Original Article

Efficacy and safety of glycopyrronium/formoterol delivered via a dry powder inhaler in patients with moderate to severe chronic obstructive pulmonary disease: Results from a multi-centre, open-label, randomised study

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ABSTRACT

Background: We designed this randomised, open-label, parallel group, multi-centre study to investigate the efficacy and safety of glycopyrronium/formoterol, a long-acting muscarinic antagonist/long-acting β2-agonist fixed dose combination, delivered through a dry powder inhaler (DPI) in patients with chronic obstructive pulmonary disease (COPD). **Material and Methods:** We randomised (1:1) patients with moderate to severe COPD (N = 356) to receive glycopyrronium 25 μg/formoterol 12 μg via DPI twice daily (GF-DPI) or glycopyrronium 50 μg monotherapy via DPI once daily (G-DPI). The primary study endpoint was the mean change from the baseline in pre-dose trough-forced expiratory volume in one second (FEV_1) at 12 weeks. **Results:** At week 12, the mean increase from the baseline in pre-dose trough FEV_1 was higher in the GF-DPI group (120 ml) than in the G-DPI (60 ml) group. The mean difference (MD) between treatment groups was 0.06 L (95% CI: 0.00–0.12 L, $P < 0.0001$ for non-inferiority). At week 12, the mean pre-dose forced vital capacity (FVC), 1 hour post-dose FEV_1, and post-dose FVC increased significantly from the baseline only in the GF-DPI group ($p < 0.0001$). The reduction in the COPD assessment test score was greater in the GF-DPI group ($p = 0.0379$). The average daily number of puffs of rescue medication and the reduction in mean modified Medical Research Council

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scale, COPD, and Asthma Sleep Impact Scale score at week 12 were similar between groups ($p > 0.05$). Overall, 35 adverse events and two serious adverse events unrelated to study drugs were reported. Both groups had similar results for overall drug safety. **Conclusion:** The results demonstrate efficacy and safety of GF-DPI in Indian patients with moderate to severe COPD. Treatment with GF-DPI significantly improved the lung function and quality of life and was well tolerated.

KEY WORDS: Bronchodilator, chronic obstructive pulmonary disease, dry powder inhaler, dual bronchodilation, formoterol, glycopyrronium

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease and is a significant cause of morbidity and mortality.[1] As per the Global Burden of Disease (GBD) study, 2017, the point prevalence of COPD was 3.9%, accounting for 5.72% of total deaths and 1068 disability-adjusted life years per 100 000 individuals.[2] In India, COPD was ranked second in terms of total number of deaths and third for total combined DALY and deaths in 2019.[3] Such a huge burden necessitates adoption of effective treatment strategies.[4]

Inhaled long-acting muscarinic antagonists (LAMAs) and long-acting β2-agonists (LABAs) are the mainstay of treatment in patients with COPD.[1] Because of their distinct mechanisms of action, the combination of LAMA and LABA, that is, dual bronchodilation, has shown to improve the lung function to a greater extent compared to LAMA or LABA monotherapy.[5] A consistently growing body of evidence led the GOLD Report Committee to lay additional emphasis on the LAMA/LABA dual therapy for COPD management since 2017.[6] With the increased adoption of LAMA/LABA combination therapy, fixed-dose combinations (FDCs) delivered via a single inhaler device have emerged to offer patient convenience and improved treatment adherence.[7]

A series of Phase III studies (GLOW 1–5) have demonstrated the efficacy of glycopyrronium, a newer generation LAMA, in improving the lung function and in reducing risk for exacerbations versus placebo.[8] Glycopyrronium has a faster onset of action and a better cardiovascular safety profile than tiotropium.[9] Glycopyrronium has also shown to improve dyspnea, the health status, rescue medication use, and exercise tolerance versus placebo.[8] Glycopyrronium bromide 25 µg twice daily (BID) provides significant bronchodilation over a 24-hour period with forced expiratory volume in 1 second (FEV_1) area under the curve (AUC) (0–24 h) that is reportedly similar to 50 µg once daily dose.[9-11] Formoterol fumarate (FF) is a potent and selective LABA, with an onset of action faster than that of salmeterol and similar to that of short-acting β_2-adrenergic receptor agonists (SABAs).[9] Studies have demonstrated formoterol 12 µg BID to be effective in improving the lung function, controlling COPD symptoms and reducing the need for rescue medications, and well tolerated in the management of COPD.[9,12]

The clinical profiles of glycopyrronium and formoterol are well established, and they are approved to be used as maintenance therapy in patients with COPD. Dual fixed-dose bronchodilator therapy containing glycopyrronium/formoterol 18/9.6 µg delivered through a single pressurised metered-dose inhaler (pMDI) has been shown to be effective in the long-term maintenance treatment of airflow obstruction in patients with COPD in a series of PINNACLE studies.[13,14] The combination also significantly improved the Transition Dyspnea Index focal score, the St George's Respiratory Questionnaire total score, and the average daily rescue medication use versus glycopyrronium monotherapy.

Recently, we developed a glycopyrronium/formoterol 25/12 µg FDC to be delivered via a dry powder inhaler (DPI), which can overcome the problem of hand-to-breath coordination required for pMDIs. Herein, we report the results from a phase III randomised study evaluating the efficacy and safety of the newly developed glycopyrronium and formoterol 25/12 µg FDC when delivered via DPI in patients with moderate to severe COPD. This was the first study evaluating the efficacy of this LABA–LAMA combination when delivered through a DPI.

MATERIAL AND METHODS

Study design and patient population

We designed this randomised, prospective, open-label, parallel group, multi-centre phase III study which was conducted at 32 centres in India between August 2017 and October 2018. The study included men and women (40–65 years of age) with moderate to severe COPD (GOLD 2015) who were randomly allocated (1:1) to either glycopyrronium 25 µg/formoterol 12 µg twice daily or glycopyrronium 50 µg once daily for their COPD management for 12 weeks. Inclusion criteria included a post-bronchodilator FEV_1/FVC ratio of <0.7, post-bronchodilator FEV_1 between ≥40% and ≤80% of the predicted normal value, and current or past smoking (cigarette/bidi) history of ≥10 pack years. Key exclusion criteria included >2 exacerbations

in the past year, clinically significant diseases other than COPD, and pregnant or lactating women (refer supplementary appendix for complete inclusion and exclusion criteria). The detailed study withdrawal criteria are provided in the supplementary appendix. Key withdrawal criteria included >1 mild or moderate COPD exacerbations (requiring out-patient treatment without hospitalisation, requiring systemic steroids/ antibiotics except macrolides), one severe COPD exacerbation (requiring emergency hospitalisation and treatment with oral steroids and antibiotics), or use of prohibited medications.

We conducted this study in accordance with Good Clinical Practice (GCP), International Council for Harmonisation (ICH) guidelines of technical requirements for pharmaceuticals for human use, the National Ethical guidelines for Biomedical and Health Research involving Human Participants (Indian Council of Medical Research 2017), and the Declaration of Helsinki, 2018. The Drug Controller General of India and Institutional Ethics Committees also approved this study. All participants provided informed consent prior to commencement of the study. We prospectively registered the study with the Clinical Trials Registry of India (CTRI) (CTRI/2017/08/009286).

