

Original Research Article

Effectiveness and tolerability of formoterol plus glycopyrronium combination in patients with chronic obstructive pulmonary disease: FINE registry

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ABSTRACT

Background: Long-term therapy for chronic obstructive pulmonary disease (COPD) is progressing fast. Dual bronchodilation with long-acting muscarinic antagonist (LAMA) and long-acting β_2 -agonist (LABA) fixed dose combinations (FDC) have been available over the past few years. To evaluate the real-world tolerability and effectiveness of formoterol plus glycopyrronium FDC inhaler, a post-marketing surveillance study was conducted in Indian population.

Methods: This was an open-label, observational registry in which COPD patients, who were prescribed forglyn (a brand of FDC of glycopyrronium 25 mcg and formoterol fumarate dihydrate 6 mcg dry powder inhalation). The effectiveness, safety and tolerability of this LAMA/LABA combination were evaluated for 4, 8 and 12 weeks. The safety and tolerability was assessed based on the incidence of adverse events (AEs). Effectiveness was evaluated based on change in total symptom score from baseline to end of 12 weeks. The forced expiratory volume in 1 second (FEV₁) was performed at baseline and end of 12 weeks.

Results: Total COPD patients enrolled were 605, of which 78.5% were males and 21.5% were females. Patients showing improvement of symptoms at week 4 were 587 (97.02%).

Overall, at the end of 8 week and 12 week 98.34 % and 99.49% patients showed improvement in the total symptoms respectively. About 0.49% did not show any improvement. AEs were reported in 64 (10.64%) patients with no serious AEs. Mean FEV₁ of 476 patients before treatment was 1.53 ± 0.68 L at baseline which changed to 1.85 ± 0.74 L at the end of 12 weeks, with was statistically significant ($p < 0.05$).

Conclusions: In real-life clinical practice in India, formoterol and glycopyrronium FDC dry powder inhaler was well tolerated in COPD patients, and can be regarded as an effective option for maintenance treatment.

Keywords: Glycopyrronium, Formoterol fumarate, LAMA, LABA, COPD

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease manifested by persistent airflow restriction, which is associated with cough, sputum production and difficulty breathing secondary to an increased chronic inflammatory response to noxious particles or gases.^{1,2} As per the World Health Organization (WHO) estimates, 65 million patients suffer from moderate-to-severe COPD worldwide. In 2005, COPD-related mortality accounted for 5% of total deaths; the data is certainly underestimated as the most epidemiological data that originate is exclusively from high-income countries. According to current estimates, WHO predicts a 30% rise in COPD deaths over the next decade, making COPD the third leading cause of death worldwide by 2030.³ In India, the prevalence of COPD has been reported at 3.49% (ranging from 1.1% in Mumbai to 10% in Thiruvananthapuram).^{4,5}

Bronchodilators continue to be the keystone of pharmacological treatment in patients with COPD. For the management of stable COPD; long-acting β_2 -agonists (LABA) and long-acting muscarinic antagonists (LAMA) are often preferred. The fixed dose combinations (FDC) of LAMA and LABA can be delivered via single inhaler because of the convenience.

The choice of therapy always depends on the disease manifestation, symptoms, previous therapies and responses to them, health status, and individual patient preference. Therefore, the optimal treatment is decided based on the medical history of every patient. Nevertheless, clinical trials data, clinical practice, and guidelines are indispensable for an evidence-based medicine approach.⁶

The earlier global initiative for chronic obstructive lung disease (GOLD) guidelines recommended LABA+inhaled corticosteroid (ICS) as the first line treatment for managing stable COPD in high risk people of categories C and D. However, the current GOLD 2020 guidelines recommend LAMA+LABA should be preferred over LABA+ICS.⁷

The combination treatment with LABA/LAMA upsurges forced expiratory volume in 1 second (FEV₁) and decreases COPD symptoms compared with monotherapy.⁶ Benefits of LABA/LAMA FDCs are widely reported; however, the availability of different FDC options approved for the treatment of COPD and the absence of head-to-head studies between all the available LABA/LAMA FDCs make choosing the most appropriate option difficult.⁸⁻¹⁰

This post-marketing observational study was conducted to determine the tolerability/safety and effectiveness of formoterol plus glycopyrronium FDCs in COPD in real world scenario.

