CLINICAL INVESTIGATION

# Glycopyrronium for chronic obstructive pulmonary disease: evidence and rationale for use from the GLOW trials

The clinical development of the long-acting muscarinic antagonist bronchodilator glycopyrronium (Seebri® Breezhaler® inhalation powder) in the GLOW (glycopyrronium bromide in chronic obstructive pulmonary disease airways) series of studies showed that, compared with placebo, once-daily glycopyrronium provided 24-h bronchodilation, improved symptoms and health status and reduced the risk and rate of moderate or severe exacerbations. Glycopyrronium also reduced dynamic hyperinflation and increased exercise tolerance. Compared with the long-acting muscarinic antagonist tiotropium, glycopyrronium had a similar effect on clinical outcomes with a faster onset of action. Added to the long-acting $\beta_2$-agonist bronchodilator indacaterol, glycopyrronium had a greater bronchodilator effect and improved dyspnea versus indacaterol alone. There were no significant safety issues in the GLOW studies. Glycopyrronium is a useful addition to the treatments for chronic obstructive pulmonary disease.

**Keywords:** chronic obstructive pulmonary disease • clinical study • efficacy • glycopyrronium • long-acting muscarinic antagonist • safety • tiotropium

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The current pharmacological management strategy for patients with stable chronic obstructive pulmonary disease (COPD) centers on inhaled long-acting bronchodilators, which feature prominently among the recommended first-choice treatment options for the different patient groups [1]. Long-acting bronchodilators may be given singly, in combination with another bronchodilator or combined with an inhaled corticosteroid (ICS), depending on the severity of a patient's symptoms and their level of risk. Two types of long-acting bronchodilator are available, the long-acting muscarinic antagonists (LAMAs) and long-acting $\beta_2$-adrenergic agonists (LABAs). The LAMA tiotropium was the first once-daily inhaled long-acting bronchodilator. Since then, the older twice daily LABAs have been superseded by once-daily LABAs such as indacaterol [2–4], and other LAMAs have become available. The once-daily inhaled LAMA, glycopyrronium, was approved for use in Europe in September 2012 as Seebri® Breezhaler® inhalation powder. Phase III clinical data supporting this approval was generated in the GLOW (glycopyrronium bromide in COPD airways) series of clinical studies. The primary aim of these studies was to provide the evidence of the efficacy and safety of glycopyrronium required to obtain regulatory approvals. However, the relevance of the patient population (symptomatic patients with moderate-to-severe COPD irrespective of ICS use) and the scope (3257 patients) and duration of the studies (up to 1 year) also provide a rationale for the utility of glycopyrronium in the everyday treatment of patients with COPD. The aim of this review is to provide an overview of the glycopyrronium clinical development program, and to highlight the value of glycopyrronium in the treatment of COPD.

## Preclinical & early-phase clinical development of glycopyrronium

Bronchoconstriction mediated via cholinergic activity (or 'tone') of the parasympathetic

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nervous system is the major bronchoconstrictor neural pathway in the airways, and the major reversible component in COPD. When stimulated, these nerves release acetylcholine, which acts at multiple muscarinic receptor subtypes. The muscarinic receptor subtypes M1, M2 and M3 are of relevance in the human lung, with the M3 receptor on airway smooth muscle primarily involved in bronchoconstriction [5,6].

Glycopyrronium is a potent antagonist at the M1, M2 and M3 muscarinic receptors. Preferential activity at M1 and M3 receptors (over M2 receptors) is considered a desirable pharmacological profile, since the former mediates bronchodilation while M2 receptor blockade may result in bronchoconstriction and (via cardiac M2 receptors) increased heart rate [5,6]. In binding studies, glycopyrronium was selective for the human M3 and M1 receptors over the human M2 receptor, with faster dissociation from the M2 receptor than from the M1 and M3 receptors. While both glycopyrronium and tiotropium share this kinetic selectivity, the M3:M2 selectivity was higher for glycopyrronium (eightfold) than for tiotropium (twofold) [7]. Receptor kinetics showing more rapid equilibration with the M3 receptor for glycopyrronium than for tiotropium [7] may relate to a difference in onset of bronchodilator effect.

Glycopyrronium (NVA237) appeared to be a promising candidate for development as a dry powder formulation for once-daily inhalation treatment for patients with COPD. The clinical development program for glycopyrronium in patients with COPD was designed to provide a comprehensive evaluation of the duration of action and clinical effects of this drug. Following initial phase clinical trials, short-term (1–4 weeks) Phase II dose ranging studies confirmed the bronchodilator efficacy of glycopyrronium at doses of 50 µg once daily and above, with a pharmacodynamic profile characterized by a fast onset of action and a sustained effect over 24 h with once-daily dosing [8–10]. The Phase II study results led to selection of glycopyrronium 50 µg once daily as the optimum dosage for further clinical investigation.

## The GLOW studies

### Overview of study designs

The study designs of the six GLOW studies are summarized in Table 1.

The similarly designed, Phase III pivotal studies GLOW1 (6 months) [11] and GLOW2 (1 year) [12] were designed to confirm the efficacy and provide long-term safety data for glycopyrronium 50 µg once daily in patients with moderate-to-severe COPD. A third Phase III study (GLOW3) was performed to investigate the effect of glycopyrronium on exercise tolerance [13]. Data from these three studies were used to support the registration of glycopyrronium in Europe and Canada. All studies were placebo controlled, and GLOW2 included open-label tiotropium 18 µg as an active control. At that time, tiotropium was the only approved once-daily LAMA in COPD.

GLOW4 was a 1-year comparison of glycopyrronium and open-label tiotropium conducted in Japanese patients with COPD, since safety and efficacy data obtained locally would be required for glycopyrronium to be registered in Japan [14].

Glycopyrronium was given in all the GLOW studies at a dose of 50 µg once daily, administered via the Breezhaler® device. Tiotropium (as Spiriva® via HandiHaler®) was administered open label in GLOW2 and GLOW4 owing to technical and copyright issues with blinding. Subsequently, a 12-week study (GLOW5) was conducted in order to compare glycopyrronium and tiotropium under blinded conditions using a double-dummy design [15].

GLOW6 investigated the potential benefits of 'dual bronchodilation' by comparing concurrent treatment with glycopyrronium and the LABA indacaterol with indacaterol alone [16].

### Outcomes evaluated

The primary efficacy variable in GLOW1, GLOW2, GLOW5 and GLOW6 was trough forced expiratory volume in 1 s ($FEV_1$; the mean of measurements at 23 h 15 min and 23 h 45 min post-dose) following 12 weeks of study treatment. The minimum clinically important difference (MCID) for trough $FEV_1$ has been estimated as 100 ml between active and placebo treatments [17]. Rigorous profiling of the bronchodilator response over 24 h using serial spirometry was included in a subgroup of approximately a third of the patients in GLOW1 and GLOW2. The bronchodilator effect of glycopyrronium in the early post-dose period was assessed at individual time points ($FEV_1$ from 5 min post-dose) and as the average $FEV_1$ over the first 4 h following dosing ($FEV_1AUC_{0-4h}$). Inspiratory capacity (IC), regarded as a surrogate for hyperinflation [18], was also measured at various post-dose time points in several of the GLOW studies.

