Original Article

Comparative efficacy and safety of glycopyrronium/formoterol fixed-dose combination versus glycopyrronium monotherapy in patients with moderate-to-severe COPD

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ABSTRACT

Background: The safety and efficacy of fixed-dose combination (FDC) of glycopyrronium bromide 12.5 μg/formoterol fumarate 12 μg (GB/FF) twice daily as dry powder inhalers (DPIs) compared to glycopyrronium 50 μg monotherapy (GLY) once daily as DPI in subjects with moderate-to-severe chronic obstructive pulmonary disease (COPD) were evaluated. **Methods:** This was a phase-3, randomized, double-blind, active-controlled, parallel-group, superiority study conducted in India. COPD patients aged ≥40 to ≤65 years, current or ex-smokers with FEV_1/FVC <0.70, using ICS, LAMA, or LABA for ≥1 month were included. Subjects were randomized (1:1) to GB/FF or GLY for 12 weeks. The primary efficacy endpoint was the change from baseline in peak FEV_1 at the end of 12 weeks. The study is registered with the Clinical Trials Registry of India (CTRI/2017/02/007814). **Results:** Between March 2017 and July 2018, 331 patients were enrolled and randomized into GB/FF FDC (165 patients) and GLY monotherapy (166 patients) groups. At week 12, the difference in change from baseline in the peak FEV_1 for GB/FF DPI versus GLY was 0.115 L (SE = 0.02; 95% CI = 0.061, 0.170; $P < 0.0001$). Trough FEV_1 increased significantly in the GB/FF group compared to the GLY group with a treatment difference of 0.078 L (SE = 0.02; 95% CI = 0.015, 0.14; $P = 0.01$). There were no significant differences in adverse events between the groups. **Conclusion:** FDC of GB/FF (12.5/12 μg twice daily) as a DPI provides superior bronchodilation and lung function improvement over GLY (50 μg once daily) monotherapy. It is safe and well tolerated in symptomatic COPD patients.

KEY WORDS: COPD, fixed-dose combination, formoterol fumarate, glycopyrronium, India, LAMA/LABA

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, treatable, and noncommunicable lung disease characterized by progressive airflow limitation that is poorly reversible.[1] Estimates indicate that globally about 545 million people had a chronic respiratory disease in 2017, with COPD accounting for more than 50%.[2] It is the third leading cause of death, causing 3.23 million deaths in 2019 worldwide.[3] In India, it is the second leading cause of death and disability-adjusted life-years.[4] India accounts for a high symptomatic COPD population with poor survival among patients with severe COPD.[5,6]

Long-acting inhaled bronchodilators, such as long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), are preferred for different stages of COPD treatment.[7] However, treatment with either LABA or LAMA does not reduce the risk of exacerbations or hospitalizations in patients with symptomatic COPD.[8] Dual bronchodilation with LAMA/LABA fixed-dose combination (FDC) that maximizes bronchodilation is associated with significant improvement in key clinical outcomes and good tolerability compared to treatment with a single bronchodilator.[9] Current guidelines also recommend the addition of LAMA/LABA in moderate-to-severe COPD patients to maximize bronchodilation.[1]

The United States Food and Drug Administration (USFDA) approved the FDC of glycopyrronium bromide/formoterol fumarate dihydrate (GB/FF; Bevespi Aerosphere®, For Bevespi- AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850) in the form of a pressurized metered-dose inhaler (pMDI) in 2016.[10] However, COPD being the disease of the elderly, there may be several factors that limit the correct use of pMDIs.[11] For proper drug administration, pMDIs require coordination between actuation–inhalation, deep inspiration, and breath-holding,[12] while dry powder inhalers (DPIs) do not. In addition, pMDIs are more prone to errors, which can lead to overdose or less than optimal dosing of medication. Dry powder inhalers are relatively easier to use as long as patients can generate sufficient inspiratory flow rates. Given this, the use of pMDIs might pose several problems with drug administration and compliance in contrast to DPIs. Moreover, DPIs are widely available and less expensive than pMDIs.[9,12]

To the best of our knowledge, (Airz-F™, For Airz-F-Glenmark Pharmaceuticals Ltd, Mumbai-400099) (12.5 μg glycopyrronium/12 μg formoterol fumarate) is the first twice-daily DPI to be launched in India for COPD treatment. Glycopyrronium is a rapidly acting LAMA, available as once- and twice-daily formulations with sustained bronchodilation and a good safety profile even at high doses.[13] Formoterol is a rapid and longer-acting LABA that offers better treatment compliance.[14]

There is a lack of data on GB/FF FDC as a DPI in Indian settings, and evidence generation in this regard is warranted. Given this, the current study was designed to evaluate the efficacy, safety, and tolerability of FDC of GB/FF (12.5/12 μg) DPI twice daily in comparison with glycopyrronium (GLY) (50 μg) monotherapy DPI given once daily.

METHODS

Study design

This was a phase 3, randomized, double-blind, double-dummy, active-controlled, parallel-group, superiority study conducted across 25 cites in India.

Patients meeting inclusion and exclusion criteria during the screening visit entered a 2-week open-label run-in period, during which they received the placebo inhaler and rescue medication (salbutamol pMDI). Prior therapy of FDC of LABA/LAMA and inhaled corticosteroids (ICS) was discontinued and subjects were switched to the nearest equivalent dose of ICS as monotherapy at the start of the run-in period (visit 2). At the end of a 2-week run-in period, subjects were randomized 1:1 to one of the two treatment groups.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice according to International Conference on Harmonization guidelines and was reviewed and approved by the ethics committee/institutional review board of the respective study centers. A properly executed, written, informed consent was obtained from each subject before entering into the trial.

Patients

Eligible patients were male or female, aged ≥40 to ≤65 years, current or ex-smokers [cigarette or bidi (thin hand-rolled tobacco available in the Indian subcontinent)], with a smoking history of at least 10 pack-years and had a clinical diagnosis of COPD [presence of respiratory symptoms (modified Medical Research Council dyspnoea grade ≥2)], postbronchodilator forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio of <0.70, and postbronchodilator FEV_1 ≥30% and <80% of predicted. The study was approved by the local institutional ethics committees, and patients were provided written informed consent before any study-related procedures.

Patients with a history of asthma, hospitalization for COPD exacerbation or pneumonia within 3 months before screening, oral/parenteral corticosteroid or depot corticosteroid use 6 weeks and 3 months before the screening, respectively, or clinically significant laboratory abnormality or a clinically significant condition (as judged by the investigator) were excluded.

Full inclusion and exclusion criteria and blinding and allocation concealment are provided in the Supplementary Appendix.

Procedures

After the run-in period, subjects were randomized in the ratio of 1:1 to GB/FF (12.5/12 μg) DPI twice daily or GLY (50 μg) DPI once daily for 12 weeks.

The total study duration was 17 weeks, which comprised nine study visits including 1 week of the screening period, 2 weeks of the placebo run-in period, and 12 weeks of the treatment period, followed by 2 weeks of the telephonic follow-up period.