METHODS

Study design

This was a post marketing, observational study conducted between February 2019 to November 2019, in which the eligible patients were treated with forglyn (glycopyrronium 25 mcg and formoterol fumarate dihydrate 6 mcg dry powder inhaler) in its approved indication at the discretion of treating physician according to the routine medical practice, over a 12-week duration. We established a registry, which was conducted in order to demonstrate the effectiveness, safety, and tolerability of formoterol/glycopyrronium in patients with COPD in real-life clinical practice in India.

Study population

In this observational study, 700 patients of COPD, age more than 18 years were treated with formoterol and glycopyrrolate FDC by treating physician as a maintenance therapy. The treatment was given at the discretion of treating physician.

Assessments

The total COPD symptom scores were evaluated by treating physician at the baseline, 4, 8 and 12 weeks post formoterol and glycopyrrolate combination therapy. The number of exacerbation at the end of 4, 8 and 12 weeks were recorded. The pulmonary function tests (FEV₁) were performed at the baseline and end of 12 week.

Safety and tolerability evaluation was done based on the incidence of AEs and serious adverse events (SAEs) during reported study duration. An AE was defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease (new disease or worsening of existing disease) occurring after the start of the study medication. Data was collected and recorded, whether volunteered by the subject, discovered by investigator questioning or detected through physical examination, laboratory test or by any other means. Anyone of the following event was regarded as an SAE, if any occurred: AE resulting in death/life-threatening condition, required hospitalisation or prolongation of hospitalization, resulted in persistent or significant disability/inability, resulted in a congenital anomaly or a birth defect, and important medical event that jeopardized the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. The severity of AEs was determined as: mild, symptom(s) not interfering with daily activities of patient and continuous treatment with same dose of is possible; moderate, symptom(s) were interfering with the daily activities of patient so that the dose lowering of or any treatment is required and severe, symptom(s) leading to patient's inability to undertake daily activities or discontinuation of due to AEs.

Statistical analysis

The data obtained were recorded in a Microsoft Excel sheet, and statistical analysis was performed using Statistical Package for Social Sciences (SPSS) (version 17). Results are presented as drawings, frequency and percentages. Categorical variables were compared using chi square test, Quantitative results were compared with Mann Whitney U test. For all tests, significant change was achieved at $p < 0.05$.

The AEs were assessed as the number of patients reporting the adverse events. Patients excluded from the safety analysis set were those who 'did not take the study drug' and 'who were lost to follow-up. Adverse events were reported as the percentage of patients experiencing AE.

RESULTS

Patient disposition

Of the 700 enrolled patients, 605 were included in the effectiveness, safety and tolerability analysis. Ninety five patients' data were not included in the analysis because they were noncompliant to the recommended treatment or were lost to follow-up. All patients received the daily treatment dose of formoterol fumarate dihydrate 6 mcg and glycopyrronium 25 mcg and the mean \pm standard deviation (SD) duration of therapy (weeks) was 12.43 ± 2.152 .

Patient demographics and baseline characteristics

Patient demographics and baseline characteristics are presented in Table 1. Of the total number of patients evaluated in the study, 78.5% were males and 21.5% were females. The mean patient age was 61.46 ± 10.57 years and weight was 62.84 ± 13.64 kg. The mean duration of COPD was 9.49 ± 7.199 years.

There were 169 (27.9%) current smokers, 290 (48%) past smokers and 146 (24.15%) non-smokers. The mean total duration of smoking amongst smokers was 19.31 ± 15.06 years and mean number of units smoked/day was 12.14 ± 14.46 . Most patients were followed up at outpatient clinic. The percentage of COPD patients reporting exacerbations in the total study duration were 46.3%, 32.1% and 21.5% at the end 4, 8 and 12 week respectively.

In our study 33.6%, patients had co-morbidities. The most common co-morbidities were hypertension (15.2%), diabetes (7.1%), acid-peptic disease (2.5%) and allergic rhinitis (0.8%).

Effectiveness assessments

Physicians subjectively evaluated the patient's overall status. Patients showing improvement of symptoms at week 4 were 587 (97.02%).

Overall, at the end of 8 week and 12 week 98.34% and 99.49% patients showed improvement in the total symptoms respectively. There was consistent improvement throughout study in 116 (19.2%) patients. About 0.49% of patients did not show any improvement.

Table 1: Patient demographics and baseline characteristics.

Basic variables	No. of patients (%)
Age (years)	
≤ 30	4 (0.7)
31-40	22 (3.6)
41-50	76 (12.6)
51-60	159 (26.3)
> 61	343 (56.7)
Mean \pm SD	61.46 ± 10.57
Gender	
Female	130 (21.5)
Male	475 (78.5)
Smoking history	
Current	169 (27.9)
Past	290 (47.9)
Non-smokers	146 (24.1)
Type of smoking	
Bidi	172 (28.6)
Cigarette	267 (44.0)
Cigarette and bidi	20 (3.3)
Non-smokers	146 (24.1)
Other medications used for COPD	
No	182 (30.08)
Yes	423 (69.92)

Table 2: The adverse events.

Adverse event	No. of patients (%)
Dry mouth	16 (2.6)
Breathlessness	10 (1.6)
Cough + cold	9 (1.5)
Irritation in throat	5 (0.9)
Headache	3 (0.5)
Constipation	2 (0.3)
Diarrhea	2 (0.3)
Tachycardia	2 (0.3)
Urinary retention	2 (0.3)
Vomiting	2 (0.3)
Gastritis	2 (0.3)
Disguise	3 (0.5)
Giddiness	1 (0.2)
Tremors	2 (0.3)
Palpitation	3 (0.5)

The total no of COPD exacerbations were 280, 194 and 130 at the end 4, 8 and 12 weeks. There was significant improvement observed in individual symptom score (cough, breathlessness, sputum and sleep disturbance) ($p < 0.001$ versus baseline) and the scores are depicted in

Figure 1. Majority patients showed an improvement in symptom score except three (0.49%) patients. The total symptom score decreased from 9.19 at baseline to 2.3 at the end of 12 weeks follow up ($p<0.001$) (Figure 2).

Mean value of FEV1 collected from 476 patients before drug administration was 1.53 ± 0.68 L at baseline which changed to 1.85 ± 4.74 L at the end of 12 weeks, with the difference being statistically significant ($p<0.05$). Global assessment of efficacy by the clinician at end of therapy

showed that majority (70%) of the patient showed good improvement in the symptoms (Figure 3).

Safety assessments

Overall, 64 patients (10.6%) reported at least one AE during entire duration of study (Table 2). The most common AEs were dry mouth (2.6%) followed by breathlessness (1.6%), cold and cough (1.5%), (no serious AEs were reported).

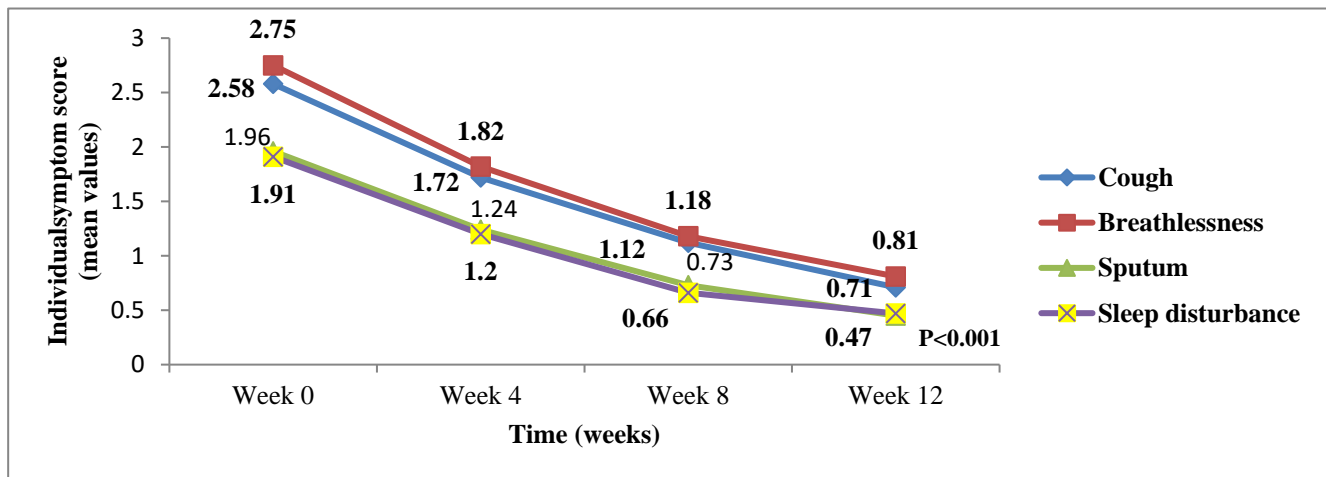


Figure 1: Efficacy assessment of individual symptom scores.

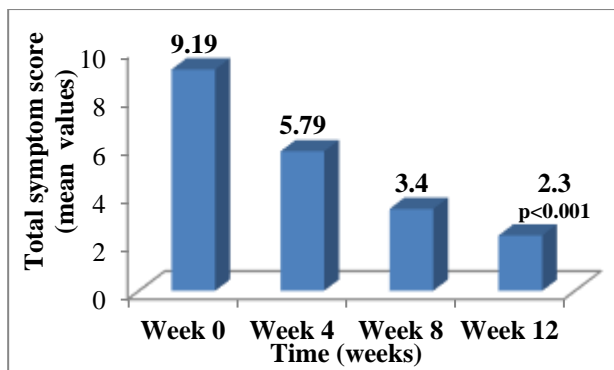


Figure 2: Assessment of total score of all symptoms.

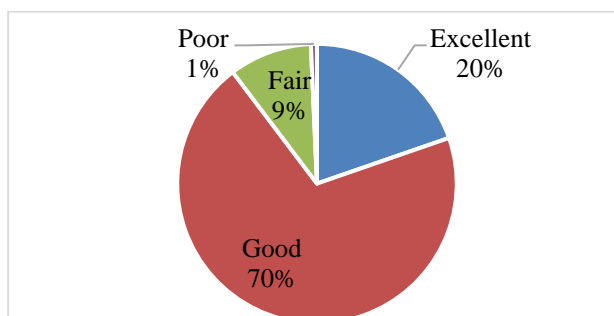


Figure 3: Global assessment of efficacy by the clinician at end of therapy.

The global assessment of tolerability by the clinician showed that 88.3%, 8%, 3.3% and 0.3% patient had excellent, good, fair and poor tolerability respectively at end of therapy.

DISCUSSION

In this registry, of the total number of COPD patients evaluated, 78.5% were males. Traditionally COPD is more prevalent in males.¹¹

COPD is an age-related disorder, and several evidences suggested a relationship with a rapidly increasing age.^{12,13} The mean patient age was 61.46 ± 10.57 years and 56.7% of patients were above 60 years of age. This distribution can be explained by the physiological decrease in FEV1 with age where the slope becomes steeper when aggravated by risk factors, particularly smoking.⁵ The mean duration of COPD was 9.49 ± 7.199 years.

Good nutritional status is considered an independent factor influencing the course of COPD. Body weight could be one of the indicator of good nutritional status. In our study, the mean weight of the patients was 62.84 ± 13.64 kg that is considered good. A study by Wilson et al demonstrated that factors related to nutritional status have an independent influence on the course of COPD.¹⁴ This could be one of the reasons for better response to therapy.

Smoking is conclusively the most common risk factor of COPD.¹⁵ About 75.9% of the evaluated patients in our study were smokers, of which, current smokers were 27.9% while the ex-smokers were 48%. The mean total duration of smoking was 19.31 ± 15.06 years and mean number of units smoked/day was 12.14 ± 14.46 . The odds of having COPD is nine and 4 times in the current and ex-smokers, respectively compared to the nonsmokers.^{15,16} Higher quantity of cigarette smoking increases the risk, i.e. each pack-year of smoking increases 15% risk for COPD. Moreover, lesser risk of COPD in the ex-smoker compared 60% to current smokers.¹⁵

Most patients were followed up at outpatient clinic. With continuation of therapy the number of COPD exacerbations in the intervening periods week 0 to end of week 4, week 5 to end of week 8 and week 9 to end of week 12 were 280 (46.3%), 194 (32.1%) and 130 (21.5%) respectively.

The mainstay of COPD treatment has been long-acting bronchodilators including LAMAs and LABAs, the latter is frequently combined with inhaled corticosteroid. Now it is established that grading COPD severity and determining treatment according to spiro metric values are one-dimensional approach, as patients exhibit a wide spectrum of spiro metric values when highly symptomatic and at risk of exacerbations. Clinical evidence suggests that inhalation corticosteroid is useful in lowering frequent exacerbations. It comes with its own risks but can be withdrawn safely in patients who are unlikely to have exacerbations. The use of LAMA-LABA combination is emerging as a safe and effective choice in this category of patients and some studies have shown superiority of this combination to LABA-ICS combination in symptom control and reduction in exacerbations. The WISDOM study demonstrated that by withdrawing inhaled steroids from the regimen of stable patients with COPD there was no worsening of symptoms or increased exacerbation rate.¹⁷ Currently, five fixed-dose LAMA-LABA combinations are available, including formoterol/acclidinium, indacaterol/glycopyrronium, olodaterol/tiotropium, umeclidinium/vilanterol, and formoterol/glycopyrronium. Formoterol/glycopyrronium is a new LAMA-LABA combination that has been recently approved in several countries globally, including India. The registry elucidates safety, tolerability and effectiveness of formoterol/glycopyrronium in patients with COPD in real-life clinical practice in India.