In the mentioned studies that used trough $FEV_1$ at 12 weeks as the primary outcome, the terms of comparison differed: GLOW1 and GLOW2 were designed to show superiority of glycopyrronium versus placebo; GLOW5 was designed to demonstrate noninferiority of glycopyrronium versus tiotropium, and the objective of GLOW6 was to show superiority of concurrent glycopyrronium and indacaterol versus indacaterol alone. Given that tiotropium was administered open label in GLOW2, all comparisons of glycopyrronium

Table 1. GLOW study designs.

| | GLOW1 [11] | GLOW2 [12] | GLOW3 [13] | GLOW4 [14] | GLOW5 [15] | GLOW6 [16] |
|---|---|---|---|---|---|---|
| Objective | Efficacy, safety and tolerability of glycopyrronium | Efficacy, safety, and tolerability of glycopyrronium | Effect of glycopyrronium on exercise endurance | Long-term safety and tolerability of glycopyrronium in Japanese patients | Efficacy, safety and tolerability of glycopyrronium vs tiotropium | Efficacy, safety and tolerability of co-administration of glycopyrronium + indacaterol |
| Study design | R, MC, PC, PG, DB | R, MC, PC, PG, DB and OL (TIO) | R, MC, PC, XO, DB | R, MC, PG, OL | R, MC, PG, DD, B | R, MC, PG, DB |
| Clinicaltrials.gov registration | NCT01005901 | NCT00929110 | NCT01154127 | NCT01119937 | NCT01613326 | NCT01604278 |
| Duration | 26 weeks | 52 weeks | 21 days per period | 52 weeks | 12 weeks | 12 weeks |
| Treatment arms (randomization ratio) | GLY 50 μg q.d. PBO (2:1) | GLY 50 μg q.d. TIO 18 μg q.d. PBO (2:1:1) | GLY 50 μg q.d. PBO (1:1) | GLY 50 μg q.d. TIO 18 μg q.d. (3:1) | GLY 50 μg q.d. TIO 18 μg q.d. (1:1) | GLY 50 μg q.d.+ IND 150 μg q.d. PBO + IND 150 μg q.d. (1:1) |
| N (randomized) | N = 822 (GLY n = 552; PBO n = 270) | N = 1060 (GLY n = 525; TIO n = 267; PBO n = 268) | N = 108 (GLY first n = 55; PBO first n = 53) | N = 163 (GLY n = 123; TIO n = 40) | N = 657 (GLY n = 327; TIO n = 330) | N = 449 (GLY + IND n = 226; PBO + IND n = 223) |
| Primary endpoint(s) | Trough $FEV_1$ at week 12 | Trough $FEV_1$ at week 12 | Exercise endurance time at day 21 | AEs and SAEs | Trough $FEV_1$ at week 12 (noninferiority vs TIO) | Trough $FEV_1$ at week 12 |
| Other endpoints | TDI; SGRQ; rescue medication use; time to first moderate-or-severe exacerbation; IC and other spirometry AEs and SAEs; ECG abnormalities | TDI; SGRQ; time to first moderate or severe exacerbation; rescue medication use; IC and other spirometry; annual rate of COPD exacerbations AEs and SAEs | Exercise endurance time at day 1; resting and dynamic IC and other spirometry at days 1 and 21; Borg symptoms and leg discomfort; TDI AEs and SAEs | Other spirometry; time to first moderate or severe exacerbation; SGRQ; rescue medication use; laboratory values; vital signs; QTc interval | Other spirometry; TDI; SGRQ; rescue medication use; symptoms; COPD exacerbations | Other spirometry; TDI; symptoms; rescue medication use; SGRQ-C AEs and SAEs |

All study treatments were given once daily via unit dose dry powder inhaler.
AE: Adverse event; COPD: Chronic obstructive pulmonary disease; DB: Double blind; ECG: Electrocardiography; $FEV_1$: Forced expiratory volume in 1 s; FVC: Forced vital capacity; GLY: Glycopyrronium; IC: Inspiratory capacity; MC: Multicenter; OL: Open label; PBO: Placebo; PC: Placebo controlled; PG: Parallel group; q.d.: Once daily; R: Randomized; SAE: Serious adverse event; SGRQ: St George's Respiratory Questionnaire; SGRQ-C: SGRQ for COPD; TDI: Transitional Dyspnea Index; TIO: Tiotropium; XO: Crossover.

and tiotropium in that study were considered to be exploratory objectives.

As recommended by regulatory guidelines, the studies also included important clinical outcomes such as dyspnea, health status and exacerbations. Dyspnea was measured using the transition dyspnea index (TDI) [19], with a 1-point increase in TDI total score denoting the MCID [20]. Results were analyzed both as the TDI total score and as the percentage of patients achieving the MCID. Shortness of breath was also recorded by patients in electronic diaries, along with other symptom-related variables such as cough, wheezing, sputum volume and color, ability to perform usual daily activities and night-time awakenings. Patients also recorded their use of rescue medication for symptom relief, to provide an indirect measure of the effect of treatment on symptoms [21].

Health status during treatment was evaluated by the St. George's Respiratory Questionnaire (SGRQ) [22]. A 4-unit decrease in the total score between placebo and active treatments or from baseline represents the MCID [23]. Again, differences in both total score and percentages of patients achieving the MCID were analyzed.

In the GLOW program, exacerbations of COPD were defined consistently either as worsening of two or more major symptoms (dyspnea, sputum volume or purulence) for at least two consecutive days; or worsening of any one of those symptoms together with any one minor symptom (sore throat, colds, fever without other cause, increased cough or wheeze) for at least two consecutive days. Assessment of symptoms was based on patient diary data. Severity was determined by the level of treatment required (moderate severity if treatment with systemic corticosteroids and/or antibiotic was required; severe if hospitalization was also required). An MCID for exacerbations has not been established.

Antimuscarinics have the potential for unwanted class effects resulting from the inhibition of cholinergic stimulation, giving rise to a sympathomimetic effect. Such effects include constipation, tachycardia, palpitations and arrhythmias, reduced bronchial secretions, urinary retention and dry mouth. Administering treatment directly to the lungs minimizes systemic exposure and extrapulmonary effects. In addition to the standard evaluation of safety through adverse event reporting, because cardiovascular co-morbidity is common among patients with COPD [24], close attention was given in the GLOW program to cardiovascular adverse events and electrocardiographic (ECG) monitoring. Furthermore, causes of deaths were reviewed by an independent adjudication committee in GLOW 1, 2, 5 and 6.

## Patients

The criteria for patient entry to the studies were designed to provide a study population that was relevant to the overall population of patients with COPD. Thus, patients were to have moderate-to-severe COPD, with a smoking history of ≥10 pack–years. Disease severity was defined by the Global initiative for chronic Obstructive Lung Disease (GOLD) strategy documents current at the time the studies were designed (GOLD 2008 and 2010), in other words, in terms of airflow limitation: post-bronchodilator $FEV_1$ ≥30% (≥40% in GLOW3) and less than 80% predicted and $FEV_1$/FVC ratio less than 0.70. Patients in GLOW1, GLOW2, GLOW5 and GLOW6 were required to be symptomatic on study entry. Concomitant use of ICS was permitted.

Patients with unstable disease (a recent history of hospitalization for an exacerbation or acute respiratory tract infection in the 6 weeks prior to or during the screening period) were excluded, as were those with any history of asthma (indicated by, but not limited to, a blood eosinophil count >600/$mm^3$ at screening or onset of symptoms prior to age 40 years). Because of potential anticholinergic class effects, the studies also excluded patients with pre-existing conditions that could be exacerbated by any such effects, including narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder neck obstruction, and moderate-to-severe renal impairment or urinary retention. Patients with cardiovascular co-morbidity (including chronic stable atrial fibrillation) could be enrolled, although not those with a clinically significant cardiovascular condition that could interfere with the study conduct, for example, unstable ischemic heart disease, left ventricular failure, history of myocardial infarction or arrhythmia.

Patients could continue with their ICS treatment at a stable dose, but bronchodilators other than study treatments (salbutamol was provided as rescue medication) were discontinued.