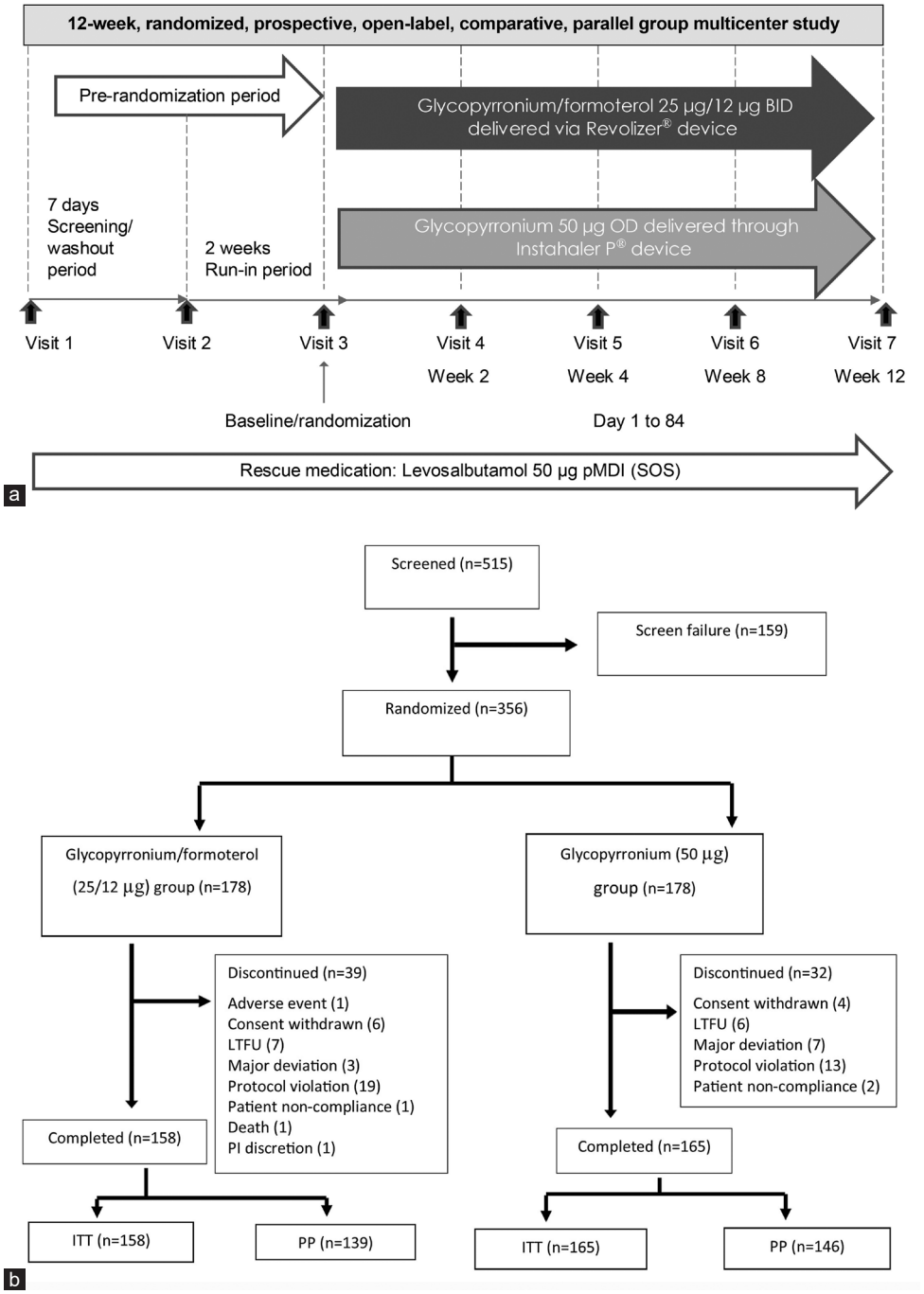

Figure 1: (a) Study design (b) Patient disposition (LTFU: lost to follow-up)

Study procedure

The study involved a screening period of up to 7 days, a 2-week run-in period, and a 12-week treatment period [Figure 1a]. During the run-in period, the investigators treated the patients with levosalbutamol 50 μg as a rescue medication. If the patients were on a stable dose of inhaled corticosteroid (ICS)/LABA combination over the past 3 months, the investigators treated the patients with budesonide pMDI as per their discretion at a dose pharmacologically equivalent to their existing ICS. At the end of the run-in period, if the change in absolute pre-dose trough FEV_1 of patients was ± 20% compared to that at screening without an exacerbation of disease, the investigators enrolled them in the study.

A trained pharmacist or clinical research coordinator randomly (1:1) allocated the patients to receive either glycopyrronium 25 μg/formoterol 12 μg twice daily (GF-DPI group; Cipla Ltd) through Revolizer® or glycopyrronium 50 μg once daily (G-DPI group, Glenmark) through Instahaler P® for 12 weeks. Both are unit-dose capsule-based DPIs. During the study period, patients were allowed to take a rescue drug, levosalbutamol 50 μg, inhalation up to a maximum of 12 puffs a day. Designated study personnel explained the study procedure thoroughly to the patients and asked them to contact their investigators for assessment and initiation of appropriate therapy if they required more than 12 puffs a day of levosalbutamol 50 μg for 2 or more consecutive days. An independent study statistician generated the randomisation sequence by using SAS statistical software version 9.3 or higher (SAS Institute Inc., USA). In this study, we followed a central randomisation procedure. A trained pharmacist or clinical research coordinator at the site dispensed the treatment drugs (either glycopyrronium 25 μg/formoterol 12 μg or glycopyrronium 50 μg) depending upon the treatment allocation envelopes selected and opened by the patients under supervision of the investigator. Each investigator received appropriate quantities of the envelopes and related quantities of treatment drugs for dispensing to the patients for the next 12 weeks. Bilcare Limited Global Clinical Supplies, Pune, did the packaging and labelling. There was no allocation bias. The biostatistician was blinded for the treatment arms as per the randomisation codes allocated.

Study assessments and endpoints

Spirometry measurements for FEV_1 and FVC were performed in accordance with the American Thoracic Society (ATS) criteria at the second screening visit and at all treatment visits.[15] At all visits, investigators confirmed that patients stopped COPD medications, including reliever medications, 6 hours prior to spirometry measurements. Pre-dose and post-dose FEV_1 and FVC were recorded at each visit.

The study team used the following tools for assessment of various parameters at screening visit 2 (i.e., baseline) and at weeks 4, 8, and 12) The modified Medical Research Council (mMRC) dyspnea scale for assessment of dyspnea,[16,17] 2) the COPD assessment test (CAT) for health-related quality of life wherein higher scores denote a more severe impact of COPD on the patient's life,[18] and 3) the COPD and Asthma Sleep Impact Scale (CASIS) for sleep impairment. Patients rated nocturnal symptoms on a scale of 1 (never) to 5 (very often). The responses to each question were summarised as frequency and the corresponding percentages. Patients used diaries to record information regarding the use and time of rescue medications (at screening visit 2 and weeks 2, 4, and 8) and any adverse events (AEs) across all time points.

The primary study endpoint was the mean change from the baseline in pre-dose trough FEV_1 at 12 weeks. Secondary endpoints included the mean change from the baseline in pre-dose trough FEV_1 at weeks 2, 4, and 8; the mean change from the baseline in 1-hour post-dose FEV_1 at weeks 2, 4, 8, and 12; the mean change from the baseline in pre-dose and 1-hour post-dose FVC at weeks 2, 4, 8, and 12; and the mean change from the baseline in CAT score, mMRC scale, average daily number of pMDI puffs of rescue medications, and CASIS score at weeks 4, 8, and 12.

Safety endpoints were AEs, changes in electrocardiography (ECG), and vital signs throughout the treatment period and mean changes from the baseline in serum potassium levels at weeks 4 and 12 in both groups.

Statistical analysis

A sample size of 138 patients was determined for each treatment arm to achieve 80% power to detect non-inferiority (upper limit: above -60 ml, standard deviation: 200 ml) of GF-DPI with G-DPI for the change from the baseline in morning pre-dose trough FEV_1 at week 12 with type I error, controlled at 5% (two-sided) using sequential testing. Considering a 30% dropout ratio, 356 patients were enrolled in the study. The sample size, non-inferiority design, and selection of the comparator group were guided by previous publications.[19-21]

The study results are presented for the intent-to-treat (ITT) population, defined as all randomised patients who received at least 1 dose of the study drug; per-protocol (PP) population, defined as all patients in the ITT analysis set without major protocol violation/deviation; and safety population (SP), defined as all randomised patients for whom there was evidence of drug intake.

