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ORIGINAL RESEARCH

Efficacy and safety of glycopyrrolate in patients with COPD by reversibility: pooled analysis of GEM1 and GEM2 12-week studies

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Purpose: Bronchodilator reversibility has been reported in patients with COPD, although correlations between reversibility and treatment response are unclear. The effect of reversibility on lung function, health status, and dyspnea was assessed in patients with moderate-to-severe COPD receiving glycopyrrolate (GLY) 15.6 µg twice daily vs placebo in the Glycopyrrolate Effect on syMptoms and lung function 1 and 2 (GEM1 and GEM2) replicate, 12-week, placebo-controlled studies.

Patients and methods: Reversibility was defined as a post-bronchodilator increase of ≥12% and ≥0.200 L in FEV_1. FEV_1 area under the curve from 0 to 12 hours ($AUC_{0–12\,h}$), trough FEV_1, St George's Respiratory Questionnaire (SGRQ) total score, COPD Assessment Test (CAT™) score, Transition Dyspnea Index (TDI) focal score, daily symptom scores, and rescue medication use were assessed by reversibility status. Incidences of adverse events and serious adverse events were also assessed.

Results: Data from 846 patients enrolled in GEM1 and GEM2 with known reversibility status were pooled for post hoc analysis. GLY significantly improved FEV_1 $AUC_{0–12\,h}$, trough FEV_1, SGRQ and CAT total scores, and rescue medication use compared with placebo in reversible and nonreversible patients. Significant improvements in TDI focal score and daily symptom scores with GLY over placebo were observed only among reversible patients. Improvements in FEV_1 $AUC_{0–12\,h}$ (0.165 vs 0.078 L; $P<0.001$) and trough FEV_1 (0.173 vs 0.070 L; $P<0.001$) were clinically relevant (based on minimal clinically important differences) and significantly greater in reversible compared with nonreversible patients receiving GLY. The safety profile of GLY was not affected by reversibility status.

Conclusion: In this post hoc analysis, GLY was associated with significant improvements in lung function and patient-reported outcomes compared with placebo, mostly independent of reversibility status. In patients receiving GLY, improvements in lung function were greater in reversible compared with nonreversible patients. Reversibility status did not meaningfully impact the safety profile of GLY.

Keywords: bronchodilator, COPD, glycopyrrolate, reversibility

Introduction

COPD is characterized by progressive airflow limitation that is not fully reversible.[1] However, several studies have shown that many COPD patients demonstrate bronchodilator reversibility.[2–6] Patients may be categorized as reversible or nonreversible based on changes in lung function measured following treatment with a bronchodilator.[2] Bronchodilator reversibility is defined as a ≥12% and ≥0.200 L improvement from baseline in lung function following bronchodilator treatment, as measured by FEV_1.[7]

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Glycopyrrolate (GLY; Seebri® Neohaler®, Sunovion Pharmaceuticals Inc., Marlborough, MA, USA; 15.6 µg twice daily [BID]) is an inhaled long-acting muscarinic antagonist (LAMA) approved in USA for the long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.[8,9] The pivotal, phase III replicate studies, Glycopyrrolate Effect on syMptoms and lung function 1 and 2 (GEM1 and GEM2), demonstrated improvements in lung function and health status compared with placebo following 12 weeks of treatment with GLY 15.6 µg BID, and a safety profile comparable between GLY 15.6 µg BID and placebo.[10,11] A post hoc analysis of pooled data from the GEM1 and GEM2 studies to investigate the efficacy and safety of GLY 15.6 µg BID compared with placebo in patients with moderate-to-severe COPD, categorized according to bronchodilator reversibility status, is reported here. Identification of patients with COPD who may achieve a greater benefit with GLY could be useful in defining an optimal treatment strategy and improving treatment outcomes.

Methods

Study design and treatment

The pivotal GEM1 (NCT01709864) and GEM2 (NCT01715298) studies were replicate, multicenter, double-blind, 12-week, placebo-controlled trials.[10,11] Following a 14-day run-in period, patients received GLY 15.6 µg or placebo via the Neohaler® device for 12 weeks, with a 30-day safety follow-up. Inhaled corticosteroid (ICS) monotherapy at a stable dose was permitted as COPD background therapy and albuterol was used as rescue medication throughout the studies.[10,11]

The study protocols were approved by the Quorum Review, Inc Institutional Review Board for each study center and conducted according to the ethical principles of the Declaration of Helsinki and in compliance with the International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent was obtained before enrollment into either study.

Patients

Patient inclusion and exclusion criteria for GEM1 and GEM2 have been previously reported.[10,11] Patients were included if they had post-bronchodilator (1 hour after inhalation of ipratropium bromide 84 µg) FEV_1 ≥30% and <80% of predicted normal, a FEV_1/FVC ratio <0.70, and modified Medical Research Council grade of ≥2 at the run-in visit. Patients with a history of asthma were excluded.

