

Effect of Gender on Lung Function and Patient-Reported Outcomes in Patients with COPD Receiving Nebulized Glycopyrrolate

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease

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Purpose: The clinical manifestation of COPD can differ by gender, with women experiencing worse lung function and health-related quality of life than men. Additionally, women tend to report more symptoms given the same disease severity. Accordingly, the impact of gender on efficacy and safety in patients with moderate-to-very-severe COPD was examined following 12 weeks of nebulized glycopyrrolate (GLY) 25 µg twice daily (BID) or placebo.

Patients and Methods: GLY and placebo pooled data from the replicate 12-week GOLDEN 3 and 4 studies (n=861) were grouped by gender. Endpoints reported were change from baseline in trough forced expiratory volume in 1 second (FEV₁), St George's Respiratory Questionnaire (SGRQ) and EXacerbations of COPD Tool-Respiratory Symptoms (EXACT-RS) total scores. Safety was evaluated by reviewing the incidence of adverse events (AEs) and serious AEs.

Results: Men (placebo: 54.7%; GLY: 56.1%) were generally older with a greater proportion of high cardiovascular risk and use of background long-acting β₂-agonists or inhaled corticosteroids. GLY treatment resulted in significant, clinically important improvements in trough FEV₁, regardless of gender. Patients treated with GLY reported significant improvements in SGRQ total score, irrespective of gender; however, the improvement was numerically higher in women. Although EXACT-RS improved in both genders, only women experienced a significant improvement. Overall, GLY was well tolerated with a numerically lower incidence of AEs in men than women.

Conclusion: Treatment with nebulized GLY resulted in lung function, SGRQ total score, and EXACT-RS total score improvements regardless of gender. However, only EXACT-RS showed significantly greater improvements in women compared with men. Treatment with GLY was generally well tolerated across genders. These data support the efficacy and safety of GLY 25 µg BID in patients with moderate-to-very-severe COPD, independent of gender. Gender similarities in airflow improvement and differences in symptom-reporting augment the evidence supporting the consideration of individualized treatment plans for COPD patients.

Keywords: COPD, gender, LAMA, nebulized glycopyrrolate

Introduction

COPD is a progressive disease characterized by persistent respiratory symptoms and airflow limitation.¹ More recently, the disease has transitioned into being more prevalent in women than in men.²⁻⁴ Women are more likely to be diagnosed with COPD compared with men, when adjusted for age, race, income, education, and smoking status.⁵ In fact, women represent ~58% of patients with COPD in the USA. Between

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2000 and 2005, the death rate for women with COPD increased by 11% compared with 5% among men with COPD,⁶ and women currently account for 53% of COPD deaths in the USA.^{5,7,8} There are clear differences in the manifestation, symptoms, and progression of COPD between genders;^{3,9-15} women are more susceptible to the effects of smoking and experience a faster decline of lung function,^{8,16,17} more frequent exacerbations, higher levels of dyspnea,^{8,12,17-20} increased number of comorbidities,^{8,21,22} and overall decreased quality of life.^{3,11-13,18,19,23} The exact reasons behind gender-related differences in COPD are not clear, but may be related to hormonal, as well as physiologic differences such as thickness of airway walls or increased immune system responsiveness among women.²⁴⁻²⁶ Importantly, response to therapy may be different between genders, particularly with long-acting muscarinic antagonists, due to greater gene expression of the M₃ muscarinic receptor relative to the M₂ receptors among women.²⁷ However, treatment recommendations do not take gender into account, and consequently women with COPD have been reported to experience a higher level of suboptimal treatments, based on guidelines.^{28,29} Currently, there are limited data regarding gender and differences in treatment outcomes among patients with COPD, and such analyses are limited by the majority of male participants in clinical trials (75–77%).^{9,30-33}

Glycopyrrolate inhalation solution (GLY; Lonhala[®], Sunovion Pharmaceuticals Inc., Marlborough, MA, USA) 25 µg twice daily (BID) delivered by the eFlow[®] Closed System (CS) nebulizer (Magnair[®], PARI Pharma GmbH, Starnberg, Germany)³⁴ was approved by the US Food and Drug

Administration (FDA) for the long-term maintenance treatment of airflow obstruction in patients with COPD in December 2017.³⁵ Data from the 12-week, placebo-controlled Glycopyrrolate for Obstructive Lung Disease via Electronic Nebulizer (GOLDEN) 3 and GOLDEN 4 Phase III studies (NCT02347761 and NCT02347774, respectively) demonstrated statistically significant and clinically important improvements in pulmonary function and patient-reported outcomes (PRO) with GLY compared with placebo in patients with moderate-to-very-severe COPD.³⁶ Unlike previous trials analyzed for gender differences in treatment response, the GOLDEN 3 and GOLDEN 4 studies included ~45% females.³⁶ The impact of gender on patient responses to nebulized GLY, compared with placebo, was investigated using pooled data from the 12-week GOLDEN 3 and GOLDEN 4 studies.

