacin (n=117)	Glycopyrronium (n=112)
Screening (visit 1)	Mean (mL)	1184.1	1184.8
	SD (mL)	326.58	315.23
Baseline (visit 2, day 0)	Mean (mL)	1176.6	1156.1
	SD (mL)	320.84	323
Week 4 (visit 3)	Mean (mL)	1286.5	1281.2
	SD (mL)	349.21	342.36
CFB at week 4	Mean (mL)	109.9	125.1
	SD (mL)	157.79	165.65
Week 12 (visit 4)	Mean (mL)	1432.9	1407.9
	SD (mL)	372.89	370.38
CFB at week 12	Mean (mL)	256.3	251.8
	SD (mL)	232.32	265.14

TABLE 2: Summary of trough forced expiratory volume in 1 second (mL) across study visits in the PP population

Values are descriptive statistics of observed data.

CFB, change from baseline; FEV_1, forced expiratory volume in 1 second; SD, standard deviation; PP, per-protocol; ANCOVA, analysis of covariance

Treatment	n	LS mean CFB (mL)	SE of LS mean (mL)	LS mean difference (mL)	95% CI lower limit (mL)	95% CI upper limit (mL)	F-value	P-value
Revefenacin 175 mcg	117	237.5	29.24	4.5	-58.21	67.16	0.02	0.89
Glycopyrronium 25 mcg	112	233	28.27					

TABLE 3: Primary efficacy endpoint: CFB in trough forced expiratory volume in 1 second (mL) at week 12 in the PP population

LS mean difference=revefenacin minus glycopyrronium. The analysis was performed using ANCOVA, with smoking status, age category, sex, and treatment as fixed effects and baseline FEV_1 as a covariate. The F-value represents the F-statistic for the treatment effect (df=1, 223). The between-group estimate, 95% CI, F-value, and p-value apply to both treatment arms and are presented in merged cells. Decision criterion: p≥0.05 indicates no statistically significant difference. Descriptive values for baseline, week 12, and CFB are presented in Table 2.

CFB, change from baseline; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; LS, least squares; SE, standard error; ANCOVA, analysis of covariance; PP, per-protocol

Secondary efficacy endpoints

All secondary efficacy endpoints demonstrated comparable outcomes between the two treatment groups, with no statistically significant differences at the 5% significance level in either the PP or mITT populations (Table *4*).

Endpoint	Revefenacin	Glycopyrronium	Between-group estimate	95% CI lower limit	95% CI upper limit	Test statistic	Test statistic value	P-value
Peak FEV_1 CFB at day 1, 2 h post-dose (mL)	130.7	127.2	3.5	-39.32	46.39	F	0.026	0.87
Peak FVC CFB at day 1, 2 h post-dose (mL)	142.4	101.3	41.1	-37.11	119.26	F	1.072	0.30
Trough FEV_1 CFB at week 4 (mL)	71.1	89.4	-18.3	-58.76	22.10	F	0.798	0.37
Trough FVC CFB at week 4 (mL)	49.1	41.0	8.1	-56.87	73.08	F	0.060	0.81
Trough FVC CFB at week 12 (mL)	249.9	250.9	-1.0	-66.81	64.83	F	0.001	0.98
SGRQ total score CFB at week 12 (units)	-17.13	-16.73	-0.40	-3.35	2.54	F	0.073	0.79
SGRQ responders at week 12 (%)	87.18	84.82	1.21	0.49	2.98	Wald χ^2	0.163	0.69

TABLE 4: Between-group comparisons of secondary efficacy endpoints in the PP population

For spirometric endpoints and the SGRQ total score, the treatment columns show LS mean CFB, and the between-group estimate is the LS mean difference (revefenacin minus glycopyrronium), obtained using ANCOVA with smoking status, age category, sex, and treatment as fixed effects and the baseline value as a covariate. The test statistic is the F-statistic for the treatment effect (df=1, 223). For SGRQ responders, the treatment columns show the percentage of responders (defined as a ≥4-unit decrease in the SGRQ total score), and the between-group estimate is the odds ratio (revefenacin vs. glycopyrronium), obtained using logistic regression with the same fixed effects and baseline SGRQ total score as a covariate. The test statistic is the Wald χ^2 statistic (df=1).