Post hoc analysis

Reversibility was defined as a post-bronchodilator increase of ≥12% and ≥0.200 L in FEV_1.[7] FEV_1 reversibility was calculated as a percentage increase of FEV_1 after inhalation of short-acting anticholinergic bronchodilators. This analysis compared GLY and placebo in patients grouped by reversibility status, for the following study endpoints: lung function, measured by the change from baseline in FEV_1 area under the curve from 0 to 12 hours (FEV_1 $AUC_{0–12\ h}$) and trough FEV_1 at week 12; changes from baseline in health status score at week 12, measured via the St George's Respiratory Questionnaire (SGRQ) and the COPD Assessment Test™ (CAT); changes in breathlessness over 12 weeks, using the Transition Dyspnea Index (TDI) score; and change from baseline over 12 weeks in symptom burden and rescue medication use, based on data from patient diaries. Safety assessments included in this analysis were the incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs).

Statistical analyses

The full analysis set included all randomized patients who received at least one dose of study drug. Changes from baseline in FEV_1 $AUC_{0–12\ h}$ were analyzed using a mixed model for repeated measures. Changes from baseline in SGRQ total score, CAT total score, rescue medication use, symptom scores, and overall changes in TDI focal score were analyzed using a linear mixed model. SGRQ and TDI responders, the proportions of patients with a reduction in SGRQ total score ≥4 units,[12] or an increase in TDI focal score ≥1 unit[13] (defined as minimum clinically important differences), respectively, were analyzed using logistic regression models. No multiplicity adjustments were made for the post hoc multiple comparisons.

The safety population, which included all patients who received at least one dose of study drug, was used for the analysis of all safety outcomes. Safety data were analyzed using descriptive statistics. AEs were coded according to the Medical Dictionary for Regulatory Activities version 15.1 and summarized by treatment, system organ class, and preferred term. Major adverse cardiovascular events (MACE) were defined as nonfatal myocardial infarction (MI), nonfatal unstable angina, nonfatal stroke, heart failure requiring hospitalization, and coronary revascularization. All potential MACE were reviewed by an independent adjudication committee. Non-MACE serious cardiovascular or cerebrovascular (CCV) AEs were also adjudicated.

All statistical procedures were performed using SAS® version 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics and baseline characteristics

Data from 846 patients enrolled in GEM1 and GEM2 with known FEV_1 reversibility status were pooled for analysis. The mean (SD) FEV_1 reversibility was 20.3% (16.3%) with 49.1% of patients meeting the criteria for reversibility. Of those with reversible lung function (n=415), 209 received GLY and 206 received placebo; of those with nonreversible lung function (n=431), 218 received GLY and 213 received placebo (Table 1).

Patient demographics and baseline characteristics were generally consistent across the reversible and nonreversible subgroups. Reversible patients, when compared with nonreversible patients, were younger and included a greater proportion of males and current smokers (Table 1). In addition, patients in the nonreversible subgroups had more severe and symptomatic COPD, with a greater proportion of patients classified as GOLD stage 3 and GOLD group D (Table 1).[1,14]

Efficacy

Changes from baseline in lung function

At week 12, improvements in lung function, as assessed by FEV_1 $AUC_{0–12\,h}$ and trough FEV_1, were significantly greater

Table 1 Pooled population demographics and baseline characteristics of patients in the GEM1 and GEM2 studies by bronchodilator reversibility (FAS)

Characteristic	Reversible (n=415)		Nonreversible (n=431)	
	GLY 15.6 µg BID (n=209)	Placebo (n=206)	GLY 15.6 µg BID (n=218)	Placebo (n=213)
Age, years, median (range)	61.0 (43–83)	61.0 (43–87)	65.0 (44–86)	65.0 (41–84)
Male, n (%)	128 (61.2)	128 (62.1)	117 (53.7)	120 (56.3)
Race, n (%)				
Caucasian	200 (95.7)	180 (87.4)	189 (86.7)	185 (86.9)
Black	6 (2.9)	22 (10.7)	21 (9.6)	22 (10.3)
Other[a]	3 (1.4)	4 (1.9)	8 (3.7)	6 (2.8)
Duration of COPD, years, mean (SD)	6.6 (4.71)	6.7 (5.02)	6.8 (4.95)	7.2 (5.62)
COPD severity (GOLD stage based on GOLD 2011),[18] n (%)[b]				
Moderate (GOLD 2)	149 (71.3)	146 (70.9)	124 (56.9)	119 (55.9)
Severe (GOLD 3)	60 (28.7)	59 (28.6)	94 (43.1)	94 (44.1)
Combined assessment of COPD (GOLD classification based on GOLD 2011),[18] n (%)[c]				
GOLD B	143 (68.4)	137 (66.5)	122 (56.0)	112 (52.6)
GOLD D	65 (31.1)	68 (33.0)	96 (44.0)	101 (47.4)
COPD exacerbations in previous year, n (%)				
0	170 (81.3)	155 (75.2)	170 (78.0)	159 (74.6)
1	33 (15.8)	38 (18.4)	39 (17.9)	39 (18.3)
≥2	6 (2.9)	13 (6.3)	9 (4.1)	15 (7.0)
Smoking status, n (%)				
Ex-smoker	77 (36.8)	69 (33.5)	105 (48.2)	111 (52.1)
Current smoker	132 (63.2)	137 (66.5)	113 (51.8)	102 (47.9)
Estimated number of pack years, mean (SD)	53.9 (27.75)	55.0 (28.04)	50.2 (23.85)	50.8 (24.69)
ICS use at baseline, n (%)	59 (28.2)	69 (33.5)	59 (27.1)	61 (28.6)
FEV_1, L, mean (SD)	1.65 (0.50)	1.63 (0.48)	1.40 (0.50)	1.43 (0.52)
FEV_1, % predicted, mean (SD)	56.3 (12.1)	56.9 (12.4)	52.8 (13.9)	52.9 (13.7)
FEV_1/FVC, %, mean (SD)	51.4 (10.3)	51.2 (9.5)	51.3 (10.9)	50.6 (11.2)
FEV_1 reversibility, %, mean (SD)	29.0 (13.1)	32.2 (19.8)	10.4 (7.0)	10.2 (7.0)