Continuous variables are presented as mean and standard deviation (SD) or as median and inter-quartile range as applicable. Categorical variables are presented as frequency with the corresponding percentages. The change in pre-dose and 1-h post-dose trough FEV_1 and FVC from the baseline to weeks 2, 4, 8, and 12 was evaluated using analysis of covariance (ANCOVA) with baseline levels as covariates and treatment as a factor. Treatment effects were estimated using the least square means and 95% confidence interval (CI) from the ANCOVA model. For remaining variables (average daily number of pMDI puffs, CAT score, mMRC scale, CASIS

scale, safety variables), the between-group or within-group comparisons for the mean change from the baseline were performed using non-parametric or parametric tests as applicable. The statistical significance was defined as a two-sided *P* value <0.05.

RESULTS

Patient demographics and clinical characteristics

From 11th August, 2017, to 30th October, 2018, 356 patients were randomised to two treatment arms (n = 158 in Glycopyrronium/formoterol arm; n = 165 Glycopyrronium arm). Of these, 323 patients completed the study on an ITT basis and 285 patients completed it on a per-protocol (PP) basis [Figure 1b]. Approximately 95% patients were men; the mean age of patients was 56 years, and the mean body mass index (BMI) was 22.14 kg/m^2. The mean duration of COPD was 4.1 years. As per the GOLD 2015 criteria, 216 (66.9%) patients had moderate and 107 (33.1%) had severe disease. Patients had a history of smoking of 23.19 ± 11.49 pack years. There was no statistical difference between the two groups at baseline for all parameters [Table 1].

Efficacy

Change in pre-dose trough FEV$_1$

In the ITT population, there was a significant improvement in the pre-dose trough FEV$_1$ in both treatment groups from baseline at 12 weeks with a statistically significant difference between both the groups (GF-DPI: 120 mL vs. G-DPI group: 60 mL, mean difference: 60 mL, 95% CI: 0.00-0.12L, $P < 0.0001$ for non-inferiority) [Figure 2]. The lower bound of 95% CI was 0 mL in the ITT population,

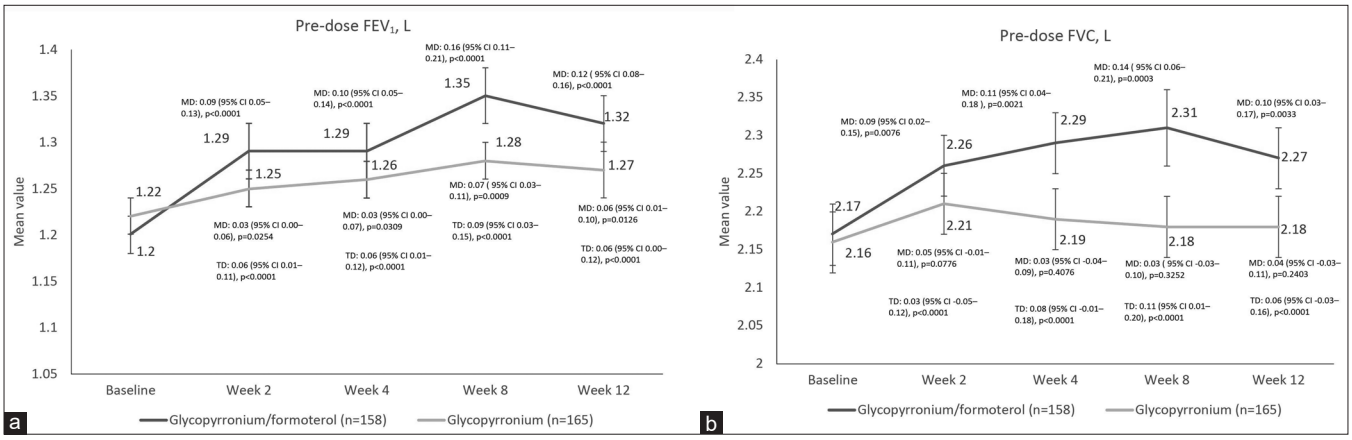

Figure 2: Changes in pre-dose trough forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) in the intention-to-treat (ITT) population (a) Changes in pre-dose trough FEV1 (b) Changes in pre-dose trough FVC (MD: Mean difference from the baseline, TD: Treatment difference between the groups, CI: Confidence interval)

Table 1: Baseline demographics and clinical characteristics

Parameters	Glycopyrronium/ formoterol (*n*=158)	Glycopyrronium (*n*=165)	*P*
Gender (M/F)	150 (94.9%)/8 (5.1%)	158 (95.8)/7 (4.2)	0.7260
Age (years)	56.53±6.35	55.85±6.56	0.3517
BMI (kg/m^2)	22.19±3.99	22.10±4.25	0.8410
Duration of COPD (years)	4.11±4.04	4.19±4.19	0.8697
Smoking history (pack years)	23.20±11.03	23.17±11.94	0.9795
Severity of disease as per GOLD 2015			
Moderate	111 (70.3)	105 (63.6)	0.2066
Severe	47 (29.8)	60 (36.4)	
Absolute eosinophil count	246.91±185.63	261.07±193.40	0.5028
Pre-bronchodilator FEV$_1$ (L)	1.21±0.28	1.24±0.30	0.4227
1 h post-bronchodilator FEV$_1$ (L)*	1.33±0.28	1.33±0.30	0.9190
Pre-dose FEV$_1$ (L)	1.20±0.29	1.22±0.31	0.4195
1 h post-dose FEV$_1$ (L)	1.35±0.32	1.36±0.37	0.7386
Pre-bronchodilator FVC (L)	2.17±0.46	2.16±0.49	0.8490
1 h post-bronchodilator FVC (L)	2.37±0.49	2.33±0.54	0.4745
Reversibility (%)	11.24±16.54	8.68±12.51	0.1170
mMRC score	2.02±0.83	2.08±0.75	0.4597
CAT score	20.52±7.65	20.80±7.62	0.7332
Patients continuing budesonide during the run-in period	93 (52.25)	89 (50.00)	0.671
Median dose of budesonide during the run-in period (µg)	400.00 (400.00,1200.00)	400.00 (400.00,1200.00)	0.533
Patients using ICS/LABA therapy prior to screening	27 (15.17%)	21 (11.80%)	0.352

Data presented as mean±SD or median (range) or n (%); * at screening. CAT: COPD assessment test, COPD: chronic obstructive pulmonary disease, FEV$_1$: forced expiratory volume in 1 second, h: hour, FVC: forced vital capacity, mMRC: modified medical research council

which was greater than the protocol-defined non-inferiority margin of -60 mL. The improvements in pre-dose trough FEV_1 in the GF-DPI group versus the G-DPI group were seen as early as week 2 [Figure 2]. Similar results were observed in the PP population [Supplementary Table 1].

Change in pre-dose trough FVC

The mean pre-dose trough FVC increased significantly at week 2 and persisted until week 12 with an increase by 100 mL at week 12 in the GF-DPI group (p = 0.0033) versus 40 mL in the G-DPI group (p = 0.2403) [Figure 2]. This led to a significant difference in the treatment effect of 30 mL, 80 mL, 110 mL, and 60 mL at weeks 2, 4, 8, and 12, respectively, for the GF-DPI group versus G-DPI group (p < 0.0001 for all comparisons). Changes in pre-dose trough FVC were similar in the PP population [Supplementary Table 1].

Changes in 1-hour FEV_1 and FVC post dose

One-hour post-dose FEV_1 significantly increased, beginning from week 2 until week 12, with an increase of 100 mL (95% CI: 0.04–0.15 L, $P = 0.0003$) for patients in the GF-DPI group, whereas it remained unchanged for patients in the G-DPI group (MD: 10 mL, 95% CI: -0.05–0.07 L, $P = 0.6846$) [Table 2]. The difference in the mean change from baseline in FEV_1 between the treatment groups was 90 mL, 90 mL, 110 mL, and 80 mL at weeks 2, 4, 8, and 12, respectively, for the GF-DPI group versus G-DPI group (p < 0.0001 for all comparisons). A similar trend was observed in the PP population [Supplementary Table 2].