Patients and Methods

Study Design

Study designs for GOLDEN 3 and GOLDEN 4 have been previously described (Figure 1).³⁶ Briefly, in the 12-week, multicenter, placebo-controlled, double-blind studies, patients (n=1293) were randomized in a 1:1:1 ratio to receive placebo or GLY (25 or 50 µg BID), via the eFlow CS nebulizer system. Randomization in each study was stratified by background long-acting β₂-agonist (LABA) use (yes/no) and cardiovascular (CV) risk (high/low). Supplemental ipratropium bromide and rescue medication (albuterol [salbutamol]) were permitted. Data for the GLY 50 µg BID treatment arm are not presented in this post hoc analysis in order to focus on the FDA-approved and clinically relevant GLY 25

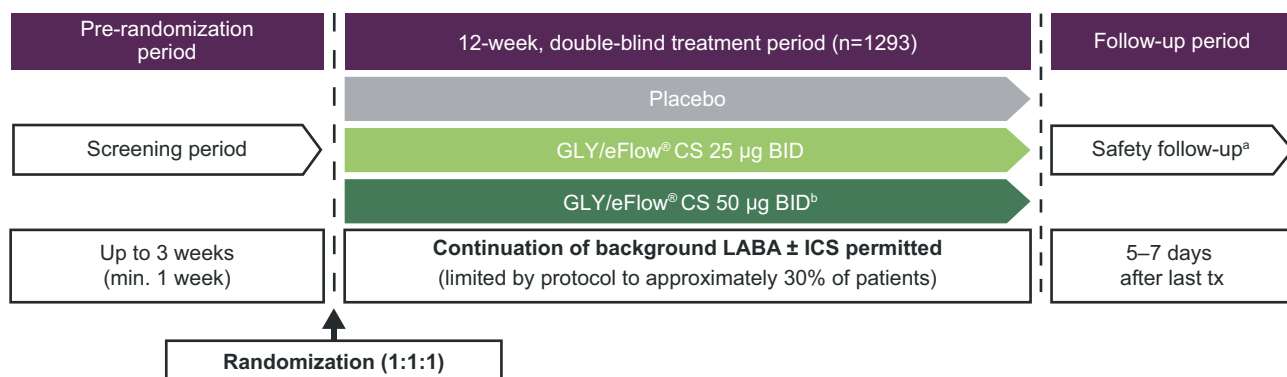


Figure 1 GOLDEN 3 and GOLDEN 4 study designs: 12-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies.³⁶

Notes: ^aSAEs were monitored for 30 days after the last dose of study treatment. ^bData for the GLY 50 µg BID treatment arm are not presented in this post hoc analysis but were used in the modeling and in defining the gender subgroups studied in this analysis; inclusion of the 50 µg BID data in the modeling does not confound the interpretation of the GLY 25 µg BID dose.

Abbreviations: BID, twice daily; CS, closed system; GLY, nebulized glycopyrrolate; ICS, inhaled corticosteroids; LABA, long-acting β₂-agonist; min, minimum; SAE, serious adverse event; tx, treatment.

µg BID dose. However, the data for the GLY 50 µg BID dose were included in the data modeling; inclusion of the 50 µg BID data in the modeling does not confound the interpretation of the findings from the GLY 25 µg BID dose.

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 (USA 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.

Patients

Detailed patient inclusion and exclusion criteria have been published previously.³⁶ Briefly, enrolled patients 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 Global Initiative for Chronic Obstructive Lung Disease 2014 Report¹), and qualifying post-bronchodilator (ipratropium 68 µg) spirometry (forced expiratory volume in 1 second [FEV₁] $\leq 80\%$ of predicted normal, FEV₁ > 0.7 L, and FEV₁/forced vital capacity ratio < 0.70).³⁶

Post Hoc Analysis

Pooled data from the GOLDEN 3 and GOLDEN 4 studies were grouped based on gender. GLY 25 µg BID and placebo treatment were compared, by gender, for the following endpoints: lung function, as assessed by changes from baseline in trough FEV₁ at Week 12; PROs, as measured by changes from baseline in St George's Respiratory Questionnaire (SGRQ) total score, EXacerbations of COPD Tool-Respiratory Symptoms (EXACT-RS) total score at Week 12, and rescue medication use over 12 weeks. The EXACT-RS is a PRO used to measure the effect of treatment on the severity of respiratory symptoms in stable COPD.³⁷ Safety data were analyzed using descriptive statistics.³⁶ Adverse events (AE) and serious adverse events (SAE) were coded according to MedDRA version 15.1 and summarized by treatment, system organ class, and preferred term.

