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Original Research

Efficacy and Safety of Twice-Daily Glycopyrrolate Versus Placebo in Patients With COPD: The GEM2 Study

Edward Kerwin, MD[1] Thomas M. Siler, MD[2] Phillip Korenblat, MD[3] Alexander White, MD[4]
Joerg H. Eckert, PhD[5] Michelle Henley, MSc[6] Francesco Patalano, MD[5] Peter D'Andrea, MD[6]

Abstract

Long-acting bronchodilators including muscarinic antagonists are central to the management of patients with COPD. The **G**lycopyrrolate **E**ffect on sy**M**ptoms and lung function (GEM2) study assessed the efficacy and safety of twice-daily glycopyrrolate 15.6µg in patients with moderate-to-severe airflow limitation.

This 12-week multicenter, double-blind study randomized (1:1) patients to glycopyrrolate 15.6µg twice daily (b.i.d.) or placebo both delivered via the Neohaler™ device. The primary objective was superiority of glycopyrrolate compared with placebo for forced expiratory volume in 1 second (FEV1) standardized area under curve (AUC) between 0 and 12 hours post dosing (FEV_1 $AUC_{0\text{-}12h}$) at week 12. Other outcomes included additional spirometry parameters, health status using St George's Respiratory Questionnaire (SGRQ), dyspnea via Transition Dyspnea Index (TDI), rescue medication use and COPD symptoms reported by patients via the electronic diary. Safety was also assessed.

Of the 432 patients randomized (glycopyrrolate, n=216; placebo, n=216), 96% completed the planned treatment phase. The study met its primary objective (superiority of glycopyrrolate compared with placebo for FEV_1 $AUC_{0\text{-}12h}$). Compared with placebo, glycopyrrolate showed significant improvements in lung function parameters ($p<0.001$). Health status (SGRQ total score and COPD assessment test), rescue medication use and daily total COPD symptom scores were significantly improved with glycopyrrolate versus placebo over 12 weeks. Improvements in dyspnea were observed with glycopyrrolate and placebo although the treatment difference was not statistically significant. Overall, differences in the incidences of adverse events and serious adverse events between the groups were not considered clinically meaningful. No deaths were reported.

Twice-daily glycopyrrolate 15.6µg showed statistically significant and clinically meaningful improvements compared with placebo in lung function, COPD symptoms, health status, and rescue medication usage in COPD patients with moderate-to-severe airflow limitation.

Clinical Trial Registration: NCT01715298

Abbreviations: Glycopyrrolate Effect on syMptoms and lung function study, **GEM2**; twice daily, **b.i.d.**; forced expiratory volume in 1 second, **FEV_1**; area under the curve, **AUC**; St. George's Respiratory Questionaire, **SGRQ**; Transition Dyspnea Index, **TDI**; Global initiative for chronic Lung Disease, **GOLD**; long-acting muscarinic antagonist, **LAMA**; long-acting β_2-agonist, **LABA**; inhaled corticosteroid, **ICS**; chronic obstructive pulmonary disease, **COPD**; U.S. Food and Drug Administration, **FDA**; forced vital capacity, **FVC**; modified Medical Research Council, **mMRC**; electronic diary, **e-diary**; minimal clinically important difference, **MCID**; COPD Assessment Test, **CAT**; adverse event, **AE**; major adverse cardiovascular events, **MACE**; cardio-and cerebrovascular, **CCV**; full analysis set, **FAS**; per protocol set, **PPS**; Baseline Dyspnea Index, **BDI**; glycopyrrolate, **GLY**; placebo, **PBO**; confidence interval, **CI**; odds ratio, **OR**; serious adverse effects, **SAEs**; Friederica's corrected QT interval, **QTcF**; least squares means, **LSM**

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1 Clinical Research Institute of Southern Oregon, Medford

2 Midwest Chest Consultants, St. Charles, Missouri

3 The Clinical Research Center, St. Louis, Missouri

4 Progressive Medical Research, Port Orange, Florida

5 Novartis Pharma AG, Basel, Switzerland

6 Novartis Pharmaceuticals Corporation, East Hanover, New Jersey

Address correspondence to:

Edward Kerwin, MD
Clinical Research Institute of Southern Oregon
3860 Crater Lake Avenue
Medford, OR 97504
Phone: 541-858-1003
Email: ekerwin@criresearch.com

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Introduction

The current Global initiative for chronic Obstructive Lung Disease (GOLD) strategy[1] and American Thoracic Society/European Respiratory Society guidelines[2] recommend inhaled bronchodilators, such as a long-acting muscarinic antagonist (LAMA) alone or in combination with a long-acting β_2-agonist (LABA) or inhaled corticosteroid (ICS), as the mainstay for treatment of patients with chronic obstructive pulmonary disease (COPD). Glycopyrrolate, also known as glycopyrronium bromide, is a fast onset (statistically significant bronchodilation within 5 and 15 minutes post-dose) and long-acting (sustained 24-hour bronchodilation) muscarinic antagonist (LAMA), developed for maintenance treatment in patients with COPD.[3-5] Preclinical studies with glycopyrrolate have demonstrated high affinity and slow dissociation from muscarinic receptors which supports the prolonged bronchodilation effect in patients with COPD.[6] Various global clinical studies have demonstrated that treatment with glycopyrrolate 63µg (equivalent to glycopyrronium 50µg) administered once-daily offers substantial benefit to patients with moderate to severe COPD with improved lung function, dyspnea, health status, rescue medication use, with overall good safety profile[4,5,7] and is an approved treatment in more than 80 countries including the European Union, Brazil, Japan, Canada, Switzerland and Australia, excluding the United States. In the United States, a separate phase III clinical trial program with glycopyrrolate 15.6µg (equivalent to glycopyrronium 12.5µg) was developed that included 2 identical pivotal 12-week efficacy and safety studies, **G**lycopyrrolate **E**ffect on sy**M**ptoms and lung function study (GEM1) and GEM2 and a long-term safety study, GEM3. The dose selection was based on a dose-ranging study[8] showing statistically significant and clinically relevant improvements in trough forced expiratory volume in 1 second (FEV_1) with twice-daily glycopyrrolate 15.6µg treatment and on discussions with the U.S. Food and Drug Administration (FDA). Seebri® Neohaler™ (glycopyrrolate) 15.6µg is now approved in the United States for the long-term maintenance treatment of airflow obstruction in patients with COPD.

