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ORIGINAL RESEARCH

Efficacy and safety of a novel, nebulized glycopyrrolate for the treatment of COPD: effect of baseline disease severity and age; pooled analysis of GOLDEN 3 and GOLDEN 4

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Background: The efficacy and safety of nebulized glycopyrrolate inhalation solution (GLY), administered twice daily (BID) via the innovative eFlow® Closed System nebulizer (PARI Pharma GmbH, Starnberg, Germany), were demonstrated in two replicate, placebo-controlled, 12-week Phase III studies (GOLDEN 3 and GOLDEN 4). This report evaluates the efficacy and safety of GLY by baseline disease severity and age in the pooled GOLDEN 3 and GOLDEN 4 patient population (N=1,294).

Methods: Patients were grouped by baseline predicted post-bronchodilator FEV_1 (<50%, ≥50%) and age (<65, ≥65, ≥75 years).

Results: GLY (25 and 50 µg BID) produced significant improvements in trough FEV_1 in FEV_1% predicted <50% (0.070 L, 0.079 L) and ≥50% (0.112 L, 0.126 L) subgroups ($P<0.01$ vs placebo), and in patients aged <65 (0.056 L, 0.086 L), ≥65 (0.140 L, 0.124 L), and ≥75 (0.144 L, 0.120 L) years ($P<0.05$ vs placebo). St George's Respiratory Questionnaire (SGRQ) total score was significantly improved with GLY 25 and 50 µg BID ($P<0.05$ vs placebo) in FEV_1% predicted <50% (–3.237, –3.061) and ≥50% (–3.392, –2.322) and in <65 years (–3.447, –2.318) and ≥65 years (–3.053, –3.098) subgroups. In patients aged ≥75 years, GLY 25 µg reduced SGRQ total score by –6.278 units ($P<0.01$ vs placebo). The incidence of treatment-emergent adverse events was similar between GLY and placebo across all subgroups, and the overall incidence of cardiovascular events was low.

Conclusions: Nebulized GLY improved lung function and health status and was well tolerated over 12 weeks in patients with moderate-to-very-severe COPD, irrespective of baseline disease severity and age.

Clinical trial registration: NCT02347761, NCT02347774.

Keywords: age, COPD, disease severity, long-acting muscarinic antagonist, LAMA, nebulizer, nebulized glycopyrrolate

Plain language summary

COPD is a debilitating illness that results from limited airflow within the lungs. Patients with COPD have symptoms such as cough and breathlessness. About four of every ten people in the US aged 65 years or older have COPD. Aging is associated with a progressive decline in lung function. This means that older patients can have more severe disease at the time of diagnosis compared with younger patients. Bronchodilators are drugs that open up the airways, help relieve symptoms, and thereby increase the ability to carry out activities of daily living. However, older age and more severe disease can make bronchodilator therapy less effective.

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This may be due to these patients finding it harder to inhale medication (for example, due to muscle weakness or problems with coordination), or having other conditions (such as arthritis or dementia) that may affect the person's ability to use the inhalation device effectively. Nebulized glycopyrrolate is a long-acting bronchodilator belonging to the LAMA (long-acting muscarinic antagonist) class of drugs, and is approved in the US for the long-term treatment of COPD. The drug is delivered through a nebulizer using normal breathing, which may be useful for patients who find it difficult to use other handheld inhalation devices. This analysis found that nebulized glycopyrrolate improved lung function and symptoms across age groups and disease severities, with a good overall safety profile.

Introduction

COPD affects a substantial proportion of older patients, with 35% of those diagnosed in the United States aged ≥65 years.[1,2] Approximately 30% of patients with COPD have severe-to-very-severe airflow limitation at diagnosis.[3,4] Lung function declines with age due to physiologic (eg, reduction in the strength of respiratory muscles) and anatomic (eg, loss of supporting structures in the lung parenchyma) changes in the peripheral airways, with a greater deterioration observed in patients aged >70 years.[5,6] This causes a decrease in FEV_1, which decreases with age to a greater extent than other commonly assessed lung volumes.[7]

Bronchodilators are central to pharmacologic therapy for COPD and are used clinically to relieve symptoms, reduce the frequency and severity of exacerbations, and improve health status.[1] For maintenance bronchodilator monotherapy, long-acting muscarinic antagonists (LAMAs) are preferred over long-acting $beta_2$-agonists (LABAs),[1] as some LAMAs have demonstrated a reduction in exacerbation rate compared with LABAs.[8,9]

Importantly, advanced age and more severe airflow limitation at treatment initiation reduce the effect of bronchodilator therapy,[7,10] and are associated with higher rates of device handling errors.[11] The presence of fewer comorbidities was significantly associated with high physician-reported confidence in inhaler use, which in turn was associated with a more favorable COPD-related health status.[12] The correct use of handheld devices, such as dry powder inhalers and metered dose inhalers, depends on several factors that may be impaired in older patients, including the ability to generate sufficient inspiratory flow, cognitive function, adequate breath/actuation coordination, dexterity, and hand strength.[6,13–17]

Nebulized therapy may be appropriate in patients who have difficulty using handheld devices, as drug administration occurs with normal tidal breathing. Glycopyrrolate inhalation solution (GLY; Lonhala®, Sunovion Pharmaceuticals Inc., Marlborough, MA, USA) 25 µg twice daily (BID) delivered by the innovative eFlow® Closed System nebulizer (Magnair®, PARI Pharma GmbH, Starnberg, Germany) was approved by the US Food and Drug Administration for the long-term maintenance treatment of airflow obstruction in patients with COPD in December 2017.[18] The efficacy and safety was demonstrated by data from the 12-week Phase III Glycopyrrolate for Obstructive Lung Disease Via Electronic Nebulizer (GOLDEN) 3 and GOLDEN 4 studies (NCT02347761 and NCT02347774, respectively).[19] This pooled subgroup analysis assessed the effect of age and disease severity (post-bronchodilator FEV_1% predicted) at baseline on physiologic and symptomatic responses, as measured by lung function, health status, and safety.