On the day of randomization (day 1) and day 85, patients were asked to be in-house till the completion of serial spirometry at predefined time points up to 2 h postdose. Morning study drug dosage was taken by all the subjects at the site after completion of predose procedures on days 1, 2, 15, 29, 57, and 85, and the evening dosage was taken at home. Efficacy parameters (FEV_1 and FVC), mean total daily symptom score (MTDSS), mean daytime total symptom score (MDTSS), and mean nighttime total symptom score (MNTSS) were assessed. Safety was assessed with physical examination, vital signs, electrocardiogram (ECG), ultrasonography (USG), intraocular pressure (IOP), chest X-ray, and adverse events (AEs). At visits 5, 6, and 7, subjects returned to the clinic for safety and efficacy assessments and were assessed for study medication compliance. At the end of the study treatment visit (visit 8), subjects returned to the clinic for efficacy assessments (FEV_1 and FVC) and safety measurements. During the 12 weeks of the treatment period, subjects were assessed for compliance with study medication, use of the subject diary, and prohibited medications from visit 3 to visit 9. Telephone follow-up and/or clinic visit was scheduled after the follow-up, if required and deemed necessary by the investigator.

Study endpoints and assessments

The primary endpoint was the change in peak FEV_1 (within 2 h postdose) from baseline to the end of the treatment on day 85. The secondary endpoints were (1) change from baseline in trough FEV_1 on days 2, 15, 29, 57, and 86; (2) change from baseline in FVC on days 2, 15, 29, 57, and 85; (3) change from baseline in standardized FEV_1 area under the curve 0–2 h (FEV_1 AUC_{0-2h}) on day 85; and (4) change from baseline in MTDSS, MDTSS, and MNTSS on day 85.

Peak FEV_1 was defined as the maximum FEV_1 over the period from 5 min to 2 h post morning dose. Baseline FEV_1 was defined as the average of the predose FEV_1 measured at 45 and 15 min on day 1 and baseline FVC was the average of the predose FVC measured at 45 and 15 min on day 1.

Safety assessments consisted of monitoring and recording of all AEs (including severity as mild, moderate, and severe, as per the investigator assessment of the severity of AEs as per Common Terminology Criteria for Adverse Events Version 5.0) and serious AEs (SAEs); regular monitoring of vital signs, ECG, USG examination for urinary retention, and ophthalmic assessment for IOP; and physical examinations.

Statistical analysis

A sample size of 266 evaluable subjects with a ratio of 1:1 (133 subjects per treatment arm) was estimated to detect a difference in means between the two treatments assuming a two-sided alpha of 5% with 90% power. An effect size of 100 mL and standard deviation (SD) of 250 mL were assumed to determine the sample size based on previously published studies.[15-18] Assuming a dropout rate of 20%, a total of 332 subjects (166 subjects per treatment arm) were planned to be randomized in the study.

The analysis population sets for efficacy assessments were the full analysis set (FAS) and per-protocol set (PPS). The FAS was the primary population for the primary endpoint, which was analyzed using analysis of covariance (ANCOVA) with categorical covariates of center and treatment, visit, and treatment-by-visit interaction as fixed-effect factors and baseline peak FEV_1 value as a continuous covariate with last observation carried forward (LOCF) to treat missing values. Data from PPS were used for sensitivity analysis of the primary endpoint. Mixed-effect model repeated measure (MMRM) without LOCF in both FAS and PPS populations was also used as a sensitivity analysis. The secondary efficacy endpoint, trough FEV_1, and FVC were analyzed using MMRM with fixed categorical terms for treatment, visit, treatment-by-visit interaction, and center and continuous fixed covariates of baseline FEV_1 and baseline FEV_1 by visit. Other secondary endpoints (standardized FEV_1 AUC_{0-2h} and MTDSS, MDTSS, and MNTSS) were analyzed by ANCOVA with categorical covariates of center and treatment and the appropriate baseline score as a continuous covariate.

Additional analyses based on the PPS were also summarized.

All safety analyses were conducted in the safety population. All the safety assessments performed were summarized descriptively by the treatment group. The incidences of treatment-emergent adverse events (TEAEs), SAEs, treatment-related AEs, and AEs leading to discontinuation were also summarized by treatment. All AEs were coded to system organ class and preferred terms using Medical Dictionary for Regulatory Activities (MedDRA) 19.0. All analyses were performed using SAS® software v9.3 or later. The study is registered with the Clinical Trials Registry of India (identifier number: CTRI/2017/02/007814). The full clinical protocol can be obtained from the corresponding author upon request.

RESULTS

The study was conducted between 23 March 2017 and 31 July 2018.

A total of 443 patients were enrolled and screened. Among them, 94 patients were screen failures and of the remaining 349 screened patients, 331 patients were competitively randomized in a 1:1 ratio to receive either FDC of GB/FF (12.5/12 µg) twice daily or GLY monotherapy (50 µg) once daily. Of the 331 randomized subjects, 330 (99.7%) were included in the safety analysis (SAF) population, 327 (98.8%) were included in the FAS population, and 326 (98.5%) were included in the PPS population. A total of 295 (89.1%) subjects completed the study. Thirty-six (10.9%) patients prematurely discontinued from the study. The most common reason for discontinuation was lost to follow-up [15 (4.5%)], followed by withdrawal of consent [9 (2.7%)], COPD exacerbation [7 (2.1%)], and protocol deviation [2 (0.6%)]. There was one death in the study [Figure 1].

Baseline demographic and clinical characteristics were generally similar between study treatment and control groups [Table 1]. All the subjects were Asians, and the majority of the subjects were male (97.9%). Overall, the mean age (±SD) of the subjects was 57.3 (±6.1) years. The mean number of smoking pack-years was 24.3 (±14.2). The number of patients with severe COPD (FEV_1 postbronchodilator <50% and ≥30% predicted) was slightly higher in the GB/FF group (71.0%) in comparison to the GLY monotherapy group (63.6%) but this was not statistically significant ($P = 0.16$). Mean FEV_1 reversibility percentage was slightly lower in the GB/FF group (8.24%) in comparison to the GLY monotherapy group (10.0%). The mean FEV_1 reversibility between the two groups was not statistically significant ($P = 0.18$).

Primary outcomes

The observed mean changes from baseline in the peak FEV_1 in patients from GB/FF and GLY monotherapy groups on day 85 were 0.3038 L and 0.1977 L, respectively. Peak FEV_1 increased significantly from baseline to day 85 in both groups.