One-hour post-dose FVC significantly improved from baseline to week 2 until week 12, with an increase of 110 mL (95% CI: 0.05–0.18 L, $P = 0.0011$) for patients in the GF-DPI group, and remained unchanged for patients in the G-DPI group (p = 0.4889) [Table 2]. The between-group difference in the treatment effect was 110 mL, 100 mL, 140 mL, and 140 mL at weeks 2, 4, 8, and 12, respectively (p < 0.0001 for all comparisons). The changes in 1-hour post-dose FVC in the PP population were identical to those in the ITT population [Supplementary Table 2].

Change in CAT score

The mean CAT score significantly reduced from baseline at weeks 4, 8, and 12 in both treatment groups [Table 3]. The differences between both groups were statistically significant with a greater reduction in the GF-DPI group than in the G-DPI group at weeks 4 and 12 (p = 0.0144 and $P = 0.0379$, respectively) [Table 3]. Changes in the mean CAT score in the PP population were comparable to those of the ITT population [Supplementary Table 3].

Change in rescue medication use

The average daily number of puffs of rescue medication significantly reduced from baseline to weeks 2, 4, 8, and 12 in both groups [Table 3], and this reduction was similar between groups at all time points. Use of rescue medications in the PP analysis was identical to that in the ITT analysis [Supplementary Table 3].

Table 2: Changes in post-dose FEV1 and FVC in the ITT population

Treatments	Post-dose FEV_1					Post-dose FVC				
	Baseline	Week 2	Week 4	Week 8	Week 12	Baseline	Week 2	Week 4	Week 8	Week 12
Glycopyrronium/formoterol (*n*=158)	1.35±0.02	1.43±0.03	1.41±0.03	1.48±0.03	1.45±0.03	2.37±0.04	2.48±0.06	2.43±0.04	2.49±0.05	2.48±0.04
MD		0.09 (0.03-0.14)	0.06 (0.01-0.12)	0.13 (0.07-0.19)	0.10 (0.04-0.15)		0.11 (0.03-0.19)	0.06 (-0.00-0.12)	0.12 (0.06-0.18)	0.11 (0.05-0.18)
P		0.0026	0.0131	<0.0001	0.0003		0.0057	0.0541	0.0003	0.0011
Glycopyrronium (*n*=165)	1.35±0.03	1.35±0.03	1.33±0.02	1.37±0.03	1.36±0.03	2.33±0.04	2.33±0.04	2.29±0.04	2.30±0.04	2.29±0.04
MD		-0.00 (-0.05-0.04)	-0.02 (-0.07-0.02)	0.02 (-0.03-0.08)	0.01 (-0.05-0.07)		-0.00 (-0.06-0.06)	-0.04 (-0.11-0.02)	-0.02 (-0.08-0.05)	-0.02 (-0.10-0.05)
P		0.8905	0.3178	0.4058	0.6846		0.9888	0.1935	0.6087	0.4889
Treatment difference	-	0.09 (0.02-0.16)	0.09 (0.02-0.16)	0.11 (0.02-0.19)	0.08 (0.00-0.16)	-	0.11 (0.01-0.21)	0.10 (0.01-0.19)	0.14 (0.05-0.23)	0.14 (0.04-0.23)
P (inter- group)	-	<0.0001	<0.0001	<0.0001	<0.0001	-	<0.0001	<0.0001	<0.0001	<0.0001

Data presented as least squares mean±standard error or least squares mean difference (95% CI). AFEV$_1$: forced expiratory volume in 1 second, FVC: forced vital capacity, MD: mean difference

Table 3: Changes in rescue medication usage, mMRC scale, and CAT score (ITT population)

Treatments	Number of puffs of rescue medication consumed daily					mMRC score					CAT score				
	Baseline	Week 2	Week 4	Week 8	Week 12	Baseline	Week 4	Week 8	Week 12	Baseline	Week 4	Week 8	Week 12
Glycopyrronium/formoterol (n=158)	1.74±1.52	1.26±1.28	0.98±0.86	1.12±1.06	0.82±0.68	2.04±0.84	1.67±0.81	1.46±0.73	1.18±0.73	20.68±7.63	17.36±7.68	15.41±6.64	13.13±6.36
MD		-0.49	-0.74	-0.61	-0.89		-0.37	-0.57	-0.85		-3.49	-5.57	-7.94
		(-0.71–-0.26)	(-0.94–-0.53)	(-0.82–-0.41)	(-1.10–-0.68)		(-0.47–-0.26)	(-0.70–-0.44)	(-1.00–-0.70)		(-4.13–-2.86)	(-6.46–-4.69)	(-9.03–-6.84)
P		<0.0001	<0.0001	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001
Glycopyrronium (n=165)	1.61±1.43	1.25±0.90	0.94±0.79	1.14±0.87	0.94±0.75	2.09±0.74	1.86±0.80	1.66±0.77	1.46±0.81	20.72±7.66	18.48±7.39	16.25±6.89	14.86±7.30
MD		-0.39	-0.72	-0.51	-0.73		-0.24	-0.44	-0.65		-2.32	-4.72	-6.21
		(-0.59–-0.20)	(-0.95–-0.50)	(-0.72–-0.30)	(-0.96–-0.49)		(-0.34–-0.14)	(-0.56–-0.33)	(-0.79–-0.51)		(-3.01–-1.62)	(-5.64–-3.80)	(-7.42–-5.00)
P		<0.0001	<0.0001	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001
Treatment difference	-	-0.10	-0.01	-0.10	-0.16	-	-0.13	-0.12	-0.20	-	-1.18	-0.86	-1.73
		(-0.39–0.20)	(-0.32–0.29)	(-0.40–0.19)	(-0.48–0.15)		(-0.27– 0.02)	(-0.30–0.05)	(-0.40–0.01)		(-2.12–-0.24)	(-2.13–0.42)	(-3.36–-0.10)
P (inter- group)	-	0.8199	0.1524	0.2588	0.211	-	0.0889	0.157	0.0568	-	0.0144	0.1892	0.0379

Data presented as mean±standard deviation and mean difference (95% CI). CAT: COPD assessment test, mMRC: modified medical research council, MD: mean difference

Change in mMRC scale

The mean mMRC scale significantly reduced from baseline at weeks 4, 8, and 12 in both treatment groups [Table 3]. The reduction was similar between the GF-DPI group and the G-DPI group at all time points ($p > 0.05$ for all time points) in both ITT [Table 3] and PP analyses [Supplementary Table 3].

Change in CASIS score

Sleep impairment improved with both treatments, indicated by a decreased percentage of patients frequently ('often' and 'very often') experiencing nocturnal symptoms and a corresponding increase in patients experiencing no symptoms ('never' or 'rarely') for the first five CASIS score domains (bad night sleep, problems staying awake during the day, trouble falling asleep, waking up at night with breathing problems, waking up and having trouble falling back asleep) for both groups [Supplementary Tables 4 and 5].

Safety

Overall safety appeared to be similar between the two groups. A total of 35 AEs were reported [Table 4]. The most common AEs reported with GF-DPI were upper respiratory tract infection (1.69%), gastritis (1.12%), arthralgia (1.12%), and headache (1.12%). One patient (0.28%) discontinued from the study because of AE (hospitalisation or prolongation of existing hospitalisation). Two serious adverse events (SAEs) of COPD exacerbation (0.28%) and pneumonia associated with acute onset exertional dyspnea leading to death (0.28%) were reported in the study but were not related to the study drugs. There were no clinically significant changes in ECG and serum potassium levels [Supplementary Tables 6 and 7].