Methods

Study design

GOLDEN 3 and GOLDEN 4 (Figure 1) were prospectively designed to enroll patients representative of the general COPD population by including those with very severe

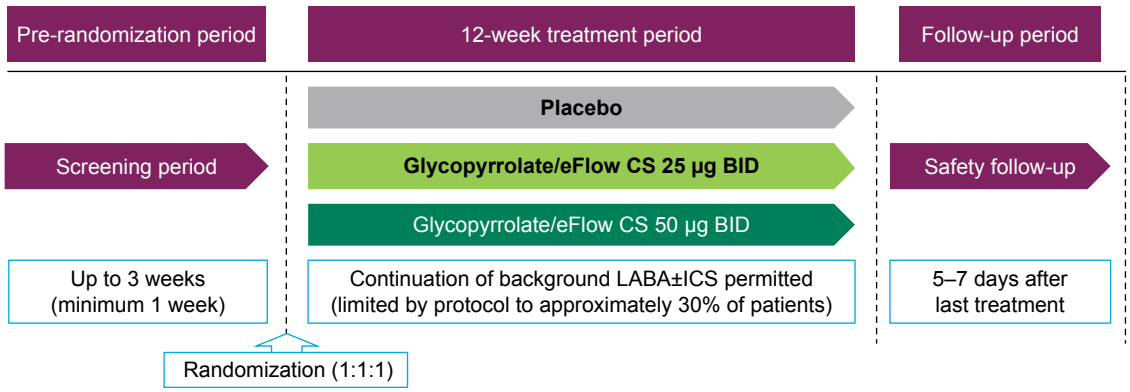

Figure 1 GOLDEN 3 and GOLDEN 4 study designs: 12-week, randomized, double-blind, placebo-controlled, parallel group, multicenter, efficacy and safety studies.
Notes: Data from Kerwin et al.[19]
Abbreviations: BID, twice daily; CS, closed system; ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist.

disease, a history of cardiovascular (CV) risk factors, and continuing background LABA therapy (limited by protocol to approximately 30% of patients), with or without additional inhaled corticosteroid therapy.

Albuterol (salbutamol), as rescue medication, and ipratropium bromide, as supplemental medication, were permitted.

Patients

Briefly, key eligibility criteria, reported previously,[19] included males or females ≥40 years of age, current or ex-smokers with ≥10 pack-year smoking history, a clinical diagnosis of moderate-to-very-severe COPD (as defined by the GOLD 2014 Report),[1] and qualifying post-bronchodilator (ipratropium 68 µg) spirometry (FEV_1 ≤80% of predicted normal, FEV_1 >0.7 L, and FEV_1/forced vital capacity ratio <0.70).

The GOLDEN 3 (SUN101–301: project approval number 28481) and GOLDEN 4 (SUN101–302: project approval number 28482) study protocols were approved by Quorum Review IRB North American (US and Canadian) Board (Panel II) prior to patient enrollment, and were conducted in accordance with the protocols, International Council for Harmonization Good Clinical Practice guidelines, and the Declaration of Helsinki. All patients provided written informed consent.

Efficacy and safety assessments

Subgroup analyses by baseline disease severity and age were prespecified. Intent-to-treat (ITT) and safety populations pooled from GOLDEN 3 and GOLDEN 4 comprised all patients receiving at least one dose of study drug and, for efficacy, one post-dose pulmonary function assessment. Efficacy was assessed in all patients who received double-blind study drug, regardless of their completion status. Treatment effect during the time patients remained on randomized therapy was analyzed (on-treatment data). Patients who discontinued the randomized treatment before week 12 continued to be followed and were analyzed using retrieved dropout data (all collected data). Efficacy and safety analyses were performed on on-treatment and all collected data, and as the primary study results were similar for both datasets,[19] only on-treatment data are presented.

The primary efficacy endpoint was change from baseline trough FEV_1 at week 12. Additional efficacy endpoints included change from baseline health status measured by St George's Respiratory Questionnaire (SGRQ) total score and SGRQ responder rate (defined as a ≥4-unit reduction in SGRQ total score) at week 12.

Treatment-emergent adverse events (TEAEs) were coded according to MedDRA v15.1. CV events of special interest were examined using standardized MedDRA query analysis and included cardiac arrhythmia, arrhythmia-related events, cardiac failure, ischemic heart disease, QT prolongation, and myocardial infarction. Other assessments in the overall population included heart rate, blood pressure, electrocardiogram (ECG), and clinical laboratory measures. Holter monitoring was conducted at visit 0 and at week 12 in a subpopulation (N=153) of GOLDEN 3.

Statistical analysis

Least square (LS) means for the difference between GLY and placebo for FEV_1 were calculated using a mixed model for repeated measures, with change from baseline trough FEV_1 as the response variable, and treatment group, CV risk, background LABA use, visit week, visit-week-by-treatment-group interaction, and baseline FEV_1 as covariates. Change from baseline SGRQ total score at week 12, as the response variable, was assessed by analysis of covariance. ORs and CIs were computed for SGRQ responder rates. No adjustments were made for multiple treatment comparisons in this post hoc analysis. Safety data were analyzed using descriptive statistics.