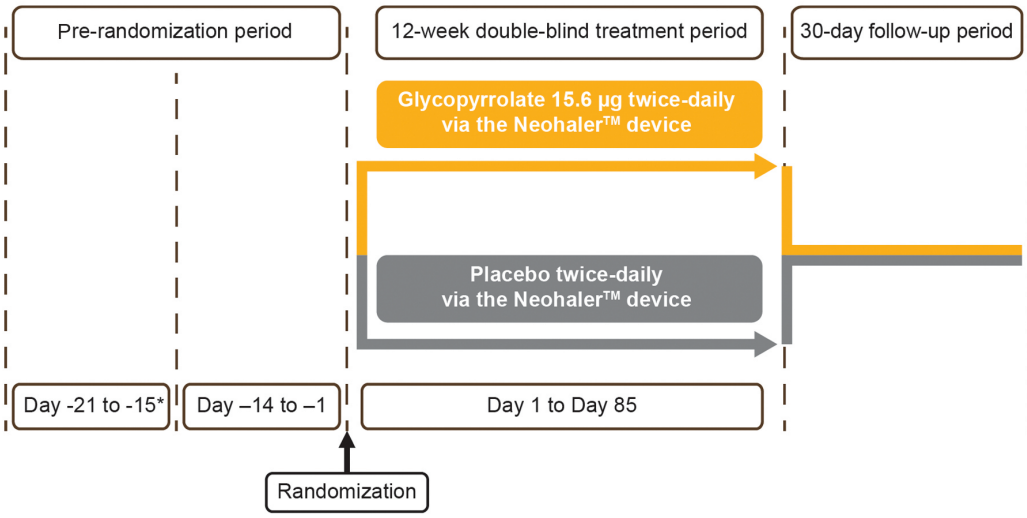
This manuscript presents the results of the 12-week Phase III GEM2 study that assessed the efficacy and safety of glycopyrrolate 15.6µg b.i.d. compared with placebo in COPD patients with moderate-to-severe airflow limitation (GOLD 2 and 3 according to the GOLD 2011 strategy).

Methods

Study Design and Treatment

GEM2 was a 12-week multicenter, randomized, double-blind, parallel-group, placebo controlled study (ClinicalTrials.gov registration number: NCT01715298). The study comprised an initial wash out period (duration of 7 to 1 days depending on washout required for prior medications), a run-in period of 2 weeks, followed by a 12-week randomized treatment period, and a 30-day safety follow-up period. Patients were randomized after the run-in period to receive glycopyrrolate 15.6µg b.i.d. or placebo (both delivered via the single-dose dry-powder inhaler [the Neohaler™ device; Novartis, Basel, Switzerland]) for the following 12 weeks using an allocation ratio of 1:1 (Figure 1). Additional details of the randomization and blinding procedures are included in the online supplementary material. This study was conducted at 64 centers within the United States. The first patient was enrolled on November 26, 2012 and the last patient visit was completed on December 26, 2013. Albuterol (100µg/puff administered from the pressurized metered-dose inhaler) was allowed as a rescue medication. The continuation of inhaled corticosteroid (ICS) monotherapy at a stable dose regimen was permitted as COPD background therapy. This study was submitted

Figure 1. Study Design



*flexible between 1 to 7 days

to the FDA, was approved by the institutional review boards/independent ethics committees/research ethics boards of participating centers, and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent before participating in the study.

Patients

The study population included male and female patients aged 40 years or older with moderate-to-severe airflow limitation (GOLD 2 or 3 as defined in GOLD 2011), current or ex-smokers with a smoking history of at least 10 pack years, post-bronchodilator FEV_1 ≥30% and <80% of predicted value, post bronchodilator FEV_1/forced vital capacity (FVC) ratio <0.70, and a modified Medical Research Council (mMRC) Dyspnea Scale grade of at least 2 at the run-in visit. Key exclusion criteria included history of asthma and COPD exacerbation requiring treatment with antibiotics, systemic corticosteroids (oral or intravenous), and/or a hospitalization within 6 weeks before screening or during screening and run-in. Detailed inclusion and exclusion criteria are provided in the online supplementary material.

Study Objectives

The primary objective was to demonstrate the superiority of glycopyrrolate 15.6µg b.i.d compared with placebo for FEV_1 standardized area under curve (AUC) between 0 and 12 hours post dose (FEV_1 $AUC_{0\text{-}12h}$) at Week 12. The secondary objectives were evaluation of glycopyrrolate compared with placebo in terms of lung function through trough FEV_1 (mean of FEV_1 measured at 23:15h and 23:45h post previous morning dose) at Day 2 and Week 12, standardized FEV_1 AUC between 0 and 4 hours post-dose ($AUC_{0\text{-}4h}$), 4 to 8 hours post-dose ($AUC_{4\text{-}8h}$), and 8 to 12 hours post-dose ($AUC_{8\text{-}12h}$) on Day 1 and Week 12, FEV_1 and FVC recording at the following time points relative to the morning dose: 5 and 15 min, 1, 2, 4, 8, and 12-hours post dose on Day 1 and Week 12. Additional lung function efficacy objectives were peak FEV_1 and FVC during 4 hours post morning dose on Day 1 and Week 12 and trough FVC on Day 2 and Week 12. The time (min) to achieve ≥100 mL improvement in FEV_1 from baseline on Day 1 was also evaluated to determine the onset of action.

