AMERICAN JOURNAL OF EDUCATION AND LEARNING
ISSN: 2996-5128 (online) | ResearchBib (IF) = 10.91 IMPACT FACTOR
Volume-3| Issue-10| 2025 Published: |30-11-2025|

LONG-TERM EFFICACY AND SAFETY OF BUDESONIDE/FORMOTEROL COMBINATION THERAPY IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

https://doi.org/10.5281/zenodo.17567450

Pulatova Nargiza Ikhsanovna
MD, DSc, Associate Professor
Zufarov Pulat Saatovich
MD, DSc, Professor
Pulatova Durdona Bakhadirovna
MD, PhD, Associate Professor
Abdumajidova Nozima Khamidullayevna
assistant
Tashkent State Medical University (Tashkent, Uzbekistan)

Abstract

Background: The long-term stability of clinical benefit from inhaled corticosteroid (ICS) and long-acting β2-agonist (LABA) combinations in Chronic Obstructive Pulmonary Disease (COPD) requires continuous evaluation in real-world settings. This study aimed to assess the sustained efficacy and safety of a fixed-dose combination (FDC) of budesonide/formoterol (B/F) over 12 months in patients with moderate-to-severe COPD.

Methods: We conducted a 12-month, single-center, prospective, open-label observational study. We enrolled 32 patients (mean age 62.5 ± 7.1 years) with moderate-to-severe COPD (GOLD 2-3) and a history of ≥1 exacerbation in the previous year, who were already prescribed B/F FDC. Patients were assessed at baseline, 6 months, and 12 months. Endpoints included changes in pre-bronchodilator FEV_1 (Forced Expiratory Volume in 1 second), exacerbation frequency, COPD Assessment Test (CAT) scores, modified Medical Research Council (mMRC) dyspnea scores, and St. George's Respiratory Questionnaire (SGRQ) scores. Safety was monitored via adverse event (AE) reporting.

Results: Twenty-nine (29) patients (90.6%) completed the 12-month follow-up. At 12 months, mean pre-BD FEV_1 showed a modest but significant improvement from baseline (1.45 ± 0.3 L vs. 1.55 ± 0.4 L; $p = 0.045$). The mean annual rate of moderate-to-severe exacerbations was significantly reduced from 1.4 ± 0.9 (in the year prior) to 0.5 ± 0.6 during the study year ($p < 0.001$). Clinically significant improvements were observed in patient-reported outcomes: CAT score decreased from 18.5 ± 4.2 to 12.0 ± 3.1 ($p < 0.001$), mMRC score from 2.2 ± 0.7 to 1.5 ± 0.6 ($p <$

AMERICAN JOURNAL OF EDUCATION AND LEARNING
ISSN: 2996-5128 (online) | ResearchBib (IF) = 10.91 IMPACT FACTOR
Volume-3| Issue-10| 2025 Published: |30-11-2025|

0.01), and SGRQ total score from 45.0 ± 8.1 to 35.5 ± 7.4 ($p < 0.001$). The B/F combination was well-tolerated. One patient (3.1%) developed pneumonia (non-hospitalized), and two (6.2%) reported oral candidiasis.

Conclusion: Long-term (12-month) treatment with budesonide/formoterol fixed-dose combination provides sustained improvements in lung function, a significant reduction in exacerbation frequency, and clinically meaningful improvements in symptom burden and quality of life in patients with moderate-to-severe COPD.

Keywords

COPD, Budesonide, Formoterol, Long-Term Efficacy, Exacerbations, Quality of Life

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide, characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible [1]. The primary goals of COPD management are to control symptoms, improve exercise tolerance, enhance quality of life (QoL), and, crucially, prevent and treat exacerbations, which accelerate disease progression [2].

Pharmacological therapy, centered on bronchodilators, is the cornerstone of management. For patients with persistent symptoms or a history of exacerbations despite bronchodilator monotherapy, guidelines recommend escalation of treatment. This often includes the addition of an inhaled corticosteroid (ICS) to a long-acting β2-agonist (LABA), particularly for patients with features of an eosinophilic phenotype or a significant history of exacerbations [2, 3].

The fixed-dose combination (FDC) of budesonide (an ICS) and formoterol (a fast- and long-acting LABA) has been well-established in the treatment of both asthma and COPD. The rapid onset of formoterol provides immediate symptom relief, while the combination acts synergistically to reduce inflammation (budesonide) and provide sustained bronchodilation (formoterol) [4]. Numerous short-term (3-6 months) randomized controlled trials (RCTs) have demonstrated the efficacy of this combination in improving lung function (FEV_1) and reducing exacerbations compared to its monocomponents [5].

However, COPD is a chronic, lifelong condition. The clinical utility of a therapy is ultimately defined by its long-term performance. There remains a need for "real-world" and long-term observational data (≥12 months) to confirm that the benefits observed in controlled RCTs are durable over time and that the safety profile, particularly concerning ICS-related risks like pneumonia, remains

acceptable during prolonged use [6]. This study was designed to address this gap by evaluating the sustained efficacy and safety of the budesonide/formoterol FDC in a "real-world" cohort of patients with moderate-to-severe COPD over a 12-month period.

Objective

The primary objective of this study was to evaluate the long-term (12-month) efficacy and safety of a fixed-dose combination of budesonide/formoterol in patients with moderate-to-severe chronic bronchial obstruction (COPD).

Specific Tasks:

To assess the change from baseline in pulmonary function (pre-bronchodilator FEV_1 and FVC) after 12 months of therapy.

To quantify the frequency of moderate-to-severe exacerbations during the 12-month study period and compare it to the 12-month period prior to enrollment.

To evaluate changes in patient-reported outcomes (PROs), including symptom load (CAT score), dyspnea (mMRC score), and health-related quality of life (SGRQ score).

To document the long-term safety and tolerability profile of the budesonide/formoterol combination by monitoring adverse events (AEs).

Materials and Methods

Study Design This was a 12-month, single-center, prospective, open-label, observational study conducted at the Department of Pulmonology of the Multidisciplinary Clinic of Tashkent State Medical University. The study protocol was approved by the local Institutional Review Board, and all patients provided written informed consent.

Patient Population A total of 32 patients were enrolled in the study.

Inclusion Criteria:

- Age ≥ 40 years.
- A confirmed diagnosis of COPD according to GOLD guidelines (post-bronchodilator FEV_1/FVC ratio < 0.70).
- Moderate-to-severe airflow limitation (GOLD 2 or GOLD 3; 30% ≤ FEV_1 < 80% predicted).
- A history of at least one moderate-to-severe COPD exacerbation (requiring systemic corticosteroids or hospitalization) in the 12 months prior to enrollment.
- Currently receiving a stable dose of budesonide/formoterol FDC (e.g., 160/4.5 mcg or 320/9 mcg, two inhalations twice daily) for at least 4 weeks prior to screening.

Exclusion Criteria:

AMERICAN JOURNAL OF EDUCATION AND LEARNING
ISSN: 2996-5128 (online) | ResearchBib (IF) = 10.91 IMPACT FACTOR
Volume-3| Issue-10| 2025 Published: |30-11-2025|

- A current diagnosis of asthma or asthma-COPD overlap.
- Hospitalization for COPD exacerbation within 4 weeks of screening.
- Clinically significant, uncontrolled comorbid conditions (e.g., heart failure, malignancy).
- Previous participation in another clinical trial within 30 days.

Study Procedures Patients were assessed at baseline (Visit 1), Month 6 (Visit 2), and Month 12 (Visit 3).

Baseline (Visit 1): Demographic data, smoking history, exacerbation history (for the previous 12 months, verified by medical records), and concomitant medications were recorded. Patients underwent pre-bronchodilator spirometry (FEV_1, FVC), and completed the CAT, mMRC, and SGRQ questionnaires.

Month 6 (Visit 2): Pre-bronchodilator spirometry, CAT, mMRC, and AE monitoring.

Month 12 (Visit 3 / Study Completion): Pre-bronchodilator spirometry, CAT, mMRC, SGRQ, and final AE monitoring.

Exacerbations were defined as a worsening of respiratory symptoms requiring treatment with systemic corticosteroids, antibiotics, or hospitalization. All exacerbations and AEs (including pneumonia, oral candidiasis) were recorded throughout the 12-month period.

The primary analysis population was the per-protocol (PP) cohort, defined as all enrolled patients who completed the 12-month study. Continuous variables were presented as mean ± standard deviation (SD). Categorical variables were presented as N (%).

Changes in continuous variables (FEV_1, CAT, SGRQ, etc.) from baseline to 12 months were analyzed using a paired t-test or Wilcoxon signed-rank test, as appropriate. A p-value of < 0.05 was considered statistically significant.

Results

Patient Disposition and Baseline Characteristics A total of 32 patients were enrolled. Three patients (9.4%) discontinued the study: one was lost to follow-up, and two withdrew consent for personal reasons. Twenty-nine (29) patients (90.6%) completed the 12-month follow-up and were included in the per-protocol analysis.

The baseline characteristics of the 32 enrolled patients are presented in Table 1. The population was predominantly male (68.8%), with a mean age of 62.5 years and a significant smoking history (mean 42.5 pack-years). The majority had moderate (GOLD 2, 59.4%) or severe (GOLD 3, 40.6%) airflow limitation.

Table 1. Baseline Patient Characteristics

Characteristic	Value

AMERICAN JOURNAL OF EDUCATION AND LEARNING
ISSN: 2996-5128 (online) | ResearchBib (IF) = 10.91 IMPACT FACTOR
Volume-3| Issue-10| 2025 Published: |30-11-2025|

Characteristic	Value
Age, years (mean ± SD)	62.5 ± 7.1
Male Gender, n (%)	22 (68.8%)
Smoking Status, n (%)	
Current Smoker	14 (43.8%)
Former Smoker	18 (56.2%)
Pack-years (mean ± SD)	42.5 ± 11.2
GOLD Stage, n (%)	
GOLD 2 (Moderate)	19 (59.4%)
GOLD 3 (Severe)	13 (40.6%)
Post-BD FEV_1/FVC (mean ± SD)	0.58 ± 0.09
Pre-BD FEV_1, L (mean ± SD)	1.45 ± 0.3
Pre-BD FEV_1, % predicted (mean ± SD)	54.5% ± 9.8%
CAT Score (mean ± SD)	18.5 ± 4.2
mMRC Dyspnea Score (mean ± SD)	2.2 ± 0.7
SGRQ Total Score (mean ± SD)	45.0 ± 8.1
Exacerbations in prior year (mean ± SD)	1.4 ± 0.9

Notes: SD = Standard Deviation; GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV_1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; CAT = COPD Assessment Test; mMRC = modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire.

Efficacy Endpoints

Pulmonary Function and Exacerbations: Patients demonstrated a stabilization and modest, statistically significant improvement in lung function over the 12-month period. The mean pre-BD FEV_1 increased from 1.45 L at baseline to 1.55 L at 12 months ($p = 0.045$) (See Table 2). The most significant finding was the reduction in exacerbations. The mean annual rate of moderate-to-severe exacerbations was significantly reduced from 1.4 ± 0.9 (in the 12 months prior to enrollment) to 0.5 ±

0.6 during the 12-month study period ($p < 0.001$). The number of patients requiring hospitalization for COPD fell from 6 (18.8%) in the prior year to 2 (6.2%) during the study year.

Patient-Reported Outcomes (PROs): All PROs showed statistically and clinically meaningful improvements by 12 months (Table 2). The mean CAT score decreased by 6.5 points (from 18.5 to 12.0), indicating a significant reduction in symptom burden. The mean SGRQ total score improved by 9.5 points, well exceeding the minimum clinically important difference (MCID) of 4 points. Dyspnea, measured by mMRC, also improved significantly.

Table 2. Changes in Efficacy Endpoints from Baseline to 12 Months

Endpoint	Baseline (Mean ± SD)	12 Months (Mean ± SD)	Mean Change (95% CI)	p-value
Pre-BD FEV_1 (L)	1.45 ± 0.3	1.55 ± 0.4	+0.10 (0.01 to 0.19)	0.045
Pre-BD FVC (L)	2.80 ± 0.6	2.95 ± 0.7	+0.15 (0.04 to 0.26)	0.012
CAT Score	18.5 ± 4.2	12.0 ± 3.1	-6.5 (-8.0 to -5.0)	<0.001
mMRC Score	2.2 ± 0.7	1.5 ± 0.6	-0.7 (-1.0 to -0.4)	<0.01
SGRQ Total Score	45.0 ± 8.1	35.5 ± 7.4	-9.5 (-12.1 to -6.9)	<0.001

Notes: FEV_1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; CAT = COPD Assessment Test; mMRC = modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire; CI = Confidence Interval.

Safety and Tolerability The budesonide/formoterol FDC was generally well-tolerated over the 12-month period. No deaths or serious adverse events (SAEs) deemed related to the study medication occurred.

Adverse Events (AEs): The most frequently reported AEs were consistent with the known profile of the medication and the disease: nasopharyngitis (n=4, 12.5%), bronchitis (n=3, 9.4%), and headache (n=2, 6.2%).

Events of Special Interest: One patient (3.1%) was diagnosed with community-acquired pneumonia (CAP) at Month 8, which was managed on an outpatient basis with oral antibiotics without requiring discontinuation of the study drug. Two

patients (6.2%) reported mild oral candidiasis (thrush), which resolved with topical antifungal treatment and reinforcement of mouth-washing technique.

Discussion

This 12-month prospective observational study provides "real-world" evidence supporting the long-term efficacy and safety of the budesonide/formoterol FDC for patients with moderate-to-severe COPD. Our findings demonstrate that the benefits seen in shorter-term RCTs are sustained over a 12-month period.

The primary finding of this study is the significant and clinically relevant reduction in exacerbation rates. By reducing the mean annual exacerbation rate from 1.4 to 0.5, the B/F combination demonstrated a profound impact on one of the most important drivers of disease progression and healthcare cost. This aligns with large-scale trials indicating the critical role of ICS/LABA combinations in managing patients with an exacerbation-prone phenotype [7].

Furthermore, we observed a statistically significant, albeit modest, improvement in FEV_1. In a progressive disease like COPD, where an annual decline in FEV_1 is expected, the sustained improvement over 12 months is a positive finding. This suggests that consistent use of the B/F combination not only provides bronchodilation but may also control the underlying inflammatory components that contribute to airflow limitation.

Perhaps most importantly, these physiological improvements translated into clinically meaningful benefits for the patient. The 6.5-point reduction in the CAT score and 9.5-point improvement in the SGRQ score are well above their respective MCIDs [8]. This indicates that patients felt significantly better, experienced fewer symptoms, and had a substantially improved quality of life while on long-term therapy.

The safety profile was consistent with previous reports. The rate of pneumonia (3.1%, non-hospitalized) was low and is reassuring, although the small sample size limits definitive conclusions on this rare but important AE. The incidence of oral candidiasis (6.2%) highlights the continuous need for patient education on post-inhalation rinsing.

Limitations This study has several limitations. First, the sample size (N=32) is small, which limits the generalizability of the findings. Second, the open-label, observational design without a control group (e.g., LAMA monotherapy or LABA/LAMA) means we cannot definitively attribute all observed improvements solely to the B/F therapy, as study participation itself (Hawthorne effect) may influence adherence. Third, as a single-center study, our population may not represent the full spectrum of COPD patients.

Conclusion

In this 12-month prospective observational study of patients with moderate-to-severe COPD and a history of exacerbations, continuous treatment with the budesonide/formoterol fixed-dose combination demonstrated sustained efficacy. This was evidenced by modest improvements in lung function, a significant reduction in exacerbation rates, and clinically meaningful improvements in symptom burden (CAT), dyspnea (mMRC), and health-related quality of life (SGRQ). The long-term safety profile was favorable and consistent with known data.

These "real-world" findings support the role of the budesonide/formoterol combination as an effective and durable long-term management strategy for this specific COPD patient population.

REFERENCES:

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for Prevention, Diagnosis and Management of COPD: 2024 Report. Bethesda: GOLD; https://goldcopd.org/2024-gold-repor
2. Agustí A, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Am J Respir Crit Care Med. 2023 Apr 1;207(7):819-837. doi: 10.1164/rccm.202301-0106PP. PMID: 36856433; PMCID: PMC10111975.
3. David B, Bafadhel M, Koenderman L, De Soyza A. Eosinophilic inflammation in COPD: from an inflammatory marker to a treatable trait. Thorax. 2021 Feb;76(2):188-195. doi: 10.1136/thoraxjnl-2020-215167. Epub 2020 Oct 29. PMID: 33122447; PMCID: PMC7815887.
4. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. Pharmacol Rev. 2012 Jul;64(3):450-504. doi: 10.1124/pr.111.004580.
5. Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, Peterson S, Olsson H. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J. 2003 Jan;21(1):74-81. doi: 10.1183/09031936.03.00031402. Erratum in: Eur Respir J. 2003 May;21(5):912. PMID: 12570112.
6. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013 Nov;68(11):1029-36. doi: 10.1136/thoraxjnl-2012-202872.
7. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA,

Martinez FJ, Singh D, Tabberer M, Wise RA, Pascoe SJ; IMPACT Investigators. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med. 2018 May 3;378(18):1671-1680. doi: 10.1056/NEJMoa1713901.

8. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009 Sep;34(3):648-54. doi: 10.1183/09031936.00102509.