The baseline demographics and clinical characteristics of the patients in the six studies are summarized in Table 2. Aside from more specialized studies (GLOW3, exercise tolerance and GLOW4 in a Japanese population), the patients in the GLOW program were well matched across the studies, as would be expected from the near-identical entry criteria. The mean age in each of the GLOW 1, 2, 5 and 6 studies was 64 years, and the majority of patients were Caucasian, males (64–82% of patients) and had moderate COPD (59–64% of patients), with similar baseline spirometry ($FEV_1$ 54–56%; $FEV_1$/FVC 47–51%). The level of ICS use at baseline was similar in GLOW1, GLOW2 and GLOW5 (51–54%), and 63% of patients in GLOW6. The majority of patients

Table 2. Baseline demographics and clinical characteristics of patients in the GLOW studies.

| | GLOW1 | GLOW2 | GLOW3 | GLOW4[††] | GLOW5 | GLOW6 |
|---|---|---|---|---|---|---|
| N[†] | 817 | 1060 | 108 | 163 | 657 | 446 |
| Mean (SD) age, years | 63.9 (9.30) | 63.6 (8.87) | 60.5 (8.64) | 68.4 (7.29)<br>69.4 (7.48) | 63.5 (8.00) | 63.8 (8.07) |
| Male, n (%) | 669 (81.9) | 680 (64.2) | 63 (58.3) | 159 (97.6) | 485 (73.8) | 365 (81.8) |
| Ethnicity, n (%) | | | | | | |
| Caucasian | 512 (62.7) | 927 (87.5) | 104 (96.3) | 0 | 457 (69.6) | 440 (98.7) |
| Asian | 289 (35.4) | 53 (5.0) | 2 (1.9) | 163 (100) | 186 (28.3) | 0 |
| Black | 6 (0.7) | 42 (4.0) | – | 0 | 0 | 0 |
| Other | 10 (1.2) | 38 (3.6) | 2 (1.9) (could include black) | 0 | 14 (2.1) | 6 (1.3) |
| Severity of COPD, n (%) | | | | | | |
| Moderate | 497 (60.8) | 678 (64.0) | [¶] | 93 (57.1) | 385[§] (58.6) | 286 (64.1) |
| Severe | 320 (39.2)[§] | 381 (36.0)[§] | | 68 (41.7) | 272 (41.4) | 160 (35.9) |
| Mean (SD) duration of COPD, years | 6.07 (6.14) | 7.32 (6.59) | [¶] | 3.41 (3.31)<br>3.97 (3.79) | 6.3 (5.09) | 7.2 (5.50) |
| COPD exacerbation history[‡] n (%) | | | | | | |
| 0 exacerbation | 643 (78.7) | 778 (73.4) | [¶] | 141 (86.5) | 502 (76.4) | 314 (70.4) |
| 1 exacerbation | 133 (16.3) | 211 (19.9) | | 19 (11.7) | 113 (17.2) | 102 (22.9) |
| ≥2 exacerbations | 41 (5.0) | 71 (6.7) | | 3 (1.8) | 42 (6.4) | 30 (6.7) |
| ICS use, n (%) | 437 (53.5) | 568 (53.6) | [¶] | 41 (25.2) | 337 (51.3) | 279 (62.6) |
| Smoking history, n (%) | | | | | | |
| Ex-smoker | 546 (66.8) | 580 (54.7) | 43 (39.8) | 110 (67.5) | 361 (54.9) | 259 (58.1) |
| Current smoker | 271 (33.2) | 480 (45.3) | 65 (60.2) | 53 (32.5) | 296 (45.1) | 187 (41.9) |
| Mean (SD) duration of smoking, pack-years | 44.8 (27.04) | 49.0 (25.61) | 46.1 (21.20) | 65.9 (29.20)<br>57.6 (28.76) | 39.9 (21.01) | 44.5 (22.81) |
| Mean (SD) post-bronchodilator $FEV_1$% predicted | 54.6 (12.98) | 56.0 (13.28) | 57.1 (8.52) | 52.7 (13.44)<br>55.2 (12.19) | 53.5 (12.88) | 54.8 (12.76) |
| Mean (SD) post-bronchodilator $FEV_1$/FVC,% | 50.0 (10.24) | 50.6 (10.47) | 50 (9.00)[#] | 47.4 (9.49)<br>50.3 (7.71) | 47.3 (10.61) | 48.4 (9.99) |
| Mean (SD) post-bronchodilator $FEV_1$ reversibility,% | 13.7 (14.07) | 15.9 (14.88) | 19.2 (11.43) | 12.8 (11.77)<br>11.3 (10.48) | 17.8 (13.50) | 19.4 (14.73) |

[†]N = number of patients evaluated for safety (safety population).
[‡]The number of moderate or severe COPD exacerbations in the year prior to screening.
[§]Included n = 4 (GLOW1) and n = 8 (GLOW2) patients with very severe COPD and n = 1 patient with mild COPD (GLOW5).
[¶]Data not available.
[#]Converted to percentage from value 0.5 (0.09) in publication [13].
[††]Where two values are given, these are for the glycopyrronium and tiotropium treatment groups, respectively.
COPD: Chronic obstructive pulmonary disease; $FEV_1$: Forced expiratory volume in 1 s; FVC: Forced vital capacity; ICS: Inhaled corticosteroid; SD: Standard deviation.

(70–79%) in these studies had been exacerbation free in the past year.

## Results & findings

The efficacy results section focuses first on the studies GLOW1, GLOW2 and GLOW5. The concurrent treatment study (GLOW6) and the special-interest studies GLOW3 (exercise) and GLOW4 (safety in Japanese patients) are described separately. Readers are referred to the published individual studies for further details [11–16].

### Bronchodilator efficacy

The spirometry results of the GLOW studies are summarized in Table 3. Trough $FEV_1$ at week 12 was 97–108 ml greater with glycopyrronium than with placebo, and glycopyrronium was noninferior to tiotropium (all $p < 0.001$). There was no difference versus tiotropium whether the latter was given open label or blinded. At day 1, similarly, trough $FEV_1$ with glycopyrronium was 91–105 ml greater than placebo and not different versus tiotropium.

The significant effect of glycopyrronium versus placebo for trough $FEV_1$ was maintained at weeks 24/26 (113–134 ml) and week 52 (108 ml) in the longer term studies (Figure 1).

At 5 min post-dose on day 1 of treatment, $FEV_1$ was 78–87 ml higher with glycopyrronium versus placebo ($p < 0.001$), and significant increases versus tiotropium of 47 ml (open label) or 51 ml (blinded) (both $p < 0.01$) were observed. Figure 2 depicts the bronchodilator effect of glycopyrronium, placebo and open-label tiotropium measured serially over the 24-h post-dose period on day 1 in the GLOW2 study. The average $FEV_1$ over the 4-h post-dose period ($FEV_1AUC_{0–4h}$) on day 1 was significantly greater with glycopyrronium versus open-label tiotropium (56 ml; $p < 0.001$). Similarly, in GLOW5, $FEV_1AUC_{0–4h}$ on day 1 was significantly greater with glycopyrronium versus blinded tiotropium (58 ml, $p < 0.001$). The significant effect of glycopyrronium versus placebo for $FEV_1AUC_{0–4h}$ observed at day 1 in GLOW2 was maintained at 12, 26 and 52 weeks.

Glycopyrronium increased trough IC by 97–129 ml versus placebo over the various time points of the 12–52 week studies (all $p \leq 0.01$), and trough IC did not differ between glycopyrronium and tiotropium. Both GLOW1 and GLOW2 demonstrated superiority of glycopyrronium over placebo in its effect on IC in the 2-h post-dose period during the course of the studies [11,12].

### Clinical outcomes (symptoms, health status, use of rescue medication and exacerbations)

These outcomes are summarized in Table 4. Glycopyrronium improved the TDI total score relative to placebo at weeks 26 and 52, with the change at week 26 exceeding the MCID. Patients receiving glycopyrronium were significantly more likely to achieve the MCID compared with placebo in GLOW1 and GLOW2. Both the open-label and blinded comparisons with tiotropium in GLOW2 and GLOW5 showed no difference between the two treatments for TDI total score or for the odds ratio for achieving the MCID. The daily diary data showed improvements in the daily symptom score with glycopyrronium versus placebo in the pooled analysis of the GLOW1 and GLOW2 studies [25], and compared with blinded tiotropium in the GLOW5 study [15]. The pooled GLOW1 and GLOW2 data also showed that glycopyrronium increased the proportion of days patients were able to perform their usual activities relative to placebo over 26 weeks (by 3.6%; $p = 0.014$) [25].

Glycopyrronium improved the SGRQ total score by approximately 3 units compared with placebo in GLOW1 and GLOW2. The odds ratio for patients achieving the MCID favored glycopyrronium over placebo at week 26 in GLOW1, but not at week 52 in GLOW2. Decreases (improvement) from baseline in the SGRQ total score in the GLOW2 study (unadjusted data) at week 52 were –4.3 units with placebo, –7.2 units with tiotropium and –7.5 units with glycopyrronium.