CFB, change from baseline; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LS, least squares; SGRQ, St. George's Respiratory Questionnaire; PP, per-protocol

SGRQ responder rates at week 12 were 87.18% (102/117) in the revefenacin arm and 84.82% (95/112) in the glycopyrronium arm, with an odds ratio of 1.21 (95% CI: 0.49 to 2.98; p=0.69). The LS mean CFB in total SGRQ score at week 12 was -17.13 for revefenacin and -16.73 for glycopyrronium (LS mean difference: -0.40; 95% CI: -3.35 to 2.54; p=0.79). Both arms showed comparable, high proportions of SGRQ responders (>84%) and substantial improvements from baseline SGRQ scores (revefenacin: 54.4 to 38.3; glycopyrronium: 53.3 to 38.3; Table 5). Between-group comparisons for the SGRQ outcomes, including test statistics, are presented in Table 4.

Parameter	Statistic	Revefenacin (n=117)	Glycopyrronium (n=112)
Baseline SGRQ total score	Mean	54.38	53.35
	SD	21.45	21.2
Week 12 SGRQ total score	Mean	38.31	38.35
	SD	15.97	15.45
CFB in SGRQ total score	Mean	-16.07	-15.00
	SD	16.36	15.99
SGRQ responders (≥4-unit decrease)	n	102	95
	%	87.18	84.82

TABLE 5: SGRQ scores and responder rates at week 12 in the PP population

A responder is defined as having a ≥4-unit decrease in the SGRQ total score from baseline. Values are descriptive statistics of the observed data. Between-group comparisons (ANCOVA for CFB in total score and logistic regression for responders), including the corresponding test statistics, are presented in Table 4.

CFB, change from baseline; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; PP, per-protocol

Safety outcomes

The mean exposure duration was 84.4 days for the revefenacin arm and 83.4 days for the glycopyrronium arm. No deaths or SAEs were reported throughout the study. A total of 29 AEs were reported in 29 participants (11.98%), with 14 events in 14 participants (11.57%) in the revefenacin arm and 15 events in 15 participants (12.40%) in the glycopyrronium arm. None of the reported AEs in the revefenacin arm had an individual incidence exceeding 3%.

The severity profile was predominantly mild. Of the 29 AEs, 25 were mild, and four were moderate in severity; no severe AEs were recorded. Nine AEs were considered treatment-related (revefenacin: 3 (2.48%); glycopyrronium: 6 (4.96%)). All AEs resolved or recovered, except for one mild, treatment-unrelated event of increased lymphocyte count in the revefenacin arm, for which the outcome was unknown at the end of the study. No participant discontinued the study due to an AE.

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) were comparable between treatment groups throughout the study period, and no clinically significant abnormalities were identified. No clinically significant ECG findings were observed. One moderate COPD exacerbation (dyspnea and cough) was reported in a participant receiving glycopyrronium; no exacerbations were reported in the revefenacin arm. A summary of AEs in the safety population is presented in Table *6*.

Variable	Revefenacin 175 mcg (n=121), n (%)	Glycopyrronium 25 mcg (n=121), n (%)
Participants with ≥1 AE	14 (11.57)	15 (12.40)
Participants with ≥1 SAE	0 (0)	0 (0)
Treatment-related AEs	3 (2.48)	6 (4.96)
Mild AEs	12 (9.92)	13 (10.74)
Moderate AEs	2 (1.65)	2 (1.65)
Severe AEs	0 (0)	0 (0)
Deaths	0 (0)	0 (0)
Discontinued due to AE	0 (0)	0 (0)
Gastrointestinal disorders	3 (2.48)	3 (2.48)
Constipation	1 (0.83)	0 (0)
Dry mouth	0 (0)	2 (1.65)
Gastritis	1 (0.83)	1 (0.83)
Nausea	1 (0.83)	0 (0)
General disorders and administration site conditions	3 (2.48)	1 (0.83)
Pyrexia	3 (2.48)	1 (0.83)
Infections and infestations	0 (0)	1 (0.83)
Candida infection	0 (0)	1 (0.83)
Investigations	1 (0.83)	0 (0)
Lymphocyte count increased	1 (0.83)	0 (0)
Musculoskeletal and connective tissue disorders	2 (1.65)	3 (2.48)
Arthralgia	0 (0)	1 (0.83)
Back pain	2 (1.65)	2 (1.65)
Nervous system disorders	4 (3.31)	7 (5.79)
Dizziness	1 (0.83)	0 (0)
Headache	3 (2.48)	7 (5.79)
Renal and urinary disorders	1 (0.83)	0 (0)
Urinary tract obstruction	1 (0.83)	0 (0)
AEs recovered/resolved (events)	13 (92.86)	15 (100)
AEs with unknown outcome (events)	1 (7.14)	0 (0)
COPD exacerbation (moderate)	0 (0)	1 (0.83)