All statistical procedures were performed using SAS v9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics and baseline characteristics

Overall, 1,111/1,294 (86%) patients randomized (GOLDEN 3, N=653; GOLDEN 4, N=641) completed treatment. The mean age was 63.2 years (range: 40–87 years), and the majority of patients were male (56.0%) and Caucasian (89.6%).

Patient subgroups were defined by baseline post-bronchodilator FEV_1% predicted (<50%: N=555; ≥50%: N=737) and age (<65 years: N=705; ≥65 years: N=588). The ≥75 years age group (N=126), a subgroup of the ≥65 years age group, was analyzed separately.

Background LABA use was higher in patients with FEV_1% predicted <50% compared with those with FEV_1% predicted ≥50%. The proportion of patients with CV risk factors was similar in all FEV_1% predicted subgroups (Table 1). Background LABA use was slightly higher and a greater proportion had existing CV risk factors among patients aged ≥65 years compared with those aged <65 years (Table 2).

Table 1 Patient demographics by post-bronchodilator baseline FEV_1% predicted (ITT population)

FEV_1% predicted	Placebo		GLY 25 µg BID		GLY 50 µg BID	
	<50% (N=177)	≥50% (N=253)	<50% (N=185)	≥50% (N=245)	<50% (N=193)	≥50% (N=239)
Baseline FEV_1, median (range), L	0.930 (0.510–2.045)	1.520 (0.710–3.145)	0.965 (0.475–2.220)	1.493 (0.605–3.225)	0.940 (0.490–2.205)	1.595 (0.690–3.260)
High CV risk	113 (63.8)	165 (65.2)	122 (65.9)	153 (62.4)	119 (61.7)	156 (65.3)
Background LABA use	70 (39.5)	62 (24.5)	74 (40.0)	60 (24.5)	77 (39.9)	58 (24.3)
Age						
<65 years	87 (49.2)	133 (52.6)	91 (49.2)	139 (56.7)	113 (58.5)	141 (59.0)
≥65 years	90 (50.8)	120 (47.4)	94 (50.8)	106 (43.3)	80 (41.5)	98 (41.0)
≥75 years[a]	19 (10.7)	22 (8.7)	17 (9.2)	30 (12.2)	18 (9.3)	20 (8.4)

Notes: Data are presented as N (%) unless otherwise stated. [a]Subset of the ≥65 years subgroup.
Abbreviations: ITT, intent-to-treat; GLY, glycopyrrolate inhalation solution; BID, twice daily; CV, cardiovascular; LABA, long-acting $beta_2$-agonist.

Table 2 Patient demographics by age (ITT population)

Age, years	Placebo			GLY 25 µg BID			GLY 50 µg BID		
	<65 (N=220)	≥65 (N=210)	≥75[a] (N=41)	<65 (N=231)	≥65 (N=200)	≥75[a] (N=47)	<65 (N=254)	≥65 (N=178)	≥75[a] (N=38)
Baseline FEV_1, median (range), L	1.380 (0.545–3.145)	1.190 (0.510–2.435)	1.075 (0.535–2.060)	1.415 (0.530–3.225)	1.130 (0.475–2.760)	1.215 (0.530–1.785)	1.323 (0.490–3.260)	1.165 (0.580–2.645)	1.140 (0.625–2.630)
High CV risk	121 (55.0)	157 (74.8)	36 (87.8)	121 (52.4)	154 (77.0)	34 (72.3)	140 (55.1)	135 (75.8)	30 (78.9)
Background LABA use	50 (22.7)	82 (39.0)	20 (48.8)	66 (28.6)	69 (34.5)	15 (31.9)	74 (29.1)	61 (34.3)	14 (36.8)
Post-bronchodilator FEV_1% predicted[b]									
<50%	87 (39.5)	90 (42.9)	19 (46.3)	91 (39.4)	94 (47.0)	17 (36.2)	113 (44.5)	80 (44.9)	18 (47.4)
≥50%	133 (60.5)	120 (57.1)	22 (53.7)	139 (60.2)	106 (53.0)	30 (63.8)	141 (55.5)	98 (55.1)	20 (52.6)

Notes: Data are presented as N (%) unless otherwise stated. [a]Subset of the ≥65 years subgroup. [b]One post-bronchodilator FEV_1 measurement was missing for a patient aged ≥65 years in the GLY 25 µg BID group.
Abbreviations: ITT, intent-to-treat; GLY, glycopyrrolate inhalation solution; BID, twice daily; CV, cardiovascular; LABA, long-acting $beta_2$-agonist.

The overall use of inhaled respiratory medication prior to the studies was lower in the FEV_1% predicted ≥50% subgroup than the FEV_1% predicted <50% subgroup, with the exception of steroids, which were used by a similar proportion of patients in each subgroup. Proton pump inhibitors were used by a numerically higher proportion of patients with FEV_1% predicted ≥50% compared with FEV_1% predicted <50%.

Prior to entering the studies, the overall use of inhaled long-acting respiratory medications (including steroids) showed numerical increase with increasing age. Generally, short-acting $beta_2$-agonist use was higher in patients aged <65 years compared with older patients, and short-acting muscarinic antagonist use was similar across age groups. Previous use of statins and antiplatelet agents showed an overall increase with age.

Efficacy

GLY 25 µg and 50 µg BID produced significant, clinically important improvements in the primary endpoint of LS mean placebo-adjusted change from baseline in trough FEV_1 at week 12 (0.094 L and 0.104 L, respectively; $P<0.001$). Placebo-adjusted change from baseline in trough FEV_1 with GLY was numerically higher in the FEV_1% predicted ≥50% subgroup (25 µg: 0.112 L; 50 µg: 0.126 L) than in the FEV_1% predicted <50% subgroup (25 µg: 0.070 L; 50 µg: 0.079 L) (Figure 2A). Placebo-adjusted change from baseline in trough FEV_1 with GLY 25 µg and 50 µg was numerically higher in the older age groups (≥65 years: 0.140 L and 0.124 L; ≥75 years: 0.144 L and 0.120 L, respectively) compared with the <65 years subgroup (0.056 L and 0.086 L, respectively) (Figure 2B).