Glycopyrronium allowed a significant reduction of approximately half a puff of rescue medication daily compared with placebo in GLOW1 and GLOW2, and was not significantly different from tiotropium in GLOW2 and GLOW5.

A significant reduction (by 31–34%) in risk of moderate or severe exacerbations for glycopyrronium compared with placebo was observed in both the 26-week and 52-week studies. Over 52 weeks, glycopyrronium and tiotropium were similarly and significantly effective relative to placebo in reducing the risk of exacerbations, with no significant difference between the two LAMAs in time to first exacerbation (Figure 3). The rate of moderate or severe exacerbations over 1 year in GLOW2 was significantly reduced relative to placebo by glycopyrronium (by 34%), but the 20% reduction with open-label tiotropium versus placebo was not statistically significant (rate ratio 0.80, 95% CI: 0.586, 1.105; $p = 0.179$) [12].

### Glycopyrronium & exercise endurance time

GLOW3 [13] was specifically designed to assess the effect of glycopyrronium on exercise tolerance in patients with moderate-to-severe COPD, using an incremental cycle endurance test. This was a cross-over comparison with placebo, with a 3-week treatment period. The primary variable, exercise endurance time during a submaximal exercise test, was increased by 89 s relative to placebo, a significant 21%

Table 3. Bronchodilator efficacy of glycopyrronium in GLOW1, GLOW2, GLOW5 and GLOW6.

| | GLOW1 | GLOW2 | | GLOW5 | GLOW6 |
|---|---|---|---|---|---|
| **Treatment difference** | **GLY vs PBO** | **GLY vs PBO** | **GLY vs TIO open label** | **GLY vs TIO blinded** | **GLY+IND vs PBO+IND** |
| **Trough $FEV_1$** | | | | | |
| Day 1 | 105 ± 10.9 p < 0.001 | 91 ± 10.9 p < 0.001 | 8 ± 1.1 p = NS | –10 (–24, 21) p = NS | 74 (46, 101) p < 0.001 |
| Week 12 | 108 ± 14.8 p < 0.001 | 97 ± 16.7 p < 0.001 | 14 ± 16.5 p = NS | 0 (–32, 31) p < 0.001 (noninferiority)[§]<br>4 (–25, 34) p = NS (superiority) | 64 (28, 99) p < 0.001 |
| Week 24/26 | 113 ± 16.5 p < 0.001 | 134 ± 18.9 p < 0.001 | 50 ± 18.5 p < 0.01 | – | – |
| Week 52 | – | 108 ± 19.5 p < 0.001 | 19 ± 19.0 p = NS | – | – |
| $FEV_1$ 5 min post-dose, day 1 | 87 ± 16.3 p < 0.001[‡] | 78 ± 15.3 p < 0.001[‡] | 47 ± 15.1 p = 0.002[‡] | 51 (36, 66) p < 0.001 | – |
| **$FEV_1$ $AUC_{0–4h}$[†]** | | | | | |
| Day 1 | 188 ± 9.9 p < 0.001 | 197 ± 9.5 p < 0.001 | 56 ± 9.5 p < 0.001 | 58 (40, 76) p < 0.001 | 106 (80, 132) p < 0.001 |
| Week 12 | 186 ± 15.9 p < 0.001 | 176 ± 17.0 p < 0.001 | 30 ± 16.5 p = NS | 23 (–6, 53) p=NS | 111 (76, 145) p < 0.001 |
| Week 26 | 197 ± 17.2 p < 0.001 | 177 ± 18.2 p < 0.001 | 50 ± 17.9 p < 0.01 | – | – |
| Week 52 | – | 165 ± 19.8 p < 0.001 | 15 ± 19.4 p = NS | – | – |
| Trough IC | | | | | |
| Day 1 | 104 ± 23.9 p < 0.001 | 114 ± 24.4 p < 0.001 | 33 ± 24.6 p = NS | 4 ± 27 p = NS | – |
| Week 12 | 97 ± 29.6 p = 0.01 | 129 ± 33.6 p < 0.001 | 15 ± 33.0 p = NS | –34 (–101, 33) p = NS | 68 (–14, 150) p = NS |
| Week 26 | 113 ± 27.5 p < 0.001 | 110 ± 33.1 p < 0.001 | 29 ± 32.8 p = NS | – | – |
| Week 52 | – | 126 ± 34.6 p < 0.001 | 42 ± 33.9 p = NS | – | – |

Data are LSM ± SE ml (95% CI) unless otherwise stated. '–' symbol indicates not applicable (owing to study duration) or variable not recorded.
[†]From 5 min to 4 h post-dose or (GLOW6) from 30 min to 4 h post-dose.
[‡]Measured in serial spirometry subgroup (approximately 30% of total patients).
[§]Noninferiority of glycopyrronium to tiotropium was demonstrated if the lower limit of the 95% confidence interval lies above –0.050 l.
COPD: Chronic obstructive pulmonary disease; $FEV_1$: Forced expiratory volume in 1 s; FVC: Forced vital capacity; GLY: Glycopyrronium; IC: Inspiratory capacity; IND: Indacaterol; LSM: Least squares mean; NS: Not significant; PBO: Placebo; SE: Standard error; TIO: Tiotropium.