DISCUSSION

This study is the first ever study to report the efficacy and safety of the newly developed glycopyrronium 25 μg/formoterol 12 μg FDC when delivered via a DPI. Our study demonstrates that treatment with glycopyrronium 25 μg/formoterol 12 μg FDC administered twice daily through a DPI provides significantly greater improvement in the lung function compared to glycopyrronium 50 μg monotherapy once daily in patients with moderate to severe COPD. The improvement in the primary endpoint, the change from the baseline in pre-dose trough FEV_1 at week 12, was 120 mL in the GF-DPI group and 60 mL in the G-DPI group (difference between groups: 60 mL; $P < 0.0001$). The post-dose FEV_1 at 12 weeks increased by 100 mL in the GF-DPI group, with a between-group treatment difference of 80 mL ($p < 0.0001$). Improvements in the other efficacy parameters, pre-dose trough FVC, 1-hour post-dose FVC, and CAT score, were also significantly greater in the GF-DPI group than in the G-DPI group. The safety and tolerability profile of GF-DPI FDC was similar to that of G-DPI. Overall, our results reiterate the efficacy and safety of glycopyrronium/formoterol FDC shown in previous studies.[14,22] In the PINNACLE 1, 2, and

Table 4: Summary of AEs

Parameters	Glycopyrronium/formoterol (n=178) *n* (%)	Glycopyrronium (*n*=178) *n* (%)
Number of AEs	18	17
Number of patients with at least 1 AE	17 (9.55%)	15 (8.43%)
Patients discontinued from study with AE	1 (0.56%)	0 (0.00%)
AEs occurring in≥2% of patients in any treatment arm (preferred term)		
Dry mouth	0 (0.00%)	2 (1.12%)
Dry throat	1 (0.56%)	3 (1.69%)
Gastritis	2 (1.12%)	1 (0.56%)
Upper respiratory tract infection	3 (1.69%)	1 (0.56%)
Arthralgia	2 (1.12%)	0 (0.00%)
Headache	2 (1.12%)	0 (0.00%)

AE: adverse events, COPD: chronic obstructive pulmonary disease

4 studies,[14,22] pre-dose FEV_1 improved by 116–126 mL at 24 weeks with a treatment difference of 54–59 mL, favoring the FDC of glycopyrronium/formoterol over glycopyrronium monotherapy. Similarly, post-dose FEV_1 improved by 350–358 mL with the FDC with a treatment difference of 126–145 mL between both groups.[14,22]

It is important to note that the benefits in terms of improvements in lung function parameters were seen early, that is, beginning in week 2 in the fixed-dose combination group, whereas it was not observed until week 12 in the monotherapy group. Greater improvements in the lung function with GF-DPI may correlate with substantial benefits in the patient's quality of life.[23,24] In our study, reduction in the CAT score was significantly different between the groups with higher reductions seen in the glycopyrronium/formoterol group at week 12, and these reductions were higher than the MCID (2 points) in both groups.[25] Improvements in the number of puffs of rescue medication consumed daily, the mMRC scale, and the CASIS score were also significant for both treatment groups at week 12 compared to the baseline. The magnitude of improvements in using rescue medication, the CAT score, and the mMRC score were in the range of those published in previous studies for LABA/LAMA combinations.[20,26-28]

Glycopyrronium/formoterol 25/12 µg FDC was well tolerated in patients with moderate to severe COPD, with most AEs of mild or moderate severity. Only one patient discontinued the study because of AEs. The safety profile of glycopyrronium/formoterol DPI in our study is comparable to that reported in previous studies evaluating this FDC in pMDI.[14,22]

A key limitation of this study was the open label nature of the study. We did not include exacerbations as an endpoint because of the relatively short study duration of 12 weeks. However, given the scarcity of evidence for published randomised studies for the glycopyrronium/formoterol fixed-dose combination in the Indian population, findings from our study have the potential to address this gap in the management of COPD patients in India.

CONCLUSION

The results of this Phase III study conducted in Indian patients with moderate to severe COPD demonstrated that glycopyrronium 25 µg/formoterol 12 µg FDC delivered through a DPI twice a day significantly improves the lung function, symptoms, and patient-reported outcomes in moderate to severe COPD and is safe and well tolerated with no untoward safety signals.

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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

M Lopez, S Sawant, A Vaidya and J Gogtay are employees of Cipla Ltd.

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SUPPLEMENTARY DATA

Contents

Eligibility criteria

Participant inclusion criteria

1. A voluntarily written, signed, and dated informed consent given by the patient and/or a legally acceptable representative
2. Patients of either gender with an age between 40 and 65 years (both inclusive)
3. Patients with moderate to severe COPD (GOLD 2015) and a documented history of COPD and a spirogram performed within at least 6 months from trial initiation
4. Post-bronchodilator FEV_1 ≥40% and ≤80% of the predicted normal value
5. Post-bronchodilator FEV_1/FVC ratio of <0.7
6. Current or ex-smoker of at least 10 pack years of cigarette/bidi smoking

$$Total\ pack\ year = \frac{No.of\ cigarettes\ /\ beedis\ smoked\ per\ day}{20} \times No.of\ years\ of\ smoking$$

7. Ability to use pMDI and DPI during the study duration and to be protocol-compliant

Participant exclusion criteria

1. Hyper-sensitivity to glycopyrronium or formoterol or levosalbutamol or budesonide or ipratropium or any of its components
2. Patients who were hospitalised for exacerbation or any serious condition 12 weeks prior study initiation
3. Patients with more than two exacerbations in the past year
4. Use of systemic corticosteroids/antibiotics 6 weeks prior to study initiation
5. Patients requiring oxygen therapy
6. Clinically significant ECG abnormality
7. Absolute blood eosinophil count > 600 cells/c mm of blood
8. Clinically significant neurologic, cardiovascular, hepatic, renal, endocrine, pulmonary (post-tuberculosis fibrosis, pulmonary fibrotic disease, pulmonary arterial hyper-tension), hematologic, psychiatric, or other medical illnesses that might interfere with study participation
9. History of asthma or any chronic respiratory disease other than COPD
10. Occupational and non-smoking COPD
11. Life-threatening/unstable respiratory disease including lower respiratory tract infection, within 4 weeks prior enrollment
12. History of lung resection of more than one full lobe
13. Scheduled for in-patient hospitalisation, including elective surgery during the trial
14. Clinically significant laboratory values as per the principal investigator
15. History of clinically significant bladder neck obstruction or urinary retention
16. History of uncontrolled glaucoma
17. History of uncontrolled diabetes mellitus

18. Patients receiving immunotherapy or live vaccines within the past year and inactivated vaccines within 1 month from screening visit 1
19. Participating in a clinic 4 weeks prior to screening visit 1
20. Participating in a clinical trial of glycopyrronium alone or as combination therapy within the past 3 months from screening visit 1
21. Women who are either pregnant or lactating or planning pregnancy
22. Woman of child-bearing potential who is unwilling to use adequate contraceptive measures unless abstinence is considered adequate in the opinion of the investigator.

Randomisation criteria

1. Change in the absolute pre-dose trough FEV1 value should be within ±20% compared to the value at screening visit 2
2. Patient should not have an exacerbation during 2 weeks of the run-in period.

Withdrawal criteria

1. Patients requiring any other COPD medication at any time during the study, except during exacerbation, will be withdrawn from the study
2. Use of prohibited medications
3. Severe exacerbation
4. Patient wishing to withdraw from the study
5. Patient requiring any other medication that affects COPD symptoms
6. Patients with <80% or >120% treatment compliance as per the investigator
7. Patients requiring any change in dose for systemic medication that could affect COPD symptoms
8. Patient withdrawn at the investigator's discretion because of safety reasons.

Participants were free to withdraw from the study at any time without giving any reason. For participants who were lost to follow-up, every effort was made to determine their whereabouts and their medical status and to recover the study medication. Every effort was made by the investigator to keep a participant from dropping out of the study. If a participant was withdrawn from the study, all efforts were made to complete and record the required observations as thoroughly as possible. If a participant prematurely discontinued from the study, the premature discontinuation observations were concluded and the reasons for removal from the study were recorded and the date of last use of medication was recorded.