Other secondary objectives included evaluation of dyspnea (assessed via the Transition Dyspnea Index [TDI] focal scores), health status (assessed via the St. George's Respiratory Questionnaire [SGRQ] total score) at Week 12, rescue medication use, and COPD symptoms reported using the patient electronic diary (e-diary) over the 12 week treatment period, which also confirmed study compliance. The percentage of patients who achieved the minimal clinically important difference (MCID) in SGRQ total score and TDI focal score in the glycopyrrolate and placebo treated groups was also analyzed. An exploratory objective of the study was to evaluate health status using the COPD assessment test (CAT) at Week 12.

Safety assessments included treatment-emergent adverse events (AEs), monitoring of vital signs (pulse rate, systolic and diastolic blood pressure), electrocardiography, and laboratory analyses (hematology, clinical chemistry assessments, and urinalysis). All serious cardio- and cerebro-vascular events (CCV), atrial fibrillation and atrial flutter, and all cases of death that occurred between randomization

and the end of the follow-up period were evaluated by an independent adjudication committee. Serious CCV events were adjudicated by major adverse cardiovascular event (MACE) outcome and atrial fibrillation/flutter events were adjudicated based on the new onset or recurrence/persistence of events.

Statistical Analysis

The full analysis set (FAS) included all randomized patients who received at least 1 dose of the study drug. The per-protocol set (PPS) included all patients in the FAS who did not have any major protocol deviations. The safety set included all patients who received at least 1 dose of the study drug. The FAS was used for the analysis of the primary objective and all other efficacy variables. The PPS was used for the supportive analysis of the primary variable. The safety set was used in the analysis of all safety variables.

FEV_1 $AUC_{0\text{-}12h}$ was calculated using the trapezoidal rule divided by length of time (12 hours).[9] For the analysis of the primary efficacy endpoint (FEV_1 $AUC_{0\text{–}12h}$), a mixed model for repeated measures was used. The model contained terms for treatment, baseline FEV_1, baseline smoking status, baseline ICS use, visit, treatment x visit interaction and baseline FEV_1 x visit interaction, with an unstructured covariance matrix. Secondary endpoints were analyzed using the same mixed model as used for the primary endpoint, with the respective baseline values replacing baseline FEV_1 as a covariate as necessary. The proportion of patients who achieved the MCID in the SGRQ total score and TDI focal score was analyzed using a logistic regression model. Details on the sample size estimation are given in the online supplementary material.

Results

Patient Disposition and Baseline Characteristics

Of the 1144 patients screened, 432 were randomized to glycopyrrolate (n=216) or placebo (n=216), and 414 patients (96%) completed the 12-week planned treatment phase (glycopyrrolate, n=209 [96.8%]; placebo, n=205 [94.9%]). Patients could continue to participate in the 12-week planned treatment phase even if they had permanently discontinued the study medication. The most common reason for study discontinuations was patient decision (glycopyrrolate, n=7; placebo, n=9) and 2 patients were discontinued in the placebo group due to lost to follow up.

Patient demographics and baseline clinical characteristics were comparable between the treatment groups (Table 1). Most of the enrolled patients were men (58.8%) and white (86.8%) with moderate airflow limitation (61.1%). Most of the patients belonged to the GOLD 2011 Group B (57.6%) and did not have COPD exacerbations in the year prior to study entry (78.0%).

Efficacy

Lung Function

The study met its primary objective with glycopyrrolate demonstrating significant improvement compared with placebo ($p<0.001$) in change from baseline in FEV_1 $AUC_{0\text{-}12h}$ at Week 12 (Figure 2). Both at Day 1 and Week 12, FEV_1 $AUC_{0\text{-}12h}$ was higher with glycopyrrolate ($p<0.001$) compared with placebo, with a statistically significant and clinically meaningful treatment difference[10] of 119mL and 123mL, respectively (Figure 2). The results of the PPS analysis (Week 12) were consistent with the primary analysis (treatment difference 128mL; 95% confidence interval 84, 171mL; $p<0.001$).

Improvement in FEV_1 $AUC_{0\text{-}12h}$ with glycopyrrolate versus placebo in all the subgroups based on age, sex, airflow limitation, baseline smoking status, and ICS use at baseline was generally consistent with the overall study population (Figure 3). Superior bronchodilation with glycopyrrolate was supported by statistically significant improvement in trough FEV_1 on Day 2 which was maintained at all timepoints through Week 12 (both Days 85 and 86) (Figure 4) confirming benefits with respect to trough FEV_1 for twice-daily glycopyrrolate. Glycopyrrolate showed an early onset of bronchodilation with statistically significant improvements in FEV_1 at 5 and 15 minutes post-dose compared with placebo at Day 1 and Week 12 (all $p<0.001$; Figure 5A and 5B). Serial spirometry showed significantly higher improvements in FEV_1 with glycopyrrolate versus placebo at all individual post-baseline timepoints from 0 to 12 hours during the study ($p<0.001$ at all timepoints; Figure 5A and 5B) . Similarly, FVC at all timepoints from 0 to 12 hours post dose at Day 1 and Week 12 was significantly improved with glycopyrrolate versus placebo (data not shown).