Notes: [a]Native American, Asian, and other. [b]One patient treated with placebo in the reversible subgroup was classified as GOLD stage 1. [c]One patient treated with GLY and one treated with placebo in the reversible subgroup were classified as GOLD group A.

Abbreviations: BID, twice daily; FAS, full analysis set; GLY, glycopyrrolate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; GEM1 and GEM2, Glycopyrrolate Effect on syMptoms and lung function 1 and 2.

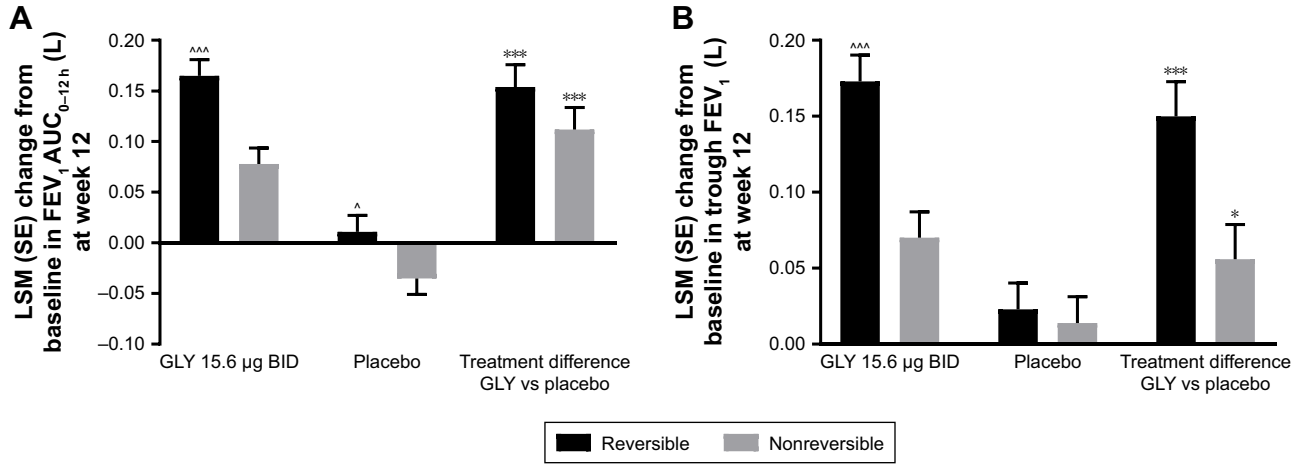

Figure 1 LSM change from baseline in (**A**) FEV_1 $AUC_{0–12\,h}$ and (**B**) trough FEV_1 at week 12 by bronchodilator reversibility status (FAS).
Notes: *$P<0.05$; ***$P<0.001$ GLY vs placebo; ^$P<0.05$; ^^^$P<0.001$ vs nonreversible subgroup.
Abbreviations: $AUC_{0–12\,h}$, area under the curve from 0 to 12 hours; BID, twice daily; FAS, full analysis set; GLY, glycopyrrolate; LSM, least squares mean; SE, standard error.

in patients treated with GLY than in those receiving placebo, regardless of reversibility status (Figure 1). Improvements in FEV_1 $AUC_{0–12\,h}$ were significantly greater among reversible patients compared with nonreversible patients, both in patients treated with GLY and those treated with placebo (Figure 1A). Similarly, improvements in trough FEV_1 were significantly greater among reversible patients compared with nonreversible patients, although only in patients treated with GLY (Figure 1B).

In patients using background ICS, improvements in trough FEV_1 were significantly greater in patients treated with GLY than in those treated with placebo, regardless of reversibility status. In patients not using background ICS, improvements in trough FEV_1 were significantly greater in patients treated with GLY than in those treated with placebo only among reversible patients (Table S1). Interestingly, improvements in trough FEV_1 with GLY were significantly greater among reversible patients compared with nonreversible patients with no background ICS use, but not with background ICS use.