In all cases, the reason for withdrawal was recorded in the CRF and in the participant's medical records. For any participant who was withdrawn, the investigator performed the following:

1. Completed the Case Report Form indicating the date and explanation for early discontinuation of medication
2. Whenever feasible, all scheduled examinations were completed by the time the medication was discontinued. Arranged for alternative medical care if necessary and recorded any follow-up data in participants withdrawn for adverse events.

Supplementary Table 1: Changes in pre-bronchodilator FEV_1 and FVC in the PP population

Parameters	Glycopyrronium/ formoterol. (*n*=139)	Glycopyrronium (*n*=146)	Treatment difference	*P* (inter- group)
Pre-bronchodilator FEV_1, L				
Baseline	1.19±0.02	1.21±0.02	-	-
Week 2	1.28±0.03	1.24±0.03	-	-
MD: Baseline-week 2	0.09 (0.06:0.13)	0.04 (0.01:0.07)	0.06 (0.01:0.10)	<0.0001
P	<0.0001	0.0161	-	-
Week 4	1.29±0.03	1.24±0.03	-	-
MD: Baseline-week 4	0.10 (0.05:0.14)	0.03 (-0.00:0.07)	0.06 (0.01:0.12)	<0.0001
P	<0.0001	0.0617	-	-
Week 8	1.35±0.03	1.27±0.03	-	-
MD: Baseline-week 8	0.16 (0.11:0.21)	0.07 (0.03:0.11)	0.09 (0.02:0.15)	<0.0001
P	<0.0001	0.0011	-	-
Week 12	1.31±0.03	1.27±0.03	-	-
MD: Baseline-week 12	0.12 (0.07:0.16)	0.06 (0.01:0.11)	0.06 (-0.01:0.12)	<0.0001
P	<0.0001	0.0111	-	-
Pre-bronchodilator FVC, L				
Baseline	2.17±0.04	2.13±0.04	-	-
Week 2	2.29±0.04	2.18±0.04	-	-
MD: Baseline-week 2	0.12 (0.05:0.18)	0.06 (-0.00:0.12)	0.06 (-0.03:0.15)	<0.0001
P	0.0003	0.0659	-	-
Week 4	2.29±0.05	2.15±0.04	-	-
MD: Baseline-week 4	0.12 (0.05:0.19)	0.02 (-0.04:0.09)	0.10 (0.00:0.19)	<0.0001
P	0.0008	0.4498	-	-
Week 8	2.31±0.05	2.17±0.04	-	-
MD: Baseline-week 8	0.14 (0.06:0.21)	0.05 (-0.02:0.11)	0.09 (-0.01:0.19)	<0.0001
P	0.0003	0.1591	-	-
Week 12	2.26±0.04	2.18±0.04	-	-
MD: Baseline-week 12	0.10 (0.03:0.16)	0.05 (-0.02:0.12)	0.05 (-0.05:0.14)	<0.0001
P	0.0062	0.1512	-	-

Data are presented as least squares mean±standard error or least squares mean (95% CI). FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, MD: mean difference

Supplementary Table 2: Changes in post-bronchodilator FEV_1 and FVC in the PP population

Parameters	Glycopyrronium/ formoterol (*n*=139)	Glycopyrronium (*n*=146)	Treatment difference	*P* (inter- group)
Post-bronchodilator FEV_1				
Baseline	1.35±0.02	1.34±0.03	-	-
Week 2	1.42±0.03	1.34±0.03	-	-
MD: Baseline-week 2	0.08 (0.02:0.13)	0.00 (-0.05:0.05)	0.08 (0.00:0.15)	<0.0001
P	0.0065	0.9931	-	-
Week 4	1.40±0.03	1.32±0.03	-	-
MD: Baseline-week 4	0.05 (0.00:0.10)	-0.02 (-0.08:0.03)	0.07 (0.00:0.15)	<0.0001
P	0.0394	0.3697	-	-
Week 8	1.47±0.03	1.37±0.03	-	-
MD: Baseline-week 8	0.13 (0.07:0.19)	0.02 (-0.04:0.09)	0.10 (0.02:0.19)	<0.0001
P	<0.0001	0.4172	-	-
Week 12	1.44±0.03	1.35±0.03	-	-
MD: Baseline-week 12	0.09 (0.04:0.14)	0.01 (-0.05:0.07)	0.08 (-0.00:0.16)	<0.0001
P	0.0006	0.7581	-	-
Post-bronchodilator FVC				
Baseline	2.37±0.04	2.31±0.04	-	-
Week 2	2.50±0.06	2.30±0.04	-	-
MD: Baseline-week 2	0.13 (0.04:0.21)	-0.01 (-0.07:0.05)	0.14 (0.03:0.24)	<0.0001
P	0.0033	0.7463	-	-
Week 4	2.43±0.05	2.26±0.04	-	-
MD: Baseline-week 4	0.06 (-0.00:0.12)	-0.05 (-0.12:0.02)	0.11 (0.02:0.20)	<0.0001
P	0.0669	0.1338	-	-
Week 8	2.49±0.05	2.29±0.04	-	-
MD: Baseline-week 8	0.11 (0.05:0.18)	-0.02 (-0.09:0.05)	0.13 (0.04:0.23)	<0.0001
P	0.0005	0.5706	-	-
Week 12	2.47±0.05	2.29±0.04	-	-
MD: Baseline-week 12	0.10 (0.04:0.17)	-0.02 (-0.10:0.05)	0.12 (0.03:0.22)	<0.0001
P	0.0028	0.5209	-	-

Data are presented as least squares mean±standard error or least squares mean (95% CI). FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, MD: mean difference

Supplementary Table 3: Changes in the number of pMDI puffs of rescue medication consumed daily, mMRC scale, and CAT score (PP population)

Parameters	Glycopyrronium/ formoterol (*n*=158)	Glycopyrronium (*n*=165)	Treatment difference	*P* (inter- group)
Number of pMDI puffs of rescue medication consumed daily				
Baseline	1.74±1.43	1.67±1.46	-	-
Week 2	1.31±132	1.28±0.90	-	-
MD: Baseline-week 2	-0.42 (-0.64:-0.21)	-0.40 (-0.61:-0.19)	-0.03 (-0.33:0.27)	0.7591
P	0.0002	0.0003	-	-
Week 4	1.00±0.86	0.97±0.81	-	-
MD: Baseline-week 4	-0.74 (-0.95:-0.53)	-0.71 (-0.94:-0.47)	-0.03 (-0.35:0.28)	0.0949
P	<0.0001	<0.0001	-	-
Week 8	1.14±0.99	1.15±0.88	-	-
MD: Baseline-week 8	-0.60 (-0.80:-0.40)	-0.52 (-0.75:-0.29)	-0.07 (-0.38:0.23)	0.2475
P	<0.0001	<0.0001	-	-
Week 12	0.83±0.69	0.96±0.75	-	-
MD: Baseline-week 12	-0.91 (-1.12:-0.70)	-0.72 (-0.96:-0.48)	-0.19 (-0.51:0.13)	0.1639
P	<0.0001	<0.0001	-	-
mMRC scale				
Baseline	2.05±0.83	2.11±0.73	-	-
Week 4	1.65±0.79	1.88±0.81	-	-
MD: Baseline-week 4	-0.40 (-0.51:-0.28)	-0.23 (-0.33:-0.12)	-0.17 (-0.33:-0.01)	0.0333
P	<0.0001	<0.0001	-	-
Week 8	1.47±0.74	1.67±0.78	-	-
MD: Baseline-week 8	-0.58 (-0.71:-0.45)	-0.44 (-0.56:-0.32)	-0.14 (-0.32:0.03)	0.1103
P	<0.0001	<0.0001	-	-
Week 12	1.18±0.73	1.47±0.82	-	-
MD: Baseline-week 12	-0.87 (-1.02:-0.72)	-0.64 (-0.78:-0.49)	-0.23 (-0.44:-0.03)	0.0281
P	<0.0001	<0.0001	-	-
CAT score				
Baseline	21.26±7.46	20.95±7.64	-	-
Week 4	17.73±7.60	18.71±7.45	-	-
MD: Baseline-week 4	-3.53 (-4.21:-2.85)	-2.24 (-2.99:-1.49)	-1.29 (-2.30:-0.28)	0.0123
P	<0.0001	<0.0001	-	-
Week 8	15.59±6.62	16.39±7.03	-	-
MD: Baseline-week 8	-5.67 (-6.58:-4.76)	-4.56 (-5.52:-3.60)	-1.11 (-2.42:0.21)	0.0991
P	<0.0001	<0.0001	-	-
Week 12	13.17±6.42	14.96±7.42	-	-
MD: Baseline-week 12	-8.09 (-9.19:-6.98)	-5.99 (-7.22:-4.76)	-2.09 (-3.74:-0.44)	0.0131
P	<0.0001	<0.0001	-	-