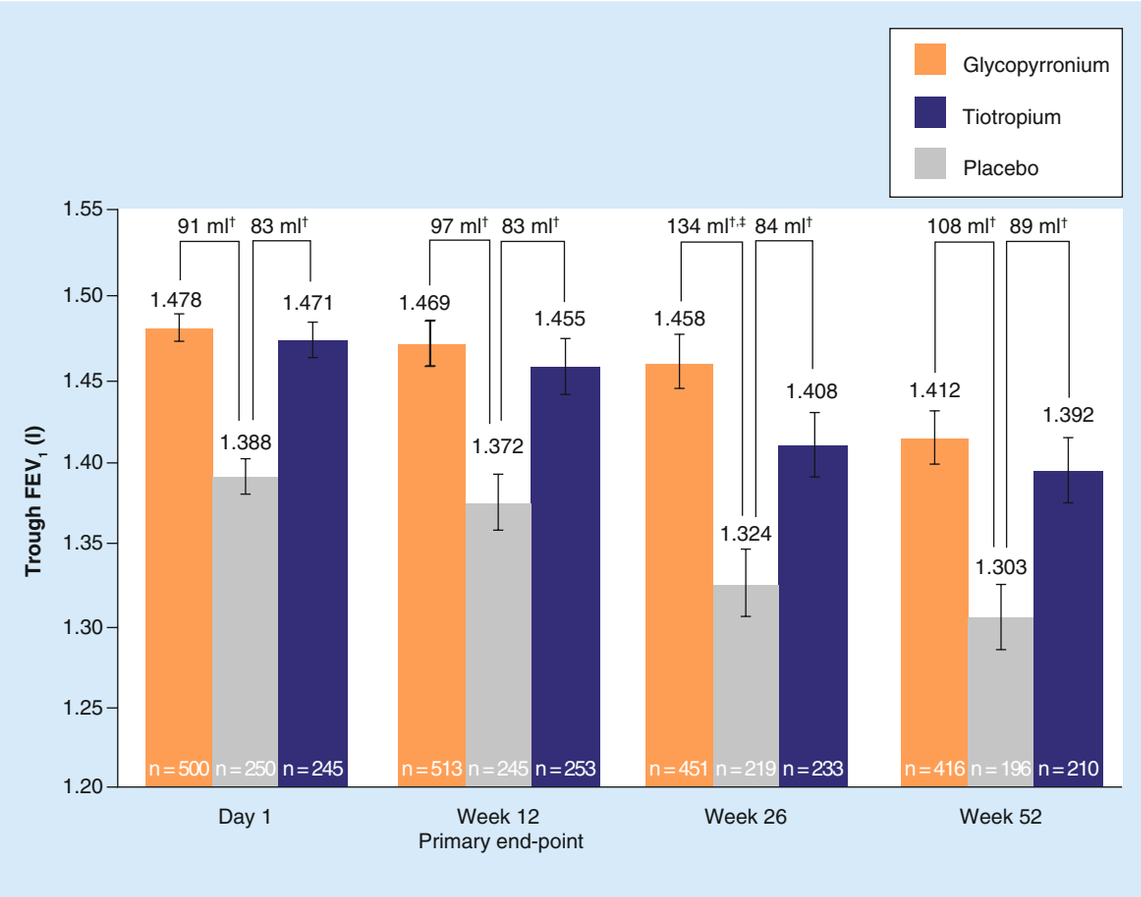


**Figure 1. Trough forced expiratory volume in 1 s at day 1 and at weeks 12 (primary end-point), 26 and 52 in GLOW2.** †p < 0.001 versus placebo; ‡p < 0.007 versus tiotropium.
$FEV_1$: Forced expiratory volume in 1 s.
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increase (p < 0.001) (Figure 4). A smaller but significant 10% improvement with glycopyrronium versus placebo was observed on the first day of treatment (43 s; p < 0.001). Both resting and dynamic IC were significantly increased, along with other measures of hyperinflation (including functional residual capacity, residual volume and total lung capacity). Glycopyrronium was superior to placebo in decreasing leg discomfort (Borg leg discomfort score) on day 21 and exertional dyspnea (modified Borg dyspnea score) on days 1 and 21.

## Concurrent treatment with glycopyrronium & LABA

The GLOW6 study [16] signals the way forward to what is likely to become a standard treatment for patients with COPD who require more than a single bronchodilator: the combination of LAMA and LABA. While the advantages of combining bronchodilators from different pharmacological classes have long been exploited with the use of combined short-acting bronchodilators (SAMA+SABA), the fixed-dose combination of two once-daily bronchodilators is a recent development [26]. GLOW6 evaluated concurrent administration of glycopyrronium and the once-daily LABA indacaterol (via separate inhalers) versus indacaterol (with concurrent placebo) in a 12-week study.

Concurrent treatment increased trough $FEV_1$ at week 12 (primary variable) and day 1, with significant improvements in $FEV_1AUC_{0–4h}$ at the same time points. Compared with indacaterol alone, concurrent treatment improved dyspnea (0.5-point difference in TDI total score) and the likelihood of achieving the MCID in the TDI total score. The difference in health status, measured using the COPD-specific version of the St George's Respiratory Questionnaire (SGRQ-C) [27], was not significant. Raw mean (not baseline-adjusted) data suggested that the change from baseline in SGRQ-C exceeded the MCID with both treatments (–6.22 units with glycopyrronium and indacaterol; –4.13 units with indacaterol alone).

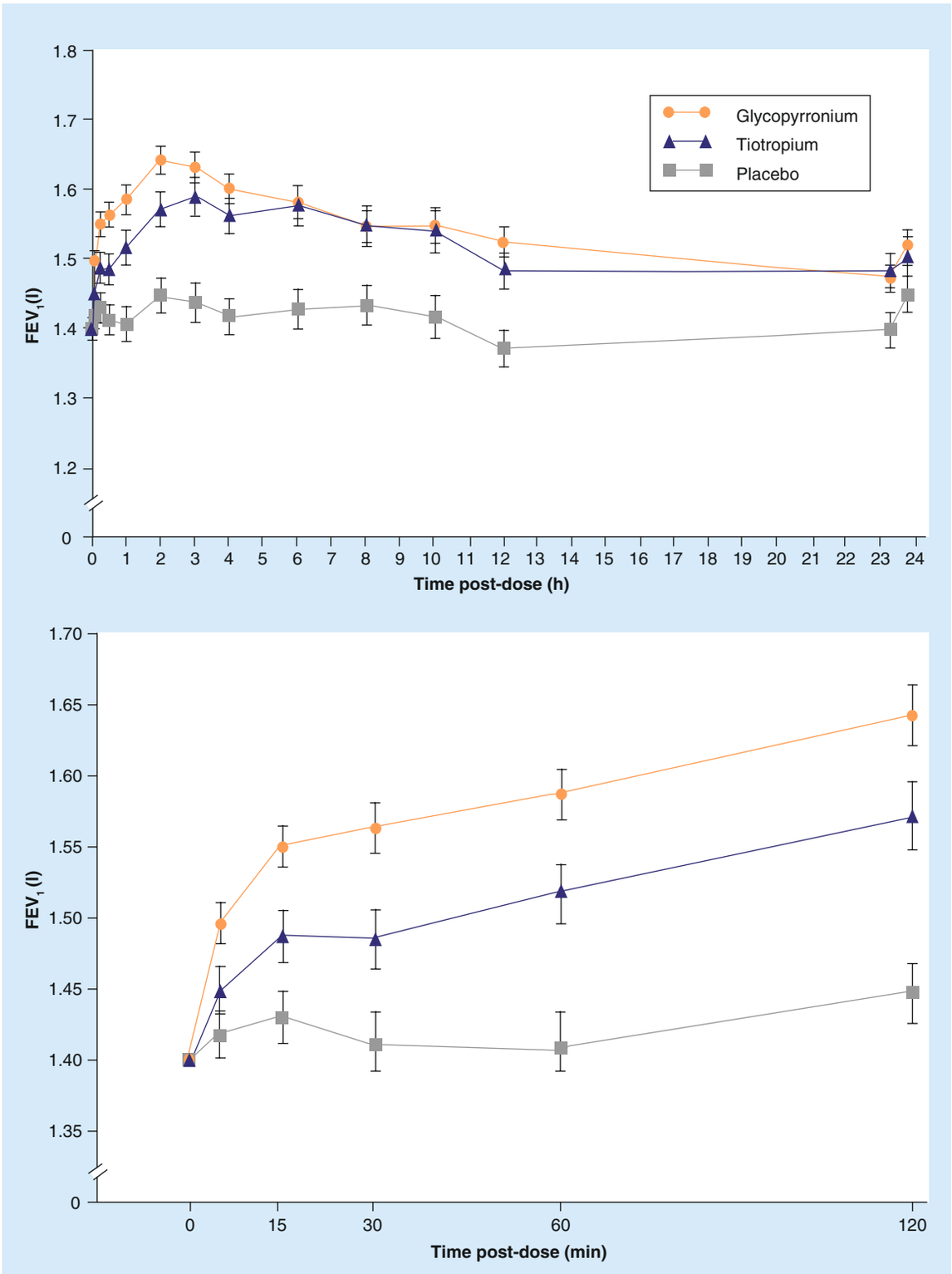


**Figure 2. Forced expiratory volume in 1 s measured during the 24-h post-dose in GLOW2 in the subgroup of patients who had serial spirometry measurements (approximately a third of total) at day 1.** Glycopyrronium versus placebo $p < 0.01$ at all time points. Lower panel shows expanded view of data at 0–2 h; glycopyrronium versus tiotropium, $p < 0.05$ at 5, 15 and 30 min, 1 and 2 h.
$FEV_1$: Forced expiratory volume in 1 s.
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### Safety & tolerability

No new statistical analysis with the safety data was planned or performed for the present publication. This review presents data from the combined safety database [28], which represents the most recent exercise in pooling the glycopyrronium safety data. This database includes data from GLOW1, GLOW2 and GLOW3, together with three Phase II studies [8–10] providing data from another 501 patients with COPD.

The overall incidence of adverse events, adjusted for exposure, was similar with glycopyrronium and tiotropium and numerically highest with placebo (Table 5). The table also lists the most common individual adverse events in each of the treatment groups. Potential anticholinergic adverse events such as dry mouth and urinary tract infection occurred in fewer than 2% of patients in the glycopyrronium and placebo groups, and in 6% of patients receiving tiotropium.

The overall incidence of serious adverse events was numerically highest in the placebo treatment group (Table 6). The most common individual serious adverse event in all treatment groups was COPD worsening (event rates per 100 patient-years were glycopyrronium 4.2; placebo 8.6; tiotropium 6.1), followed by pneumonia (glycopyrronium 1.5; placebo 2.6; tiotropium 1.7).

Major cardiovascular adverse events were rare and occurred at a similar incidence in the three treatment groups (Table 7). There were no clinically meaningful changes in ECGs across the treatment groups (data not shown).