Significant improvements ($P<0.05$) in LS mean SGRQ total score were observed at week 12 in the overall population with GLY 25 µg (–3.710) and 50 µg (–3.078) vs placebo (–0.364).

Improvement in SGRQ total score was observed with GLY in both the <50% and ≥50% FEV_1% predicted subgroups (25 µg: –3.237 and –3.392, $P<0.01$ vs placebo; 50 µg: –3.061 and –2.322, $P<0.05$ vs placebo; Figure 3A). GLY produced significant improvement in placebo-adjusted SGRQ total score in both <65 years and ≥65 years subgroups (25 µg: –3.447 and –3.053, $P<0.01$ and $P<0.05$; 50 µg: –2.318 and –3.098, both $P<0.01$). The minimum clinically important difference, defined as a reduction of ≥4 units in SGRQ total score, was exceeded in the GLY 25 µg ≥75 years subgroup (–6.278; $P<0.01$ vs placebo), but not in the corresponding GLY 50 µg subgroup (–2.441; Figure 3B).

In the FEV_1% predicted <50% subgroup, GLY 50 µg was associated with a significant increase in SGRQ responder rate vs placebo (OR: 1.658; 95% CI: 1.029–2.672), while GLY 25 µg resulted in a significant increase vs placebo in the FEV_1% predicted ≥50% subgroup (OR: 1.730; 95% CI: 1.166–2.567; Figure 4A). Significant improvement in SGRQ responder rate was observed with GLY 25 µg and 50 µg doses in patients aged ≥65 years (1.985; 95% CI: 1.253–3.143 and OR: 2.008; 95% CI: 1.250–3.224 respectively; Figure 4B).

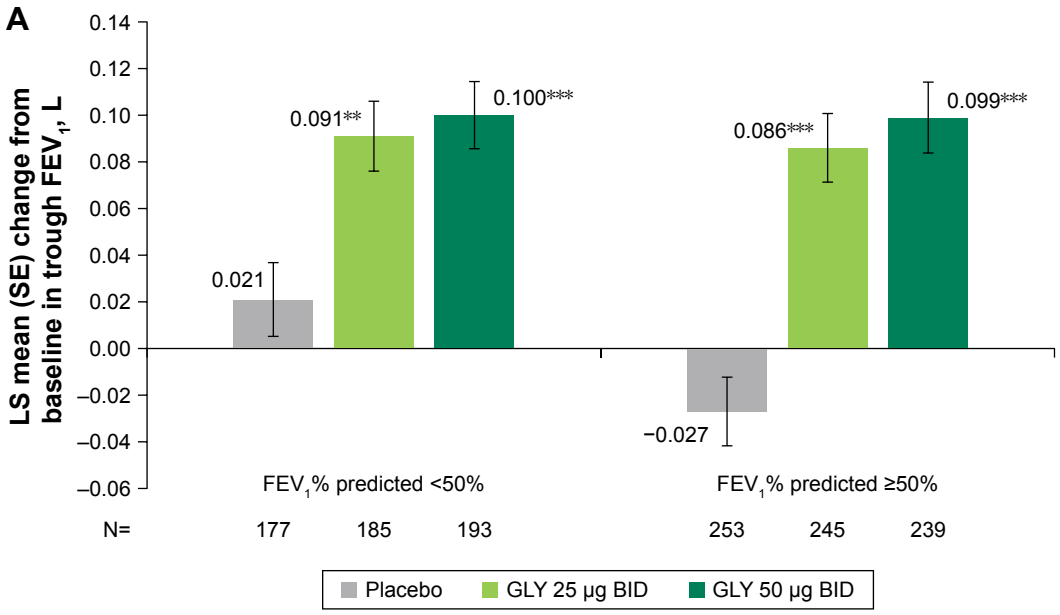

Figure 2 (*Continued*)

