

Efficacy and safety of coadministration of once-daily indacaterol and glycopyrronium versus indacaterol alone in COPD patients: the GLOW6 study

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Background: Addition of a second bronchodilator from a different pharmacological class may benefit patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) whose symptoms are insufficiently controlled by bronchodilator monotherapy. GLOW6 evaluated the efficacy and safety of once-daily coadministration of the long-acting β_2 -agonist indacaterol (IND) and the long-acting muscarinic antagonist glycopyrronium (GLY) versus IND alone in patients with moderate-to-severe COPD.

Materials and methods: In this randomized, double-blind, parallel group, placebo-controlled, 12-week study, patients were randomized 1:1 to IND 150 μg and GLY 50 μg daily (IND + GLY) or IND 150 μg daily and placebo (IND + PBO) (all delivered via separate Breezhaler[®] devices). The primary objective was to demonstrate the superiority of IND + GLY versus IND + PBO for trough forced expiratory volume in 1 second (FEV_1) at week 12. Other end points included trough FEV_1 at day 1, FEV_1 area under the curve from 30 minutes to 4 hours ($\text{AUC}_{30\text{min}-4\text{h}}$), peak FEV_1 , inspiratory capacity and trough forced vital capacity (FVC) at day 1 and week 12, and transition dyspnea index (TDI) focal score, COPD symptoms, and rescue medication use over 12 weeks.

Results: A total of 449 patients were randomized (IND + GLY, 226; IND + PBO, 223); 94% completed the study. On day 1 and at week 12, IND + GLY significantly improved trough FEV_1 versus IND + PBO, with treatment differences of 74 mL (95% CI 46–101 mL) and 64 mL (95% CI 28–99 mL), respectively (both $P < 0.001$). IND + GLY significantly improved postdose peak FEV_1 , $\text{FEV}_1 \text{AUC}_{30\text{min}-4\text{h}}$, and trough FVC at day 1 and week 12 versus IND + PBO (all $P < 0.01$). TDI focal score and COPD symptoms (percentage of days able to perform usual daily activities and change from baseline in mean daytime respiratory score) were significantly improved with IND + GLY versus IND + PBO ($P < 0.05$). The incidence of adverse events was similar for the two treatment groups.

Conclusion: In patients with moderate-to-severe COPD, once-daily coadministration of IND and GLY provides significant and sustained improvement in bronchodilation versus IND alone from day 1, with significant improvements in patient-centered outcomes.

Keywords: indacaterol, glycopyrronium, inhalation therapy, bronchodilation, COPD, Breezhaler[®]

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Introduction

Bronchodilators are central to the pharmacological management of chronic obstructive pulmonary disease (COPD).¹ Whereas short-acting bronchodilators are used for immediate relief from symptoms, one or more long-acting bronchodilators (long-acting

β_2 -agonists [LABAs] and long-acting muscarinic antagonists [LAMAs]) are recommended for long-term maintenance therapy in patients with moderate-to-very severe COPD.^{1,2} Long-acting bronchodilators include well-established agents, such as the LAMA tiotropium (once-daily [od]) and the LABAs formoterol and salmeterol (both twice-daily [bid]), and the more recently introduced LAMAs glycopyrronium (NVA237; od)^{3,4} and aclidinium (bid),⁵⁻⁷ and the LABA indacaterol (od).

The efficacy and safety of glycopyrronium and indacaterol, given as long-acting bronchodilator monotherapies in patients with moderate-to-severe COPD, has been demonstrated in several Phase III studies.⁸⁻¹⁴ The effect of indacaterol on lung-function outcomes was shown to be superior to twice-daily LABAs^{11,14,15} and comparable to tiotropium.^{12,16,17} Clinical outcomes, such as dyspnea and health status, have also been shown to improve to a significantly greater extent with indacaterol compared with tiotropium.¹⁶ Glycopyrronium was shown to have a comparable effect to tiotropium on lung function, symptoms, exacerbations, and rescue medication use, with a significantly more rapid onset of action on day 1 compared with tiotropium.¹³ Glycopyrronium has also demonstrated an immediate and significant improvement in exercise tolerance over 3 weeks compared with placebo, beginning with the first dose; this was accompanied by sustained reductions in lung hyperinflation.⁸

In patients whose symptoms are insufficiently controlled by bronchodilator monotherapy, the Global initiative for chronic Obstructive Lung Disease (GOLD) strategy for the management of COPD recommends the addition of a second bronchodilator¹; this is supported by evidence showing that the addition of a second bronchodilator from a different pharmacological class improves lung function, symptoms, and health status compared with monotherapy, without significantly increasing the risk of side effects.¹⁸⁻²⁰

Several studies have established the superior efficacy of free combinations of LABAs and LAMAs in bronchodilation, symptom control, and rescue medication use versus the LAMA monocomponent²¹⁻²⁵ and versus the LABA monocomponent.^{18,20,26} Recently, INTRUST-1 and INTRUST-2 study investigators reported that concurrent administration of a LABA (indacaterol) and a LAMA (tiotropium) provided superior bronchodilation and lung deflation compared with LAMA (tiotropium) monotherapy.²¹ Furthermore, QVA149, a once-daily, fixed-dose combination of glycopyrronium 50 μ g and indacaterol 150 μ g (in development), has demonstrated superior efficacy compared with both monocomponents in a recent study.²⁷

In the present GLOW6 (GLycopyrroonium bromide in COPD airWays clinical study 6), we aimed to evaluate the efficacy and safety of the coadministration of a LABA (indacaterol 150 μ g od) and a LAMA (glycopyrronium 50 μ g od) versus the LABA (indacaterol 150 μ g od) alone in patients with moderate-to-severe COPD.

Materials and methods

Patients

The GLOW6 study enrolled men and women ≥ 40 years of age, with moderate-to-severe stable COPD (GOLD stage II or III according to the 2010 GOLD guidelines),²⁸ who were current or ex-smokers with a smoking history of at least 10 pack-years, and had a post-bronchodilator forced expiratory volume in 1 second (FEV_1) $\geq 30\%$ and $< 80\%$ of the predicted normal and postbronchodilator FEV_1 /forced vital capacity (FVC) ratio of < 0.70 at screening (GOLD stage II or III).²⁸ Postbronchodilator refers to 1 hour after sequential inhalation of 84 μ g ipratropium bromide (or equivalent dose) and 400 μ g salbutamol (or equivalent dose).

The main exclusion criteria included respiratory tract infection within 6 weeks prior to screening; COPD exacerbation requiring treatment with antibiotics and/or oral corticosteroids and/or hospitalization 6 weeks prior to screening; concomitant pulmonary disease (such as lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, clinically significant bronchiectasis, pulmonary tuberculosis); history of asthma, diabetes (with the exception of controlled type II diabetes), malignancy of any organ system, long QT syndrome or QTc > 450 ms at screening, symptomatic prostatic hyperplasia, bladder-neck obstruction, moderate/severe renal impairment, urinary retention, narrow-angle glaucoma, a known history of α_1 -antitrypsin deficiency, or paroxysmal atrial fibrillation; clinically significant renal, cardiovascular (such as, but not limited to, unstable ischemic heart disease, New York Heart Association class III/IV left ventricular failure, myocardial infarction), neurological, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormality that could have interfered with the assessment of efficacy and safety of the study treatment; participation in the active phase of a supervised pulmonary rehabilitation program; and contraindications for tiotropium or ipratropium, or history of adverse reactions to inhaled anticholinergics.

All patients gave written, informed consent to participate in the study (NCT01604278).²⁹ The study protocol was reviewed and approved by institutional review boards and

ethics committees at participating centers. The study was conducted in compliance with Good Clinical Practice (GCP). Table S1 lists the study centers.

Study design and treatment

GLOW6 was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-week study. After a washout period (up to 7 days), followed by a 14-day run-in period, patients were randomized 1:1 to indacaterol 150 µg od and glycopyrronium 50 µg od (IND + GLY; 50 µg refers to the quantity of the glycopyrronium moiety present in the capsule, which corresponds to a delivered dose of 44 µg) or indacaterol 150 µg od and placebo (IND + PBO). All treatments were delivered via separate Breezhaler® (Novartis, Basel, Switzerland) devices, and were taken each morning between 8 and 11 (Figure 1). The devices were not to be used interchangeably by the patients, and alternative inhalation devices were not permitted.

An automated, interactive, voice-response technology was used to assign randomization numbers to patients who met the study criteria. Randomization numbers were used to link patients to treatment groups and these were not communicated to the caller. Patients, investigators, site staff, persons performing the assessments and data analysts were blind to the identity of the treatment from the time of randomization. Randomization data were kept strictly confidential until the time of unblinding.

Patients were to discontinue taking long-acting bronchodilator therapy before starting the run-in period (for at least 7 days for LAMAs and the LABA indacaterol, and for 48 hours for other LABAs or LABA/inhaled corticosteroid

[ICS] combinations). Those on fixed-dose LABA/ICS combinations were switched to ICS monotherapy at a dose equivalent to that contained in the fixed-dose combination. Patients were provided with a salbutamol (short-acting β_2 -agonist) inhaler to be used as rescue medication during the study. They were instructed to abstain from taking rescue medication within 6 hours of the start of each study visit. Further details are provided in Table S2.

Efficacy assessments

The primary efficacy variable was trough FEV₁ (defined as the mean of the 23 hour 15 minute and 23 hour 45 minute postdose values, imputed with last observation carried forward) at week 12. Secondary variables included trough FEV₁ at day 1, FEV₁ area under the curve from 30 minutes to 4 hours (AUC_{30min-4h}), peak FEV₁, FEV₁ and inspiratory capacity (IC) at individual time points, trough FVC at day 1 and week 12, transition dyspnea index (TDI) focal score, COPD symptoms collected via patient diaries, and mean change from baseline in daily number of puffs of rescue medication over the 12-week treatment period. Effects on the St George's Respiratory Questionnaire – COPD (SGRQ-C) total score at week 12 versus baseline were assessed as an exploratory objective.

Spirometric measurements (recorded via centralized spirometry) were taken prior to the run-in period to determine study eligibility and to record postbronchodilator FEV₁ 1 hour after sequential inhalation of four 21 µg puffs of ipratropium bromide (or equivalent dose) and four 100 µg puffs of salbutamol. FEV₁ and FVC were recorded at all clinic visits

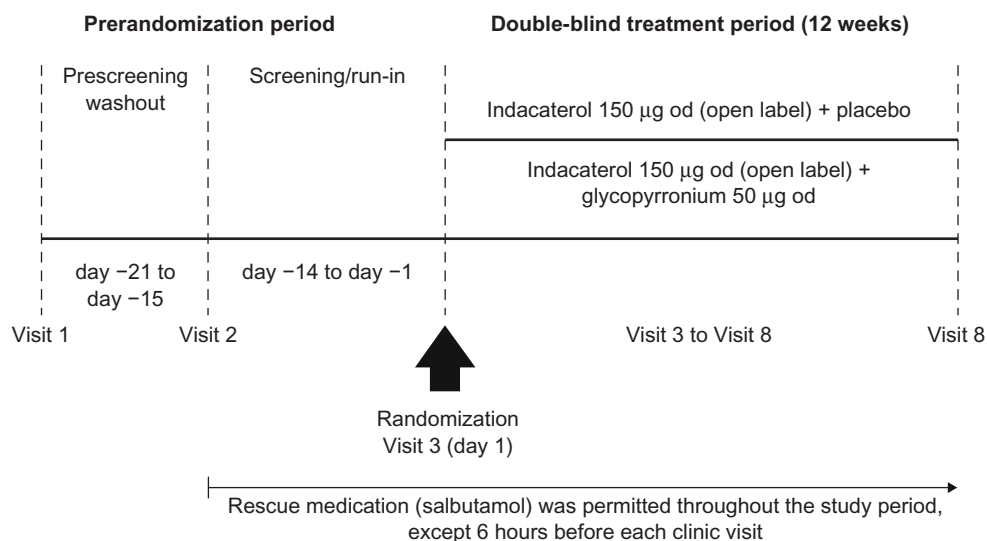


Figure 1 GLOW6 study design.

Abbreviation: od, once-daily.

at the following time points relative to the morning dose: 45 and 15 minutes predose, and 30 minutes, 1 hour, 4 hours, and 24 hours postdose on day 1 and week 12. Dyspnea was assessed by an investigator-administered baseline dyspnea index and TDI, and health status by self-administered SGRQ-C at day 1 and week 12.

All patients were provided with an eDiary to record morning and evening daily clinical symptoms: cough, wheezing, shortness of breath, sputum volume, sputum purulence, cold, fever, sore throat, nighttime awakenings and rescue medication use, and time of study-drug administration. Patients were instructed to complete the eDiary routinely at the same time each morning (prior to taking the study drug) and again (approximately 12 hours later) each evening, considering events over the previous 12 hours. Patient diaries were reviewed at each clinic visit.

Safety assessments

Safety was assessed by recording all treatment-emergent adverse events (AEs) and serious AEs (SAEs), monitoring vital signs (pulse rate and systolic and diastolic blood pressure), and performing laboratory analyses (hematology, clinical chemistry, and urinalysis). AEs starting on or after the time of first inhalation of the study drug but not later than 7 days (30 days in the case of SAEs) after last inhalation of the study drug were classified as treatment-emergent AEs. AEs were coded using the Medical Dictionary for Regulatory Activities³⁰ and summarized by primary system organ class, preferred term, maximum severity, and relationship to study drug. An independent adjudication committee classified the reported serious cardio- and cerebro-vascular (CCV) events.

Statistical analysis

Three populations were defined in the GLOW6 study for the purpose of analysis. The full analysis set (FAS) included all randomized patients who received at least one dose of the study drug; patients were analyzed according to the treatment they were assigned to at randomization. The per-protocol set (PPS) included all patients in the FAS who had no major protocol deviations; patients were analyzed according to the treatment to which they were randomized. The safety population included all patients who received at least one dose of the study medication, irrespective of randomization; patients were analyzed according to the treatment they received.

The primary analysis for trough FEV₁ at week 12 was performed on the FAS using a mixed model. The mixed model contained treatment as a fixed effect, with the baseline

FEV₁ and FEV₁ prior to and post inhalation of short-acting bronchodilator as covariates. The model also included smoking status at baseline (current/ex-smoker), history of baseline ICS use (yes/no) and region as fixed effects, and center (nested in the region) as a random effect. If any of the values contributing to trough FEV₁ were collected within 6 hours of rescue medication or within 7 days of systemic corticosteroid use, then the individual FEV₁ value was not included in the analysis. Superiority of IND + GLY versus IND + PBO was claimed if the difference in trough FEV₁ was statistically significant at the 5% level and the 95% confidence interval (CI) was entirely to the right of (higher than) 0.0 L.

Other secondary variables were analyzed in the FAS using the same mixed model as the primary analysis, with the respective baseline values replacing baseline FEV₁ as a covariate. Results are shown as least squares means (LSMs) with standard errors for group mean values and with 95% CIs for differences between treatments. The procedure for handling missing data is detailed in Table S3.

Additionally, exploratory subgroup analyses were performed for the primary end point to explore the treatment effect by age (<65 and ≥65 years), sex (male/female), smoking history (ex-smokers/current smokers), severity of disease, use of ICS at baseline (yes/no) and body mass index (BMI; >30 kg/m² or ≤30 kg/m²) in the FAS. The analysis was performed with the appropriate interaction term in the model and the additional covariate as a fixed effect, if necessary. All safety end points were summarized for the safety population.

Sample-size calculation

To detect statistical significance in the primary end point (at $\alpha=0.05$, with 80% power) for a treatment differential of 70 mL in trough FEV₁ at week 12, and assuming a standard deviation of 250 mL and a 10% dropout rate, it was calculated that an estimated total sample size of 450 patients (225 per group) would be required (404 completers).

Results

Patient disposition and baseline characteristics

A total of 671 patients were screened, of whom 449 were randomized (IND + GLY, 226; IND + PBO, 223; Figure 2); 94% (422 patients) completed the study. The percentage of patients who discontinued was similar in both groups. The two most common reasons for discontinuing treatment were protocol deviation and AEs. Discontinuations were more frequent due to protocol deviation in the IND + GLY

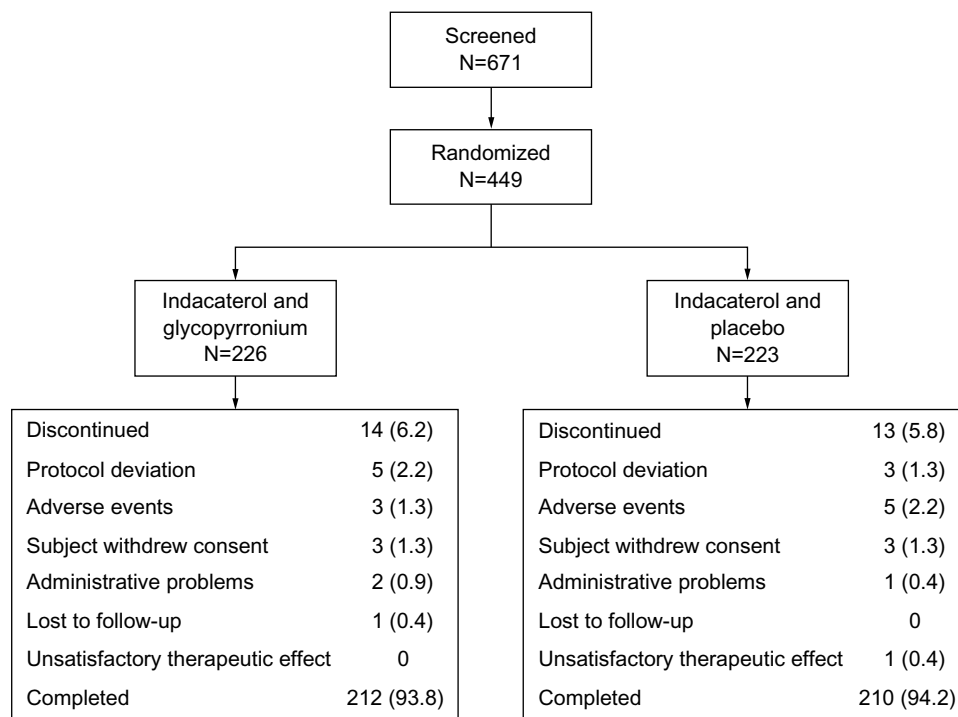


Figure 2 Patient disposition, n (%).

group (five of 14 patients; 2.2%) than in the IND + PBO group (three of 13 patients; 1.3%); they were more frequent due to AEs in the IND + PBO group (five of 13 patients; 2.2%) than in the IND + GLY group (three of 14 patients; 1.3%).

All baseline characteristics were similar between the treatment groups (Table 1). The mean age of the patients was 63.7 years, 82% of the patients were male and the majority (99%) were Caucasian. All patients had moderate (64%) or severe (36%) airflow limitation.¹ All patients were smokers (42%) or ex-smokers (58%), and the mean smoking history was 44.5 pack-years. The mean duration of COPD was 7.1 years; 30% of the patients had a documented history of at least one exacerbation in the previous year; 63% of the patients used ICS. Mean postbronchodilator FEV₁ was 54.8% predicted, and mean postbronchodilator FEV₁/FVC ratio was 48.5%.

Efficacy

Spirometry

The primary end point in GLOW6 was met, as the LSM trough FEV₁ at week 12 was significantly higher in the IND + GLY group than in the IND + PBO group, with a treatment difference of 64 mL (95% CI 28–99 mL, $P < 0.001$; Table 2 and Figure 3). Similar results were seen in the supportive analysis in the PPS, with a treatment difference of 64 mL (95% CI 28–101 mL, $P < 0.001$). After first dose, the treatment difference for trough FEV₁ (measured at the end of day 1 as

the mean of the values at 23 hours 15 minutes and 23 hours 45 minutes) was 74 mL (95% CI 46–101 mL, $P < 0.001$) in favor of IND + GLY versus IND + PBO (Table 2 and Figure 3). IND + GLY was also statistically significantly superior to IND + PBO for FEV₁ AUC_{30min–4h} postdose and peak FEV₁ on day 1 and at week 12 (all $P < 0.001$, Table 2).

On day 1 and at week 12, FEV₁ at all time points from 30 minutes to 4 hours and at 24 hours was significantly higher in the IND + GLY group compared with the IND + PBO group, with statistically significant treatment differences at each time point (all $P < 0.001$ [except at 24 hours on week 12 $P < 0.01$], Figure 4).

Trough FVC on day 1 and at week 12 was significantly higher in the IND + GLY treatment group than in the IND + PBO group (LSM treatment differences, 111 mL [$P < 0.001$] and 93 mL [$P = 0.006$], respectively; Table 2). IC at 2 hours and 4 hours postdose on day 1 and at 30 minutes, 2 hours, and 4 hours postdose at week 12 was significantly higher in the IND + GLY treatment group compared with the IND + PBO treatment group (Table 2).

The exploratory subgroup analyses of trough FEV₁ at week 12 demonstrated superiority of IND + GLY versus IND + PBO for most subgroups evaluated, consistent with the result for trough FEV₁ in the overall FAS; younger patients (<65 years), patients with severe airflow limitation,¹ ICS users at baseline, and current smokers in the IND + GLY treatment group had a

Table 1 Baseline demographics, background characteristics, and spirometry (safety population)

	IND + GLY (N=226)	IND + PBO (N=221)
Mean (SD) age, years	63.4 (8.44)	64.1 (7.67)
Male, n (%)	180 (79.6)	186 (84.2)
Ethnicity, n (%)		
Caucasian	224 (99.1)	217 (98.2)
Native American	0	1 (0.5)
Other	2 (0.9)	3 (1.4)
Severity of airflow limitation (GOLD 2013), n (%)		
Moderate	139 (61.5)	148 (67.0)
Severe	87 (38.5)	73 (33.0)
Mean (SD) duration of COPD, years	7.1 (5.65)	7.2 (5.35)
Baseline COPD exacerbation history,* n (%)		
0 exacerbations	158 (69.9)	156 (70.6)
1 exacerbation	57 (25.2)	46 (20.8)
≥2 exacerbations	11 (4.9)	19 (8.6)
ICS use at baseline, n (%)	138 (61.1)	142 (64.3)
Smoking history, n (%)		
Ex-smoker	130 (57.5)	129 (58.4)
Current smoker	96 (42.5)	92 (41.6)
Mean (SD) duration of smoking, pack-years	44.5 (23.40)	44.4 (22.24)
Mean (SD) FEV ₁ postbronchodilator, L	1.5 (0.46)	1.6 (0.46)
Mean (SD) postbronchodilator FEV ₁ % predicted	54.2 (12.90)	55.5 (12.62)
Mean (SD) postbronchodilator FEV ₁ reversibility, %	19.4 (14.82)	19.6 (14.71)
Mean (SD) postbronchodilator FEV ₁ /FVC, %	48.8 (9.83)	48.1 (10.21)

Notes: *In the year prior to screening; duration of COPD calculated from the date first diagnosed with COPD until visit 1; pack-years = total years of smoking multiplied by cigarette packs smoked per day.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GLY, glycopyrronium; GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; IND, indacaterol; PBO, placebo; SD, standard deviation.

significantly higher improvement in trough FEV₁ at week 12 versus patients in the IND + PBO group (Figure 5).

Symptoms, diary-card data, health status

TDI focal score at week 12 showed a greater reduction in dyspnea with IND + GLY than with IND + PBO, with an LSM difference of 0.49 units (95% CI 0.03–0.96 units, $P=0.037$; Table 2 and Figure 6). Patients receiving IND + GLY were significantly more likely to achieve a minimum clinically important improvement (MCID; ≥ 1 unit improvement) in dyspnea³¹ than those taking IND + PBO (76.6% versus 62.2%, respectively; odds ratio [OR] 1.97, 95% CI 1.24–3.11; $P=0.004$).

Over the 12-week treatment period, diary-card data showed a significant improvement in the percentage of days

Table 2 Differences between treatments for primary and secondary efficacy outcomes on day 1 and at week 12 (FAS)

Variable	LSM (95% CI) treatment difference (IND + GLY vs IND + PBO)	P-value
Day 1		
Trough FEV ₁ , L	0.074 (0.046–0.101)	<0.001
Peak FEV ₁ , L	0.108 (0.079–0.137)	<0.001
FEV ₁ AUC _{30min–4h} , L	0.106 (0.080–0.132)	<0.001
Trough FVC, L	0.111 (0.054–0.167)	<0.001
IC at 30 min postdose, L	0.059 (–0.001–0.118)	0.054
IC at 2 h postdose, L	0.109 (0.039–0.179)	0.003
IC at 4 h postdose, L	0.083 (0.014–0.152)	0.019
Week 12		
Trough FEV ₁ , L (primary end point)	0.064 (0.028–0.099)	<0.001
Trough FEV ₁ in the PPS, L	0.064 (0.028–0.101)	<0.001
Peak FEV ₁ , L	0.106 (0.070–0.143)	<0.001
FEV ₁ AUC _{30min–4h} , L	0.111 (0.076–0.145)	<0.001
Trough FVC, L	0.093 (0.027–0.160)	0.006
IC at 25 min predose, L	0.081 (0.002–0.160)	0.043
IC at 30 min postdose, L	0.159 (0.073–0.246)	<0.001
IC at 2 h postdose, L	0.122 (0.037–0.207)	0.005
IC at 4 h postdose, L	0.138 (0.051–0.225)	0.002
IC at 24 h postdose, L	0.068 (–0.014–0.150)	0.105
TDI focal score	0.494 (0.030–0.958)	0.037
SGRQ-C total score	–1.47 (–3.42–0.48)	0.140
Over 12 weeks		
Rescue-medication use		
Change from baseline in mean daily number of puffs	–0.1 (–0.5–0.2)	0.471
Percentage of days with no rescue-medication use	0.2 (–6.0–6.5)	0.945
Change from baseline in mean daily total symptom score	0.0 (–0.3–0.3)	0.810
Change from baseline in mean daytime respiratory symptom score	–0.1 (–0.1–0.0)	0.025
Percentage of days able to perform usual activities	6.2 (1.2–11.3)	0.016

Note: Results of analysis in the FAS, unless otherwise stated.

Abbreviations: AUC, area under the curve; CI, confidence interval; FAS, full analysis set; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GLY, glycopyrronium 50 µg; IC, inspiratory capacity; IND, indacaterol 150 µg; LSM, least squares mean; PBO, placebo; PPS, per protocol set; SGRQ-C, St George's Respiratory Questionnaire – COPD; TDI, transition dyspnea index; vs, versus; COPD, chronic obstructive pulmonary disease.

able to perform usual activities in patients receiving IND + GLY, compared with patients receiving IND + PBO (LSM difference 6.2%, $P=0.016$; Table 2). Significant differences were also observed in change from baseline in mean daytime respiratory symptom score with IND + GLY versus IND + PBO (LSM difference –0.1, 95% CI –0.1–0.0; $P=0.025$; Table 2).

No significant differences were seen between the two treatment groups in the change from baseline in mean daily

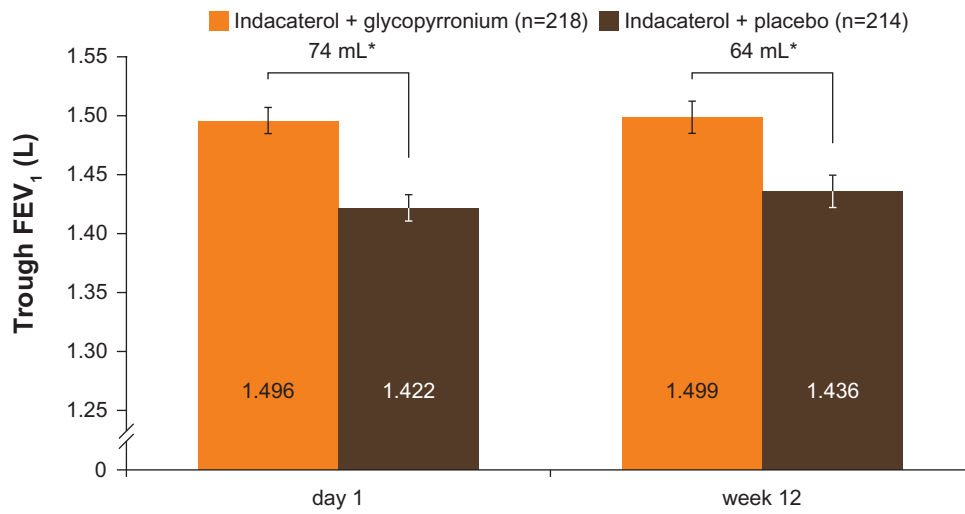


Figure 3 Trough FEV₁ after first dose (end of day 1) and week 12 (FAS).

Notes: * $P < 0.001$. Data are least squares means \pm standard error.

Abbreviations: FAS, full analysis set; FEV₁, forced expiratory volume in 1 second.

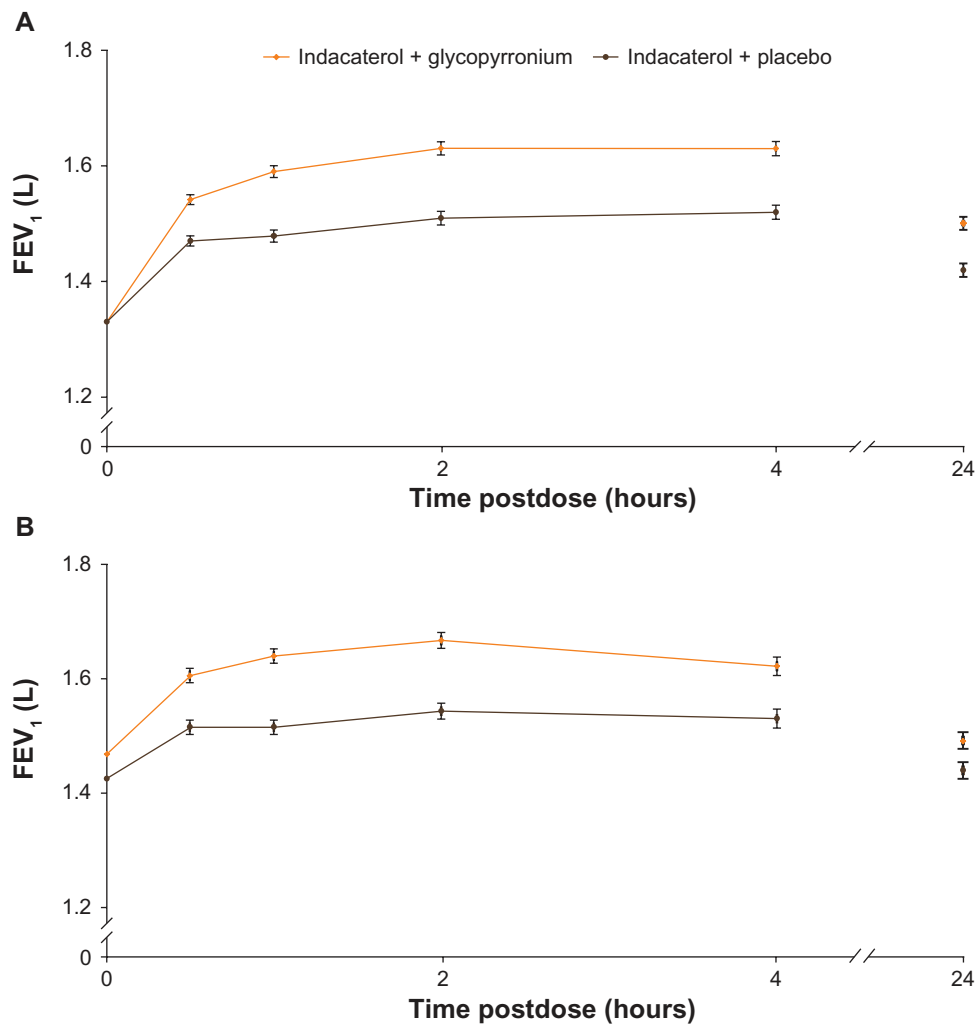


Figure 4 FEV₁ from 30 minutes to 4 hours postdose and 24 hours postdose (**A**) on day 1 and (**B**) at week 12 (FAS).

Notes: $P < 0.001$ at all time points from 30 minutes to 4 hours and at 24 hours, except at 24 hours on week 12 where $P < 0.01$. Data are least-squares means \pm standard error.

Abbreviations: FEV₁, forced expiratory volume in 1 second; FAS, full analysis set.

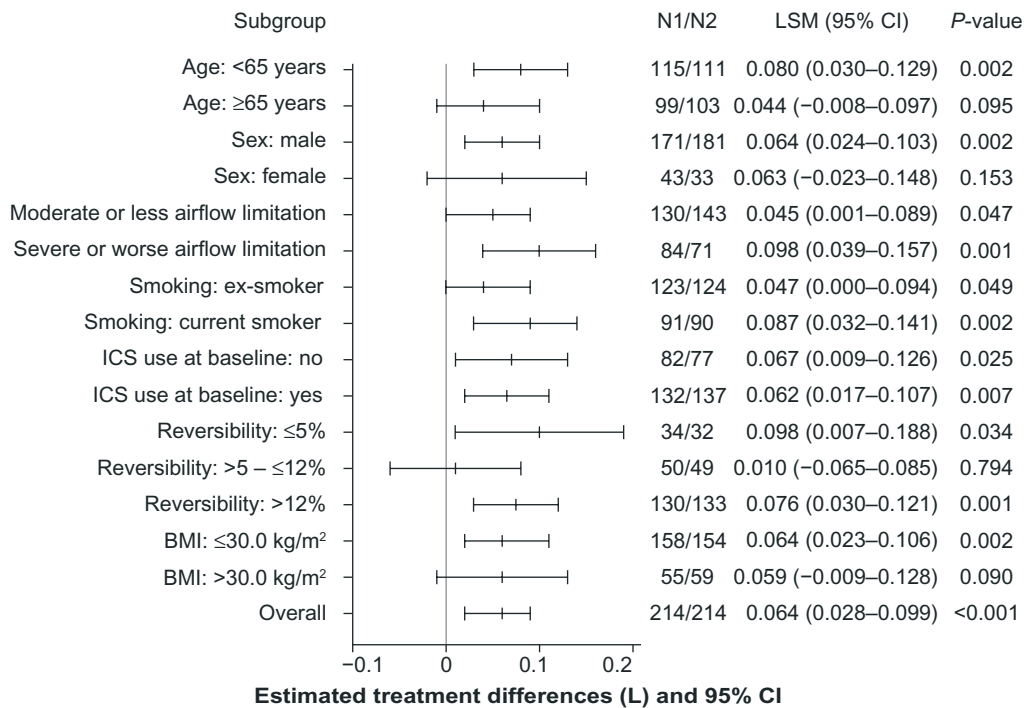


Figure 5 Subgroup analyses of treatment differences in trough FEV₁ at week 12 (FAS).

Note: Data are least squares mean ± 95% CI.

Abbreviations: BMI, body mass index; CI, confidence interval; FAS, full analysis set; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LSM, least squares mean; N1, number of patients analyzed in the indacaterol + glycopyrronium treatment group; N2, number of patients analyzed in the indacaterol + placebo treatment group.

number of puffs of rescue medication (treatment difference –0.1, 95% CI –0.5–0.2; $P=0.471$), in the percentage of days with no rescue medication use (treatment difference 0.2, 95% CI –6.0–6.5; $P=0.945$), or in the change from baseline in mean daily total symptom score (treatment difference 0.0, 95% CI –0.3–0.3; $P=0.810$) over the 12-week treatment period (Table 2).

In the exploratory assessment of health status, there was a numerical difference in the SGRQ-C total score between IND + GLY versus IND + PBO at week 12; the LSM treatment difference was –1.47 points (95% CI –3.42–0.48 points;

$P=0.140$; Table 2). Raw mean (standard deviation) changes (improvements) from baseline were –6.22 (11.47) and –4.13 (10.38) with IND + GLY and IND + PBO, respectively. A higher percentage of patients taking IND + GLY achieved an MCID in SGRQ-C score (≥ 4 -point reduction) versus patients taking IND + PBO, but the difference was not statistically significant (56.5% versus 46.8%, respectively; OR 1.43 95% CI 0.95–2.17; $P=0.089$).³²

Safety

The overall incidence of AEs was similar between the two treatment groups (IND + GLY 37.6%, IND + PBO 33.9%; Table 3). The most frequently reported AE was COPD worsening, seen with similar frequency in both treatment groups (Table 3). Other frequently occurring AEs (at least three patients in either treatment group) included nasopharyngitis, lower respiratory tract infection, cough, back pain, upper respiratory tract infection and oropharyngeal pain. Lower respiratory tract infection occurred with higher frequency in the IND + GLY group, while the frequency of cough was higher in the IND + PBO group (Table 3). AEs leading to discontinuation occurred in a comparable number of patients in both groups (Table 3).

SAEs occurred with similar frequency in both treatment groups (Table 4). The proportion of patients with newly

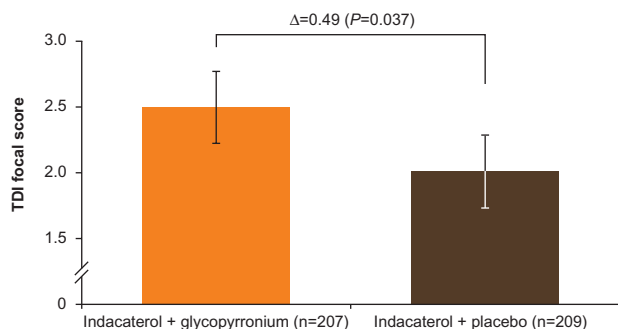


Figure 6 TDI focal score at week 12 (FAS).

Note: Data are least squares means ± standard error.

Abbreviations: FAS, full analysis set; TDI, transition dyspnea index.

Table 3 Most frequent AEs (at least three patients in either treatment group) and discontinuations due to AEs (safety population), n (%)

Preferred term	IND + GLY (N=226), n (%)	IND + PBO (N=221), n (%)
Any AE(s)	85 (37.6)	75 (33.9)
COPD worsening*	33 (14.6)	28 (12.7)
Nasopharyngitis	10 (4.4)	11 (5.0)
Lower respiratory tract infection	7 (3.1)	2 (0.9)
Cough	6 (2.7)	10 (4.5)
Back pain	4 (1.8)	3 (1.4)
Upper respiratory tract infection	4 (1.8)	5 (2.3)
Bacterial infection	3 (1.3)	0
Headache	3 (1.3)	2 (0.9)
Influenza	3 (1.3)	1 (0.5)
Pain in extremity	3 (1.3)	1 (0.5)
Upper respiratory tract infection, bacterial	3 (1.3)	4 (1.8)
Viral upper respiratory tract infection	3 (1.3)	5 (2.3)
Oropharyngeal pain	0	5 (2.3)
Discontinuation from study drug due to AE(s)	3 (1.3)	4 (1.8)

Note: *Including COPD exacerbations.

Abbreviations: AE, adverse event; GLY, glycopyrronium 50 µg; IND, indacaterol 150 µg; PBO, placebo; COPD, chronic obstructive pulmonary disease.

occurring or worsening clinically notable QT interval with Fridericia's correction (QTcF) values was similar in the IND + PBO group (3.8%) and the IND + GLY group (2.8%). The percentage of patients with an increase in QTcF of 30–60 ms from baseline was slightly higher in the IND + GLY group (6.5%) than in the IND + PBO group (4.2%). The incidence of CCV events was low in both groups: 1.3% patients in the IND + GLY group and 2.3% patients in the IND + PBO group. Only angina pectoris was experienced by more than one patient in either treatment group; two patients in the IND + PBO group reported these events, and only one of these events was classified as serious. No deaths were reported in the study.

Discussion

In the GLOW6 study, once-daily coadministration of IND + GLY provided significantly greater improvement in trough FEV₁ on day 1 and at week 12 versus indacaterol alone, with treatment differences of 74 mL and 64 mL, respectively ($P < 0.001$). Peak FEV₁ and FEV₁ AUC_{30min–4h} at day 1 and week 12 were also significantly superior with IND + GLY versus indacaterol alone. Coadministration of IND + GLY also provided statistically significant improvements in dyspnea ($P = 0.037$) and COPD symptoms (percentage of days able to perform usual activities [$P = 0.026$] and change from baseline in mean daytime respiratory symptom score [$P = 0.025$])

Table 4 SAEs (safety population), n (%)

Primary system organ class Preferred term	IND + GLY (N=226), n (%)	IND + PBO (N=221), n (%)
Patients with any SAE(s)	5 (2.2)	5 (2.3)
Respiratory, thoracic and mediastinal disorders	2 (0.9)	2 (0.9)
COPD worsening*	1 (0.4)	2 (0.9)
Hemoptysis	1 (0.4)	0
Gastrointestinal disorders	1 (0.4)	0
Inguinal hernia	1 (0.4)	0
Immune system disorders	1 (0.4)	0
Hypersensitivity	1 (0.4)	0
Infections and infestations	1 (0.4)	1 (0.5)
Bacterial infection	1 (0.4)	0
Urinary tract infection	0	1 (0.5)
Musculoskeletal and connective tissue disorders	1 (0.4)	0
Osteitis	1 (0.4)	0
Cardiac disorders	0	1 (0.5)
Angina pectoris	0	1 (0.5)
Injury, poisoning, and procedural complications	0	1 (0.5)
Rib fracture	0	1 (0.5)
Renal and urinary disorders	0	1 (0.5)
Renal failure, acute	0	1 (0.5)

Notes: *Including COPD exacerbations; a patient with multiple occurrences of an SAE was counted only once in the SAE category.

Abbreviations: COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium 50 µg; IND, indacaterol 150 µg; PBO, placebo; SAE, serious adverse event.

over the 12-week treatment period versus monotherapy. Both treatments had an acceptable safety profile.

In the 2013 GOLD strategy document, the free combination of a LABA plus LAMA is a recommended treatment option for all patients except those with the mildest severity of the disease.¹ The additional benefit provided by combining bronchodilators from different pharmacological classes is a recognized phenomenon. This has been demonstrated in studies combining two short-acting agents^{33,34} and also in studies investigating the combination of the LAMA tiotropium and twice-daily LABAs.^{18,20,25,26} More recently, the additional benefits of combining a once-daily LAMA with a once-daily LABA has been explored, and the results have demonstrated superior efficacy versus the respective monotherapies.^{21,27,35}

Results from the present GLOW6 study support these findings and also the GOLD recommendation. The treatment difference of 64 mL in trough FEV₁ between IND + GLY versus IND + PBO observed at week 12 in the GLOW6 study was consistent with results from the SHINE study, where treatment with QVA 149 (a fixed-dose combination of glycopyrronium and indacaterol in Phase III development) resulted in a treatment difference of 70 mL in trough FEV₁

($P < 0.001$) versus indacaterol at week 26.²⁷ The magnitude of improvement in trough FEV₁ at week 12 in the present study was also comparable to that reported in the INTRUST-1 and INTRUST-2 studies, where differences of 80 mL and 70 mL, respectively (both $P < 0.001$), were observed with indacaterol plus tiotropium versus tiotropium plus placebo.²¹

In GLOW6, coadministration of IND + GLY demonstrated a greater improvement in FEV₁ AUC_{30min-4h} compared with indacaterol alone on day 1 (106 mL) and at week 12 (111 mL). Furthermore, FEV₁ at all time points from 30 minutes to 4 hours and at 24 hours on day 1 and at week 12 was significantly higher with IND + GLY versus indacaterol. These results indicate an early onset and sustained 24-hour bronchodilation with the coadministration of the two once-daily long-acting bronchodilators; this may have particular relevance for patients who struggle to undertake morning activities due to COPD symptoms.³⁶ It is noteworthy that in the GLOW2 study, which evaluated glycopyrronium 50 µg od versus open-label tiotropium 18 µg od, FEV₁ AUC_{0-4h} was significantly higher with glycopyrronium versus tiotropium on day 1 (treatment difference 56 mL, $P < 0.001$) and at week 26 (treatment difference 50 mL; $P < 0.01$).¹³ Thus, the coadministration of IND + GLY appears to provide an additional improvement in FEV₁ AUC_{0-4h}. This improvement in FEV₁ AUC_{30min-4h} at week 12 with the coadministration in the GLOW6 study was similar in magnitude to that seen in the SHINE study, where a treatment difference of 110 mL was observed in FEV₁ AUC_{0-4h} between QVA149 and indacaterol at week 26 ($P < 0.001$).²⁷ Furthermore, in GLOW6, the significantly greater improvement in IC observed with the coadministration of IND + GLY at almost all assessed time points on day 1 (except 30 min post dose) and at week 12 (except predose trough IC, ie 24 hours postdose) compared with indacaterol monotherapy indicates a superior reduction in hyperinflation.

In the present study, coadministration of IND + GLY also significantly improved dyspnea (measured by TDI) compared with indacaterol alone (treatment difference 0.49 units, $P = 0.037$), suggesting that the coadministration results in additional improvement in dyspnea compared with monotherapy. Although the MCID of ≥ 1 -unit improvement in TDI score is widely applied in COPD trials for comparisons versus placebo as well as between active treatments, it is not actually validated for comparison between different active treatments, only against placebo.³¹ Indacaterol has been shown to achieve the MCID in TDI focal score versus placebo,^{11,12} as well as active treatment (tiotropium),^{12,16} and in GLOW6, the improvement in TDI focal score seen with

coadministration of IND + GLY is an incremental benefit over indacaterol alone. Also, it is noteworthy that in the BLAZE study, QVA149 provided a clinically meaningful improvement in TDI focal score versus placebo (treatment difference 1.37 units, $P < 0.001$), while the mean improvement over tiotropium was 0.49 units ($P = 0.021$).³⁵

The percentage of patients in the current study who achieved a clinically meaningful improvement in dyspnea (≥ 1 -unit improvement) was significantly higher in the IND + GLY treatment group than in the IND + PBO group (76.3% and 62.2%, respectively). In addition to the improvement in dyspnea, coadministration of IND + GLY also significantly improved patient-reported COPD symptoms versus indacaterol alone (the percentage of days able to perform usual activities and the change from baseline in mean daytime respiratory symptom score over 12 weeks), indicating better symptom control when using two long-acting bronchodilators from different classes.

Although the exploratory assessment of health status did not demonstrate a statistically significant difference between the two treatments, a numerical improvement was observed with the coadministration of IND + GLY versus indacaterol alone. The study duration of the GLOW6 study (12 weeks) might have impacted on this evaluation, and a longer-term study might potentially be able to demonstrate a greater and more significant separation between the two treatments for this end point. Studies of 6–12 months' duration are proposed as the optimal length to capture data on patient-reported outcomes.³⁶

Overall, the results of the subgroup analyses were consistent with those of the overall analyses, and demonstrated the benefit of coadministration of two long-acting bronchodilators over monotherapy. Results of the subgroup analysis also provided an indication of the patient groups who could potentially derive immediate, greater benefit from the coadministration of IND + GLY compared with indacaterol alone, ie, patients with severe or worse airflow limitation, younger patients (<65 years), ICS users, and patients who are current smokers. However, it is not known whether these trends for the subgroups are maintained over the longer term.

The safety profile of the coadministration of IND + GLY was acceptable. A small imbalance was observed in the cardiac disorders AEs (IND + GLY, two patients [0.9%]; IND + PBO, seven patients [3.2%]), but was not considered clinically meaningful. This could potentially be attributed to the aging COPD population, and also to the multiple comorbidities that are usually prevalent in patients with COPD.³⁷

The study duration of GLOW6 was 12 weeks, which may be too short a period of time to detect improvements

in outcomes for chronic diseases such as COPD, especially symptomatic end points. This could be a reason why significant separation was not seen on all secondary end points. Further, 63% of the patients in the study were on baseline ICS, and these patients continued on a stable daily dose of ICS throughout the study, which may have impacted on the magnitude of the treatment effects observed. Our study population did not enroll patients with all severities of COPD who may benefit from coadministration of two long-acting bronchodilators. It has been shown that it is patients with moderate COPD who show the greatest improvements in lung function,^{38,39} and the primary aim of our study was to assess the additional benefit in lung function from the coadministration of two long-acting bronchodilators versus one.

For the pharmacological management of COPD, long-acting bronchodilators given once-daily have been shown to be superior to short-acting bronchodilators and are also preferred.^{1,40} As demonstrated by the current study, once-daily combination therapy with a LABA plus a LAMA provides further benefits over LABA monotherapy, providing superior bronchodilation and symptom relief, with an acceptable safety profile. Hence, in COPD patients who are insufficiently controlled by long-acting bronchodilator monotherapy, a step up to long-acting bronchodilator combination therapy appears to be an effective and safe next step, potentially preferable over therapy with a combination of a LABA plus an ICS. Indeed, in non-frequent exacerbators, combination therapy with the fixed-dose, dual-bronchodilator QVA149 was more efficacious in terms of improvement in pulmonary function and symptom relief versus combination therapy with a LABA plus an ICS,⁴¹ at the same time avoiding safety issues (such as pneumonia) encountered in COPD patients treated with ICS.⁴²

Conclusion

The results from the GLOW6 study demonstrate that in patients with moderate-to-severe COPD, coadministration of indacaterol 150 µg od and glycopyrronium 50 µg od via the Breezhaler[®] device was safe and well tolerated and provided a rapid onset of effect on day 1 and significant and sustained improvements in bronchodilation along with reduction in symptoms over 12 weeks, compared with indacaterol 150 µg od, demonstrating the benefits of adding a second long-acting bronchodilator for the treatment of patients with COPD.

Author contributions

All authors read and approved the final manuscript. WV was the principal investigator of this multicenter study, reviewed

the clinical study report and manuscript drafts, and discussed and cowrote the final manuscript. JA was an investigator in the study, reviewed and revised the manuscript drafts at all stages, and approved the final draft. HC, MH, DMcB, and PG, as employees of the sponsor, contributed to the design, preparation, conduct, analysis, and interpretation of the study.

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Disclosure

WV has acted as consultant for Boehringer Ingelheim/Pfizer, GlaxoSmithKline, AstraZeneca, Meda Pharmaceuticals, Chiesi, Mundipharma, Novartis, and MSD. JA has no conflicts of interest. HC, MH, DMcB, and PG are employees of the study sponsor and have no other conflicts to declare.

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Supplementary materials

Table S1 List of study centers

Belgium: UZ Brussel, 101 Avenue de Laerbeek, Brussels 1090; Longartsenpraktijk, 5 Winterslagstraat, Genk 3600; UCL Mont-Godinne, 1 Avenue Terrasse, Yvoir 5530; Saint-Joseph, Sainte-Thérèse, and IMTR, 6 Rue de la Duchère, Gilly 6060; AZ Sint-Elisabeth, 133 Nederrij, Herentals 2200; Hôpital Erasme, 808 Route de Lennik, Brussels 1070; Centre Hospitalier du Luxembourg, 4 Rue Barblé, Luxembourg 1210; private practice – Dr Martinot, 93 Boulevard de la Meuse, Jambes 5100; private practice – Dr Aumann, 36/2A Prins Bisschopssingel, Hasselt 3500; private practice – Dr Delobbe, 6A Chemin des quartiers, Malmedy 4960; Centre Hospitalière Universitaire André Vésale, 706 Rue de Gozée, Montigny-le-Tilleul 6100; Centre Hospitalière Universitaire Sart Tilman, Bâtiment B 35 Sart Tilman, Liège 4000; Clinique Notre-Dame De Grâce, 212 Chee de Nivelles, Gosselies 6041; Sint-Elisabeth Ziekenhuis, 166 Rubensstraat, Turnhout 2300

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Table S2 Medications allowed in the GLOW6 study under certain conditions

Class of medication	Condition under which medication is permitted
SSRIs	Stable dose for at least 30 days prior to the screening visit and during the study; screening ECG is normal, with no clinical evidence of prior ECG abnormalities
Inhaled corticosteroids	Stable dose for at least 30 days prior to the screening visit and during the study
Intranasal corticosteroids	Stable dose for at least 30 days prior to the screening visit
H ₁ antagonists	Stable dose for at least 5 days prior to the screening visit (except mizolastine or terfenadine)
Inactivated influenza, pneumococcal, or any other inactivated vaccine	Not administered within 48 hours prior to a study visit

Abbreviations: ECG, electrocardiogram; SSRIs, selective serotonin reuptake inhibitors.

Table S3 Procedure for handling missing data in the GLOW6 study

Spirometry

- FEV₁, FVC, and IC measurements within 6 hours of rescue-medication use or within 7 days of systemic corticosteroid use were set to missing. Trough FEV₁ was defined as the average of the postdose 23 hour 15 minute and the 23 hour 45 minute FEV₁ values. The allowable window for these scheduled measurements was 22 hours 45 minutes to 24 hours 15 minutes. Values measured outside of this window were set to missing. If one of the 23 hour 15 minute or 23 hour 45 minute values was missing, the remaining nonmissing value was taken as trough FEV₁. If both values were missing, trough FEV₁ was regarded as missing.
- For the primary analysis, if trough FEV₁ was missing at visit 8 (week 12) the latest nonmissing predose trough FEV₁ (the mean of 45 and 15 minute predose measurements) from visits 5, 6, or 7 (days 29, 57, 84) was carried forward (LOCF). These measurements were required to have been taken before the next dose of study medication.
- Missing values for the analysis of secondary spirometry variables were not imputed.

Rescue-medication use

- The total number of puffs of rescue medication per day over the 12 weeks was calculated and divided by the total number of days with nonmissing rescue-medication data to derive the mean daily number of puffs of rescue medication taken for the patient. If the number of puffs was missing for part of the day (either morning or evening), then a half day was used in the denominator.

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; LOCF, last observation carried forward.

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