The combined safety database described above does not include GLOW4, GLOW5 and GLOW6. GLOW5 was the 12-week, blinded comparison of glycopyrronium (n = 327) and tiotropium (n = 330). Results supported the previous open-label comparisons, with similar rates of adverse events (glycopyrronium, 40.4%; tiotropium, 40.6%) and serious adverse events (3.4 and 3.9%). Dry mouth was similar with tiotropium (five patients, 1.5%) and with glycopyrronium (one patient, 0.3%). The cardio- and cerebrovascular safety profiles of the two treatments were comparable, including the results of ECG evaluations [15].

Safety was a primary objective of GLOW4, the 52-week study in Japanese patients with moderate-to-severe COPD treated with glycopyrronium (n = 123) or open-label tiotropium (n = 40) [14]. The safety and tolerability profiles of the two treatments proved similar, with an overall adverse event rate of 82.9% with glycopyrronium and 82.5% with tiotropium. Some typically anticholinergic-mediated events had small numerical variations between the glycopyrronium and tiotropium treatments (constipation, 4.9 vs 7.5%; dry mouth, 1.6 vs 5.0%, respectively).

In GLOW6, the comparison of concurrent glycopyrronium and indacaterol with indacaterol alone, the investigators reported that there were no clinically significant differences in the safety and tolerability profiles of the two treatment approaches.

## Discussion

The GLOW program demonstrated the bronchodilator efficacy of glycopyrronium 50 µg once daily via the Breezhaler® device, with 24-h bronchodilation maintained over treatment periods of up to 1 year. Glycopyrronium and tiotropium (18 µg once daily via the HandiHaler® device) had similar effects on trough $FEV_1$, and the results of the 12-week blinded comparison confirmed the previous findings of the 12-month comparison with open-label tiotropium. In terms of distinguishing the two LAMAs, it appears that glycopyrronium may have the faster onset of action.

Glycopyrronium was consistently superior to placebo in its early (up to 4 h) bronchodilator effect following morning dosing throughout the study treatment periods. Effective bronchodilation during this time may help reduce the dyspnea that limits patients' ability to undertake activities. The morning is a difficult time for many patients with COPD, who often struggle with their activities [29] and find that symptoms are more troublesome in the morning than at other times of day [30,31]. Morning symptoms in particular have been associated with an increased risk of exacerbations [32].

The GLOW studies showed that glycopyrronium provided significant bronchodilation on the first day of treatment, from 5 min post-dose (for $FEV_1$) or 25–30 min post-dose (the first IC measurement) to the trough effect at 24 h. An early onset of effect was also demonstrated in the exercise tolerance study, GLOW3, in which improved exercise tolerance was observed on day 1 of glycopyrronium treatment. This was associated with a reduction in dynamic hyperinflation, as shown by the significant increase in IC at isotime versus placebo on day 1. COPD patients who can improve their ability to exercise are more likely to have better health status and functional status [33]. Physical inactivity, on the other hand, is associated with adverse clinical outcomes, including hospitalization and all-cause mortality [34,35]. Increasing activity levels is an important goal of COPD management and could lead to improved long-term outcomes [36]. By removing the limitations that hyperinflation and dyspnea put upon exercise capacity, optimal bronchodilation (as recommended in the context of pulmonary rehabilitation programs) should allow patients to exercise their peripheral muscles to a greater extent, with the aim of a greater overall improvement in exercise performance [37].

Table 4. Efficacy of glycopyrronium on symptoms, health status, use of rescue medication and exacerbations in GLOW1, GLOW2, GLOW5 and GLOW6.

| | GLOW1 | GLOW2 | | GLOW5 | GLOW6 |
|---|---|---|---|---|---|
| Treatment difference | GLY vs PBO | GLY vs PBO | GLY vs TIO open-label | GLY vs TIO blinded | GLY+IND vs PBO+IND |
| Trial duration (weeks) | 26 | 52 | 52 | 12 | 12 |
| TDI total score difference at final time point | 1.04 ± 0.235 p < 0.001 | 0.57 ± 0.276 p < 0.05[†] | –0.08 ± 0.269 p = NS | –0.19 (–0.61, 0.24) p = NS | 0.49 (0.03, 0.96) p = 0.037 |
| Patients with ≥1-point increase in TDI at final time point,% | 61.3 vs 48.3 OR 1.74 p = 0.001 | 54.3 vs 44.0 OR 1.54, p = 0.015[†] | 54.3 vs 53.8 OR 0.97, p = NS | 58.6 vs 58.6 OR 1.06, p = NS | 76.3 vs 62.2 OR 1.97, p = 0.004 |
| SGRQ total score at final time point | –2.81 ± 0.961 p = 0.004 | –3.32 ± 1.004 p < 0.001 | –0.48 ± 1.002 p = NS | 0.65 (–1.19, 2.50) p = NS | –1.47 (–3.42, 0.48) p = NS (SGRQ-C) |
| Patients with ≥4-unit decrease in SGRQ at final time point,% | 56.8 vs 46.3 OR 1.58, p = 0.006 | 54.3 vs 50.8 OR 1.18, p = NS | 54.3 vs 59.4 OR 0.84, p = NS | 55.2 vs 54.0 OR 1.11, p = NS | 56.5 vs 46.8, OR 1.43, p = NS |
| Average change from baseline in rescue medication use, puffs per day | –0.46 ± 0.164 p = 0.005 | –0.37 ± 0.181 p < 0.05 | 0.25 ± 0.181 p = NS | 0 (–0.3, 0.3) p = NS | –0.1 (–0.5, 0.2) p = NS |
| Time to first moderate or severe COPD exacerbation, HR (95% CI) | 0.69 (0.500, 0.949) p = 0.023 | 0.66 (0.520, 0.850) p = 0.001 | 1.09 (0.833, 1.417) p = NS | 1.33 (0.76–2.33)[‡] p = NS | – |
| Rate of moderate or severe exacerbation, rate ratio (95% CI) | 0.72 (0.503, 1.029) p = NS (0.071) | 0.66 (0.496, 0.869) p = 0.003 | 0.82 (0.614, 1.085) p = 0.161 | 1.10 (0.62, 1.93) p = NS | – |
| Daily total symptom score (diary data) | –0.38 ± 0.098[§] p ≤ 0.001 | | 0.06 ± 0.135[§] p = NS | –0.3 (–0.5, 0.0)[#] p = 0.035 | |

All data are LSM ± SE, unless stated otherwise. '–' symbol indicates not applicable (owing to study duration) or variable not recorded.
[†]The effect of glycopyrronium versus placebo on TDI at 26 weeks was the key secondary variable in this study: for TDI total score, the difference was 0.81 ± 0.260 points; p = 0.002. Percentages of patients achieving the MCID were, respectively, 55.3 versus 44.2%; odds ratio 1.58 (95% CI: 1.118, 2.245); p = 0.01.
[‡]This hazard ratio should be interpreted with caution since the proportional hazards assumption was not met.
[§]Pooled 26-week data from GLOW1 and GLOW2 [25].
[#]Difference in change from baseline (12-week data).
CI: Confidence interval; GLY: Glycopyrronium; HR: Hazard ratio; IND: Indacaterol; LSM: Least squares mean; NS: Not significant; OR: Odds ratio; PBO: Placebo; SD: Standard deviation; SGRQ: St George's Respiratory Questionnaire; SGRQ-C: SGRQ for COPD; TDI: Transition Dyspnoea Index; TIO: Tiotropium.