Statistical Analyses

Data are presented for the FDA-approved GLY 25 µg BID dose.³⁵ Changes from baseline in trough FEV₁ and EXACT-RS total score at Week 12 were analyzed using a mixed-model for repeated measures. Changes from baseline in

SGRQ total score at Week 12 and rescue medication use over 12 weeks were analyzed by analysis of covariance. The proportions of patients with reduction in SGRQ total score ≥ 4 units³⁸ or reduction in EXACT-RS total score ≥ 2 ³⁹ (defined as minimum clinically important differences) were analyzed using a logistic regression model and a longitudinal logistic regression analysis, respectively. All models included factors for baseline level of the appropriate outcome measure, CV risk, LABA use, gender, treatment effect, and its interaction by gender. Efficacy and safety data were analyzed by randomized and actual treatment received, respectively. Both the efficacy intent-to-treat (ITT) population and the safety population consisted of all patients randomized to treatment who received ≥ 1 dose of study drug. Only data that were measured while on randomized, blinded study treatment (ie on-treatment data) were analyzed. No multiplicity adjustments were made for the comparisons. All p-value interpretations are made at the 5% significance level.

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

Results

Patient Demographics and Baseline Characteristics

Of 1293 patients treated in the GOLDEN 3 and GOLDEN 4 studies, 861 patients were included in this analysis. Men (n=477 [55.4%]; placebo n=235, GLY n=242), compared with women (n=384 [44.6%]; placebo n=195, GLY n=189), were generally older, with higher overall proportions of ex-smokers (average, 51.4% vs 41.1%; Table 1), high CV risk (average, 67.7% vs 59.9%) and use of background LABA (average, 33.8% vs 27.6%) or an inhaled corticosteroid (average, 31.2% vs 27.1%). Numerically, baseline FEV₁ was lower and baseline SGRQ total score was higher in women; the baseline EXACT-RS total scores were similar across genders. Study completion rate was similar across genders (placebo: women, 88.7%, men, 87.7%; GLY: women, 91.5%, men, 92.1%), but on-treatment study completion was lower among women compared with men in the GLY arm (84.7% vs 89.7%, respectively), whereas the rate was similar for patients receiving placebo (81.5% vs 82.6%, respectively).

Efficacy

Lung Function

At Week 12, GLY treatment resulted in significant and clinically important improvements in placebo-adjusted change from baseline in trough FEV₁ in both men and

Table 1 Patient Demographics and Baseline Characteristics, by Gender

Parameters	Male		Female	
	Placebo (n=235)	GLY 25 µg BID (n=242)	Placebo (n=195)	GLY 25 µg BID (n=189)
Age, years, median (range)	66.0 (41–84)	64.0 (41–83)	61.0 (42–84)	63.0 (40–80)
BMI, kg/m ² , median (range)	28.38 (18.3–71.6)	27.24 (16.7–53.4)	28.02 (16.3–56.2)	27.10 (14.7–53.1)
Ex-smoker, n (%)	132 (56.2)	113 (46.7)	80 (41.0)	78 (41.3)
Pack years, median (range)	51.0 (11–147)	48.5 (12–192)	44.0 (10–240)	43.0 (10–129)
High CV risk, n (%)	166 (70.6)	157 (64.9)	112 (57.4)	118 (62.4)
Background LABA, n (%)	81 (34.5)	80 (33.1)	51 (26.2)	55 (29.1)
Background ICS, n (%)	77 (32.8)	72 (29.8)	50 (25.6)	54 (28.6)
COPD exacerbation within past 12 months, n (%)	44 (18.7)	48 (19.8)	49 (25.1)	36 (19.0)
Pre-BD FEV ₁ , L, median (range)	1.380 (0.57–3.03)	1.330 (0.52–2.80)	1.110 (0.49–2.05)	1.110 (0.50–2.26)
Post-BD FEV ₁ , L, median (range)	1.670 (0.73–3.43)	1.620 (0.71–3.28)	1.280 (0.71–2.34)	1.300 (0.71–2.40)
Post-BD FEV ₁ , % predicted, median (range)	51.0 (22–79)	49.0 (20–79)	54.0 (27–77)	56.0 (29–79)
FEV ₁ , L, median (range)	1.395 ^a (0.51–3.15)	1.415 ^b (0.53–3.23)	1.130 ^c (0.52–2.19)	1.085 ^d (0.48–2.41)
SGRQ total score, median (range)	46.40 ^e (1.1–90.5)	46.87 ^b (0.8–95.9)	49.03 ^f (6.2–98.2)	51.84 ^g (0–90.3)
EXACT-RS total score, median (range)	12.30 ^b (0–34.7)	12.29 ^h (0–30.4)	11.38 ⁱ (0–30.4)	12.43 ^j (0–32.4)
Average rescue medication puffs per day, median (range)	2.75 ^k (0–14.1)	3.17 ^l (0–10.4)	2.09 ^m (0–11.3)	2.90 ⁿ (0–8.5)

Notes: ^an=227; ^bn=228; ^cn=188; ^dn=181; ^en=224; ^fn=186; ^gn=179; ^hn=235; ⁱn=192; ^jn=185; ^kn=207; ^ln=218; ^mn=182; ⁿn=174.