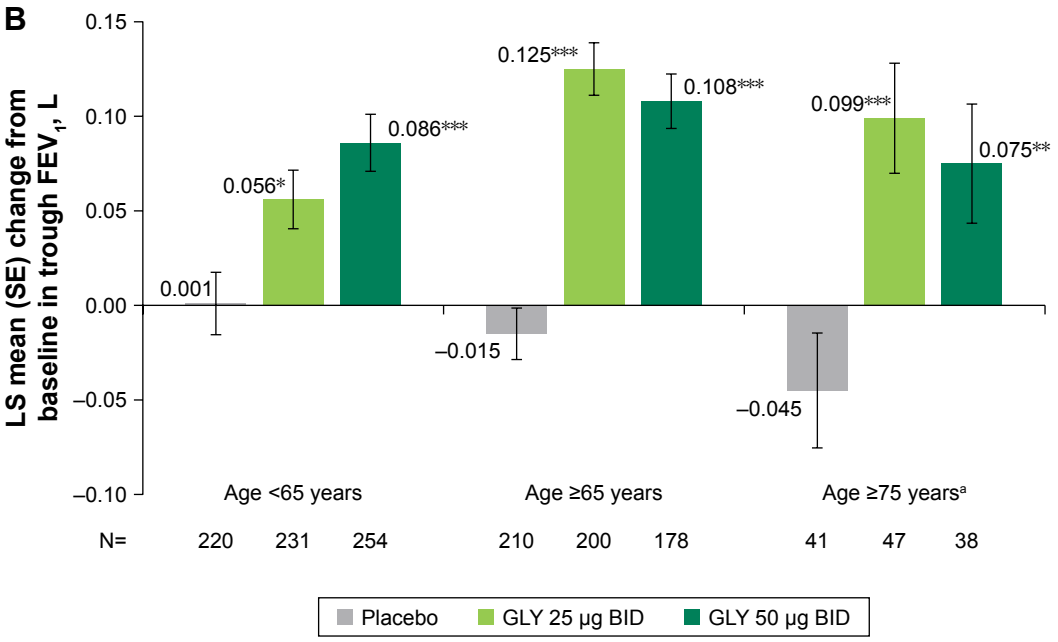

Figure 2 LS mean change from baseline in trough FEV_1 by (**A**) baseline FEV_1% predicted and (**B**) age.
Notes: *$P<0.05$ vs placebo; **$P<0.01$ vs placebo; ***$P<0.001$ vs placebo. [a]Subset of the ≥65 years subgroup.
Abbreviations: LS, least squares; SE, standard error; GLY, glycopyrrolate inhalation solution; BID, twice daily.

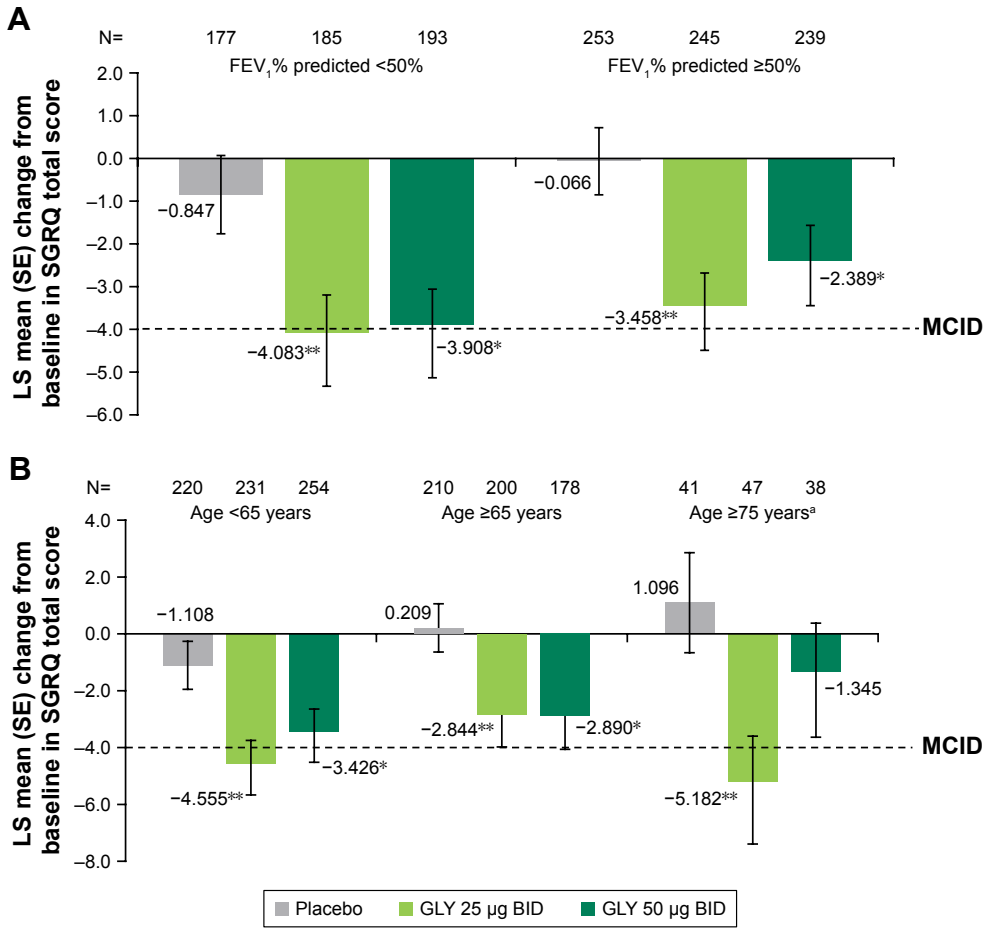

Figure 3 LS mean SGRQ total score by (**A**) baseline FEV_1% predicted and (**B**) age.
Notes: *$P<0.05$ vs placebo; **$P<0.01$ vs placebo. [a]Subset of the ≥65 years subgroup.
Abbreviations: LS, least squares; SE, standard error; SGRQ, St George's Respiratory Questionnaire; GLY, glycopyrrolate inhalation solution; BID, twice daily; MCID, minimum clinically important difference.