At Week 12, peak FEV_1 and peak FVC for glycopyrrolate were significantly higher compared to placebo (peak FEV_1 treatment difference 148mL; $p<0.001$ and peak FVC treatment difference 201mL;

Table 1. Baseline Demographics and Clinical Characteristics

	GLY (15.6 µg b.i.d.) N=216	PBO N=216
Age, years	63.9 (8.55)	64.2 (8.41)
Men, n (%)	128 (59.3)	126 (58.3)
Race, n (%)		
White	190 (88)	185 (85.6)
Black	19 (8.8)	27 (12.5)
Smoking History, n (%)		
Ex-smoker	101 (46.8)	101 (46.8)
Current smoker	115 (53.2)	115 (53.2)
Severity of COPD[a], Airflow Limitation, n (%)		
GOLD 2	139 (64.4)	125 (57.9)
GOLD 3	73 (33.8)	85 (39.4)
Severity of COPD[a], Combined Assessment of COPD, n (%)		
GOLD B	133 (61.6)	116 (53.7)
GOLD D	78 (36.1)	94 (43.5)
Duration of COPD (years)	6.6 (4.7)	7.2 (5.4)
COPD Exacerbation History, n (%)		
0	176 (81.5)	161 (74.5)
1	30 (13.9)	40 (18.5)
≥2	10 (4.6)	15 (6.9)
Discontinuation of LAMA prior to baseline, n (%)	72 (33.3)	54 (25.2)
Discontinuation of ICS/LABA prior to baseline, n (%)	72 (33.3)	74 (34.6)
ICS Use at Baseline, n (%)	68 (31.5)	70 (32.4)
mMRC Dyspnea Scale, n (%)		
Grade 2	141 (65.3)	130 (60.2)
Grade 3	66 (30.6)	75 (34.7)
Grade 4	8 (3.7)	10 (4.6)
Number of Pack Years	50.6 (25.34)	50.5 (23.59)
BDI Focal Score	5.8 (1.95)	6 (1.93)
SGRQ Total Score	48.7 (16.37)	49.9 (16.9)
CAT Score	19.1 (7.49)	19.3 (8.06)
Pre-bronchodilator FEV_1 (L)	1.31 (0.45)	1.26 (0.46)
Post-bronchodilator FEV_1 (L)	1.53 (0.49)	1.48 (0.49)
Post-bronchodilator FEV_1, % Predicted	54.8 (12.77)	53.8 (13.59)
Post-bronchodilator FEV_1 Reversibility, %[b]	18.3 (12.88)	21.3 (21.27)

Data are presented as mean (standard deviation) unless otherwise stated.
[a]COPD severity is based on the GOLD 2011 criteria.
[b]Assessed after administration of 84 µg ipratropium bromide.
BDI=Baseline Dyspnea Index; CAT=COPD assessment test; COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; GOLD=Global initiative for chronic Obstructive Lung Disease; GLY=glycopyrrolate; ICS=inhaled corticosteroid; LABA=long-acting β2-agonist; LAMA=long-acting muscarinic antagonist; mMRC=modified Medical Research Council; PBO=placebo; SGRQ=St George's Respiratory Questionnaire

Pack years=total years of smoking multiplied by cigarette packs smoked/day

$p<0.001$; online supplementary material Table 1).

Health Status and Dyspnea

With respect to health status, glycopyrrolate showed a statistically significant and clinically relevant improvement in the SGRQ total score compared with placebo ($p<0.001$; Figure 6A) and 29.8% more patients in the glycopyrrolate group achieved a clinically relevant ≥4 units improvement versus placebo ($p<0.01$; Figure 6B). The TDI focal score showed a numerical reduction in dyspnea with glycopyrrolate compared with placebo (Figure 7A) but the difference was not statistically significant. Overall, more patients receiving glycopyrrolate (46.3%) achieved the MCID of ≥1 unit in dyspnea than those receiving placebo (39.5%; Figure 7B). The CAT score significantly improved by -1.5 units at Week 12 (online supplementary material Table 1).

Rescue Medication Use and Symptom Scores

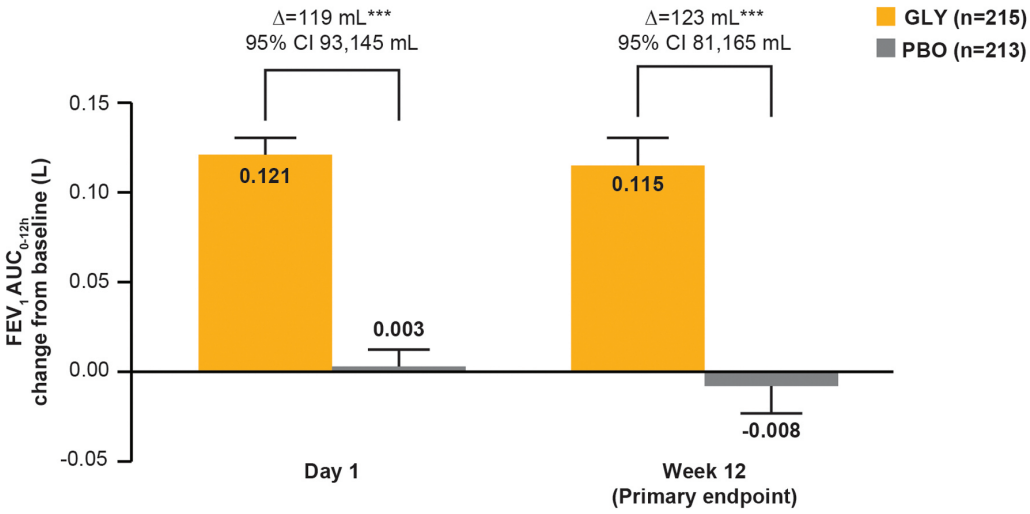
The change from baseline in the use of rescue medication was significantly lower in daily (treatment difference -0.53 puffs/day; $p<0.05$), daytime (treatment difference -0.30 puffs/day; $p<0.05$), and nighttime (treatment difference -0.25 puffs/night; $p<0.05$) number of puffs in patients treated with glycopyrrolate compared with placebo over the 12 week treatment period (online supplementary material Table 2). Glycopyrrolate also showed a significant improvement in the daily total symptom score (derived from data recorded in the patient e-diary) compared with placebo (online supplementary material Table 2).