Abbreviations: BD, bronchodilator; BID, twice daily; BMI, body mass index; CV, cardiovascular; EXACT-RS, EXacerbations of COPD Tool-Respiratory Symptoms; FEV₁, forced expiratory volume in 1 second; GLY, nebulized glycopyrrolate; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; SGRQ, St George's Respiratory Questionnaire.

women (Figure 2). Among patients treated with GLY, there was no significant difference in change from baseline in trough FEV₁ between genders (p=0.221; Figure 2).

PROs

SGRQ Total Score and Responders

Placebo-adjusted improvements from baseline in SGRQ total score with GLY treatment at 12 weeks were

significant in both men and women (Figure 3A). There was no significant difference (p=0.299) between men and women in the GLY treatment group. The odds of being an SGRQ responder (≥4-unit reduction) were significantly greater with GLY than placebo in men and women (Figure 4A), and similar to the SGRQ total score, there was no significant difference in the SGRQ responder rate

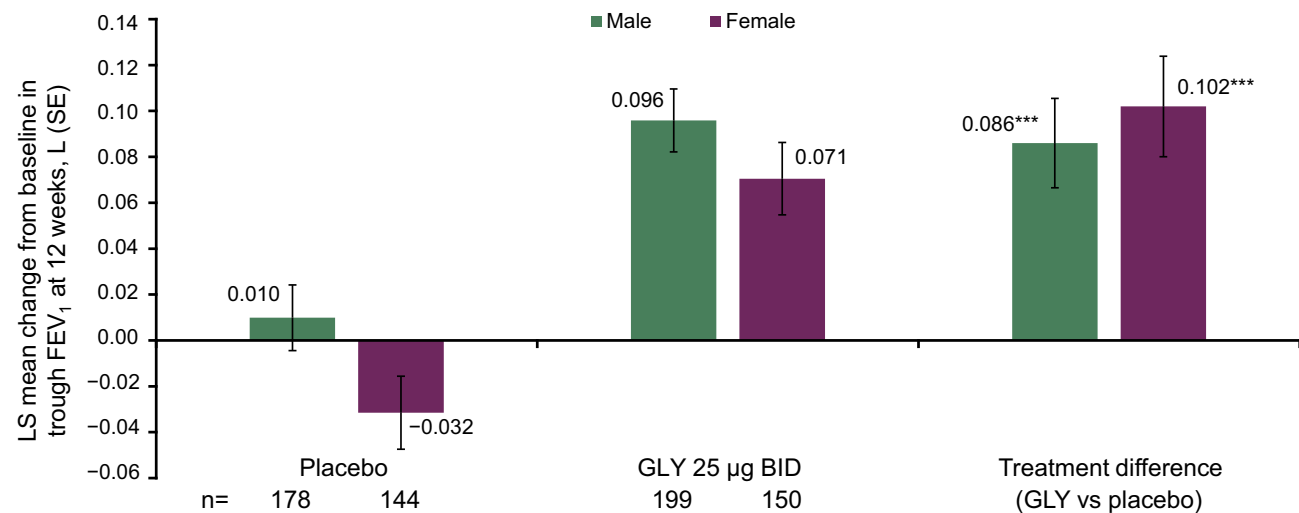


Figure 2 Pooled analysis of trough FEV₁ at 12 weeks, by gender (ITT population).

Note: ***p<0.001 vs placebo.

Abbreviations: BID, twice daily; FEV₁, forced expiratory volume in 1 second; GLY, nebulized glycopyrrolate; ITT, intent-to-treat; LS, least squares; SE, standard error.