Change from baseline in SGRQ and CAT total scores

At week 12, improvements in SGRQ total scores were significantly greater in patients treated with GLY than in those treated with placebo, regardless of reversibility status (Figure 2A). Improvements in SGRQ total scores were not significantly different between reversible and nonreversible

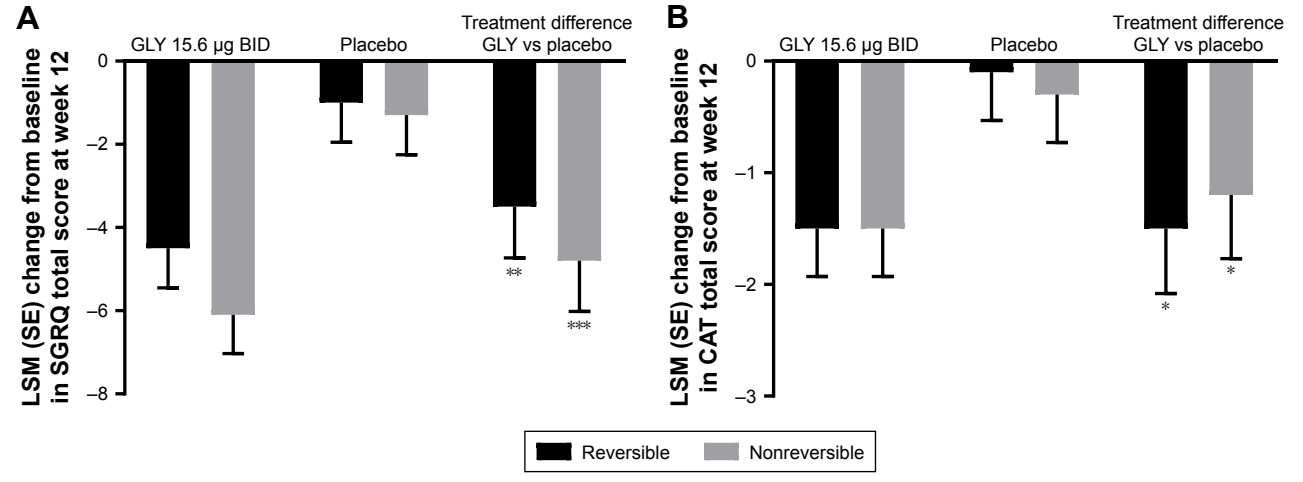

Figure 2 LSM change from baseline in (**A**) SGRQ and (**B**) CAT total scores at week 12 by bronchodilator reversibility status (FAS).
Notes: *$P<0.05$; **$P<0.01$; ***$P<0.001$ GLY vs placebo.
Abbreviations: BID, twice daily; CAT, COPD assessment test; FAS, full analysis set; GLY, glycopyrrolate; LSM, least squares mean; SE, standard error; SGRQ, St George's Respiratory Questionnaire.

patients. The odds of being an SGRQ responder were similar between treatment groups in the reversible subgroup (GLY, 45.9%; placebo, 42.5%; OR [95% CI]: 1.20 [0.79, 1.81], *P*=0.398), but were significantly greater in patients receiving GLY vs placebo in the nonreversible subgroup (GLY, 56.6%; placebo, 38.4%; OR [95% CI]: 2.15 [1.42, 3.26], *P*<0.001). In patients treated with GLY, the odds of being an SGRQ responder were numerically lower among reversible vs nonreversible patients (OR [95% CI]: 0.656 [0.43, 0.99], *P*=0.046).

Reductions from baseline in CAT total scores were also significantly greater in patients treated with GLY than in those treated with placebo, regardless of reversibility status (Figure 2B). Reductions in CAT total scores were not significantly different between reversible and nonreversible patients.

TDI focal score

At 12 weeks, TDI focal scores were clinically and significantly greater with GLY vs placebo in reversible patients, but not in nonreversible patients (Figure 3).[13] While TDI focal scores were significantly greater in nonreversible patients than in reversible patients receiving placebo, no such differences were observed among patients treated with GLY (Figure 3).

The odds of being a TDI responder were significantly greater with GLY vs placebo in the reversible subgroup (GLY, 54.5%; placebo, 36.2%; OR [95% CI]: 2.36 [1.54, 3.62], *P*<0.001), but were similar between GLY and placebo in the nonreversible subgroup (GLY, 51.8%; placebo, 45.7%; OR [95% CI]: 1.20 [0.78, 1.84], *P*=0.410). Reversible and nonreversible patients treated with GLY had similar odds of being a TDI responder (OR [95% CI]: 1.21 [0.79, 1.84], *P*=0.389).

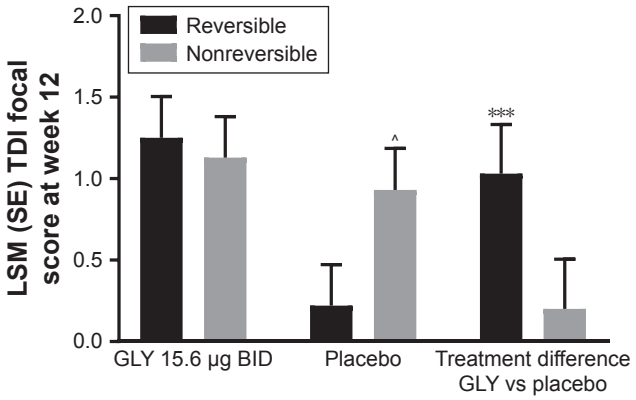

Figure 3 LSM TDI focal score at week 12 by bronchodilator reversibility status (FAS).
Notes: ***P<0.001 GLY vs placebo; ^P<0.05 vs reversible subgroup.
Abbreviations: BID, twice daily; FAS, full analysis set; GLY, glycopyrrolate; LSM, least squares mean; SE, standard error; TDI, Transition Dyspnea Index.