TABLE 6: Summary of AEs in the safety population

AEs were coded using MedDRA Version 28.0. Percentages are based on the number of participants in each treatment arm. Percentages for AE outcomes are based on the number of AEs (events) in each treatment arm. No between-group statistical tests were performed for safety data.

AE, adverse event; COPD, chronic obstructive pulmonary disease; SAE, serious adverse event

Discussion

This phase III, multicenter, randomized, active-controlled clinical trial is the first systematic evaluation of revefenacin inhalation solution in Indian patients with moderate-to-very-severe COPD. The principal finding of this study is that once-daily nebulized revefenacin 175 mcg produced a 12-week improvement in trough FEV_1 that was statistically comparable to that achieved with twice-daily glycopyrronium 25 mcg (LS mean difference: 4.5 mL; 95% CI: -58.21 to 67.16; p=0.89). The clinical importance of this study lies not in demonstrating superiority but in establishing that revefenacin's sustained bronchodilatory effect with once-daily administration is comparable to that of an established twice-daily regimen in the Indian COPD

population.

The magnitude of trough FEV_1 improvement observed in both arms (revefenacin: +256.3 mL; glycopyrronium: +251.8 mL from baseline) is numerically larger than the placebo-adjusted improvements of approximately 100-150 mL typically reported for LAMA monotherapies over comparable treatment durations [20,35]. Specifically, the replicate phase III trials (Studies 0126 and 0127) reported placebo-adjusted improvements in trough FEV_1 of 146 mL and 147 mL, respectively, for revefenacin 175 mcg over 12 weeks [20]. The larger changes observed in the present study are not directly comparable to these placebo-adjusted differences because they represent within-group changes from baseline in an open-label, active-controlled study without a placebo arm.

Secondary spirometric endpoints, including peak FEV_1 and FVC within two hours of the first dose and trough FVC at weeks 4 and 12, further support the comparable outcomes observed with the two treatment regimens. The rapid peak bronchodilatory response observed on day 1 with revefenacin is consistent with its known pharmacokinetic profile, characterized by rapid pulmonary onset and lung-selective deposition following nebulization [18,19]. The convergence of peak and trough spirometric measures supports the conclusion that revefenacin provides both a rapid onset and a sustained duration of action with once-daily dosing.

The SGRQ responder rate exceeded 84% in both treatment arms, with revefenacin yielding a numerically higher responder proportion (87.2% vs. 84.8%). Although this difference was not statistically significant (OR: 1.21; p=0.69), the high responder rates in both groups are clinically meaningful. A reduction of ⩾4 units in the SGRQ total score constitutes the established minimal clinically important difference (MCID) for health-related quality of life in COPD, and the substantial mean improvements observed in both arms (observed mean change: -16.1 for revefenacin vs. -15.0 for glycopyrronium; Table *5*) exceed this threshold, reflecting clinically meaningful patient-reported benefits [34]. These findings corroborate data from earlier revefenacin trials in which improvements in patient-reported outcomes aligned with objective lung function improvements [20,23].

The safety profile of revefenacin observed in this study was favorable and comparable to that of glycopyrronium. The overall AE incidence was low (11.57% vs. 12.40%), and all events were mild to moderate in severity. No deaths, SAEs, or treatment discontinuations due to AEs occurred in either arm. Headache was the most commonly reported AE, occurring in 2.48% of revefenacin-treated and 5.79% of glycopyrronium-treated participants, consistent with the revefenacin prescribing information, in which headache is listed among the most common adverse reactions [17]. The numerically higher incidence of headache in the glycopyrronium arm was based on a small number of events and should be interpreted with caution.

Based on the outcomes of this phase III clinical study and subsequent presentation to the Subject Expert Committee (SEC) of the CDSCO, India's national regulatory authority, the DCGI granted manufacturing and marketing permission for revefenacin 175 mcg/3 mL to M/s. Zydus Healthcare Limited on April 20, 2026, for the maintenance treatment of patients with COPD [36]. It will be a worthy addition to the arsenal of COPD treatment options for Indian patients.

The clinical relevance of once-daily dosing with revefenacin warrants emphasis in the context of COPD management in India. Suboptimal treatment adherence remains a pervasive challenge in COPD management globally and is particularly pronounced in India, where socioeconomic constraints, limited disease knowledge, and treatment complexity frequently compromise adherence to inhaled therapy [25,26]. Once-daily dosing has been associated with better adherence than more frequent dosing regimens in COPD, and the advantage of once-daily revefenacin over twice-daily glycopyrronium in this regard may translate into tangible real-world benefits in patient populations where adherence monitoring is limited [37].

The Indian COPD patient profile differs in several important respects from populations studied in pivotal Western trials. Biomass fuel exposure, particularly among rural women, contributes to a distinct COPD phenotype characterized by a higher proportion of never-smokers and younger patients [6,24]. Although the present study population was predominantly male and tobacco-exposed, reflecting recruitment from urban and semi-urban tertiary referral centers, the multicenter design, spanning nine sites that randomized participants across seven states, enhances the geographic representativeness of the findings within the Indian COPD population.

Nebulized bronchodilator therapy occupies a distinct and important niche within the Indian COPD therapeutic landscape. For patients who are unable to use DPIs or pressurized metered-dose inhalers (pMDIs) effectively due to hand-breath coordination difficulties, a subset that includes many elderly patients with comorbid arthritis or cognitive decline, nebulized administration represents the preferred or sole feasible modality [11]. In these clinical settings, revefenacin's once-daily nebulized formulation provides a practical therapeutic advantage over twice-daily nebulized glycopyrronium.

Strengths and limitations

This study is the first randomized controlled trial to systematically evaluate revefenacin in an Indian COPD population, thereby generating nationally relevant evidence aligned with the regulatory requirements of the CDSCO [27]. The study was conducted at multiple geographically distributed sites, employed robust spirometric endpoints and validated patient-reported outcome instruments, achieved a high completion rate

(>96%), and demonstrated high treatment compliance in both arms [33].

Study limitations include the open-label design, necessitated by differences in the physical characteristics of the two investigational products, which introduces the potential for performance and detection bias, especially in patient-reported outcomes. The 12-week treatment duration, while consistent with the duration of the pivotal phase III trials of nebulized LAMAs, precludes conclusions regarding long-term efficacy beyond the study period, including effects on exacerbation rates and disease progression [13,20]. The predominantly male and tobacco-exposed study population may limit generalizability to female patients and those with biomass fuel-associated COPD.

Future investigations should address the long-term safety and tolerability of revefenacin in Indian patients through extended follow-up studies, evaluate its efficacy in combination with ICSs or LABAs in the context of GOLD group E patients with frequent exacerbations, and assess clinical outcomes specifically in biomass fuel-associated COPD phenotypes. Real-world effectiveness studies across diverse Indian healthcare settings would further strengthen the evidence base for clinical adoption.

Conclusions

This prospective, randomized, multicenter, active-controlled phase III clinical trial demonstrates that revefenacin inhalation solution 175 mcg, administered once daily via nebulization, produces improvements in trough FEV_1, FVC, and health-related quality of life that are statistically comparable to those achieved with glycopyrronium inhalation solution 25 mcg, administered twice daily, over a 12-week treatment period in Indian patients with moderate-to-very-severe COPD. The safety and tolerability profiles of the two treatments were comparable, with no deaths, SAEs, or AE-related discontinuations observed in either arm.

Revefenacin inhalation solution represents the first once-daily nebulized LAMA to be systematically evaluated in the Indian COPD population, and the data from this study support its efficacy, safety, and clinical utility within current GOLD guideline-recommended treatment paradigms. The simplified once-daily dosing of revefenacin may offer a clinically meaningful advantage in optimizing adherence relative to twice-daily alternatives, particularly in the Indian real-world clinical setting. These findings provide an evidence base for the clinical adoption of revefenacin inhalation solution for the maintenance treatment of COPD in India.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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