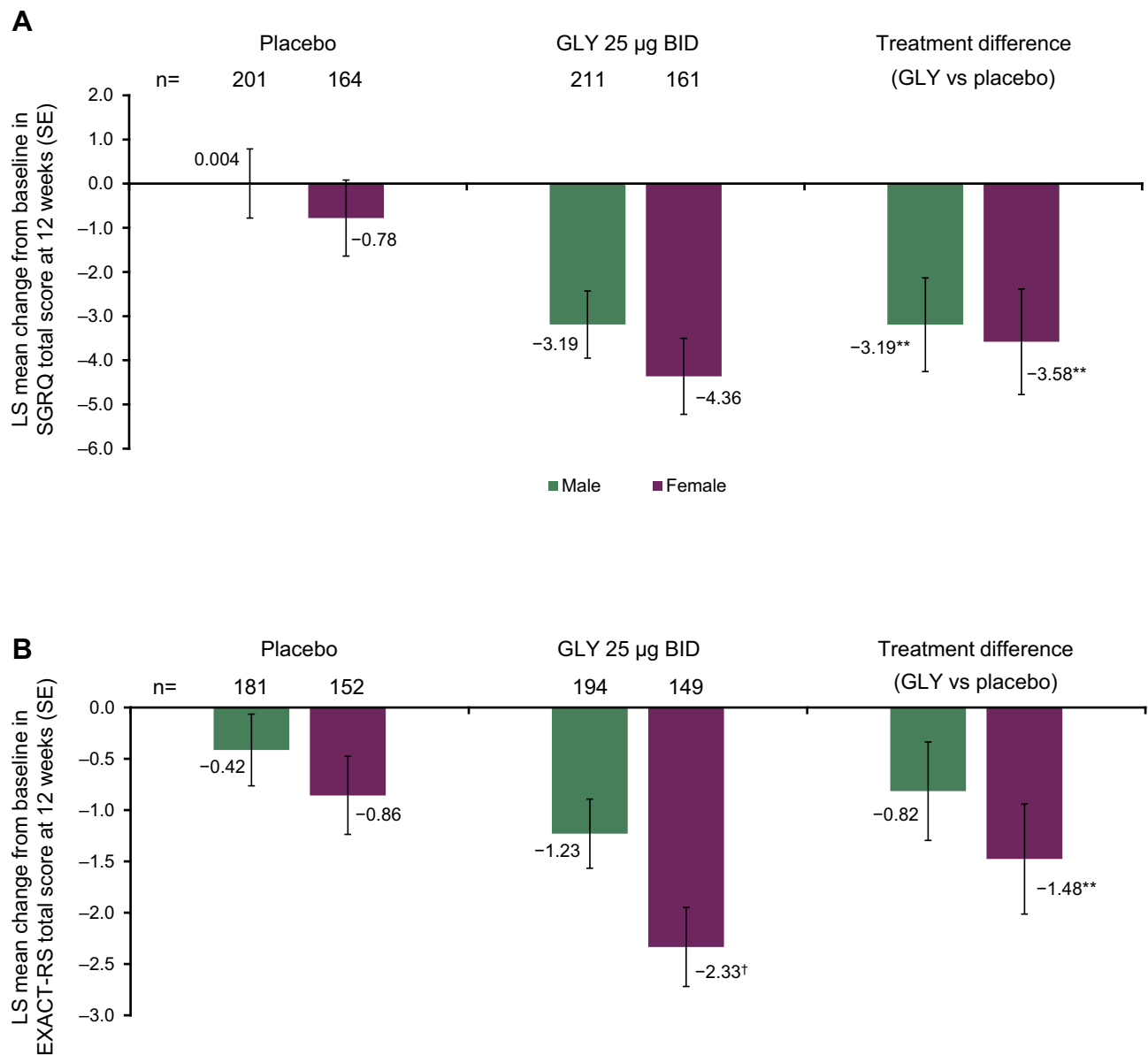


Figure 3 Pooled analysis of (A) SGRQ total score, (B) EXACT-RS total score at 12 weeks, by gender (ITT population).

Notes: ** $p < 0.01$ vs placebo; [†] $p < 0.01$ vs male

Abbreviations: BID, twice daily; EXACT-RS, EXAcacerbations of COPD Tool-Respiratory Symptoms; GLY, nebulized glycopyrrrolate; ITT, intent-to-treat; LS, least squares; SE, standard error; SGRQ, St George's Respiratory Questionnaire.

between genders among patients receiving GLY ($p=0.443$).

EXACT-RS Total Score and Responders

At 12 weeks, the placebo-adjusted change from baseline in EXACT-RS total score with GLY treatment was only significant in women ($p < 0.01$) (Figure 3B). Among patients receiving GLY, the improvement from baseline in EXACT-RS total score in women was significantly greater than in men ($p=0.0028$; Figure 3B). Notably, the odds of being an EXACT-RS responder (≥ 2 -unit reduction) in the GLY

treatment group were significantly higher than placebo for men (Figure 4B), but not for women ($p=0.177$); there was no significant difference in EXACT-RS responder rate between genders among patients receiving GLY ($p=0.457$).

Rescue Medication Use

Placebo-adjusted changes from baseline in rescue medication use over 12 weeks were not significant for either gender (Figure 5). There were no significant differences in rescue medication use between genders in patients treated with GLY ($p=0.100$).