For patients in the FAS population, a significant difference was observed in the mean change in peak FEV_1 levels from baseline (day 1) to day 85 for patients receiving GB/FF in comparison to those receiving GLY monotherapy ($P < 0.0001$). The estimated least square

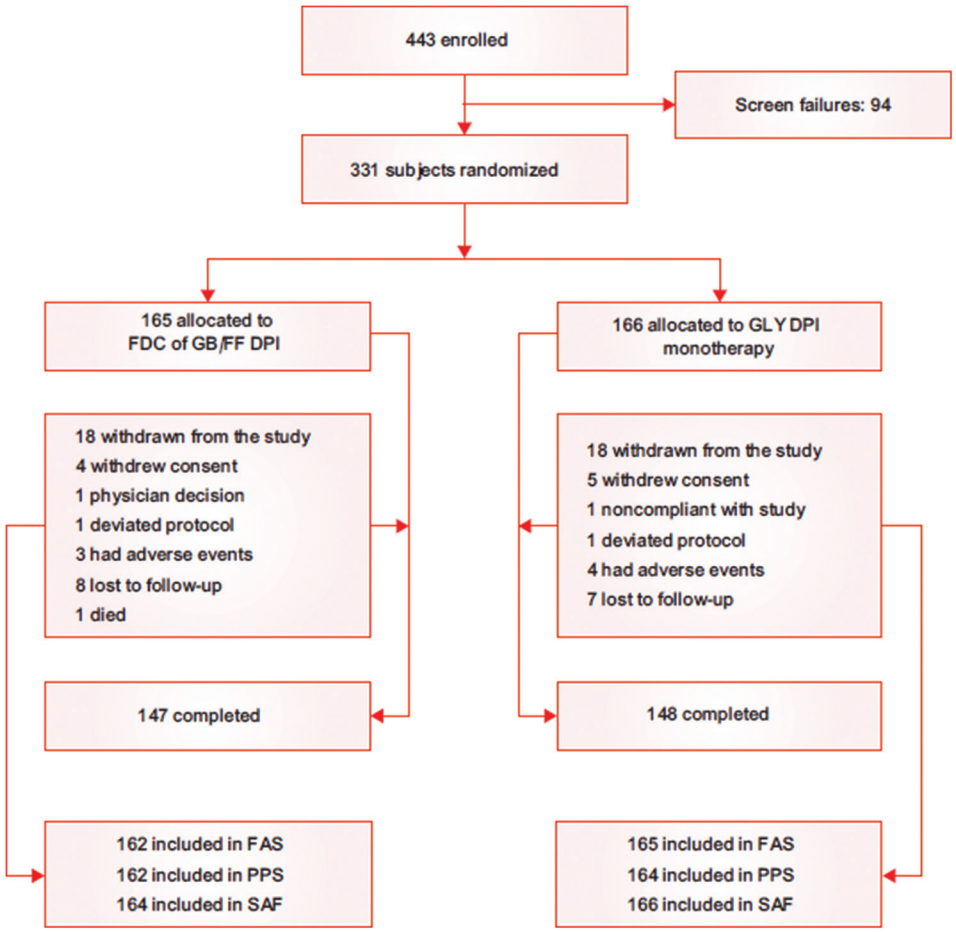

Figure 1: Study CONSORT diagram

Table 1: Patient demographics and baseline characteristics

Parameter	GLY (50 µg) once daily (*n*=165)	GB/FF FDC (12.5/12 µg) twice daily (*n*=162)	Total (*n*=327)
Age, years (mean±SD)	57.3±6.24	57.2±6.02	57.3±6.13
Severity, *n* (%)			
Moderate COPD: FEV_1 post-bronchodilator <80% and ≥50% predicted	60 (36.4)	47 (29.0)	107 (32.7)
Severe COPD: FEV_1 post-bronchodilator <50% and ≥30% predicted	105 (63.6)	115 (71.0)	220 (67.3)
Sex, *n* (%)			
Female	4 (2.4)	3 (1.9)	7 (2.1)
Male	161 (97.6)	159 (98.1)	320 (97.9)
FEV_1 reversibility (mL) (mean±SD)	96.12±152.88	76.12±115.49	86.21±135.82
FEV_1 reversibility (%) (mean±SD)	10±13.07	8.24±11.7	9.12±12.43
Smoking pack-years (*n*) (mean±SD)	23.7±12.97	25.03±15.5	24.34±14.27

COPD: Chronic obstructive pulmonary disease; FDC: Fixed-dose combination; FEV_1: Forced expiratory volume in 1 second; GB/FF: Glycopyrronium/formoterol fumarate dihydrate; GLY: Glycopyrronium; SD: Standard deviation

mean (LSM) (±SE) increase in peak FEV_1 from baseline to day 85 using ANCOVA and LOCF was significantly higher in the GB/FF group [0.318 L (±0.0249)] in comparison to the GLY group [0.203 L (±0.0240)] with an LSM difference of 0.115 L [95% confidence interval (CI) = 0.061, 0.170; $P < 0.0001$; Table 2]. Plots of LS means of change from baseline in peak FEV_1 with ANCOVA in the FAS population are provided in Figure 2.

Similar results were obtained in the FAS population when changes from baseline were derived from the ANCOVA analysis using smoking pack-years at baseline and baseline ICS as additional covariates. The LSM difference in the mean change of peak FEV_1 from baseline to day 85 for patients in the GB/FF in comparison to the GLY group was 0.114 L (95% CI = 0.059, 0.169; $P < 0.0001$).

Analysis of peak FEV_1 and change from baseline by visits with MMRM in the FAS population are provided in Table 2. The LSM difference in the mean change of peak FEV_1 from baseline to day 85 for patients in the GB/FF group in comparison to the GLY monotherapy group was 0.105 L (95% CI = 0.036, 0.174). The addition of smoking pack-years at baseline and baseline ICS as additional covariates yielded similar results.

The sensitivity analysis of the primary efficacy endpoint results with ANCOVA in the PPS population yielded similar results compared to the primary analysis. The mean increase from baseline in the peak FEV_1 on day 85 was significantly higher in the GB/FF group in comparison to the GLY monotherapy group. The LSM difference in the mean change of peak FEV_1 from baseline to day 85 for patients in the GB/FF group in comparison to the GLY group was 0.105 (95% CI = 0.036, 0.174; $P = 0.0029$). Similar results were also obtained in the sensitivity analysis with MMRM in FAS and PPS.

Secondary outcomes

Trough FEV_1 increased from baseline to day 86 in both the treatment groups. The observed mean (SD) change from baseline in trough FEV_1 on day 86 was 0.1931 L (±0.2774)

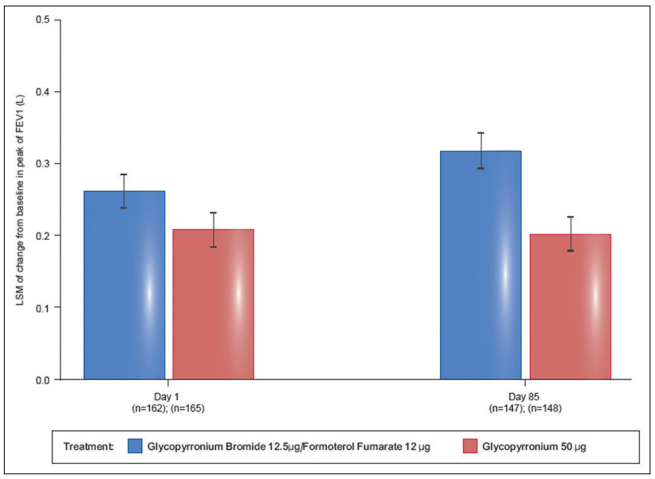

Figure 2: Plot of LS means of change from baseline of peak FEV_1 (L) with ANCOVA—FAS population

in the GB/FF group and 0.1184 L (±0.2481) in the GLY monotherapy group. Based on MMRM analysis, the difference between the two treatment groups was 0.078 L (±0.028; 95% CI = 0.015, 0.14; $P = 0.01$) and favored the FDC of GB/FF.

An increase in trough FEV_1 from baseline was also observed on days 2, 15, 29, 57, and 85 in both the treatment groups. Based on MMRM analysis, the LS mean increase in trough FEV_1 from baseline was greater in the GB/FF group in comparison to the GLY monotherapy group at all visits; the treatment differences were statistically significant at all visits, with the exception on day 57 [Figure 3].

Both the treatment groups demonstrated an increase from baseline in FVC. The mean increase from baseline in FVC was higher and statistically significant at all visits in subjects in the GB/FF FDC group in comparison to the GLY monotherapy group, except day 29 [Table S1].

On day 85, the increase from baseline in FEV_1 AUC_{0-2h} was greater in subjects in the GB/FF FDC group in comparison to the GLY monotherapy group (LSM difference: 0.111 L), and the treatment difference was statistically significant ($P < 0.0001$; Table S2).

Table 2: Summary of lung function peak FEV_1 (L) and change from baseline by visits—FAS population

Visit	GLY (50 µg) once daily (*n*=165)	GB/FF FDC (12.5/12 µg) twice daily (*n*=162)
Mean change in FEV_1 (L) from baseline on day 1 (visit 3), LSM (SE)	0.209 (0.02)	0.262 (0.02)
Difference: LSM (SE)		0.053 (0.0267)
95% CI		0.000, 0.105
P[a]		0.0491
Mean change in FEV_1 (L) from baseline on day 85 (visit 8), LSM (SE)	0.203 (0.02)	0.318 (0.02)
Difference: LSM (SE)		0.115 (0.02)
95% CI		0.061, 0.17
P[a]		<0.0001

CI: Confidence interval; FDC: Fixed-dose combination; FEV_1: Forced expiratory volume in 1 second; GB/FF: Glycopyrronium/formoterol fumarate dihydrate; GLY: Glycopyrronium; LSM: Least square mean, SE: Standard error. [a]*P*-value was calculated for the comparison of treatment groups using ANCOVA with treatment, center, visit, and treatment-by–visit interaction as fixed-effect factors and lung function FEV_1 (L) at baseline as covariate. The 95% CIs for the difference in mean change from baseline (visit 3) of GB/FF vs. GLY; LOCF was used to deal with missing data

The observed mean decrease from baseline in symptom scores of MTDSS, MDTSS, and MNTSS was numerically greater in the GB/FF FDC group in comparison to the GLY monotherapy group. However, the difference between the treatment groups was not found to be statistically significant [Figures S1-S3].

Safety outcomes

Overall, the incidence of AEs in the safety population was low (39.7%; 131/330) and comparable across the two treatment groups [37.8% (62/164) in the GB/FF group vs. 41.6% (69/166) in the GLY monotherapy group] [Table S3]. The majority of the AEs were mild or moderate in intensity.

The incidence of study drug-related TEAEs was comparable between the two treatment groups (6.7% in the GB/FF group vs. 9.0% in the GLY monotherapy group). One death due to a serious TEAE (cardiac arrest) was reported during the study; it was not related to the study drug. Serious TEAEs were reported in three patients [severe sudden cardiac arrest (n = 1) and severe COPD exacerbation (n = 2)], all in the GB/FF FDC group. None of the serious TEAEs were considered to be study drug related according to the investigator.

In total, five patients discontinued the study due to treatment-emergent COPD exacerbations, and none of them assessed were related to the study drug according to the investigator. The most commonly reported TEAEs (occurring in at least five subjects) in both groups were urinary retention, pyrexia, COPD exacerbation, upper respiratory tract infection, and hyperglycemia. The incidences of clinically significant abnormalities in laboratory parameters were low in this study. No clinically significant vital sign parameters or ECG abnormalities were reported in the study [Table 3].

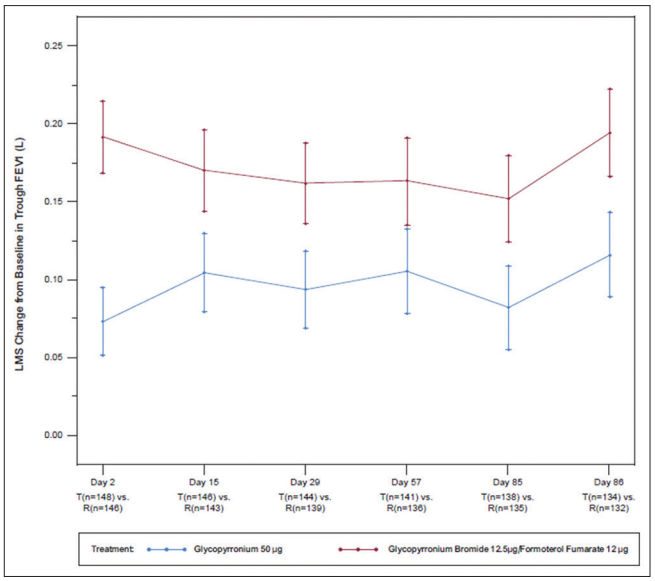

Figure 3: Plot of least square means of change from baseline of trough FEV_1 (L)—FAS population

DISCUSSION

Current GOLD 2021 guidelines recommend the combined use of LABA and LAMA when symptoms are not adequately improved by a single bronchodilator in COPD patients.[1] Evidence indicates that the LABA/LAMA combination is associated with better improvements in patient-centered outcomes, such as dyspnea, COPD symptoms, rescue medication use, and quality of life, than monotherapy.[19] The FDC of GB/FF DPI (12.5/12 µg) given twice daily in subjects with moderate-to–severe COPD was associated with superior bronchodilation compared to GLY DPI monotherapy given once daily, an effect that was sustained over 12 weeks in the current study. In general, a study duration of 12 weeks is considered sufficient to establish the efficacy and safety of LABA for the treatment of COPD.[20,21]

The change from baseline in FEV_1 in the GB/FF group was in line with the previous combination of LAMA and LABA either as FDC or separately administered via pMDI or DPI.[20,22] In a meta-analysis of 1868 patients from randomized trials of ≥2 weeks duration, LAMA/LABA combination (TIO/FORMO) significantly improved average FEV_1 compared to tiotropium only.[23] In another large meta-analysis of 34,617 patients from randomized controlled trial studies of ≥10 weeks, all licensed FDC of LAMA/LABA showed significant improvement in lung function in terms of trough, peak, and AUC_{0-24h} FEV_1 compared to placebo. In particular, FDC of GB/FF MDI significantly improved peak FEV_1 compared to UMEC/VIL.[24] Both PINNACLE studies have shown a difference of more than 100 mL for peak change from baseline in FEV_1 (within 2 h postdose) with GB/FF MDI vs. GLY MDI at week 24 (PINNACLE 1: 133 mL and PINNACLE 2: 126 mL).[25] In the current study, the difference was also more than 100 mL between GB/FF

Table 3: Summary of TEAEs in at least 2% of patients in any treatment group by system organ class and preferred term—safety population

System organ class Preferred term, *n* (%) (Y)	GLY (50 µg) once daily (*n*=165)	GB/FF FDC (12.5/12 µg) twice daily (*n*=162)	Total (*n*=330)
Number of patients with any TEAE	43 (25.9) (51)	41 (25.0) (60)	84 (25.5) (111)
Gastrointestinal disorders	11 (6.6) (12)	13 (7.9) (21)	24 (7.3) (33)
Abdominal pain	3 (1.8) (3)	4 (2.4) (4)	7 (2.1) (7)
Constipation	4 (2.4) (4)	1 (0.6) (1)	5 (1.5) (5)
Diarrhea	1 (0.6) (1)	5 (3.0) (5)	6 (1.8) (6)
Hyperchlorhydria	2 (1.2) (2)	4 (2.4) (4)	6 (1.8) (6)
Vomiting	2 (1.2) (2)	5 (3.0) (7)	7 (2.1) (9)
General disorders and administration site conditions	10 (6.0) (10)	7 (4.3) (9)	17 (5.2) (19)
Chest pain	4 (2.4) (4)	0	4 (1.2) (4)
Pyrexia	6 (3.6) (6)	7 (4.3) (9)	13 (3.9) (15)
Infections and infestations	6 (3.6) (6)	6 (3.7) (8)	12 (3.6) (14)
Upper respiratory tract infection	6 (3.6) (6)	6 (3.7) (8)	12 (3.6) (14)
Metabolism and nutrition disorders	6 (3.6) (6)	6 (3.7) (6)	12 (3.6) (12)
Hyperglycemia	6 (3.6) (6)	6 (3.7) (6)	12 (3.6) (12)
Renal and urinary disorders	11 (6.6) (11)	9 (5.5) (9)	20 (6.1) (20)
Urinary retention	11 (6.6) (11)	9 (5.5) (9)	20 (6.1) (20)
Respiratory, thoracic, and mediastinal disorders	6 (3.6) (6)	7 (4.3) (7)	13 (3.9) (13)
Chronic obstructive pulmonary disease	6 (3.6) (6)	7 (4.3) (7)	13 (3.9) (13)

FDC: Fixed-dose combination; GB/FF: Glycopyrronium/formoterol fumarate dihydrate; GLY: Glycopyrronium; N: Number of randomized patients in the respective treatment group; TEAE: Treatment-emergent adverse event; Y: Total number of events in safety population in each treatment. Percentages are based on the number of randomized patients in the respective treatment groups. At each level of summarization, a patient was counted once if the patient reported one or more events in a given level of summarization

DPI and GLY DPI (115 mL) at week 1.[25] A previous randomized dose-finding study has shown that twice-daily glycopyrronium 12.5 µg produced a marginally higher improvement in trough FEV_1 vs. placebo than 50 µg once daily.[13] Similarly, bronchodilation and other clinical outcomes were similar with glycopyrronium (12.5 µg twice daily) in the FDC group and the GLY monotherapy group (50 µg once daily) in the current study.

Sensitivity analysis in the PPS population as well as secondary endpoints in the current study supported the results of the primary endpoint. Significant differences were observed between the FDC group and the GLY group ($P > 0.05$) for change from baseline in trough FEV_1 ($P = 0.0153$), FVC ($P = 0.0055$), and FEV_1 $AUC_{0–2h}$ ($P < 0.0001$) at week 12. These findings were similar to other FDCs of GB/FF vs. GLY,[25,26] TIO/FORMO vs. TIO,[23] UMEC/VI vs. UMEC,[27] and other licensed FDCs.[24] Further, the findings from this study are in line with the exploratory analysis of the Asian subpopulation of the PINNACLE 4 study.[28] Previous studies of GB/FF MDI in moderate-to–severe COPD patients from the global population[23,25,26] and Asian population[28] have shown improvements in daily, daytime, and nighttime symptom scores compared to monocomponents. Similarly, in the current study, improvement in these symptom scores seems to favor GB/FF DPI compared to GLY monotherapy at week 12.

Overall, the incidences of AEs and TEAEs were low and comparable across the two treatment groups. The majority of the TEAEs were mild or moderate in intensity and not related to the study drug. The incidence of clinically significant abnormalities in laboratory parameters, physical examination parameters, and USG findings was low. No clinically significant abnormalities in vital sign parameters or ECG were reported in the study. In summary, the FDC of GB/FF (12.5/12 µg) as a DPI in adult subjects with COPD was found to be safe and well tolerated. The safety profile of GB/FF DPI and GLY monotherapy in Indian patients was comparable to global[25] and Asian populations[28] and other licensed LAMA/LABA FDCs.[24]

The strength of the study was the robust, double-blind, randomized, active-controlled, parallel-group, superiority study design, which helped in minimizing the effect of bias and confounding on the study results. In this study, all the subjects received a placebo during the 2-week run-in period and were then randomized to one of the two treatment groups. Thus, the study practically compared the true effects of efficacy and safety of twice-daily GB/FF 12.5 µg vs. once-daily GB/FF 50 µg in subjects receiving background treatment of ICS. In this study, statistical analysis was conducted in both FAS and PPS populations, using MMRM and ANCOVA with LOCF with and without outlier treatments in accordance with the guidance from the USFDA.

Limitations of the study include the noninclusion of the placebo arm; the placebo arm was not included due to the ethical concern of denying treatment in patients with group "D" COPD. Further, the study was of short duration and not designed to assess the effect of GB/FF on exacerbations.

CONCLUSION

In conclusion, both GLY DPI and FDC DPI of GB/FF were associated with improvements from baseline in peak FEV_1 and trough FEV_1. Compared to GLY given once daily, treatment with FDC of GB/FF given twice daily showed superior improvement from baseline in peak FEV_1 at week 12. Both treatments as DPI were found to be safe and well tolerable for use in patients with symptomatic COPD.

Take home messages

Fixed-dose combination of glycopyrronium bromide 12.5 μg/formoterol fumarate 12 μg (twice daily) as a DPI provides superior bronchodilation and lung function improvement over glycopyrronium (50 mg once daily) monotherapy in symptomatic COPD patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY FIGURES AND TABLES

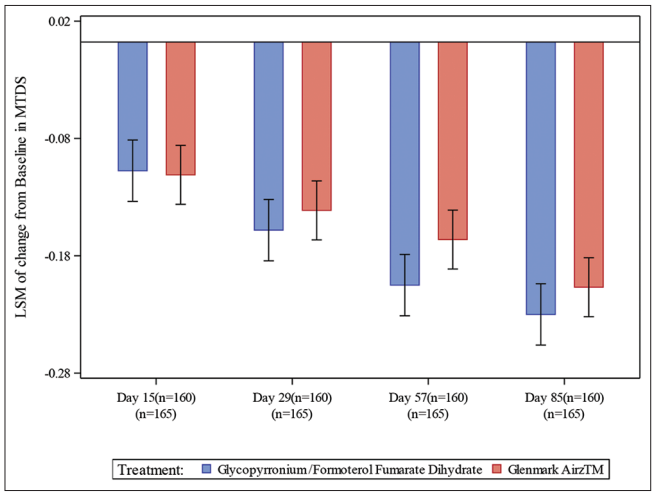

Figure S1: Plot of Least Square Means of Change from Baseline of MTDS - FAS population

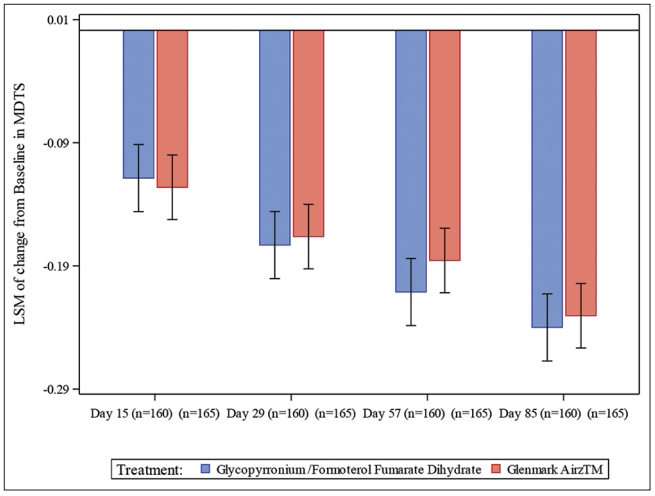

Figure S2: Plot of Least Square Means of Change from Baseline of MDTS - FAS Population

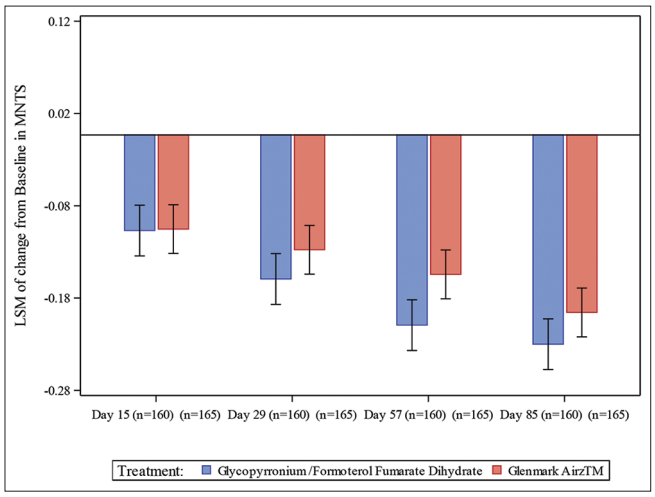

Figure S3: Plot of Treatment Difference of Change from Baseline of MNTS - FAS Population

Table S1: Analysis of Lung Function FVC (L) and Change from baseline by Visits – FAS Population

Visit	Statistics	GLY 50 once daily (*n*=165)	GB/FF FDC (12.5/12) twice daily (*n*=162)
Mean Change from baseline at Day 2 (Visit 4)	LSM (SE)	0.139 (0.0327)	0.258 (0.0347)
	Difference: LSM (SE)		0.118 (0.0355)
	95% CI		[0.048, 0.188]
	p-value1		0.0010
Mean Change from baseline at Day 15 (Visit 5)	LSM (SE)	0.151 (0.0348)	0.253 (0.0365)
	Difference: LSM (SE)		0.102 (0.0391)
	95% CI		[0.025, 0.179]
	p-value1		0.0093
Mean Change from baseline at Day 29 (Visit 6)	LSM (SE)	0.143 (0.0356)	0.223 (0.0372)
	Difference: LSM (SE)		0.079 (0.0404)
	95% CI		[-0.000, 0.159]
	p-value1		0.0503
Mean Change from baseline at Day 57 (Visit 7)	LSM (SE)	0.112 (0.0375)	0.224 (0.0389)
	Difference: LSM (SE)		0.112 (0.0436)
	95% CI		[0.026, 0.197]
	p-value1		0.0110
Mean Change from baseline at Day 85 (Visit 8)	LSM (SE)	0.062 (0.0371)	0.183 (0.0387)
	Difference: LSM (SE)		0.121 (0.0430)
	95% CI		[0.036, 0.205]
	p-value1		0.0055

CI – Confidence interval, FAS – Full analysis set, FVC – Forced volume capacity, LSM – Least square mean, SE – standard error. 1 *P* value is calculated for the comparison of treatment groups using MMRM with treatment, centre, visit, and treatment-by-visit interaction as fixed-effect factors and Lung Function FVC (L) at baseline as covariate. The 95% CIs for the difference in mean change from baseline (Visit 3) of Glycopyrronium/Formoterol Fumarate dihydrate vs Glycopyrronium monotherapy.

Table S2: Analysis of Lung Function Standardized FEV1 (L) AUC and Change from baseline by Visits – FAS Population

Visit	Statistics	GLY 50 once daily (*n*=165)	GB/FF FDC (12.5/12) twice daily (*n*=162)
Mean Change from baseline at Day 1 (Visit 3)	LSM (SE)	0.138 (0.0213)	0.194 (0.0228)
	Difference: LSM (SE)		0.056 (0.0254)
	95% CI		[0.006, 0.106]
	p-value1		0.0279
Mean Change from baseline at Day 85 (Visit 8)	LSM (SE)	0.139 (0.0211)	0.249 (0.0221)
	Difference: LSM (SE)		0.111 (0.0248)
	95% CI		[0.062, 0.159]
	p-value1		<0.0001

AUC – Area under the curve, CI – Confidence interval, FAS – Full analysis set, FEV1 – Forced expiratory volume in 1 second, LSM – Least square mean, SE – standard error. 1p-value was calculated for the comparison of treatment groups using ANCOVA with treatment, centre, visit, and treatment-by-visit interaction as fixed-effect factors and lung function FEV1 (AUC) at baseline as covariate. The 95% CIs for the difference in mean change from baseline (Visit 3) of Glycopyrronium/Formoterol Fumarate dihydrate vs Glycopyrronium monotherapy.

Table S3: Overall Summary of Subjects with Adverse Events – Safety Population

	GLY 50 once daily (*n*=166) *n* (5)	GB/FF FDC (12.5/12) twice daily (*n*=164) *n*(%)	Total (*n*=330) *n*(%)
AE	69 (41.6)	62 (37.8)	131 (39.7)
Serious Adverse Event (SAE)	0	4 (2.4)	4 (1.2)
AE Leading to Death	0	1 (0.6)	1 (0.3)
AE Leading Permanent discontinuation of IP	3 (1.8)	2 (1.2)	5 (1.5)
AE Leading to early Termination	4 (2.4)	3 (1.8)	7 (2.1)
SAE Leading to Death	0	1 (0.6)	1 (0.3)
SAE Leading to early Termination	0	2 (1.2)	2 (0.6)
AE by Relationship			
Yes	15 (9.0)	11 (6.7)	26 (7.9)
No	54 (32.5)	51 (31.1)	105 (31.8)
AE by Severity			
Mild	42 (25.3)	36 (22.0)	78 (23.6)
Moderate	27 (16.3)	22 (13.4)	49 (14.8)
Severe	0	4 (2.4)	4 (1.2)