Change from baseline in mean total symptom scores

At 12 weeks, decreases from baseline in mean daily total symptom scores were significantly greater in patients treated with GLY than in those treated with placebo among reversible patients, but not among nonreversible patients (Figure 4A). Improvements in daytime symptoms were significantly greater with GLY vs placebo, regardless of reversibility status (Figure 4B), whereas improvements in nighttime symptoms were only significantly greater with GLY vs placebo among reversible patients (Figure 4C). Of the symptoms assessed, improvements in breathlessness were significantly greater with GLY vs placebo among both reversible and nonreversible patients (*P*<0.001 and *P*<0.05, respectively), whereas improvements in cough (*P*=0.797 and *P*=0.295, respectively) and sputum production (*P*=0.089 and *P*=0.254, respectively) were not significantly different between GLY and placebo. Improvements in daily symptom scores were not significantly different between reversible and nonreversible patients (Figure 4).

Change from baseline in rescue medication use

Reductions from baseline in the number of daily puffs of rescue medication were significantly greater in patients treated with GLY than in those treated with placebo, regardless of reversibility status (Figure 5A); reductions in daytime and nighttime rescue medication use were comparable to reductions in daily rescue medication use (Figure 5B and C). Percentages of days with no rescue medication use were significantly higher with GLY vs placebo in reversible patients, but not in nonreversible patients (Figure 5D). Reversible patients treated with GLY had a significantly greater number of days with no rescue medication use than nonreversible patients treated with GLY (Figure 5D).

Safety

AEs and SAEs

The incidence of AEs was similar between treatment groups, irrespective of reversibility status (Table 2). AEs were reported by 48.1% of patients treated with GLY in the reversible subgroup and 47.3% of patients receiving GLY in the nonreversible subgroup. COPD worsening was the most common AE, with a similar incidence between treatment arms and reversibility subgroups (reversible: GLY 16.5%, placebo 19.0%; nonreversible: GLY 14.9%, placebo 16.4%). The number of patients with at least one SAE was similar