Safety

Adverse events were reported for 111 (51.4%) patients in the glycopyrrolate group versus 91 (42.5%) patients in

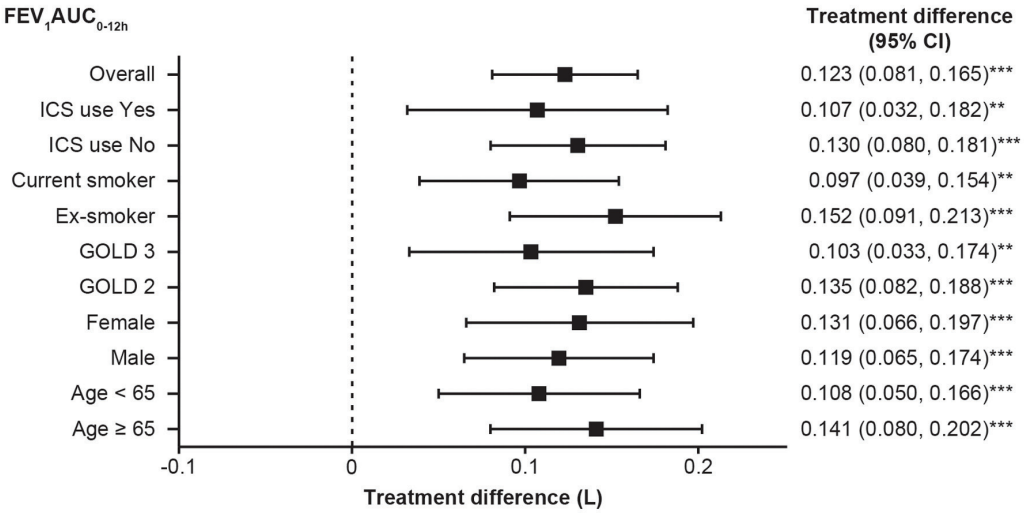
the placebo group (Table 2). The incidence of serious AEs (SAEs) was 4.2% with glycopyrrolate versus 2.3% with placebo (Table 2). The majority of SAEs were respiratory-related, and the incidence rate was the same across both treatment groups (1.9% in both the treatment groups). COPD (exacerbation) was the most commonly reported AE, and was comparable across the treatment groups (glycopyrrolate 20.8% versus placebo 21.5%; Table 2). Oropharyngeal related AEs (upper respiratory infection, nasopharyngitis, and oropharyngeal pain) that are commonly seen with orally inhaled LAMAs, occurred at low frequencies in both groups (Table 2). Potential anti-cholinergic AEs occurred infrequently with less than 1.5% of patients reporting urinary tract infections (Table 2) and less than 1% reporting dry mouth, constipation and bladder outflow obstruction and urinary retention. The majority of AEs reported during the treatment period were of mild or moderate severity; 5.6% of patients in the glycopyrrolate group and 2.8% in the placebo group experienced severe AEs. No death occurred in either group. The proportion of patients who discontinued the study treatment due to AEs (with COPD being the most common AE [≥1% in any group] leading to discontinuation) and SAEs was similar between the treatment groups (Table 2). An adjudicated serious CCV AE was reported for 1 patient in the glycopyrrolate group only; this event was adjudicated as MACE and classified as a non-fatal myocardial infarction. No patient in the placebo group had an adjudicated serious CCV event. Atrial fibrillation/flutter events occurred in 4 patients (1.9%) in the glycopyrrolate

Figure 2. FEV_1 $AUC_{0\text{-}12h}$ (FAS)



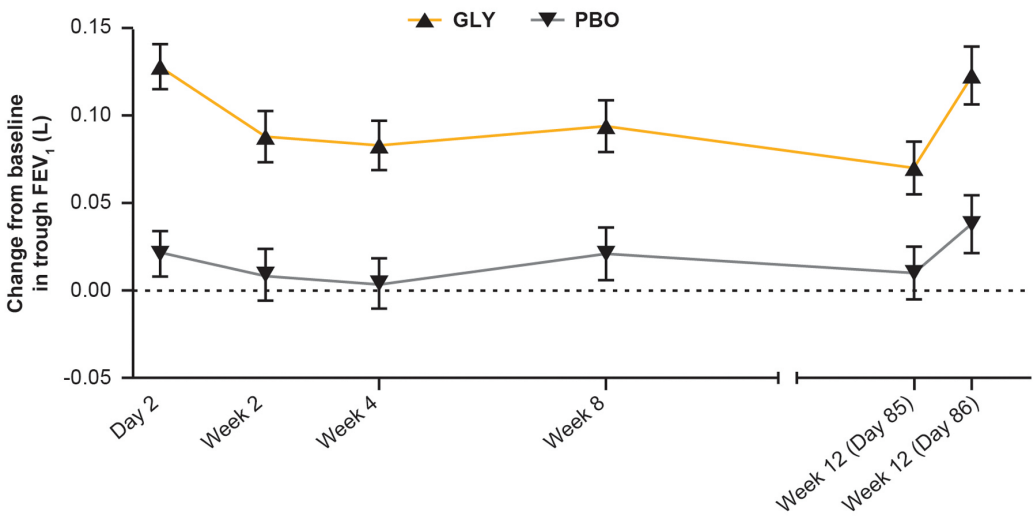
Data are least squares mean (standard error).
n=number of patients included in the analysis per treatment group.
AUC_{0-12h}= area under the curve from 0 to 12 hours is defined as the mean FEV_1 over 0 to 12 hours;
FAS=full analysis set; FEV_1=forced expiratory volume in 1 second; GLY=glycopyrrolate; PBO=placebo.
***p<0.001 GLY versus PBO

Figure 3. Analysis of The Primary Endpoint FEV_1 $AUC_{0\text{-}12h}$ Overall and by Subgroup



CI=confidence interval, GOLD=Global initiative for chronic Obstructive Lung Disease.
ICS=Inhaled corticosteroid.
**p<0.01, ***p<0.001 versus placebo

Figure 4. Trough FEV_1



Note break in x-axis. Trough FEV_1 was measured at visits on Days 2, 15, 29, 57, 85 and 86.