Unlike salmeterol, formoterol has a rapid onset of action. The relative water solubility of formoterol enables it to diffuse rapidly to the β_2 -adrenergic receptors and produces bronchodilation within 1 to 3 minutes. Moreover, formoterol is a full agonist whereas salmeterol is a partial agonist, suggesting formoterol to be a better bronchodilator with higher potency. Formoterol has rapid onset of action, which provides quick relief of symptoms.¹⁸

Glycopyrronium has a sustained 24-hour bronchodilator effect and higher selectivity for the muscarinic (M) M_3 receptor than the M_2 receptor. Dissociation from the M_3 receptor occurs four times faster than tiotropium and almost twice as fast as aclidinium. This suggests that glycopyrronium would have a more rapid onset of action.¹⁸

In this study, effectiveness of LAMA-LABA combination was proved by improvement in the individual symptom scores as well as the total score at week 4, 8 and 12. Almost 97.02% patients showed improvement of symptoms at week 4. Overall, at the end of 8 week and 12 week 98.34% and 99.49% patients showed improvement in the total symptoms respectively. About 0.49% did not show any improvement. There was also improvement observed in the FEV1 value at 12 week from baseline. Our study results are similar to the trends in the earlier studies.¹⁹⁻²¹

Several studies including a Cochrane database review have revealed an increased risk of pneumonia with the use of inhaled steroids.²² Hence, inhaled steroids should be avoided in COPD patients. Patients who have severe activity limitation but are not frequent exacerbations, can achieve maximum bronchodilation and improved quality of life by using LAMA-LABA combination. However, steroids should be withdrawn carefully in patients who have been stable on LABA-ICS combination because a statistically significant decline in FEV1 was demonstrated after withdrawal of inhaled steroids in WISDOM and GLUCOLD studies.^{17,23}

In our study, symptom score assessment was used for the evaluation of effectiveness as the focus of COPD management is shifting from FEV1-based treatment escalation to symptoms and risk-based treatment.²⁴ This will be the paradigm shift in COPD treatment with early introduction of LAMA-LABA combination as a single inhaler.

The first LAMA-LABA (FDC) studied was umeclidinium/vilanterol. This combinations has shown non-inferiority to fluticasone propionate/salmeterol (FP/SAL) in control of symptoms and superiority in one trial.²⁵ In 2015, a Cochrane database review revealed that there was a modest increase in mean FEV1 and in health-related quality-of-life with addition of LABA to LAMA therapy.²⁶ Since then, several LAMA-LABA FDCs have been developed, including glycopyrrolate/indacaterol, tiotropium/olodaterol, and aclidinium/formoterol. All of these FDCs were formulated either as dry-powder inhalers (DPIs) or as soft mist inhaler.

PINNACLE 1 and 2 were both double blind, placebo-controlled phase III, 24-week trials that evaluated the safety as well as efficacy of the combination glycopyrronium/formoterol fumarate (GFF). The regimens studied included GFF metered-dose inhaler (MDI), GP (glycopyrrolate) MDI 18 mcg, FF (formoterol fumarate) MDI 9.6 mcg, or placebo MDI (all twice daily), or tiotropium 18 mcg DPI (once daily in PINNACLE-1

only: open-label active comparator).¹⁹ GFF combination showed significant improvement versus placebo and mono-components in morning pre-dose trough FEV₁ at 24 weeks ($p<0.0001$) as well as in 2-hour post-dose FEV₁ ($p<0.0001$). Pooled St. George's respiratory questionnaire score (SGRQ) data showed a statistically significant decrease in total score with GFF at week 24 versus placebo ($p=0.0051$) and GP ($p<0.0094$) in PINNACLE-1. Hazard ratio (HR) of time to first exacerbation was lower with GFF compared to placebo (HR 0.736, $p<0.002$) and glycopyrronium (HR 0.781, $p<0.002$), but not formoterol. Patients also needed less rescue inhaler medication use compared to placebo ($p<0.0001$) or GP ($p<0.0001$). In this study, 10.6% patients reported at least one AE. The most common AEs were dry mouth (2.6%) followed by breathlessness (1.6%). The incidence of cold and cough (1.5%), which were in congruence with those reported by PINNACLE 1 and 2. No serious AEs were reported. In PINNACLE 1 and 2, treatment emergent adverse events were similar across all the active-treatment groups. Adverse events with higher rate than the placebo were cough, sinusitis, COPD, back pain, and bronchitis. Adverse events leading to discontinuation were highest in the placebo group. Cardiovascular (CV) side effects were low and comparable in all groups at 0.4-0.7%.¹⁹ All cause deaths were also comparable in all groups. In our study palpitation was reported in 0.5% of patients which was the only the cardiac adverse event.

PINNACLE 3 was extension of the previous two studies in which 892 patients who completed the original studies continued the same treatment, including mono-components and open-label tiotropium for another 52 weeks.²⁷ No unexpected safety findings were observed. Overall incidence of AEs was similar across all groups (60-69%). The most frequent AE's reported were nasopharyngitis (6.8%), cough (4.3%), and upper respiratory tract infection (3.8%). GFF showed significant improvement in trough and 2-hour post-dose peak FEV₁ versus FF (65 and 88 ml, respectively), GP (57 and 129 ml, respectively), and tiotropium (25 and 93 ml, respectively). GFF also showed significant improvement versus GP ($p<0.0001$) and open-label tiotropium ($p=0.0002$) for average daily use of rescue medication.²⁸ Our study results had similar efficacy and safety trends as in PINNACLE 3 study.

Glycopyrronium/formoterol was generally well tolerated in patients with moderate to very severe COPD, with most AEs of mild or moderate severity.²⁰ Long-acting bronchodilators have been found to be relatively safe in COPD patients in multiple other studies. In the study by Hanrahan et al, 1429 patients treated with LABA are formoterol and salmeterol underwent Holter monitoring. Although atrial tachycardia was relatively frequent at baseline, there was only minimal rise in atrial tachycardia with the use of beta agonists. None of the study participants had increased risk of serious arrhythmias such as ventricular tachycardia.²⁹ A randomized placebo-controlled trial by Campbell et al, evaluated cardiac safety

in COPD patients given formoterol 12 µg twice daily demonstrated low evidence of ventricular arrhythmia in both groups, with no significant difference between the active and placebo groups.³⁰ Wise et al demonstrated that inhaled tiotropium was safe in several studies including the large-scale TIOSPIR trial.³¹ Our study did not find any cardiovascular AE, wherein our findings were in congruence with the cardiac safety of glycopyrronium demonstrated in several randomized controlled trials, with no increase in cardiac side effects over placebo.^{32,33} The PINNACLE studies demonstrated acceptable safety profile of the GFF combination compared to its mono-components. In our study 88.3%, clinicians rated the tolerability of Formoterol and glycopyrronium combination to be good to excellent.

The GOLD guidelines suggested that the addition of ICS to dual bronchodilation should be reserved mainly for patients with symptomatic disease and history of frequent exacerbations (two or more in the previous year or one or more exacerbations leading to hospitalization).³⁴ In our study the concomitant medication was required for 8.2% patients. The ICS was most common medication used in this study. The recent clinical evidence indicates that triple therapy is the most effective treatment in moderate/severe symptomatic patients with COPD at risk of exacerbations, with marginal if any risk of side effects including pneumonia.³⁴

Real-world studies such as registries demonstrate a more realistic picture of effectiveness and safety of an approved drug in clinical-practice across different populations. Since a registry is an observational study in which there are no placebo or comparators, one must be cautious in interpreting the results as confounding factors may influence the AEs and the effectiveness of the study drug. The limitation of this registry could be inherent reporting bias, stability of concomitant medications, and physician's subjective evaluation. However, proven effectiveness and lower number of reported AEs and SAEs along with glycopyrronium and formoterol combination, in this study confirms the outcomes of clinical trials, indicating FDC of glycopyrronium and formoterol DPI as an effective and well-tolerated bronchodilator option for the maintenance treatment of COPD patients.

CONCLUSION

Forglyn (a brand of FDC of glycopyrronium 25 mcg and formoterol fumarate dihydrate 6 mcg dry powder inhalation) is found to be effective in controlling COPD symptoms and exacerbation episodes in patients of moderate to severe COPD patients and the treatment was found to be safe and well tolerated in real world clinical scenario.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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