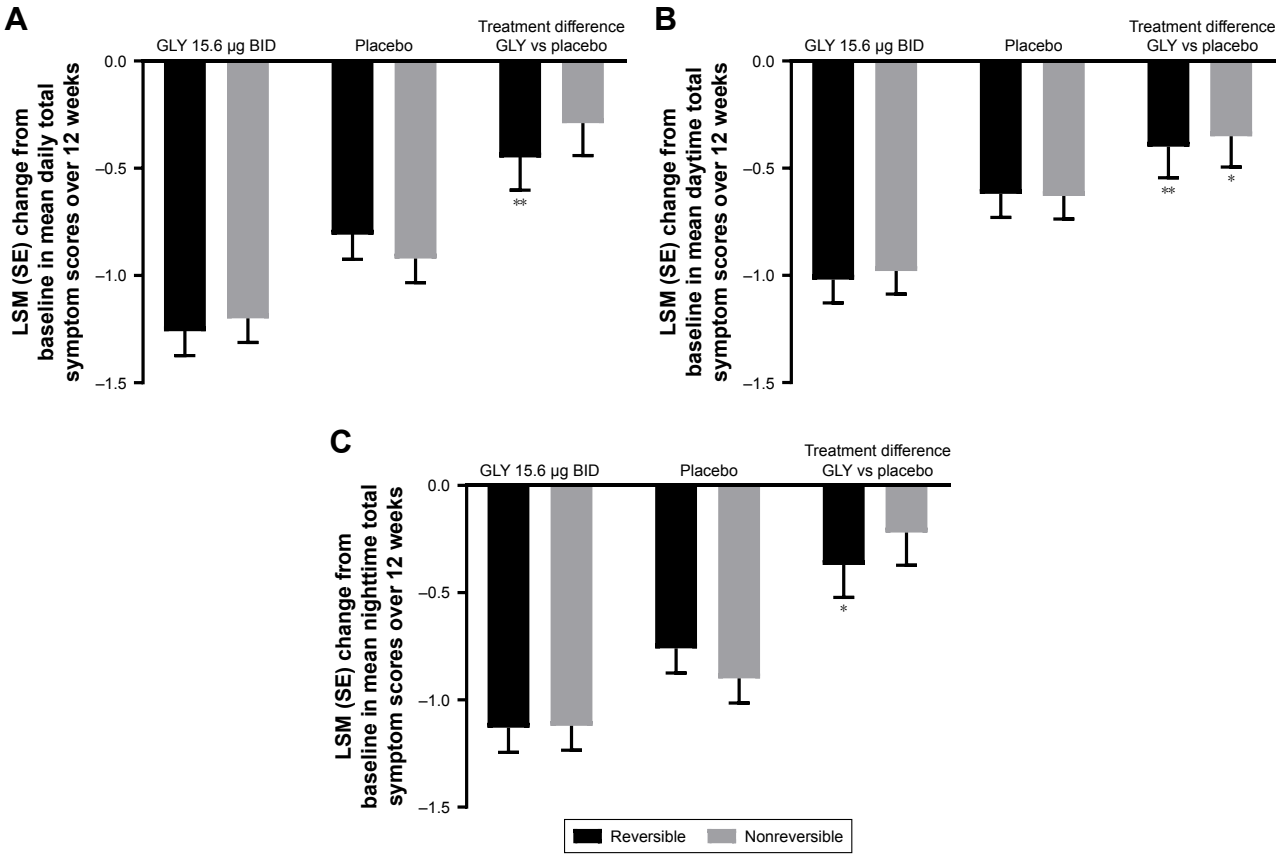

Figure 4 Pooled analysis of mean total (**A**) daily, (**B**) daytime, and (**C**) nighttime symptom scores over 12 weeks by bronchodilator reversibility status (FAS).
Notes: *$P<0.05$; **$P<0.01$ vs placebo.
Abbreviations: BID, twice daily; FAS, full analysis set; GLY, glycopyrrolate; LSM, least squares mean; SE, standard error.

between patients receiving GLY and those receiving placebo (reversible: GLY 5.3%, placebo 4.4%; nonreversible: GLY 4.1%, placebo 3.3%).

Serious CCV AEs and MACE

The incidence of CCV AEs was similar between treatment groups in both reversible and nonreversible patients (reversible: GLY n=3 [1.5%], placebo n=3 [1.5%]; nonreversible: GLY n=3 [1.4%], placebo n=3 [1.4%]). In the reversible subgroup, there was one MACE in a patient treated with GLY (nonfatal MI), and three among patients receiving placebo (one nonfatal MI, one heart failure requiring hospitalization, and one coronary revascularization). In the nonreversible subgroup, two patients treated with GLY had MACE (two nonfatal MIs), and there were three MACE among patients receiving placebo (one nonfatal stroke, two coronary revascularizations).

In the reversible subgroup there were also two non-MACE serious CCV AEs in each of the GLY and placebo treatment arms, while in the nonreversible subgroup, there was one non-MACE serious CCV AE among patients treated with GLY and two non-MACE serious CCV AEs among patients receiving placebo.

Discussion

Several studies have shown that a considerable proportion of patients with COPD may exhibit clinically significant bronchodilator reversibility.[2–6] A study with the LAMA tiotropium previously found that reversibility status correlated with lung function improvements but did not influence treatment response in terms of health status assessment using SGRQ total score.[5] This post hoc analysis of pooled data from the GEM1 and GEM2 studies showed that, among patients treated with GLY, reversibility was associated with significantly greater improvements in lung function, as assessed by the change from baseline in FEV_1 $AUC_{0–12\,h}$ and trough FEV_1, and some patient-reported outcomes (PROs), such as TDI and the number of days without rescue medication use. The results also showed that treatment with GLY resulted in significant improvements in lung function and PROs compared with