Differences between GLY and PBO were significant ($p<0.001$) at each visit during the treatment period. Trough FEV_1 on Day 2 and Day 86 is the mean of FEV_1 at 23 hours 15 minutes and 23 hours 45 minutes after the morning dose of the previous day and the mean of FEV_1 at -45 minutes and -15 minutes before morning dose at all other visits.

Data are least-squares means; error bars show standard error.

FEV_1=forced expiratory volume in 1 second; GLY=glycopyrrolate; PBO=placebo; Number of patients included in the analysis, GLY (n=208-213); PBO (n=204-208)

group compared to 1 patient (0.5%) in placebo, of which new onset events were reported by 2 patients (0.9%) in the glycopyrrolate group versus none in the placebo group. The proportion of patients with newly occurring or worsening clinically notable Fridericia's corrected QT interval (QTcF) values was similar between the treatment groups. One patient in the glycopyrrolate group had a QTcF value >480 msec. No meaningful differences between treatment groups were seen for laboratory evaluations and clinically notable vital signs.

Discussion

Bronchodilation with a LAMA and/or LABA is central to the management of COPD.[1] As per the current clinical guidelines, LAMAs are recommended as a potential first choice therapy, alone or in combination, for patients at high risk of exacerbations.[1] Glycopyrrolate 15.6µg twice-daily provides an additional LAMA option which has proven to be clinically effective with an early onset of bronchodilatory action and is generally well tolerated with a low incidence of anticholinergic effects, as shown in this study. The overall results of the GEM2 study demonstrate that twice-daily glycopyrrolate is efficacious and safe compared with placebo in patients with moderate-to-severe COPD. The selection of the glycopyrrolate dose used in this study was based on the findings of a dose-ranging study in which glycopyrrolate 15.6µg b.i.d. was demonstrated as an effective dose that showed clinically meaningful improvement in trough FEV_1 versus placebo.[8]

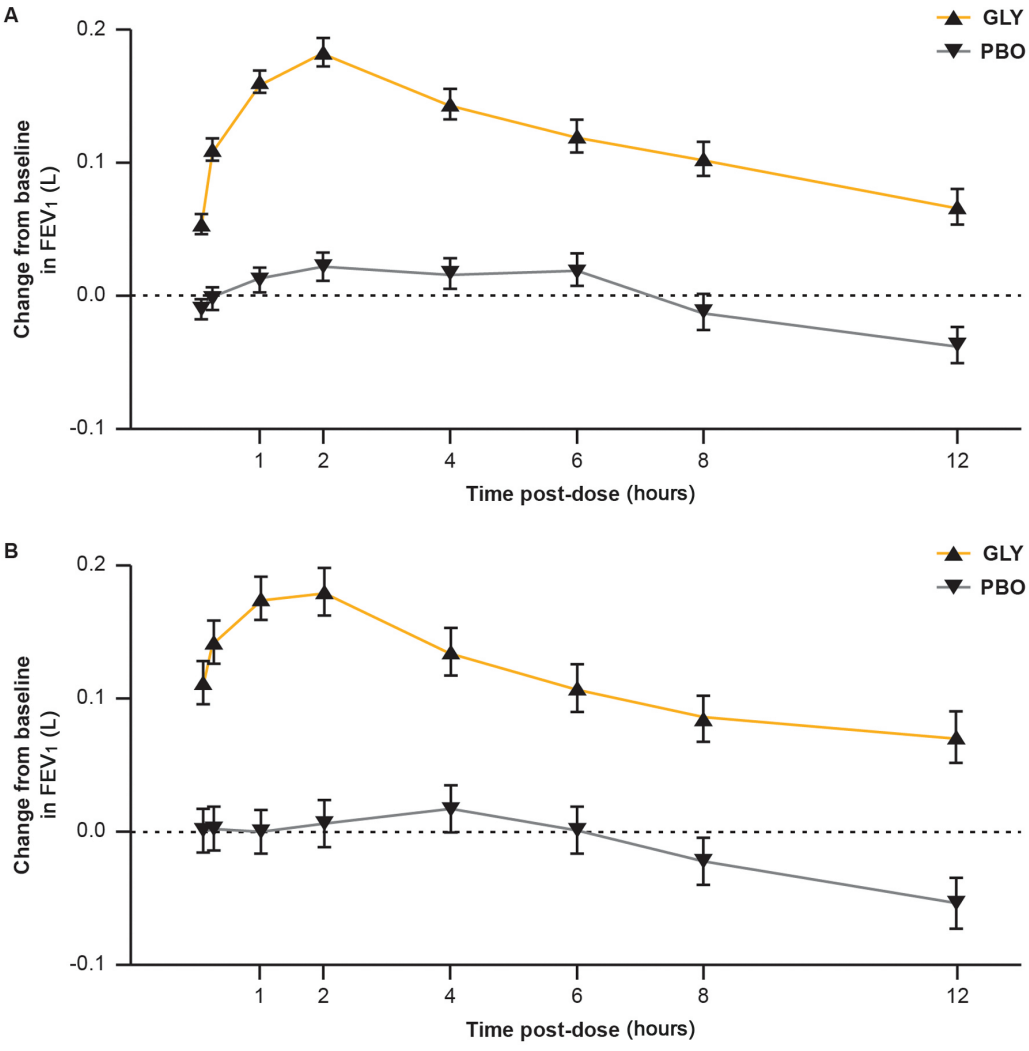
The study met its primary objective with glycopyrrolate demonstrating superiority to placebo in terms of FEV_1 $AUC_{0\text{-}12h}$ at Week 12. The magnitude of improvement (glycopyrrolate versus placebo) was 123mL, which was considered clinically meaningful thus supporting the efficacy of glycopyrrolate 15.6µg b.i.d. Glycopyrrolate was also statistically significantly superior to placebo for this endpoint on Day 1. Other secondary lung function parameters supported the primary endpoint with significant improvements in trough FEV_1, pre-dose trough FEV_1, peak FEV_1, peak FVC, and FVC $AUC_{0\text{-}12h}$. Bronchodilation with glycopyrrolate was evident at Day 1 and was maintained over the 12-week treatment duration. Compared to the GLOW1[4] and GLOW2[5] studies, generally, similar improvements in lung function were seen with glycopyrrolate versus placebo in this study at Week 12 (least square mean [LSM] treatment difference [trough FEV_1] 108 to 97mL in GLOW1 and GLOW2 studies [12-week data], respectively, versus 86mL in this study). Notably, glycopyrrolate in this study has shown similar lung function improvement compared to other twice-daily LAMAs such as aclidinium in the ACCORD COPD II trial (change from baseline in trough FEV_1 was 51 and 72mL versus placebo at doses of 200µg and 400µg respectively).[11] Of note, patient baseline characteristics, disease history and severity were comparable between the glycopyrrolate and placebo groups.