Data are presented as least squares mean±standard error or least squares mean (95% CI). CAT: COPD assessment test, mMRC: modified medical research council, MD: mean difference

Supplementary Table 4: Changes in the COPD and Asthma Sleep Impact Scale in ITT population

Parameters	Glycopyrronium/formoterol (*n*=158) *n* (%)				Glycopyrronium (*n*=165) *n* (%)			
	Baseline	Week 4	Week 8	Week 12	Baseline	Week 4	Week 8	Week 12
Question 1	Have a bad night sleep?							
Never	24 (15.19)	27 (17.09)	20 (12.66)	31 (19.62)	23 (13.94)	19 (11.52)	28 (16.97)	25 (15.15)
Rarely	30 (18.99)	61 (38.61)	53 (33.54)	44 (27.85)	39 (23.64)	43 (26.06)	53 (32.12)	52 (31.52)
Sometimes	59 (37.34)	61 (38.61)	53 (33.54)	44 (27.85)	60 (36.36)	67 (40.61)	58 (35.15)	62 (37.58)
Often	36 (22.78)	21 (13.29)	13 (8.23)	7 (4.43)	41 (24.85)	30 (18.18)	15 (9.09)	13 (7.88)
Very often	9 (5.70)	3 (1.90)	3 (1.90)	1 (0.63)	2 (1.21)	2 (1.21)	2 (1.21)	1 (0.61)
Question 2	Have problems staying awake during the day?							
Never	23 (14.56)	30 (18.99)	28 (17.72)	35 (22.15)	19 (11.52)	19 (11.52)	30 (18.18)	28 (16.97)
Rarely	44 (27.85)	65 (41.14)	56 (35.44)	53 (33.54)	53 (32.12)	53 (32.12)	62 (37.58)	63 (38.18)
Sometimes	66 (41.77)	40 (25.32)	50 (31.65)	48 (30.38)	51 (30.91)	67 (40.61)	47 (28.48)	50 (30.30)
Often	20 (12.66)	16 (10.13)	8 (5.06)	6 (3.80)	37 (22.42)	20 (12.12)	16 (9.70)	11 (6.67)
Very often	5 (3.16)	1 (0.63)	1 (0.63)	0 (0.00)	5 (3.03)	2 (1.21)	1 (0.61)	1 (0.61)
Question 3	Have trouble falling asleep?							
Never	24 (15.19)	27 (17.09)	27 (17.09)	31 (19.62)	30 (18.18)	24 (14.55)	34 (20.61)	30 (18.18)
Rarely	46 (29.11)	38 (24.05)	52 (32.91)	66 (41.77)	42 (25.45)	53 (32.12)	63 (38.18)	56 (33.94)
Sometimes	60 (37.97)	69 (43.67)	54 (34.18)	38 (24.05)	54 (32.73)	59 (35.76)	42 (25.45)	46 (27.88)
Often	23 (14.56)	16 (10.13)	8 (5.06)	6 (3.80)	33 (20.00)	23 (13.94)	16 (9.70)	20 (12.12)
Very often	5 (3.16)	2 (1.27)	2 (1.27)	1 (0.63)	6 (3.64)	2 (1.21)	1 (0.61)	1 (0.61)
Question 4	Wake up at night with breathing problems (shortness of breath coughing chest tightness, etc.)?							
Never	20 (12.66)	27 (17.09)	25 (15.82)	36 (22.78)	19 (11.52)	18 (10.91)	31 (18.79)	29 (17.58)
Rarely	38 (24.05)	53 (33.54)	56 (35.44)	57 (36.08)	44 (26.67)	56 (33.94)	54 (32.73)	61 (36.97)
Sometimes	55 (34.81)	50 (31.65)	52 (32.91)	41 (25.95)	58 (35.15)	56 (33.94)	52 (31.52)	41 (24.85)
Often	37 (23.42)	22 (13.92)	9 (5.70)	8 (5.06)	40 (24.24)	31 (18.79)	18 (10.91)	20 (12.12)
Very often	8 (5.06)	0 (0.00)	1 (0.63)	0 (0.00)	4 (2.42)	0 (0.00)	1 (0.61)	2 (1.21)
Question 5	Wake up during the night and have trouble falling back asleep?							
Never	23 (14.56)	24 (15.19)	22 (13.92)	38 (24.05)	23 (13.94)	18 (10.91)	33 (20.00)	28 (16.97)
Rarely	44 (27.85)	61 (38.61)	72 (45.57)	58 (36.71)	40 (24.24)	66 (40.00)	60 (36.36)	61 (36.97)
Sometimes	51 (32.28)	47 (29.75)	39 (24.68)	41 (25.95)	57 (34.55)	48 (29.09)	45 (27.27)	44 (26.67)
Often	36 (22.78)	17 (10.76)	9 (5.70)	5 (3.16)	40 (24.24)	25 (15.15)	17 (10.30)	19 (11.52)
Very often	4 (2.53)	3 (1.90)	1 (0.63)	0 (0.00)	5 (3.03)	4 (2.42)	1 (0.61)	1 (0.61)
Question 6	Have a good night sleep?							
Never	3 (1.90)	3 (1.90)	4 (2.53)	1 (0.63)	9 (5.45)	7 (4.24)	9 (5.45)	6 (3.64)
Rarely	32 (20.25)	19 (12.03)	20 (12.66)	25 (15.82)	26 (15.76)	31 (18.79)	35 (21.21)	33 (20.00)
Sometimes	64 (40.51)	62 (39.24)	41 (25.95)	32 (20.25)	67 (40.61)	59 (35.76)	35 (21.21)	37 (22.42)
Often	55 (34.81)	62 (39.24)	72 (45.57)	57 (36.08)	59 (35.76)	56 (33.94)	66 (40.00)	62 (37.58)
Very often	4 (2.53)	6 (3.80)	6 (3.80)	27 (17.09)	4 (2.42)	8 (4.85)	11 (6.67)	15 (9.09)
Question 7	Wake up feeling rested?							
Never	4 (2.53)	8 (5.06)	4 (2.53)	6 (3.80)	4 (2.42)	5 (3.03)	11 (6.67)	13 (7.88)
Rarely	36 (22.78)	26 (16.46)	30 (18.99)	33 (20.89)	32 (19.39)	34 (20.61)	38 (23.03)	41 (24.85)
Sometimes	61 (38.61)	52 (32.91)	39 (24.68)	30 (18.99)	68 (41.21)	62 (37.58)	41 (24.85)	31 (18.79)
Often	55 (34.81)	59 (37.34)	62 (39.24)	55 (34.81)	59 (35.76)	52 (31.52)	59 (35.76)	60 (36.36)
Very often	2 (1.27)	7 (4.43)	8 (5.06)	18 (11.39)	2 (1.21)	8 (4.85)	7 (4.24)	8 (4.85)