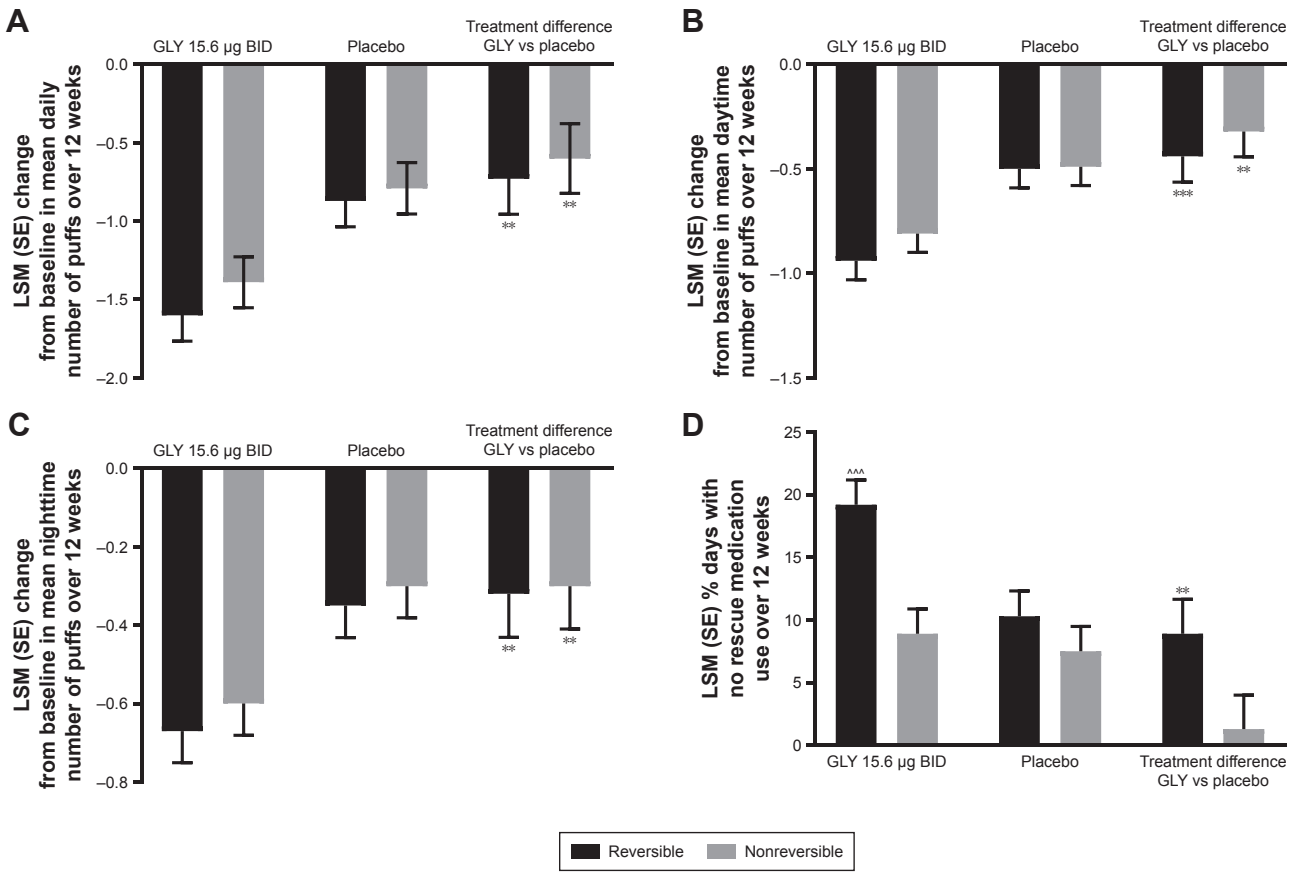

Figure 5 Pooled analysis of change from baseline in (**A**) daily, (**B**) daytime, (**C**) nighttime rescue medication use, and (**D**) days with no rescue medication use over 12 weeks of treatment by bronchodilator reversibility status (FAS).
Notes: **$P<0.01$; ***$P<0.001$ vs placebo; ^^^$P<0.001$ vs nonreversible subgroup.
Abbreviations: BID, twice daily; FAS, full analysis set; GLY, glycopyrrolate; LSM, least squares mean; SE, standard error.

Table 2 Pooled analysis of the most common AEs[a] by bronchodilator reversibility (safety population)

	Reversible (n=415)		Nonreversible (n=431)	
	GLY 15.6 µg BID (n=206)	Placebo (n=205)	GLY 15.6 µg BID (n=222)	Placebo (n=214)
Any AE	99 (48.1)	88 (42.9)	105 (47.3)	88 (41.1)
COPD worsening	34 (16.5)	39 (19.0)	33 (14.9)	35 (16.4)
Cough	5 (2.4)	4 (2.0)	7 (3.2)	7 (3.3)
Oropharyngeal pain	7 (3.4)	3 (1.5)	2 (0.9)	2 (0.9)
Nasal congestion	3 (1.5)	5 (2.4)	1 (0.5)	4 (1.9)
Nasopharyngitis	2 (1.0)	3 (1.5)	6 (2.7)	6 (2.8)
Upper respiratory tract infection	8 (3.9)	3 (1.5)	7 (3.2)	6 (2.8)
Pneumonia	5 (2.4)	0	0	0
Urinary tract infection	1 (0.5)	4 (2.0)	5 (2.3)	1 (0.5)
Headache	5 (2.4)	6 (2.9)	4 (1.8)	6 (2.8)
Back pain	2 (1.0)	0	5 (2.3)	2 (0.9)
Fatigue	0	4 (2.0)	0	0

Notes: Data are presented as n (%). The minor differences in the n values within reversible and nonreversible categories between the FAS and the safety population are due to a slight difference in specifications with regards to rounding, when deriving the reversibility categories. In addition, one patient in the safety population was excluded from the FAS due to a key procedure not being performed per protocol. [a]Occurring in ≥2 patients in either treatment group.
Abbreviations: AE, adverse event; BID, twice daily; FAS, full analysis set; GLY, glycopyrrolate.

placebo, in both reversible and nonreversible patients. Importantly, there were no major differences in the safety profile of GLY between reversible and nonreversible patients.

Improvements in lung function were significantly greater with GLY than placebo, regardless of bronchodilator reversibility, consistent with a previous study of tiotropium.[5] Furthermore, in the current analysis and previous tiotropium study,[5] reversible patients receiving GLY showed a significantly greater improvement in lung function compared with nonreversible patients. These data suggest that achieving greater short-term bronchodilator responses may correlate with greater improvements in lung function with long-term maintenance treatment and highlight the efficacy of long-acting bronchodilators in improving lung function, irrespective of bronchodilator reversibility. Further analyses using different definitions of reversibility may yield additional insight into the impact of reversibility on the efficacy of long-acting bronchodilators in patients with COPD.

A retrospective analysis of >23,000 patients with COPD from 23 clinical trials showed that post-bronchodilation FEV_1 improvements correlated with improvements in PROs.[14] However, a study with tiotropium showed that patient reversibility status did not affect the improvements observed in SGRQ total score.[5] In this analysis, improvements in health status, as measured by SGRQ and CAT total scores, were significantly greater in patients receiving GLY than in those receiving placebo regardless of bronchodilator reversibility status. There were no differences in improvements in SGRQ or CAT total scores between reversible and nonreversible patients treated with GLY. The SGRQ responder rates were numerically lower among reversible compared with nonreversible patients receiving GLY, whereas the previous tiotropium study showed similar SGRQ responder rates between reversible and nonreversible patients.[5]

Improvements with GLY over placebo in TDI focal score at 12 weeks were observed among reversible patients but not nonreversible patients. While there were no significant differences in improvements between reversible and nonreversible patients receiving GLY, nonreversible patients receiving placebo showed greater improvements in TDI focal score compared to reversible patients. The reason behind this improved response among nonreversible patients receiving placebo is unclear, and may be due to a placebo effect on breathlessness. Similarly, the TDI responder rate was significantly greater with GLY than placebo in reversible patients, but not in nonreversible patients; the odds of being a TDI responder were not significantly different between reversible and nonreversible patients receiving GLY. These results are not consistent with previous reports that showed significantly greater improvements in TDI focal score in reversible compared with nonreversible patients, and significantly greater TDI responder rate, regardless of reversibility status.[5,14]

Changes in mean daily symptom scores over 12 weeks were significantly greater with GLY over placebo in reversible patients, but not in nonreversible patients. Changes in mean daytime symptoms with GLY were significantly greater than placebo in both reversible and nonreversible patients. This highlights the observed positive effect of treatment with GLY on daytime symptoms, irrespective of reversibility status; this is important, as morning symptoms in COPD are commonly overlooked[15] and often represent patients' worst symptoms of the day.[16] In contrast, changes in mean nighttime symptoms were greater with GLY over placebo in reversible patients only, but not in nonreversible patients. Nighttime symptoms are driven in part by sleep quality,[17] and may have been impacted by the fact that, in the GEM1 and GEM2 studies, patients with sleep apnea were not excluded.[10,11] These results suggest that reversible patients may obtain greater improvements in nighttime symptoms compared with nonreversible patients.

The improvements observed with GLY treatment compared with placebo on rescue medication use were similar regardless of reversibility status, with no significant difference between reversible and nonreversible patients. This is in contrast to a previous study that showed lower rescue medication use in reversible patients compared with nonreversible patients;[5,14] however, the number of days without rescue medication use was significantly higher in reversible compared with nonreversible patients receiving GLY.

The differing results between this analysis and other studies regarding the correlation between reversibility status and PROs may be due to different study durations. This analysis included data from two 12-week studies, whereas the tiotropium study was 12 months in duration.[5,14] Additional long-term studies with GLY are needed to assess the impact of reversibility on PROs over the course of treatment.

There were no differences in the safety profile of GLY in reversible vs nonreversible patients, even though nonreversible patients had more severe disease at baseline. The overall incidence of AEs, SAEs, MACE, and serious CCV AEs was similar across treatments and independent of reversibility status. These results support the tolerability of GLY in patients with moderate-to-severe COPD, independent of their baseline reversibility status.

Conclusion

In this pooled post hoc analysis of data from the GEM1 and GEM2 studies, patients treated with GLY showed significant

improvements in lung function and PROs compared with placebo, irrespective of reversibility status. In addition, reversible patients receiving GLY were associated with greater improvement in lung function and number of days without rescue medication use compared with nonreversible patients. The safety profile of GLY was not affected by patients' reversibility status at baseline. These data support the use of GLY 15.6 µg BID in patients with moderate-to-severe COPD, regardless of bronchodilator reversibility status.

Data sharing statement

Sunovion Pharmaceuticals Inc. is part of a clinical trial data-sharing consortium that facilitates access for qualified researchers to selected anonymized clinical trial data. For up-to-date information on data availability, please visit https://www.clinicalstudydatarequest.com/Study-Sponsors.aspx and click on Sunovion.

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Disclosure

JAO has served on advisory boards for Sunovion Pharmaceuticals Inc., AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Mylan, and Theravance, and has provided expert witness testimony for Wallace & Graham; Levy Konigsberg; Goldenberg Heller & Antognoli; Simon Greenstone Panatier Bartlett; Williams Kherkher Hart; Gori Julian & Associates; Simmons Hanly Conroy; and Elrod Pope. AB, TG, BP, AO-G, SSh, and SSa are employees of Sunovion Pharmaceuticals Inc. The authors report no other conflicts of interest in this work.

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Supplementary material

Table S1 LSM change from baseline in trough FEV_1 (L) by reversibility status and ICS use at baseline (FAS)

	No background ICS use				Background ICS use			
	Reversible		Nonreversible		Reversible		Nonreversible	
	GLY 15.6 µg BID (n=148)	Placebo (n=136)	GLY 15.6 µg BID (n=156)	Placebo (n=149)	GLY 15.6 µg BID (n=59)	Placebo (n=67)	GLY 15.6 µg BID (n=59)	Placebo (n=61)
LSM (SE)	0.190 (0.020)	0.031 (0.021)	0.057 (0.020)	0.013 (0.020)	0.133 (0.030)	0.008 (0.029)	0.109 (0.031)	0.020 (0.031)
LSM difference from placebo (SE)	0.159 (0.028), $P<0.001$		0.044 (0.027), $P=0.100$		0.125 (0.041), $P<0.01$		0.089 (0.043), $P<0.05$	

Abbreviations: BID, twice daily; FAS, full analysis set; GLY, glycopyrrolate; ICS, inhaled corticosteroids; LSM, least squares mean; SE, standard error.