As per the GOLD guidelines, an improvement in symptoms is an important goal in the disease

management of patients with COPD.[1] Clinical guidelines and systematic reviews suggest that the effectiveness of COPD treatments should not be assessed by lung function alone but should also include a variety of other measures, in particular patient-reported outcomes such as dyspnea, health related quality of life and improved exercise endurance.[1,12,13] Also, there is clear evidence that improvements in mean trough FEV_1 is associated with improvements in SGRQ.[14] In this study, glycopyrrolate showed significant improvements in health status, mean daily total symptom scores and mean daily rescue medication use over 12 weeks' treatment and these were generally consistent with the known efficacy results of glycopyrrolate from other clinical trials.[15] The reduced usage of rescue medication in patients receiving glycopyrrolate compared with placebo also suggests an improvement in symptoms. This overall improvement was also reflected in the SGRQ total scores which correlated well with symptom and rescue medication parameters. MCID for the SGRQ is a reduction of 4 units in the total score and is well established.[16] In this study, the proportion of patients who achieved the MCID in the SGRQ total score was significantly higher with glycopyrrolate than with placebo. In addition, CAT was also used as an exploratory objective to evaluate the improvement in health status and it was observed that glycopyrrolate significantly improved the CAT score compared with placebo. With regards to dyspnea, there was a trend towards improvement in TDI focal score which might have achieved significance with longer study duration.

The safety profile of glycopyrrolate 15.6µg b.i.d observed in this study was consistent with the known safety profile of glycopyrrolate.[5,7,8,17,18] Anti-muscarinic side effects, such as dry mouth, constipation, urinary retention, and urinary tract infections, occurred with a low frequency in both the

Figure 5. Serial Measurements of FEV_1 by Timepoints (0-12h Post Dose) on (A) Day 1 and (B) Week 12



Data are least squares mean (standard error). First 2 time points shown in graph are 5 min and 15 min post dose. Treatment differences: $p<0.001$ for GLY versus PBO at each assessed timepoint.

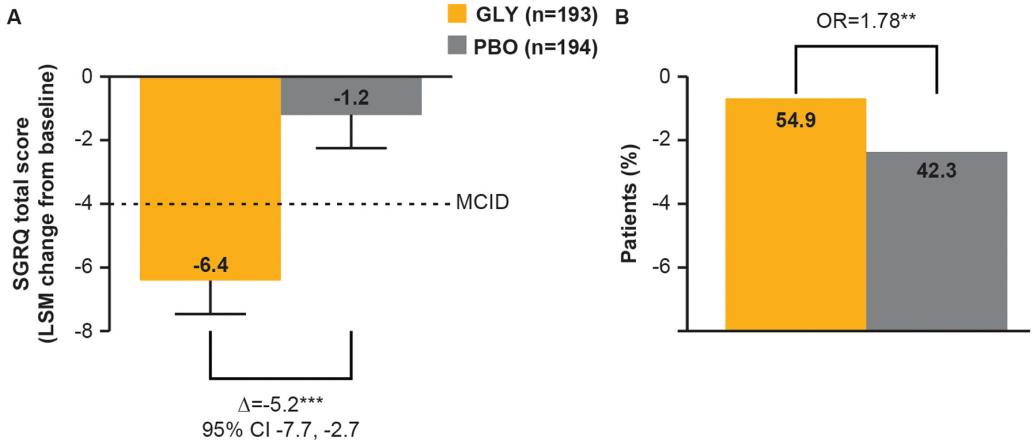
FEV_1=forced expiratory volume in 1 second; GLY=glycopyrrolate; PBO=placebo.

(A) Number of patients included in the analysis: GLY (n=203-215). PBO (n=202-213)
(B) Number of patients included in the analysis: GLY (n=203-215). PBO (n=202-213)

treatment groups. Overall, glycopyrrolate 15.6µg b.i.d. was generally well tolerated over a treatment period of 12 weeks. In spite of some minor imbalances in the frequency of some individual AEs, no clinically relevant differences between the groups could be observed with respect to any type of AE. In patients with moderate-to-severe COPD, it had been previously demonstrated that glycopyrrolate was well tolerated and had a similar incidence of MACEs, when compared with placebo or active treatments.[4,7] Similarly, in this study, based on the adjudicated findings, there was no imbalance in MACEs between the treatment groups and no deaths were observed in either group. The incidence of atrial fibrillation/flutter was low and comparable to that reported with other marketed LAMAs such as umeclidinium and tiotropium.[19]

The study has certain limitations. First, it should be considered that the study duration of 12 weeks with the current sample size was not powered for analysis of exacerbations or for the assessment of some of the patient-reported outcomes. Similarly, the long-term safety profile could not be established in a 12-week study. Furthermore, no active comparator arm was included. Longer duration studies or studies enriched for COPD exacerbations would be needed to further clarify effects on exacerbations and long term safety findings.