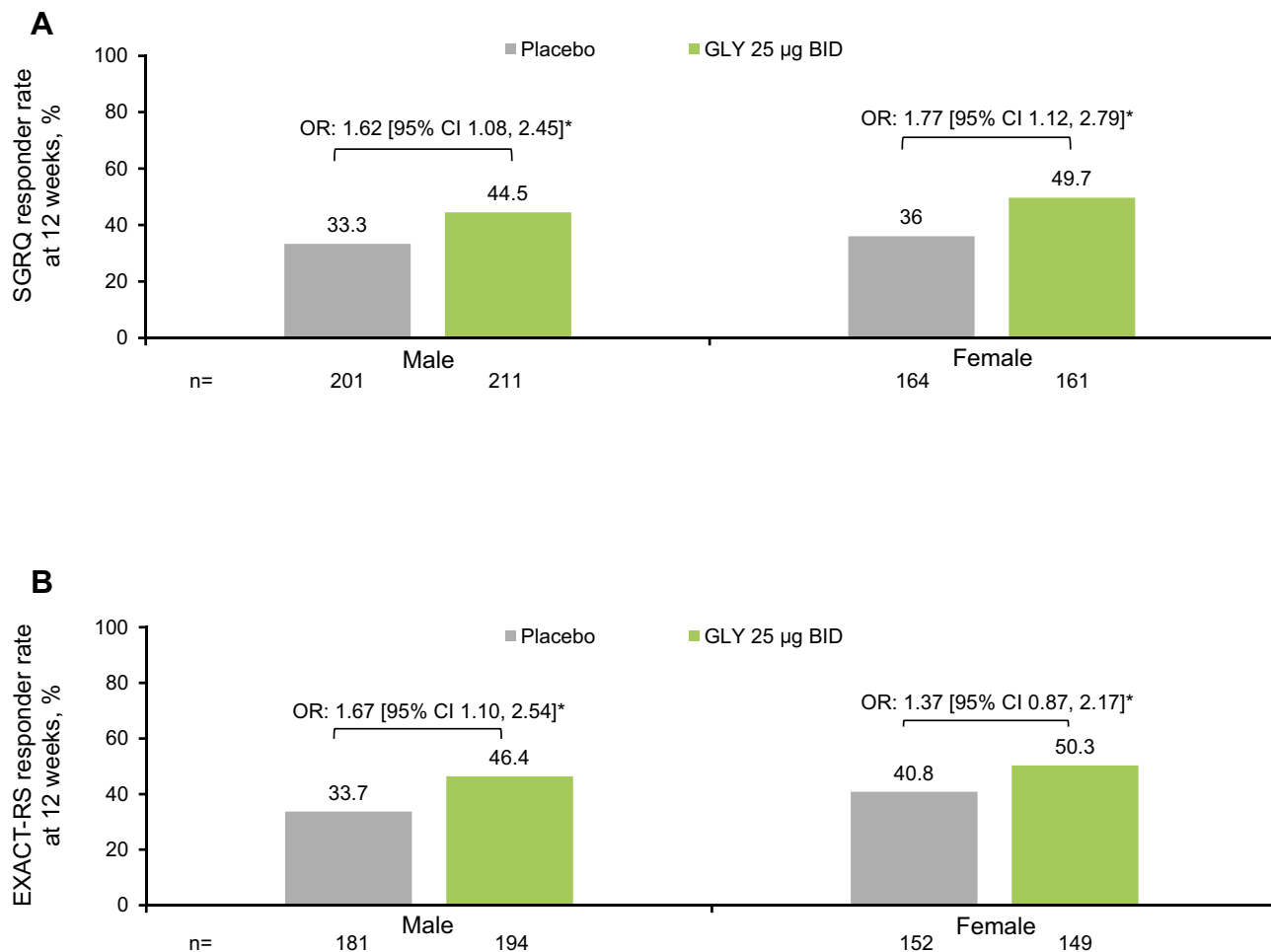


Figure 4 Pooled analysis of (A) SGRQ responder rates, (B) EXACT-RS responder rates at 12 weeks, by gender (ITT population).

Note: * $p < 0.05$ vs placebo.

Abbreviations: BID, twice daily; CI, confidence interval; EXACT-RS, EXAcerbations of COPD Tool-Respiratory Symptoms; GLY, nebulized glycopyrrolate; ITT, intent-to-treat; OR, odds ratio; SGRQ, St George's Respiratory Questionnaire.

Safety

Overall, GLY was generally well tolerated, regardless of gender, and incidences of all AEs and SAEs were lower in GLY treatment groups compared with placebo (Table 2). Within treatment groups, women reported a higher overall incidence of AEs compared with men, whereas men reported a higher incidence of SAEs than women. The most common AEs across treatment groups were cough and worsening of COPD, both of which had higher incidences among women compared with men in both treatment groups. Discontinuation due to AEs was greater among women compared with men (8.3% vs 6.3%, respectively); the most common AE leading to discontinuation in women was cough (placebo, 3.1%; GLY, 0.5%) and in men was dyspnea (placebo, 0.4%; GLY, 1.7%).