AE – Adverse event; IP – Investigational product; N – Number of subjects in safety population in respective treatment group. Percentages are based on on the total number of subjects in safety population in respective treatment group. Study drug related adverse event is defined as adverse event with relationship with IP as 'Yes'. Subjects with more than one AE are counted only once. Counted subjects with highest severity (Severe) and relationship (Related)

SUPPLEMENTARY APPENDIX

Selection of study population

Inclusion criteria

Subjects who met the following inclusion criteria were eligible for enrolment in the study:

1. Male or female, aged ≥40 to <65 years at the time of informed consent.
2. Current or previous cigarette/beedi smokers with a history of cigarette/beedi smoking of at least 10 pack-years (number of pack years = (number of cigarettes per day/20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years). Previous smokers defined as those who had stopped smoking for at least 6 months prior to Visit 1.
3. Diagnosis of COPD (as defined by the GOLD Guidelines, 2016).
4. Post-bronchodilator FEV_1 ≥30% and <80% of the predicted normal value and post-bronchodilator FEV_1/FVC ratio <0.7. *(Post-bronchodilator refers to 30 minutes ±10 minutes after sequential inhalation 400 mcg salbutamol [or equivalent dose] delivered at 30 seconds interval. Spacer devices were not permitted during the testing*)
5. An mMRC grade 2 or greater.
6. Had a chest X-ray or computed tomography (CT) scan that was consistent with the diagnosis of COPD and taken less than or equal to 6 months before study start. If there was no chest X-ray/CT scan taken less than or equal to 6 months before study start, a chest x-ray was performed at Visit 1.
7. Provided written informed consent.
8. Female subjects who had a negative pregnancy test at Visit 1, and agreed to use an adequate forms of non-hormonal contraception during the study (i.e., women of child bearing potential used a highly effective method of birth control, such as condom and spermicide, diaphragm or cervical cap and spermicide, condom and diaphragm or cervical cap, nonhormonal intrauterine device) , or females who were of non-child bearing potential i.e., who were surgically sterile (history of hysterectomy or bilateral tubal ligation or bilateral oophorectomy; partial hysterectomy was not sufficient or vasectomized partner) or postmenopausal (12 months of spontaneous amenorrhea) or who agreed to remain abstinent.
   Males: Subjects who agreed to either remain abstinent or used a highly effective method of birth control as described above.
9. Were willing and able to comply with all aspects of the protocol.
10. Were able to use the inhalation devices independently and correctly.

Exclusion criteria

Subjects who met any of the following criteria were not eligible for enrolment in the study:

1. Subjects who had current diagnosis of asthma (subjects with a prior history of asthma were eligible if COPD was currently their primary diagnosis).
2. Known respiratory disorders other than COPD including but not limited to alpha-1 antitrypsin deficiency as the underlying cause of COPD, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease.
3. Any previous lung resection surgery (e.g., lung volume reduction surgery or lobectomy).
4. Chest X-ray or CT scan which revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD (e.g., evidence of pneumonia, other infection, atelectasis, or pneumothorax).
5. Type I or uncontrolled Type II diabetes.
6. History of narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder-neck obstruction or moderate-to-severe renal impairment or urinary retention (subjects with a transurethral resection of prostate, subjects who underwent full re-section of the prostate was considered for the study, as well as subjects who were asymptomatic and stable on pharmacological treatment for the condition).
7. Clinically significant elevated IOP on ophthalmic assessment.
8. Clinically significant urinary retention on USG examination.
9. Used oral/depot corticosteroids or antibiotics for COPD within 6 weeks prior to Visit 1 or subject who had a change in dose or type of any medications for COPD within 14 days before the Visit 1.
10. Hospitalized for COPD exacerbation or pneumonia within 3 months prior to Visit 1.
11. Had a clinically relevant laboratory abnormality or a clinically significant condition, in the judgment of the investigator, such as (but not limited to):
    a. Unstable ischemic heart disease, left ventricular failure (New York Heart Association Class III and IV), history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation). Subjects with such events were not considered clinically significant by the investigator were considered for inclusion in the study.
    b. Uncontrolled hypo-or hyperthyroidism, hypokalemia or hyperadrenergic state or any condition which might compromise subject safety or compliance, interfere with evaluation, or preclude completion of the study.

12. An abnormal and clinically significant 12-lead ECG as per investigator's discretion. For the purposes of this study, an abnormal ECG was defined as a 12-lead tracing which was interpreted with (but not limited to) any of the following:
    a. Clinically significant conduction abnormalities (e.g., left bundle branch block, Wolff- Parkinson-White syndrome)
    b. Myocardial ischemia
    c. Clinically significant arrhythmias (e.g., atrial fibrillation, ventricular tachycardia)
    d. A mean QTcB value at screening ≥450 msec (for males) /≥470 msec (for females) and , the QTc(B) of all 3 screening ECGs are not within 10% of the mean, or an ECG that was not suitable for QT measurements (e.g. poorly defined termination of the T wave)
13. A known case of positive hepatitis B surface antigen or positive hepatitis C antibody at Visit 1.
14. A known case of positive human immunodeficiency virus (HIV).
15. A current malignancy or previous history of cancer in remission for <5 years prior to Visit 1 (localized basal cell or squamous cell carcinoma of the skin that was resected which was not exclusionary). Subjects with a history of cancer that was considered surgically cured and without a recurrence within the past 5 years may participate in the study. History of hematologic/lymphatic malignancy treated with chemotherapy or radiation was not allowed, under any condition.
16. History of allergy or hypersensitivity to the investigational products (IPs) or any of the excipients.
17. Additional Medications - Unable to stop following medications at the defined times prior to screening spirometry:
18. Subjects who were on long-term oxygen therapy or supplemental oxygen was required for greater than 12 hours a day. Oxygen prn use was not prohibited.
19. Subjects with clinically significant sleep apnoea that required continuous positive airway pressure.
20. Subjects with history of regular use of nebulized therapy.
21. Subjects with history of use of nocturnal positive pressure or non-invasive positive pressure ventilation.
22. Participated in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1. Subjects in the maintenance phase of a pulmonary rehabilitation program were not excluded.
23. Study investigators, sub-investigators, study coordinators, employees of a participating investigator or study site, or an immediate family member of the aforementioned were excluded from participation in this study.
24. History of psychiatric disease, intellectual deficiency, poor motivation, substance abuse in the 2 years prior to Visit 1 (including drug and alcohol), or other conditions as per investigator's discretion.
25. Subject with history of use of any prescription drug for which concomitant β-agonist administration was contraindicated (e.g., β_2-blockers).
26. Pregnant or lactating women.
27. Currently enrolled in another interventional clinical study or used any IP, study drug, or device within 30 days or 5 times the half-life, whichever was longer preceding informed consent or were scheduled to participate in another clinical study involving an IP.