Data are presented as number (%)

Supplementary Table 5: Changes in the COPD and Asthma Sleep Impact Scale in per-protocol population

Parameters	Glycopyrronium/formoterol (*n*=139) *n* (%)				Glycopyrronium (*n*=146) *n* (%)			
	Baseline	Week 4	Week 8	Week 12	Baseline	Week 4	Week 8	Week 12
Question 1	Have a bad night sleep?							
Never	18 (12.95)	22 (15.83)	19 (13.67)	31 (22.30)	23 (15.75)	17 (11.64)	27 (18.49)	24 (16.44)
Rarely	26 (18.71)	35 (25.18)	51 (36.69)	56 (40.29)	31 (21.23)	38 (26.03)	48 (32.88)	49 (33.56)
Sometimes	50 (35.97)	58 (41.73)	53 (38.13)	44 (31.65)	54 (36.99)	59 (40.41)	55 (37.67)	59 (40.41)
Often	36 (25.90)	21 (15.11)	13 (9.35)	7 (5.04)	36\ (24.66)	30 (20.55)	14 (9.59)	13 (8.90)
Very often	9 (6.47)	3 (2.16)	3 (2.16)	1 (0.72)	2 (1.37)	2 (1.37)	2 (1.37)	1 (0.68)
Question 2	Have problems staying awake during the day?							
Never	16 (11.51)	24 (17.27)	27 (19.42)	35 (25.18)	14 (9.59)	16 (10.96)	29 (19.86)	28 (19.18)
Rarely	38 (27.34)	61 (43.88)	54 (38.85)	50 (35.97)	49 (33.56)	51 (34.93)	57 (39.04)	59 (40.41)
Sometimes	63 (45.32)	37 (26.62)	49 (35.25)	48 (34.53)	46 (31.51)	59 (40.41)	43 (29.45)	47 (32.19)
Often	17 (12.23)	16 (11.51)	8 (5.76)	6 (4.32)	33 (22.60)	18 (12.33)	16 (10.96)	11 (7.53)
Very often	5 (3.60)	1 (0.72)	1 (0.72)	0 (0.00)	4 (2.74)	2 (1.37)	1 (0.68)	1 (0.68)
Question 3	Have trouble falling asleep?							
Never	17 (12.23)	20 (14.39)	25 (17.99)	30 (21.58)	25 (17.12)	20 (13.70)	31 (21.23)	28 (19.18)
Rarely	41 (29.50)	36 (25.90)	51 (36.69)	65 (46.76)	38 (26.03)	44 (30.14)	58 (39.73)	53 (36.30)
Sometimes	54 (38.85)	65 (46.76)	53 (38.13)	37 (26.62)	47 (32.19)	58 (39.73)	40 (27.40)	44 (30.14)
Often	22 (15.83)	16 (11.51)	8 (5.76)	6 (4.32)	31 (21.23)	22 (15.07)	16 (10.96)	20 (13.70)
Very often	5 (3.60)	2 (1.44)	2 (1.44)	1 (0.72)	5 (3.42)	2 (1.37)	1 (0.68)	1 (0.68)
Question 4	Wake up at night with breathing problems (shortness of breath coughing chest tightness etc)?							
Never	13 (9.35)	21 (15.11)	23 (16.55)	35 (25.18)	17 (11.64)	15 (10.27)	28 (19.18)	28 (19.18)
Rarely	34 (24.46)	48 (34.53)	54 (38.85)	55 (39.57)	35 (23.97)	51 (34.93)	50 (34.25)	57 (39.04)
Sometimes	49 (35.25)	48 (34.53)	52 (37.41)	41 (29.50)	52 (35.62)	49 (33.56)	49 (33.56)	41 (28.08)
Often	35 (25.18)	22 (15.83)	9 (6.47)	8 (5.76)	39 (26.71)	31 (21.23)	18 (12.33)	18 (12.33)
Very often	8 (5.76)	0 (0.00)	1 (0.72)	0 (0.00)	3 (2.05)	0 (0.00)	1 (0.68)	2 (1.37)
Question 5	Wake up during the night and have trouble falling back asleep?							
Never	16 (11.51)	17 (12.23)	21 (15.11)	37 (26.62)	18 (12.33)	15 (10.27)	32 (21.92)	26 (17.81)
Rarely	39 (28.06)	57 (41.01)	69 (49.64)	56 (40.29)	35 (23.97)	59 (40.41)	55 (37.67)	58 (39.73)
Sometimes	45 (32.37)	45 (32.37)	39 (28.06)	41 (29.50)	52 (35.62)	43 (29.45)	41 (28.08)	42 (28.77)
Often	35 (25.18)	17 (12.23)	9 (6.47)	5 (3.60)	36 (24.66)	25 (17.12)	17 (11.64)	19 (13.01)
Very often	4 (2.88)	3 (2.16)	1 (0.72)	0 (0.00)	5 (3.42)	4 (2.74)	1 (0.68)	1 (0.68)
Question 6	Have a good night sleep?							
Never	1 (0.72)	1 (0.72)	3 (2.16)	1 (0.72)	8 (5.48)	6 (4.11)	8 (5.48)	6 (4.11)
Rarely	29 (20.86)	19 (13.67)	20 (14.39)	25 (17.99)	22 (15.07)	29 (19.86)	34 (23.29)	32 (21.92)
Sometimes	58 (41.73)	58 (41.73)	40 (28.78)	32 (23.02)	63 (43.15)	56 (38.36)	34 (23.29)	37 (25.34)
Often	48 (34.53)	57 (41.01)	70 (50.36)	54 (38.85)	49 (33.56)	48 (32.88)	59 (40.41)	56 (38.36)
Very often	3 (2.16)	4 (2.88)	6 (4.32)	27 (19.42)	4 (2.74)	7 (4.79)	11 (7.53)	15 (10.27)
Question 7	Wake up feeling rested?							
Never	2 (1.44)	7 (5.04)	3 (2.16)	6 (4.32)	4 (2.74)	4 (2.74)	10 (6.85)	13 (8.90)
Rarely	32 (23.02)	24 (17.27)	30 (21.58)	33 (23.74)	28 (19.18)	33 (22.60)	37 (25.34)	40 (27.40)
Sometimes	56 (40.29)	51 (36.69)	39 (28.06)	30 (21.58)	62 (42.47)	58 (39.73)	40 (27.40)	31 (21.23)
Often	48 (34.53)	52 (37.41)	59 (42.45)	52 (37.41)	50 (34.25)	44 (30.14)	52 (35.62)	54 (36.99)
Very often	1 (0.72)	5 (3.60)	8 (5.76)	18 (12.95)	2 (1.37)	7 (4.79)	7 (4.79)	8 (5.48)

Data are presented as number (%)

Supplementary Table 6: Changes in serum potassium levels

Endpoints	Glycopyrronium/ formoterol (*n*=178)	Glycopyrronium (*n*=178)	*P* (inter-group)
Baseline	4.41±0.63	4.41±0.60	-
Week 4	4.41±0.55	4.48±0.58	0.2802
Week 12	4.39±0.52	4.36±0.54	0.5822

Data are presented as mean±standard error

Supplementary Table 7: Changes in the ECG findings

Parameters	Glycopyrronium/ formoterol (*n*=178)	Glycopyrronium (*n*=178)
Baseline		
Normal	163 (91.57)	153 (85.96)
Abnormal	14 (7.87)	23 (12.92)
Week 2		
Normal	157 (88.20)	146 (82.02)
Abnormal	14 (7.87)	24 (13.48)
Week 4		
Normal	148 (83.15)	138 (77.53)
Abnormal	17 (9.55)	28 (15.73)
Week 8		
Normal	135 (75.84)	141 (79.21)
Abnormal	20 (11.24)	19 (10.67)
Week 12		
Normal	138 (77.53)	134 (75.28)
Abnormal	15 (8.43)	20 (11.24)

Data are presented as number (%)