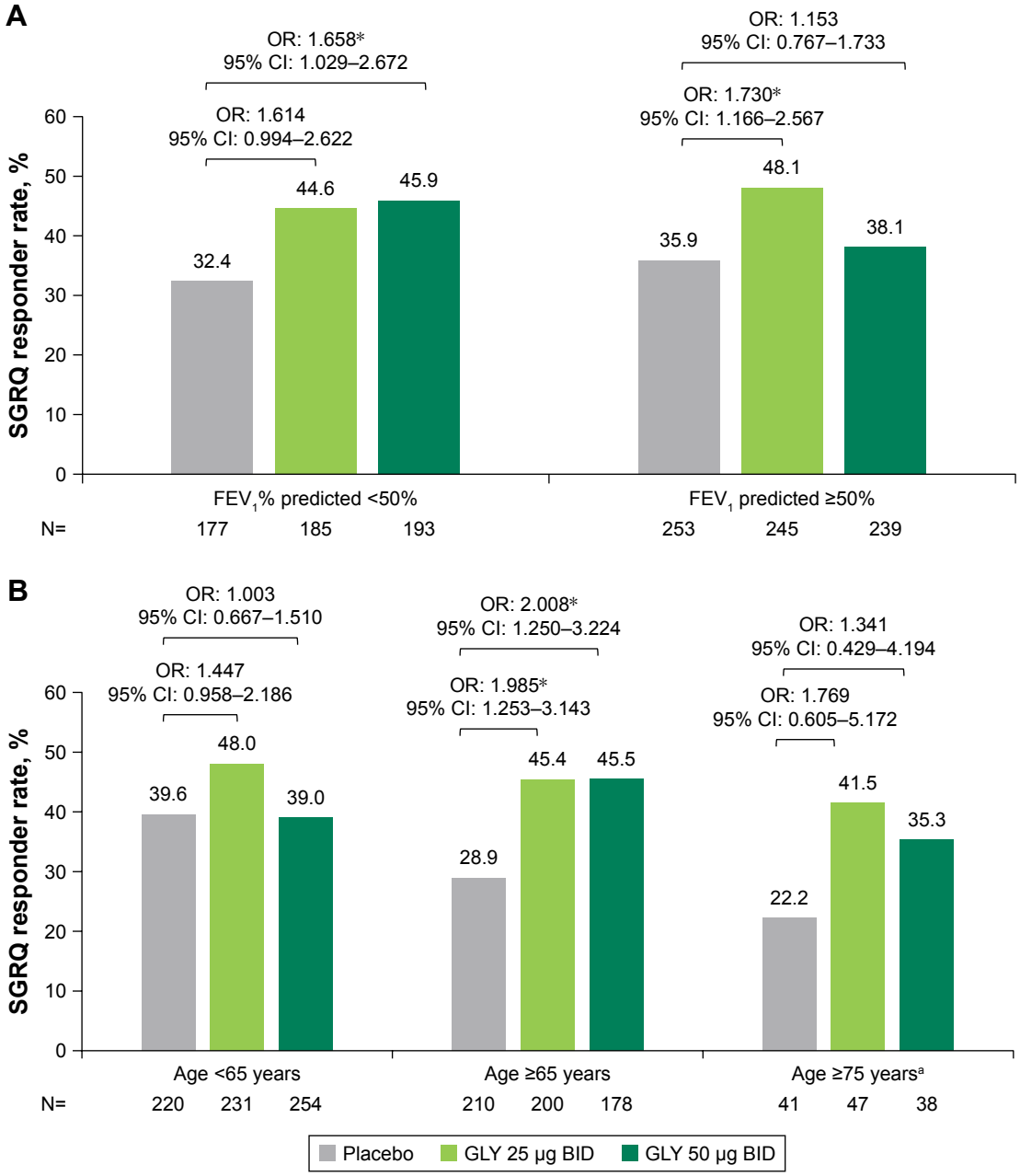

Figure 4 SGRQ responder (≥4-unit reduction in SGRQ total score) rates by (**A**) baseline FEV_1% predicted and (**B**) age.
Notes: *$P<0.05$ vs placebo. [a]Subset of the ≥65 years subgroup.
Abbreviations: SGRQ, St George's Respiratory Questionnaire; GLY, glycopyrrolate inhalation solution; BID, twice daily.

Safety

Overall, treatment with GLY 25 µg and 50 µg BID led to a lower incidence of TEAEs vs placebo (43.4%, 50.7%, and 52.3%, respectively), serious TEAEs (3.0%, 4.2%, and 5.6%, respectively), and TEAEs leading to discontinuation of study drug (5.1%, 3.9%, and 9.3%, respectively).

In the FEV_1% predicted subgroups, the incidence of TEAEs was similar for GLY and placebo (Table 3). Overall, cough and COPD worsening were the most frequent TEAEs, occurring in 7.9% and 9.5% of the FEV_1% predicted <50% subgroup and 8.3% and 6.6% of the FEV_1% predicted ≥50% subgroup, respectively. Incidence of COPD worsening and dyspnea was higher in all treatment groups in the FEV_1% predicted <50% subgroup compared with the ≥50% subgroup. The incidence of serious TEAEs was lower with GLY than placebo in both FEV_1% predicted subgroups, with a higher overall incidence in the <50% subgroup compared with the ≥50% subgroup.

The incidence of TEAEs was numerically higher for all treatment groups in patients aged ≥65 years compared with <65 years (Table 4). Cough and COPD worsening were the most frequent TEAEs overall (<65 years: 7.4% and 8.2%; ≥65 years: 9.0% and 8.0%; ≥75 years: 7.9% and

Table 3 TEAEs^ and serious TEAEs by baseline FEV_1% predicted subgroup (safety population)

Preferred term, %	FEV_1% predicted <50%			FEV_1% predicted ≥50%		
	Placebo	GLY		Placebo	GLY	
	(N=177)	25 µg BID (N=185)	50 µg BID (N=193)	(N=253)	25 µg BID (N=245)	50 µg BID (N=239)
Any TEAE	49.2	40.0	54.4	54.5	46.1	47.7
Cough	9.6	5.4	8.8	7.5	8.2	9.2
COPD worsening	9.6	7.6	11.4	7.9	5.7	6.3
Dyspnea	4.0	8.1	6.2	2.4	2.4	0.8
Urinary tract infection	1.1	2.2	4.1	1.6	2.0	1.7
Upper respiratory tract infection	1.1	1.1	4.7	0.8	1.6	2.5
Headache	2.8	0.5	1.6	2.0	2.4	2.1
Chest discomfort	2.3	1.1	1.6	2.0	1.2	0.4
Edema peripheral	1.1	1.1	3.1	0.8	0.8	1.3
Arthralgia	0.6	0.5	1.0	1.6	0.8	2.9
Any serious TEAEs	6.8	3.8	5.2	4.7	2.4	3.3

Note: ^≥2% incidence in any treatment group in the overall safety population.
Abbreviations: TEAE, treatment-emergent adverse event; GLY, glycopyrrolate inhalation solution; BID, twice daily.

4.0%, respectively). The incidence of serious TEAEs was lower with GLY than placebo across all age subgroups, with fewer events in the <65 years subgroup versus ≥65 years subgroup.

Incidence of TEAEs leading to discontinuation was similar in both FEV_1% predicted <50% and ≥50% subgroups, and lower with GLY (25 µg: 4.9% and 5.3%; 50 µg: 3.6% and 4.2%, respectively) vs placebo (10.7% and 8.3%, respectively). In GLY patients in the FEV_1% predicted <50% and ≥50% subgroups, the most common TEAEs leading to discontinuation were dyspnea and cough, respectively.

Across age subgroups, GLY 25 µg and 50 µg resulted in a lower incidence of TEAEs leading to discontinuation compared with placebo (<65 years: 3.9%, 3.9%, and 5.9%; ≥65 years: 6.5%, 3.9%, and 12.9%; ≥75 years: 6.4%, 2.6%, and 9.8%, respectively). In patients aged <65 years and ≥65 years treated with GLY, the most common TEAEs leading to discontinuation were cough and dyspnea, respectively.

Few CV events of special interest were seen; the incidence with placebo was similar to GLY in patients with baseline FEV_1% predicted <50% (placebo: 2.3%; GLY 25 µg: 1.1%; GLY 50 µg: 3.1%), and higher than GLY in the baseline FEV_1% predicted ≥50% subgroup (placebo: 2.8%; GLY 25 µg: 2.0%; GLY 50 µg: 1.3%). Incidence rates for CV events of special interest were generally similar between the <65 (placebo: 1.8%; GLY 25 µg: 2.2%; GLY 50 µg: 1.6%) and ≥65 years age groups (placebo: 3.3%; GLY

Table 4 TEAEs^ and serious TEAEs by age (safety population)

Preferred term, %	Age <65 years			Age ≥65 years			Age ≥75 years[a]		
	Placebo	GLY		Placebo	GLY		Placebo	GLY	
	(N=220)	25 µg BID (N=231)	50 µg BID (N=254)	(N=210)	25 µg BID (N=200)	50 µg BID (N=178)	(N=41)	25 µg BID (N=47)	50 µg BID (N=38)
Any TEAEs	51.4	40.7	47.6	53.3	46.5	55.1	46.3	42.6	52.6
Cough	8.2	5.6	8.3	8.6	8.5	10.1	7.3	10.6	5.3
COPD worsening	8.6	7.4	8.7	8.6	5.5	8.4	4.9	4.3	2.6
Dyspnea	2.7	3.5	1.6	3.3	6.5	5.6	0	6.4	2.6
Urinary tract infection	0.9	2.2	2.0	1.9	2.0	3.9	2.4	4.3	0
Upper respiratory tract infection	1.4	0.9	3.9	0.5	2.0	2.8	0	2.1	2.6
Headache	3.2	0.4	1.2	1.4	3.0	2.8	0	6.4	0
Chest discomfort	1.4	1.3	0.8	2.9	1.0	1.1	2.4	0	2.6
Edema peripheral	0.9	0.9	2.8	1.0	1.0	1.1	4.9	0	0
Arthralgia	0.9	0.4	2.0	1.4	1.0	2.2	0	0	0
Any serious TEAEs	4.1	2.6	3.9	7.1	3.5	4.5	7.3	0	5.3

Notes: ^≥2% incidence in any treatment group in the overall safety population. [a]Subset of the ≥65 years subgroup.
Abbreviations: TEAE, treatment-emergent adverse event; GLY, glycopyrrolate inhalation solution; BID, twice daily.

Table 5 MACE by FEV_1% predicted subgroup (safety population)

MACE category, N (%) [IR]	FEV_1% predicted <50%			FEV_1% predicted ≥50%		
	Placebo	GLY		Placebo	GLY	
	(N=177)	25 µg BID (N=185)	50 µg BID (N=193)	(N=253)	25 µg BID (N=245)	50 µg BID (N=239)
MACE	0	0	1 (0.5) [17.1]	2 (0.8) [27.4]	0	2 (0.8) [28.5]
CV death	0	0	1 (0.5) [17.1]	0	0	0
Non-fatal MI	0	0	0	2 (0.8) [27.4]	0	1 (0.4) [14.3]
Non-fatal stroke	0	0	0	0	0	1 (0.4) [14.3]

Abbreviations: MACE, major adverse cardiovascular events; IR, incidence rate per 1,000 patient-years; GLY, glycopyrrolate inhalation solution; BID, twice daily; CV, cardiovascular; MI, myocardial infarction.

25 µg: 1.0%; GLY 50 µg: 2.8%), but numerically higher in the ≥75 years subgroup (placebo: 4.9%; GLY 25 µg: 4.3%; GLY 50 µg: 5.3%).

The overall number of major adverse CV events was small (Tables 5 and 6); the overall incidence rate (IR) for GLY 50 µg was similar to placebo (IR: 23.3 and 16.4 per 1,000 patient-years, respectively). There were no clinically relevant changes in laboratory measures, blood pressure, heart rate, Holter monitoring (GOLDEN 3 only), or ECG parameters in the overall population.

Discussion

Analysis of pooled data from the GOLDEN 3 and GOLDEN 4 studies showed efficacy of nebulized GLY in subgroups of older patients and those with moderate-to-very-severe airflow limitation, resulting in significant improvements in change from baseline trough FEV_1 at 12 weeks and in patient-reported outcomes. GLY produced a decrease in SGRQ total score in all subgroups, as well as improved responder rates compared with placebo, including older age group and lower FEV_1% predicted subgroups.

As with GLY, a non-inferiority study found that treatment with the LAMAs tiotropium and umeclidinium significantly improved change from baseline in trough FEV_1 at 12 weeks regardless of disease severity, and patients with moderate COPD showed a substantially larger increase in trough FEV_1 compared with patients with severe COPD.[20] A comparable LAMA monotherapy study investigating age subgroups is not evident in the literature. The improvement in FEV_1 and SGRQ irrespective of age[21] or disease severity at baseline,[22–24] observed with GLY are similar to those found with several LAMA/LABA combinations.

GLY was well tolerated and generated no additional safety signals. The most common TEAEs across all treatments and subgroups were cough, dyspnea, and COPD worsening. TEAE incidences were similar across FEV_1 subgroups and were higher in patients aged ≥65 years compared with those aged <65 years.

Table 6 MACE by age subgroup (safety population)

MACE category, N (%) [IR]	Age <65 years			Age ≥65 years			Age ≥75 years[a]		
	Placebo	GLY		Placebo	GLY		Placebo	GLY	
	(N=220)	25 µg BID (N=231)	50 µg BID (N=254)	(N=210)	25 µg BID (N=200)	50 µg BID (N=178)	(N=41)	25 µg BID (N=47)	50 µg BID (N=38)
MACE	0	0	2 (0.8) [26.7]	2 (1.0) [33.8]	0	1 (0.6) [18.6]	1 (2.4) [82.0]	0	1 (2.6) [84.7]
CV death	0	0	1 (0.4) [13.4]	0	0	0	0	0	0
Non-fatal MI	0	0	1 (0.4) [13.4]	2 (1.0) [33.8]	0	0	1 (2.4) [82.0]	0	0
Non-fatal stroke	0	0	0	0	0	1 (0.6) [18.6]	0	0	1 (2.6) [84.7]

Note: [a]Subset of the ≥65 years subgroup.
Abbreviations: MACE, major adverse cardiovascular events; IR, incidence rate per 1,000 patient-years; GLY, glycopyrrolate inhalation solution; BID, twice daily; CV, cardiovascular; MI, myocardial infarction.

Treatment with GLY resulted in fewer TEAEs leading to discontinuation compared with placebo in all subgroups. There were few CV events of special interest; the incidence was numerically higher in the ≥75 years subgroup for all treatments, which may be due to a numerically higher percentage of patients ≥75 years having high CV risk at baseline (72.3%–87.8%) compared with patients <65 years (52.4%–55.1%).

The main limitation of this paper is the post-hoc nature of the analyses which precludes controlling for multiplicity. However, this limitation is mitigated by the size of the observed differences in the subgroups, the consistency of the results across variables and both doses, and the clinical meaningfulness of the results. Although the individual studies were not powered to provide differences between subgroups, combining the data did allow for meaningful statistical analyses. Results for the ≥75 years subgroup should be interpreted with caution due to the small number of patients, even though significant improvements in trough FEV_1 in both GLY dose groups, and a significant reduction in SGRQ total score for the GLY 25 µg group were reported for this subgroup. It must be noted that although the subgroup definitions used herein (disease severity: FEV_1% predicted ≥50% and <50%; age: <65 years and ≥65 years, with an additional subgroup of ≥75 years) differed from those in the study protocols (disease severity: FEV_1% predicted ≥50%, ≥30% to <50%, and <30%; age: <65 years, 65–74 years, and ≥75 years), we believe that the results support our conclusion that efficacy and safety were not affected by disease severity and age of the patient at baseline.

Due to the increase in the global incidence of COPD[25,26] and the aging population (it is estimated that approximately 20% of the US population will be aged ≥65 years by 2030),[27] optimizing disease management in those patients who have age-related physical, functional, and cognitive impairments is an important goal. These impairments can increase errors in handling inhalers[11] and, consequently, have a substantial impact on patients' compliance with therapeutic regimen to administer treatment correctly. In addition, chronic comorbidities increase the risk for treatment nonadherence.[6,13] Treatment options that do not rely on the requirement for specific coordination or attainment of an inspiratory flow threshold during administration may be preferable in this patient population.[28,29]

Conclusion

In this secondary analysis of two Phase III clinical trials, nebulized GLY demonstrated statistically significant and clinically important improvements in lung function and health status over 12 weeks in patients with moderate-to-very-severe COPD, irrespective of baseline disease severity and age, including those aged ≥75 years. Both doses of GLY were well tolerated and generated no additional overall or CV safety signals across all baseline FEV_1% predicted and age subgroups. Nebulized GLY provides an additional treatment option for the management of COPD, including in patients who may have difficulty using handheld inhalers. Appropriate selection of the drug delivery device is important in COPD management and may depend on disease severity, age, cognitive function, and physical ability.

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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Author contributions

All authors had full access to the study data, conducted the analysis, and take responsibility for the integrity of the data and the accuracy of the analysis. All authors contributed to drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. Jill Ohar contributed to data collection; Robert Tosiello contributed to study design.

Disclosure

Jill Ohar 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 Greensone Panatier Bartlett, Williams Kherkher Hart, Gori Julian & Associates, Simmons Hanley Conroy, and

Elrod Pope. Robert Tosiello, Thomas Goodin, and Shahin Sanjar are employees of Sunovion Pharmaceuticals Inc. The authors report no other conflicts of interest in this work.

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