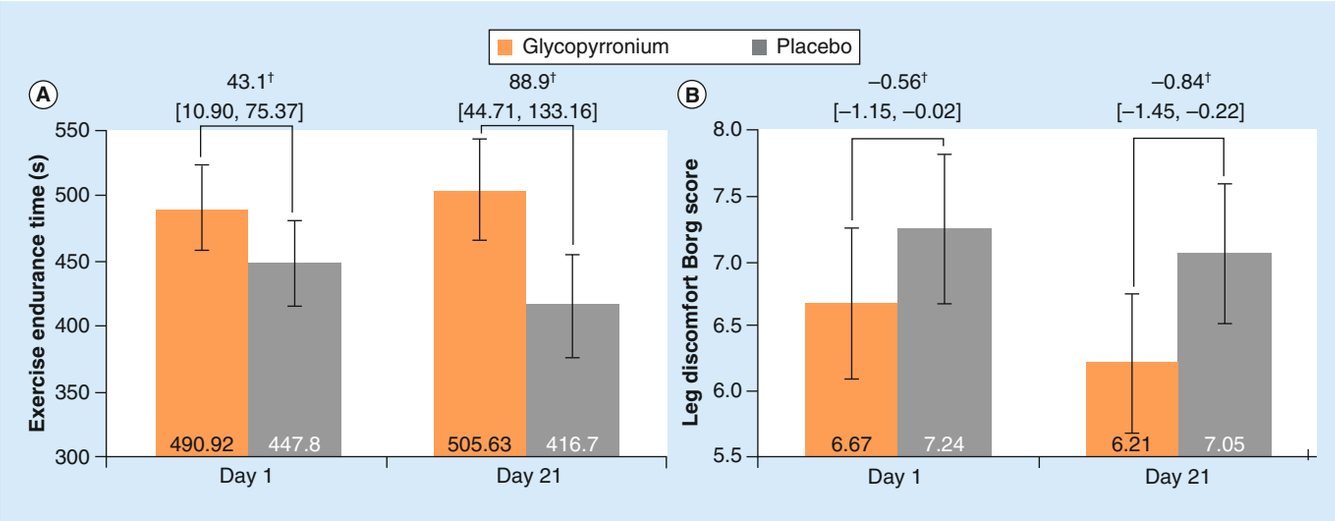


**Figure 3. (A) Exercise endurance and (B) leg discomfort measured at day 1 and day 21 of treatment in GLOW3.** Values are least squares means (95% CI). †p < 0.001 for exercise endurance time and p < 0.05 for leg discomfort.
LSM: Least squares mean.
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Significant improvements in symptom-based outcomes were observed with glycopyrronium treatment in the GLOW series of studies. Glycopyrronium improved dyspnea relative to placebo and patients receiving glycopyrronium were significantly more likely to achieve a clinically important improvement in dyspnea. The reduction in dyspnea was not achieved by increased use of salbutamol for as-needed symptom relief, since a modest but statistically significant reduction of approximately half a puff a day in the use of rescue medication was observed during glycopyrronium treatment versus placebo. Although the patient diaries were a nonvalidated instrument, the data were largely supportive of a positive effect of glycopyrronium on symptoms and related variables such as daily activities and night-time awaken-

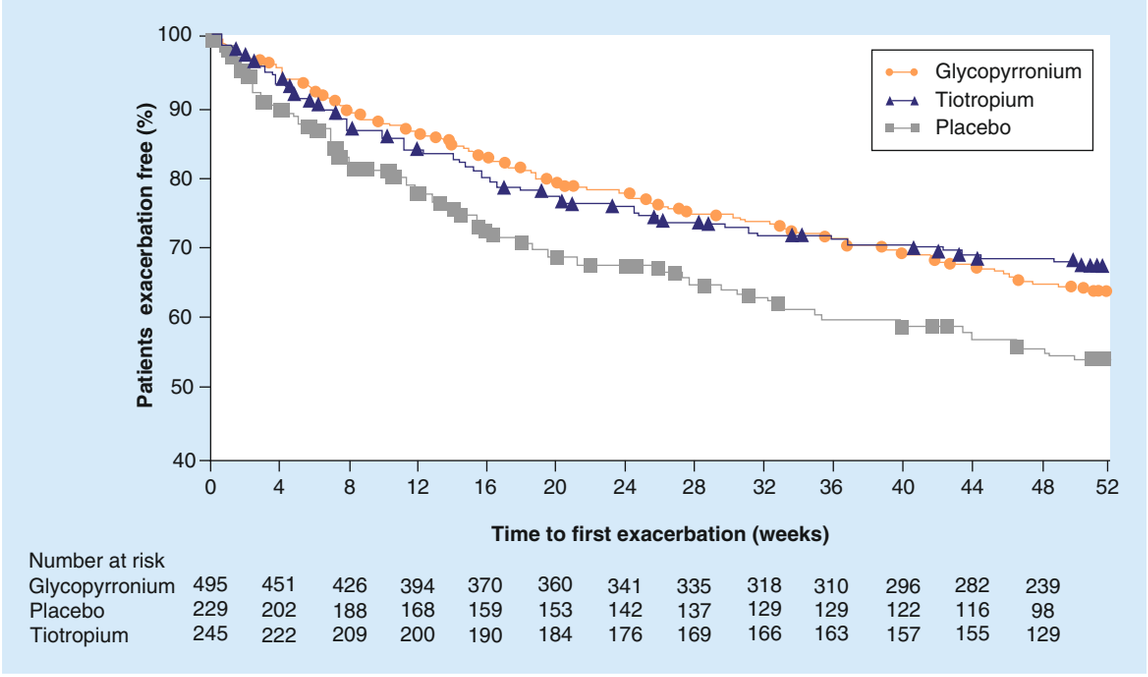


**Figure 4. Kaplan–Meier plot of time to first moderate or severe chronic obstructive pulmonary disease exacerbation in GLOW2.**
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Table 5. Adverse events overall and the 20 most commonly occurring†.

| MedDRA preferred term | Glycopyrronium N = 1353 | Placebo N = 816 | Tiotropium N = 267 |
|---|---|---|---|
| Number of AEs per 100 patient-years | 362.0 | 430.4 | 386.0 |
| Any preferred term, n (%) | 787 (58.2) | 444 (54.4) | 198 (74.2) |
| COPD worsening | 304 (22.5) | 196 (24.0) | 90 (33.7) |
| Nasopharyngitis | 84 (6.2) | 47 (5.8) | 21 (7.9) |
| Upper respiratory tract infection | 80 (5.9) | 55 (6.7) | 30 (11.2) |
| Cough | 50 (3.7) | 31 (3.8) | 12 (4.5) |
| Headache | 46 (3.4) | 34 (4.2) | 12 (4.5) |
| Upper respiratory tract infection bacterial | 45 (3.3) | 41 (5.0) | 21 (7.9) |
| Back pain | 43 (3.2) | 19 (2.3) | 12 (4.5) |
| Dyspnea | 35 (2.6) | 24 (2.9) | 6 (2.2) |
| Sinusitis | 35 (2.6) | 16 (2.0) | 10 (3.7) |
| Hypertension | 33 (2.4) | 18 (2.2) | 14 (5.2) |
| Lower respiratory tract infection | 31 (2.3) | 16 (2.0) | 10 (3.7) |
| Bronchitis | 29 (2.1) | 15 (1.8) | 12 (4.5) |
| Dry mouth | 26 (1.9) | 8 (1.0) | 4 (1.5) |
| Urinary tract infection | 25 (1.9) | 11 (1.3) | 16 (6.0) |
| Diarrhea | 23 (1.7) | 9 (1.1) | 5 (1.9) |
| Pyrexia | 23 (1.7) | 16 (2.0) | 4 (1.5) |
| Pneumonia | 20 (1.5) | 15 (1.8) | 7 (2.6) |
| Arthralgia | 18 (1.3) | 14 (1.7) | 7 (2.6) |
| Influenza | 17 (1.3) | 9 (1.1) | 3 (1.1) |
| Oropharyngeal pain | 16 (1.2) | 11 (1.3) | 2 (0.8) |

†Combined safety database; see text for details [28].
Only AEs reported while on study drug or within 7 days of the last dose are included. A patient with multiple occurrences of an AE was counted only once in the AE category. A patient with multiple adverse events is counted only once in the 'Any preferred term' row.
AE: Adverse event; MedDRA: Medical Dictionary for Regulatory Activities.

ings. The effect on health status (an improvement in SGRQ total score of 3 units vs placebo) was statistically significant, although below the MCID of 4 units. A significant effect versus placebo on the likelihood of patients achieving the MCID was observed in GLOW1, although not in GLOW2. However, large changes from baseline in SGRQ total score, exceeding the MCID, occurred in all three treatment groups in GLOW2, illustrating the substantial placebo response that can occur in clinical studies. No differences were observed between glycopyrronium and tiotropium in their effect on these outcomes in the GLOW series of studies.

Last, but probably most important in terms of an outcome that has prognostic value, glycopyrronium significantly reduced the risk of moderate or severe exacerbations compared with placebo in both the GLOW1 and GLOW2 studies, with a significant 34% reduction in the rate of moderate/severe exacerbations over 1 year in the GLOW2 study. (Results for exacerbations in GLOW5 should be viewed most cautiously since the 12-week treatment duration is far too short to assess an effect on exacerbations, given their typical clustering and seasonal variation [38–40]. A study treatment period of at least 6 months is needed to study exacerbations as an outcome [41].) Frequent exacerbations of COPD are associated with a poor prognosis [42,43] and diminished quality of life [44,45], and severe exacerbations are a major factor in healthcare costs associated with COPD [46]. A patient's exacerbation history is now used as a prognostic factor for their level of risk and, thus, as a guide to the level of treatment required [1]. The protective effect of bronchodilators on exacerbations is likely due to a reduction in hyperinflation (as shown with glycopyrronium in its effect on IC and related lung function variables in the GLOW studies) [47]. An anti-inflammatory effect of LAMA treatment may also play a role, although the potential for such is based largely on preclinical data [48]. LAMAs appear to be more effective than LABAs in reducing exacerbations of COPD [49,50].

Table 6. Serious adverse events overall and those reported in ≥1.5% of any treatment group†.

| MedDRA preferred term | Glycopyrronium N = 1353 | Placebo N = 816 | Tiotropium N = 267 |
|---|---|---|---|
| Number of SAEs per 100 patient-years | 27.4 | 40.0 | 27.3 |
| Total SAEs, n (%) | 111 (8.2) | 70 (8.6) | 40 (15.0) |
| **SAE(s) by system organ class (≥1.5% in any treatment group), n (%)** | | | |
| Respiratory, thoracic and mediastinal disorders | 37 (2.7) | 28 (3.4) | 16 (6.0) |
| Infections and infestations | 27 (2.0) | 22 (2.7) | 14 (5.2) |
| Cardiac disorders | 18 (1.3) | 13 (1.6) | 2 (0.7) |
| Injury, poisoning and procedural complications | 13 (1.0) | 6 (0.7) | 6 (2.2) |

†Combined safety database; see text for details [28].
MedDRA: Medical Dictionary for Regulatory Activities; SAE: Serious adverse event.

The comparisons in the GLOW studies between glycopyrronium 50 µg once daily and tiotropium 18 µg once daily (administered via dry powder inhaler) showed a similar bronchodilator effect on repeated dosing; glycopyrronium had the faster onset on day 1. There were no observed differences between the two bronchodilators in their effects on dyspnea, use of rescue medication, health status and exacerbations. In terms of safety and tolerability, including cardiovascular safety, the GLOW program showed no major differences between glycopyrronium and tiotropium. The overall incidence of anticholinergic class effects with glycopyrronium and tiotropium were generally similar.

As well as its use as a LAMA, glycopyrronium also forms part of the LAMA/LABA fixed-dose combination QVA149 (with indacaterol as the LABA) for the treatment of patients with COPD. Both glycopyrronium and the combination are supplied in the same type of unit-dose dry powder inhaler, providing continuity for those patients already receiving one treatment to progress if necessary to the dual bronchodilator when increased control of symptoms is required, without having to familiarize themselves with a different inhaler. QVA149 has proved to have greater efficacy than either of its components [51,52]. Studies with QVA149 have also provided further evidence of the efficacy and safety of glycopyrronium, for example in the 6-month study of QVA149 that included glycopyrronium, tiotropium and placebo as separate treatment arms [51], and the 64-week study comparing QVA149 with glycopyrronium and tiotropium in patients with severe or very severe COPD [52]. The choice between LAMA and LABA bronchodilators, or between different LAMAs, may depend on physician and patient preference and experience. The type of inhaler device and the patient's ability to use it are important factors to consider, together with the efficacy and safety of treatment.

## Conclusion

As stated in the GOLD strategy document for COPD management, pharmacological therapy is used with the aim of reducing symptoms, reducing frequency

Table 7. Major adverse cardiovascular events (MACE) by preferred term†.

| | Glycopyrronium N = 1353 | Placebo N = 816 | Tiotropium N = 267 |
|---|---|---|---|
| Number of MACE per 100 patient-years | 0.8 | 0.6 | 1.3 |
| Patients with ≥1 MACE, n (%) | 6 (0.4) | 2 (0.2) | 3 (1.1) |
| Cerebrovascular accident | 2 (0.1) | 0 | 1 (0.4) |
| Myocardial infarction | 2 (0.1) | 1 (0.1) | 1 (0.4) |
| Acute myocardial infarction | 1 (<0.1) | 1 (0.1) | 0 |
| Sudden death | 1 (<0.1) | 0 | 0 |
| Hemorrhagic stroke | 0 | 0 | 1 (0.4) |

†Combined safety database; see text for details [28].

and severity of exacerbations and improving health status and exercise tolerance [1]. All these outcomes were included as objectives in the GLOW clinical development program, and all these objectives were successfully met with glycopyrronium for the treatment of patients with moderate-to-severe COPD. The GLOW program of clinical studies demonstrated that the efficacy of glycopyrronium was superior to placebo and similar to tiotropium, and that benefits in lung function and symptoms were obtained when glycopyrronium was added to indacaterol, compared with indacaterol alone. Glycopyrronium had an acceptable safety and tolerability profile compared with placebo and tiotropium.

### Financial & competing interests disclosure

M Miravitlles has received speaker fees from Almirall, Boehringer Ingelheim, Pfizer, AstraZeneca, Chiesi, Esteve, GlaxoSmithKline, Menarini, Talecris-Grifols, Takeda-Nycomed and Novartis, and consulting fees from Almirall, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Gebro Pharma, MedImmune, Novartis, Talecris-Grifols and Takeda-Nycomed. K-M Beeh has received compensation for organizing or participating in advisory boards for Almirall Hermal, Cytos, Chiesi, Boehringer Ingelheim, AstraZeneca, Mundipharma, Novartis and Revotar Biopharmaceuticals, and participated as a speaker in scientific meetings or courses supported by various pharmaceutical companies (Almirall Hermal, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer and Takeda) in the past 3 years. He has received consulting fees from Ablynx, Apellis Pharmaceuticals, Chiesi and Cytos. The institution where KM Beeh is employed has received compensations for the design, performance or participation in single or multicenter clinical trials in the past 3 years from several companies including Almirall, Boehringer Ingelheim, Cytos, GSK, Mundipharma, Novartis, Pfizer, Revotar Biopharmaceuticals, Sterna AG and TEVA. P Altman is an employee of Novartis Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

### Executive summary

- The current pharmacological management strategy for patients with stable chronic obstructive pulmonary disease (COPD) centers on inhaled long-acting bronchodilators. The once-daily inhaled long-acting muscarinic antagonist, glycopyrronium, was approved for use in Europe in September 2012 as Seebri® Breezhaler® inhalation powder. Phase III clinical data supporting this approval was generated in the GLOW (glycopyrronium bromide in COPD airways) series of six clinical studies including a total of 3257 evaluated patients with moderate-to-severe COPD.
- In the GLOW studies, glycopyrronium (50 μg once daily) provided effective 24-h bronchodilation with once-daily dosing over treatment periods of up to 1 year. Compared with placebo and the LAMA tiotropium (18 μg once daily), it had a significant bronchodilator effect within 5 min of the first dose.
- The GLOW studies showed that glycopyrronium improved symptoms and health status and reduced exacerbations compared with placebo; these effects were similar to those seen with tiotropium. Glycopyrronium reduced hyperinflation and increased exercise tolerance time relative to placebo.
- Glycopyrronium had an acceptable profile of safety and tolerability.
- Future investigation of an association between an early post-dose bronchodilator effect and ability to undertake morning and daily activities is warranted.

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