Discussion

Heightened awareness of the prevalence of COPD in women has highlighted the need to adjust treatment guidelines and patient management based on gender-related differences in disease etiology and presentation.^{3,9,10,12-15} Outcomes from post hoc analyses of several clinical trials have shown no marked differences in responses to bronchodilators between men and women.³⁰⁻³³ However, most of those clinical trials included a majority of male patients (75–77%), which may have impacted the outcomes, and limited the conclusions of these analyses.^{9,30-33} In contrast to other studies, the proportion of females in the GOLDEN 3 and GOLDEN 4 studies was ~45%.³⁶ Consistent with previous studies, the analysis of pooled data from the GOLDEN 3 and GOLDEN 4 studies demonstrated similar improvements in lung function and SGRQ total score

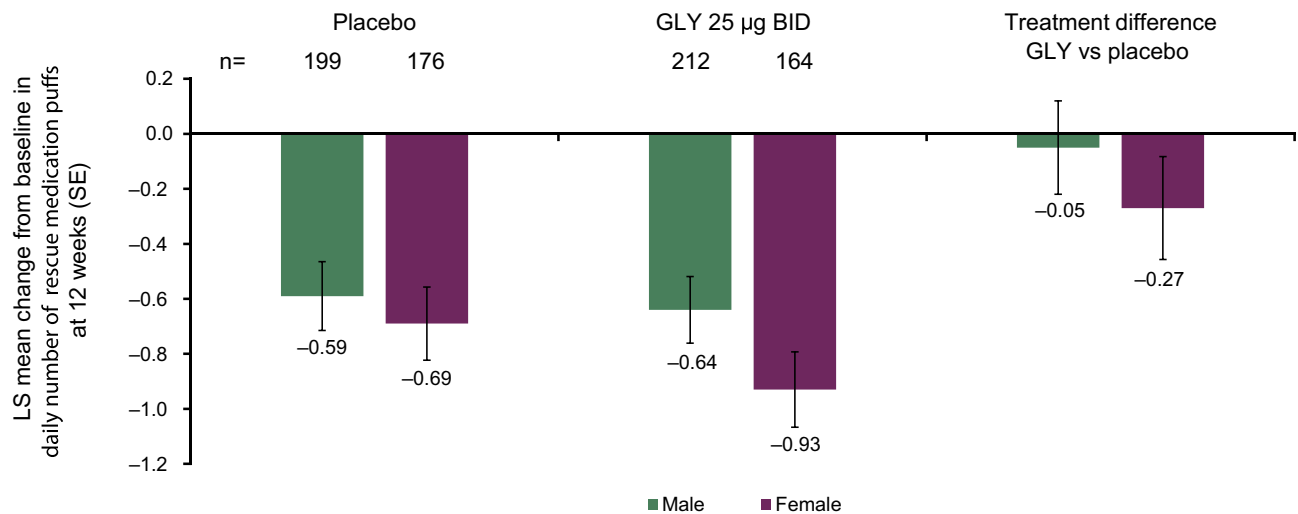


Figure 5 Pooled analysis of rescue medication use over 12 weeks, by gender (ITT population).

Abbreviations: BID, twice daily; GLY, nebulized glycopyrrolate; ITT, intent-to-treat; LS, least squares; SE, standard error.

across genders, whereas EXACT-RS total score showed greater improvements among women only. The safety profile of GLY was not different between genders, and the incidences of AEs and SAEs were lower in GLY treatment groups compared with placebo.

In our analysis, women were younger than men and included a greater proportion of current smokers, consistent with observations in other studies.^{9,30-33} CV risk was greater among men than women, consistent with previous studies.^{9,31} In addition, baseline lung function and SGRQ scores were worse in women compared with men in the pooled GOLDEN 3 and GOLDEN 4 studies. The lower baseline lung function is consistent with other studies^{2,9,30,32,33} and may reflect anatomical differences in the lung between genders, leading to smaller lung volume.²⁶ Similarly, other studies have shown that women tend to have worse health-related quality of life and dyspnea;^{9,30,31} these

are consistent with worsened quality of life among female patients with COPD in our and other analyses.^{3,10-13,18,23}

Lung function improvements with GLY were similar across genders and significantly greater than placebo. These results are similar to those observed in other studies, which showed no differences in lung function improvements between men and women in response to bronchodilator therapy.³⁰⁻³³ While women presented with lower baseline lung function compared with men, the overall similar improvements from baseline further support the treatment benefit of GLY in patients with moderate-to-very-severe COPD, independent of gender.

In this study, improvements in SGRQ total score were similar between men and women, and significantly improved in both compared with placebo. In contrast, improvements from baseline in EXACT-RS total score were only significant compared with placebo among women, and were significantly

Table 2 Summary of AEs and SAEs, Including Individual AEs with Incidence $\geq 3\%$ in Any Treatment Group, by Gender (Safety Population)

Preferred Term, n (%)	Male		Female	
	Placebo (n=235)	GLY 25 µg BID (n=242)	Placebo (n=195)	GLY 25 µg BID (n=189)
Any AE	119 (50.6)	96 (39.7)	106 (54.4)	91 (48.1)
Cough	15 (6.4)	15 (6.2)	21 (10.8)	15 (7.9)
COPD worsening	17 (7.2)	13 (5.4)	20 (10.3)	15 (7.9)
Dyspnea	7 (3.0)	16 (6.6)	6 (3.1)	5 (2.6)
Urinary tract infection	4 (1.7)	2 (0.8)	2 (1.0)	7 (3.7)
Any AE leading to discontinuation	21 (8.9)	9 (3.7)	19 (9.7)	13 (6.9)
Any SAE	14 (6.0)	9 (3.7)	10 (5.1)	6 (3.2)

Abbreviations: AE, adverse event; BID, twice daily; GLY, nebulized glycopyrrolate; SAE, serious adverse event.

greater among women than men. Changes in rescue medication use were similar across treatment arms and genders, with no significant improvements in either. Variability in the placebo response among men for the SGRQ and EXACT-RS total scores, compared with those in women, as well as differences in sample size and discontinuations between genders, may have contributed to the differences in placebo-adjusted improvements. However, these results suggest that treatment with GLY may lead to numerically greater improvements among women compared with men; this may be important, particularly with the worse quality of life scores generally observed among female patients with COPD.

GLY was generally well tolerated across genders, and the incidence of all AEs and SAEs was lower compared with placebo. However, the incidence of overall AEs was numerically higher in women, whereas the incidence of SAEs was higher among men in these studies. The higher incidence of SAEs among men is similar to that observed in the Understanding the Potential Long-term Impact of Tiotropium (UPLIFT) trial with tiotropium, in which males showed higher incidence of SAEs, particularly those related to CV or neoplastic systems.³⁰ In our analysis, women experienced a numerically higher incidence of overall AEs compared with men. These results contrast previous studies that showed similar incidence of AEs between genders;^{30,32} the higher proportion of women included in GOLDEN 3 and GOLDEN 4 may reflect possible differences in comorbidities between the genders and the incidence of treatment-emergent AEs. However, our study may also be limited by the 12-week duration of the 2 studies, compared to the longer durations of the studies that previously reported no differences in AEs between genders.^{30,32} It is important to note that the incidence of treatment-emergent AEs was similar between males and females in the GOLDEN 5 long-term (12 months) safety study of GLY, suggesting that the differences observed in this analysis at 12 weeks were not observed with long-term treatment.⁴⁰ Additional long-term studies would be needed to assess safety differences with GLY between genders.

Conclusions

Patients treated with GLY demonstrated improvements in lung function, SGRQ total score, and EXACT-RS total score compared with placebo, regardless of gender, although changes in EXACT-RS total score with GLY at 12 weeks were significantly greater among women compared with men. Treatment with GLY was generally well tolerated across genders. These data support the efficacy and safety of GLY

25 µg BID in patients with moderate-to-very-severe COPD, independent of gender. Importantly, the similarities in airflow improvement and differences in symptom reporting between genders augment the evidence supporting the consideration of individualized treatment plans for COPD patients.

Abbreviations

AE, adverse event; BID, twice daily; CS, closed system; CV, cardiovascular; EXACT-RS, EXacerbations of COPD Tool-Respiratory Symptoms; FDA, US Food and Drug Administration; FEV₁, forced expiratory volume in 1 second; GLY, glycopyrrolate; GOLDEN, Glycopyrrolate for Obstructive Lung Disease via Electronic Nebulizer; ITT, intent-to-treat; LABA, long-acting β₂-agonist; PRO, patient-reported outcome; SAE, serious adverse event; SGRQ, St George's Respiratory Questionnaire; UPLIFT, Understanding the Potential Long-term Impact of Tiotropium.

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.

Acknowledgments

The authors would like to thank Shane Hornbrook from Sarepta Therapeutics, Inc., Diane Hall from Sunovion Pharmaceuticals Inc., and Rajeshwari Sammishetty from Sage Therapeutics, Inc. for support with statistical analyses performed. This post hoc analysis was supported by funding from Sunovion Pharmaceuticals Inc. Medical writing support was provided by Hashem Dbouk, PhD, of FireKite, an Ashfield company, part of UDG Healthcare plc, and funded by Sunovion Pharmaceuticals Inc. The abstract of this paper was presented at the American Thoracic Society 2019 International Conference as a poster with interim findings. The poster's abstract was published in the "Abstracts Issue" of American Journal of Respiratory and Critical Care Medicine: <https://doi.org/10.1164/ajrccm-conference.2019.199.1.MeetingAbstracts.A3869>.

Funding

Studies were supported by funding from Sunovion Pharmaceuticals Inc.

Disclosure

JO has participated in advisory boards for Sunovion Pharmaceuticals Inc., AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Mylan, and Theravance and has received grant funding from Sunovion Pharmaceuticals Inc and Boehringer Ingelheim. AOG, TG, and SS are employees of Sunovion Pharmaceuticals Inc. The authors report no other conflicts of interest in this work.

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