Removal of subjects from therapy or assessment

Subjects were removed from study by the investigator or the sponsor if any of the following circumstances occurred:

1. Withdrawal of consent by the subject to continue in the study.
2. Development of a serious or intolerable AE that necessitated discontinuation, at the discretion of the investigator.
3. The investigator believed continued participation was not in the best interest of the subject.
4. The investigator believed the subject had not adhered to the study procedures or restrictions.
5. Protocol deviation (PD) occurred that in the opinion of sponsor warranted discontinuation from the study.
6. The investigator withdrew the subject from the study where the subject suffered from significant inter-current illness or underwent surgery during the course of the study.
7. Clinically significant elevated IOP on ophthalmic assessment during the study.
8. Clinically significant urinary retention on USG examination during the study.

9. Subject was unable to comply with spirometry washout criteria.
10. Experienced a COPD exacerbation (defined: A worsening of the following 2 or more major symptoms for at least 2 consecutive days:
    a. Dyspnoea
    b. Sputum purulence

    Or
    a. worsening of any 1 major symptom together with an increase in any 1 of the following minor symptoms for at least 2 consecutive days:
        i. Sore throat
        ii. Cold (nasal discharge and/or nasal congestion)
        iii. Fever without other cause
        iv. Cough
        v. Wheeze

    A COPD exacerbation was considered moderate in severity if the treatment with systemic glucocorticosteroids or antibiotics or both was required. A COPD exacerbation was considered severe if hospitalization was required. An emergency room visit of longer than 24 hours was considered a hospitalization. Demonstrated clinically significant changes in laboratory parameters or ECG recordings.

    Subjects who had any event of a COPD exacerbation occurred at any time during the study were treated for the exacerbation by the investigator. All moderate or severe COPD exacerbations events were recorded on the COPD exacerbation case report form (CRF).
11. Became pregnant during the study period.

    Subjects who were discontinued from the study for any reason were not replaced. In case of a subject withdrawal, all efforts were made to complete and report the observations and an explanation for the withdrawal was recorded on the CRF. Subjects discontinued from the study at any stage were considered for safety analysis.

Blinding

This was a randomized, double-blind study wherein the investigator, subject, staff, sponsor, data analysts and all other personnel directly involved in the study conduct were blinded to the treatment until database lock. The study drugs were identical in terms of shape, size, colour, smell, taste and were supplied in identical packaging. The dosing regimen of the test (twice daily) and comparator (once daily) products being different, subjects were given placebo capsules to be inhaled in evening in order to ensure treatment blinding. Thus, to maintain identical dosing schedule all subjects had to self-administer 2 inhalation capsules daily.

Sealed envelopes with the randomization codes were provided to the investigator before study initiation and were advised to keep the envelopes in a safe and secure location at the site. During the study, the integrity of the sealed envelopes were examined by the study monitor during the routine monitoring visits. The randomization code-break envelopes were to be opened only in the case of a medical emergency (AEs or serious adverse events [SAEs]) where knowledge of treatment allocation was essential for the management of the subject's condition. The investigators followed the trial's randomization procedure, and ensured that the code was broken only in accordance with the protocol. In case of any premature unblinding (e.g., accidental, due to a SAEs) of the IPs, the investigators promptly documented and explained the same to the sponsor and also documented it in the CRF. Before breaking the code, the investigator contacted the Glenmark medical monitor or delegates and asked for the approval for breaking the code. If any code-break envelope was opened, the person who opened it signed and dated the envelope and recorded the reason for opening it. The overall randomization code was broken only after the database lock.

Determination of sample size

A sample size of 266 evaluable subjects with a ratio of 1:1 (133 subjects per treatment arm) was estimated to detect a difference in means between the two treatments assuming a two-sided alpha of 5% with 90% power. An effect size of 100 mL and standard deviation (SD) of 250 mL, were assumed to determine sample size based on previous published studies. Assuming a dropout rate of 20%, a total of 332 subjects (166 subjects per treatment arm) were planned to be randomized in the study.

Randomization scheme and codes

At Visit 3, subjects were randomly assigned based on the computer generated blinded randomization list in a 1:1 ratio to receive FDC product or comparator.

STUDY SUBJECTS

Disposition of subjects

A total of 443 subjects were enrolled and screened. Of the 443 subjects screened, 94 (21.2%) were screen failures, and were not randomized. Of the remaining 349 screened subjects, a total of 331 subjects were competitively randomized across 25 centres in India (18 subjects were not randomized to receive the study drug though they met the inclusion/exclusion criteria). Of the 331 randomized subjects, 330 (99.7%) were included in SAF population, 327 (98.8%) were included in FAS population, and 326 (98.5%) were included in PPS population. A total of 295 (89.1%) subjects completed the study. The number of subjects completing the treatment period was comparable across the treatment groups (Table S4). Thirty six (10.9%) subjects prematurely discontinued from the study and did not complete the study period. The most common reason for discontinuation was lost to follow-up (15 [4.5%]), followed by withdrawal of consent (9 [2.7%]), COPD exacerbation (7 [2.1%]), and protocol deviation (2 [0.6%]). There was 1 death in the study.

Table S4: Summary of Subject Disposition (Overall)- Randomized Population

Parameter	Statistics	Glycopyrronium/ Formoterol Fumarate dihydrate (*n*=165)	Glenmark Airz™ (*n*=166)	Total (*n*=331)
Final Subject Status				
Randomized subjects	*N*	165	166	331
Subject Completed Study	*n* (%)	147 (89.1)	148 (89.2)	295 (89.1)
Subject Withdrawn	*n* (%)	18 (10.9)	18 (10.8)	36 (10.9)
Analysis sets				
FAS	*n* (%)	162 (98.2)	165 (99.4)	327 (98.8)
PPS	*n* (%)	162 (98.2)	164 (98.8)	326 (98.5)
SAF	*n* (%)	164 (99.4)	166 (100)	330 (99.7)
Reason for Early Termination				
Withdrawal of consent	*n* (%)	4 (2.4)	5 (3.0)	9 (2.7)
Adverse Event	*n* (%)	0	0	0
investigator's Discretion	*n* (%)	1 (0.6)	0	1 (0.3)
Noncompliance with Study Procedures	*n* (%)	0	1 (0.6)	1 (0.3)
Protocol Deviation	*n* (%)	1 (0.6)	1 (0.6)	2 (0.6)
Significant inter-current illness or surgery during the course of the study	*n* (%)	0	0	0
Concomitant medication interfering the pharmacokinetic property of the study medication	*n* (%)	0	0	0
Clinically significant elevated IOP	*n* (%)	0	0	0
Clinically significant urinary retention	*n* (%)	0	0	0
Unable to comply with spirometry washout criteria	*n* (%)	0	0	0
COPD exacerbation	*n* (%)	3 (1.8)	4 (2.4)	7 (2.1)
Pregnancy	*n* (%)	0	0	0
Lost to follow up	*n* (%)	8 (4.8)	7 (4.2)	15 (4.5)
Death	*n* (%)	1 (0.6)	0	1 (0.3)
Others	*n* (%)	0	0	0

COPD – Chronic obstructive pulmonary disorder, FAS – Full analysis set, IOP – Ophthalmic examination, PPS – Per protocol set, SAF – Safety analysis set, *n*=Number of randomized subjects in respective treatment group. Percentages are based on the number of randomized subjects in respective treatment group