Figure 6. SGRQ Total Score at Week 12 (FAS)

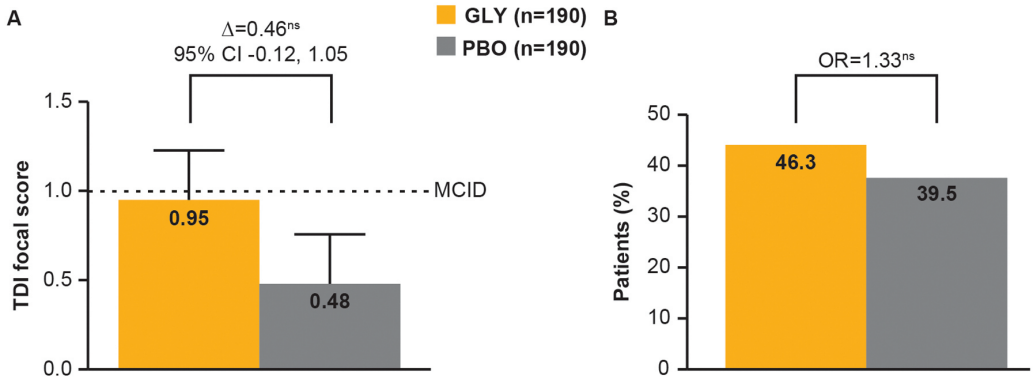


(A) LSM Change From Baseline in SGRQ Total Score and

(B) Percentages of Patients Achieving the Minimum Clinically Important Difference (≥4 Units) in SGRQ Score

Data are LSM (standard error) in Figure 6A. FAS=full analysis set; GLY=glycopyrrolate; LSM=least squares mean; PBO=placebo; SGRQ=St.George's Respiratory Questionnaire; MCID=minimal clinically important difference. OR=odds ratio; **p<0.01, ***p<0.001, GLY versus PBO

Figure 7. TDI Focal Score at Week 12 (FAS)



A) TDI Focal Score and
(B) Percentages of Patients Achieving the Minimum Clinically Important Difference (≥1 Units) (FAS)

Data are LSM (Standard error) in Figure 7A. FAS=full analysis set; GLY=glycopyrrolate; LSM, least squares mean; ns=not significant; OR=odds ratio; PBO=placebo; TDI=transition dyspnea index

Conclusion

The results from the GEM2 study demonstrated that twice-daily glycopyrrolate 15.6µg showed an early onset of action, apparent within 5 and 15 minutes post-dose and sustained 24-hour bronchodilation over 12 weeks compared with placebo. Glycopyrrolate also showed statistically significant improvements in COPD symptoms, health status, and rescue medication use. Overall, glycopyrrolate 15.6µg b.i.d. was generally well tolerated in patients with moderate-to-severe COPD.

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Table 2. AEs and Serious AEs (≥1% of Patients in Either Treatment Group) and Death (Safety Set)

	GLY (15.6 µg b.i.d.) N=216	PBO N=216
Patients with any AE	111 (51.4)	91 (42.5)
Preferred term		
COPD[a]	45 (20.8)	46 (21.5)
Upper Respiratory Tract Infection	7 (3.2)	3 (1.4)
Cough	6 (2.8)	6 (2.8)
Back Pain	5 (2.3)	1 (0.5)
Nasopharyngitis	5 (2.3)	2 (0.9)
Oropharyngeal Pain	5 (2.3)	1 (0.5)
Candida Infection	3 (1.4)	0
Cellulitis	3 (1.4)	0
Dizziness	3 (1.4)	2 (0.9)
Urinary Tract Infection	3 (1.4)	3 (1.4)
Rhinitis Allergic	3 (1.4)	0
Sinusitis	3 (1.4)	2 (0.9)
Gastroenteritis Viral	2 (0.9)	3 (1.4)
Diarrhea	2 (0.9)	3 (1.4)
Dyspnea	3 (1.4)	3 (1.4)
Upper Respiratory Tract Infection, viral	2 (0.9)	3 (1.4)
Headache	2 (0.9)	7 (3.3)
Peripheral Edema	1 (0.5)	3 (1.4)
Bronchitis	0	4 (1.9)
Rhinorrhea	1 (0.5)	3 (1.4)
Nasal Congestion	0	5 (2.3)
Patients with SAE(s)	9 (4.2)	5 (2.3)
COPD[a]	3 (1.4)	3 (1.4)
Discontinuation of Study Treatment		
Due to AEs	10 (4.6)	9 (4.2)
Due to SAEs	2 (0.9)	2 (0.9)
Due to non-SAEs	8 (3.7)	7 (3.3)
Deaths	0	0

Data are presented as n (%) unless otherwise stated;
AEs=adverse events; b.i.d.=twice-daily; COPD=chronic obstructive pulmonary disease; GLY=glycopyrrolate; PBO=placebo; SAEs=serious adverse events;
[a]worsening of COPD which includes COPD exacerbation

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Declaration of Interest

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References

1. Global initiative for chronic Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2015. GOLD website. www.goldcopd.com. Published 2015. Accessed January 2016.
2. American Thoracic Society and European Respiratory Society. Standards for the Diagnosis and Management of Patients with COPD, 2004. American Thoracic Society website. http://www.thoracic.org/copd-guidelines/ Published 2004. Accessed January 2016.
3. European Medicines Agency. Seebri breezhaler, glycopyrronium bromide: summary of product characteristics. European Medicines Agency website. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002430/WC500133769.pdf. Accessed January 2016.
4. D'Urzo A, Ferguson GT, van Noord JA, et al. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. *Respir Res*. 2011;12:156. doi: http://dx.doi.org/10.1186/1465-9921-12-156
5. Kerwin E, Hebert J, Gallagher N, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. *Eur Respir J*. 2012; 40(5):1106-1114. doi:http://dx.doi.org/10.1183/09031936.00040712
6. Haddad EB, Patel H, