e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2025; 17(11); 1020-1024

Original Research Article

Comparative Efficacy and Safety of Glycopyrronium/Formoterol Fixed-Dose Combination versus Glycopyrronium Monotherapy in COPD Patients

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Received: 23-09-2025 / Revised: 21-10-2025 / Accepted: 24-11-2025
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Conflict of interest: Nil

Abstract:

Aim: The aim of this study is to compare the efficacy and safety of glycopyrronium/formoterol fixed-dose combination (FDC) to glycopyrronium monotherapy in the management of patients with moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD).

Materials and Methods: A randomized, open-label, parallel-group study was conducted in tertiary care centers. Eligible patients (aged 40–75 years) with diagnosed moderate-to-severe COPD were randomized to receive either glycopyrronium/formoterol FDC (12.5/12 µg BID) via inhaler or glycopyrronium monotherapy (50 µg OD) for 12 weeks. Primary endpoints were improvement in FEV_1, symptom scores (mMRC, CAT), and exacerbation frequency. Secondary endpoints included quality of life (QoL), rescue inhaler use, and adverse events. Safety was monitored by recording all adverse events and routine laboratory parameters.

Results: A total of 220 patients were analyzed (112 in FDC group, 108 in monotherapy group). The FDC group showed a significantly greater improvement in mean FEV_1 (+225 mL vs +125 mL; $p<0.01$), greater reduction in mMRC and CAT scores, and fewer exacerbations over 12 weeks compared to monotherapy. Improvements in QoL scores were more pronounced in the FDC group (SGRQ score change, -14.7 vs -8.9; $p<0.01$). Adverse events were similar between groups, with dry mouth and cough most reported but mild. No significant cardiovascular or metabolic events were noted. Compliance and satisfaction were high in both groups.

Conclusion: Glycopyrronium/formoterol FDC demonstrated superior efficacy in improving lung function and symptoms, reducing exacerbations, and enhancing quality of life compared to glycopyrronium monotherapy, without increased safety risks, in moderate-to-severe COPD patients.

Keywords: COPD, Glycopyrronium, Formoterol, Fixed-Dose Combination, Bronchodilator, Efficacy, Safety.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of mortality and morbidity worldwide, marked by persistent respiratory symptoms, progressive airflow limitation, and frequent exacerbations.[1] Although long-acting bronchodilators are the mainstay of COPD management, there is growing evidence supporting the use of fixed-dose combinations (FDCs) of long-acting muscarinic antagonists (LAMAs) and long-acting beta2-agonists (LABAs) for improved patient outcomes.[2,3]

Glycopyrronium is a potent LAMA offering significant bronchodilation, reduced exacerbation rates, and notable safety. Formoterol, as a LABA, complements this action with rapid onset and sustained symptom improvement. [4,5] The combination of glycopyrronium with formoterol FDC is expected to provide additive benefits over monotherapy by targeting distinct pathways of bronchial smooth muscle relaxation.[6] While international studies have explored efficacy of such FDCs, head-to-head comparisons against monotherapy, particularly in diverse populations, remain limited.

This study aims to address this gap by evaluating the comparative efficacy and safety of glycopyrronium/formoterol FDC versus glycopyrronium alone in patients with moderate-to-severe COPD, focusing on clinical, functional, and quality-of-life outcomes over a 12-week period.

Materials & Methods

Study Design: This was a prospective, randomized, open-label, parallel-group clinical study conducted

between January 2023 and February 2025 in two tertiary care centers.

Inclusion Criteria:

- Age 40–75 years
- Diagnosed COPD (GOLD stage II–III, post-bronchodilator FEV_1 30–80% predicted)
- History of ≥1 moderate exacerbation in past year
- mMRC dyspnea score ≥2
- Stable clinical condition (no exacerbation in last 4 weeks)

Exclusion Criteria:

- Current diagnosis of asthma, bronchiectasis, or lung cancer
- Significant cardiovascular, renal, or hepatic comorbidity
- Use of systemic steroids or antibiotics within past 4 weeks
- Pregnancy or lactation

Randomization and Intervention Participants were randomized (1:1) to receive:

- **Group A (FDC):** Glycopyrronium 12.5 µg + Formoterol 12 µg, inhaled BID via dry powder inhaler
- **Group B (Monotherapy):** Glycopyrronium 50 µg, inhaled OD via DPI

Treatment duration: 12 weeks. All patients received training on inhaler technique.

Outcomes

Primary efficacy endpoints:

- Change in post-bronchodilator FEV_1 from baseline at 12 weeks
- Change in mMRC and CAT symptom scores
- Number of moderate/severe exacerbations

Secondary endpoints:

- Quality of life assessed by SGRQ score
- Rescue inhaler use (mean puffs per week)
- Treatment satisfaction (TSQM-9 scale)

Safety endpoints:

- Adverse events (nature, frequency, severity)
- Discontinuation rates
- Cardiovascular/metabolic parameters

Observation Tables

Table 1: Baseline Demographics and Clinical Characteristics of Study Participants

Demographics and Clinical Characteristics	FDC Group (n=112)	Monotherapy (n=108)	p-value
Age (years), mean ± SD	63.1 ± 8.3	62.8 ± 8.0	0.72
Male (%)	84 (75.0%)	82 (75.9%)	0.88
Smoking status (current/ex/never)	62/41/9	58/40/10	0.97
COPD duration (years)	6.8 ± 3.4	7.1 ± 3.7	0.64
FEV_1 (% predicted)	51.4 ± 12.9	50.7 ± 12.2	0.68
mMRC score	2.6 ± 0.5	2.7 ± 0.4	0.35
CAT score	19.7 ± 5.1	20.1 ± 4.9	0.61
SGRQ score	48.4 ± 12.3	49.0 ± 12.8	0.73

Table 2: Comparison of Key Efficacy Endpoints at 12 Weeks

Pulmonary Function and Symptom Scores	FDC Group	Monotherapy	p-value
Δ FEV_1 (mL)	+225 ± 72	+125 ± 68	<0.01
Δ mMRC score	-1.3 ± 0.6	-0.7 ± 0.7	<0.01
Δ CAT score	-6.3 ± 2.2	-3.1 ± 2.5	<0.01
Exacerbations (n, mean)	0.14 ± 0.42	0.31 ± 0.59	0.04

Table 3: Changes in Quality-of-Life Indices and Rescue Medication Requirements

Quality of Life and Rescue Medication	FDC Group	Monotherapy	p-value
Δ SGRQ score	-14.7 ± 5.3	-8.9 ± 5.7	<0.01
Δ TSQM-9 score	+12.6 ± 4.7	+8.2 ± 5.1	<0.01
Rescue inhaler use (puffs/week)	2.2 ± 1.1	4.9 ± 1.7	<0.01

Table 4: Incidence of Adverse Events and Discontinuation Rates

Adverse Events and Safety Outcomes	FDC Group (n=112)	Monotherapy (n=108)	p-value
Dry mouth	7 (6.3%)	6 (5.6%)	0.82
Cough	5 (4.5%)	4 (3.7%)	0.74
Palpitation	2 (1.8%)	2 (1.9%)	1.00
Headache	2 (1.8%)	1 (0.9%)	0.59
Serious AEs	0 (0%)	0 (0%)	—
Discontinuation (AEs)	2 (1.8%)	1 (0.9%)	0.59

Result

In this study of 220 moderate-to-severe COPD patients, the glycopyrronium/formoterol FDC group exhibited significantly greater improvement in FEV_1 at week 12 compared to the glycopyrronium monotherapy group (mean difference +100 mL, $p<0.01$). Symptom relief, assessed via mMRC and CAT scores, was also superior in the FDC group. A marked reduction in the number of moderate/severe exacerbations was noted in the FDC group (0.14 vs 0.31, $p=0.04$). Quality of life, as measured by the SGRQ score, improved more in the FDC group. Rescue inhaler uses and patient satisfaction scores favored FDC. Both groups had comparable adverse event rates, with no significant cardiovascular or severe adverse outcomes.

Statistical Analysis: Sample size calculation estimated 100 participants per group ($\alpha=0.05$, 80% power, detecting 100 mL FEV_1 difference), accounting for 10% attrition. Data were analyzed using SPSS v27. Continuous variables are expressed as mean ± SD; categorical variables as percentages. Independent t-test/Mann–Whitney U test and chi-square/Fisher's exact test were used as appropriate. A p-value <0.05 was considered statistically significant. The primary endpoint (improvement in post-bronchodilator FEV_1) showed statistically significant superiority of FDC over monotherapy ($p<0.01$, independent t-test). Secondary endpoints—change in SGRQ, CAT, mMRC scores, and rescue medication use—were also significantly better in the FDC group (all $p<0.05$). The incidence of adverse events did not differ significantly between groups (chi-square test). No cases of serious AE, hospitalization, or mortality were observed. A per-protocol and intention-to-treat analysis yielded similar findings, confirming robustness of results.

Discussion

COPD remains a significant global health challenge, with an estimated worldwide prevalence exceeding 10% among adults over age 40. Current guidelines endorse the use of long-acting bronchodilators, either as monotherapy or in combination, with the rationale that dual bronchodilation offers additive benefits for patients inadequately controlled on monotherapy. Glycopyrronium and formoterol, representing LAMA and LABA classes, respectively, have been widely investigated for their individual and synergistic efficacy in COPD management.

The present study demonstrated that glycopyrronium/formoterol FDC provides superior improvements in lung function, as evidenced by a mean FEV_1 increase of 225 mL, significantly greater than glycopyrronium alone. Moreover, the improvements in symptomatic scores (mMRC, CAT) align with previous meta-analyses wherein FDCs consistently reduced dyspnea, improved health status, and minimized daily symptoms in COPD populations compared to either agent alone.

A noteworthy finding was the lower frequency of exacerbations in the FDC arm (mean 0.14 vs 0.31), corroborating literature that dual bronchodilation reduces exacerbation risk, likely by optimizing airway patency and mucus clearance. Rescue medication usage was almost halved in the FDC group, suggesting not only enhanced day-to-day control of symptoms but potentially higher patient confidence in primary therapy, an important outcome in real-world management.

The substantial reduction in SGRQ scores in both groups reflects meaningful improvement in health-related quality of life, more pronounced in the FDC arm (-14.7 vs -8.9). This difference exceeds the minimum clinically important difference (MCID) for SGRQ, supporting the value of FDCs in addressing overall patient wellness. The TSQM-9 scale further suggested higher treatment satisfaction with FDC, echoing the potential role of simpler administration and better disease control in enhancing compliance and patient experience.

The safety profile observed in this study is consistent with previous large-scale trials: both treatments were well-tolerated, with low rates of mild adverse effects (dry mouth, cough), and no serious cardiovascular or metabolic events. Our findings indicate that adding formoterol to glycopyrronium does not increase the frequency or severity of adverse events, addressing concerns regarding safety of dual bronchodilation, particularly in patients with cardiovascular comorbidities.

Strengths: Strengths of this study include its randomized design, adequate power for detecting meaningful differences, use of validated symptom and quality-of-life measures, and robust statistical analysis (both ITT and per-protocol). Additionally, the study aligns with clinical practice through inhaler technique reinforcement and assessment of patient-relevant endpoints.

Limitations include its open-label design (potential for bias), relatively short follow-up (12 weeks), and a predominantly male, smoker population, potentially limiting generalizability. Biomarkers of inflammation and long-term exacerbation prevention were not evaluated. The study also excluded patients with significant comorbidities or recent exacerbations, so findings may not extend to more severe or unstable COPD patients.

Comparison with Previous Studies: Our findings are concordant with the results from pivotal clinical trials such as PINNACLE-1 and PINNACLE-2, which showed glycopyrronium/formoterol FDC superiority over monotherapy in FEV_1 improvement and symptom reduction.[8,18] Real-world studies,

such as those by Wedzicha et al., similarly observed benefits of dual therapy regarding exacerbation rates and patient-reported outcomes.[19,20] Meta-analyses and Cochrane reviews consistently endorse dual LABA/LAMA as providing greater efficacy than monotherapy, with a low additive risk of adverse effects.[3,17]

Future studies should focus on longer-term outcomes, diversity of populations (including women and non-smokers), and the impact of dual therapy on inflammation, disease progression, healthcare resource utilization, and cost-effectiveness. Additionally, assessment of adherence and inhaler technique over extended periods will inform the sustained benefits of fixed-dose combinations in real-world settings.

Conclusion

This randomized comparative study demonstrates that glycopyrronium/formoterol FDC offers significantly greater efficacy than glycopyrronium monotherapy in improving lung function, symptom burden, exacerbations, and quality of life in moderate-to-severe COPD patients, with a comparable safety profile. These findings support the early introduction of dual bronchodilator therapy in appropriate COPD populations to optimize clinical outcomes and patient satisfaction.

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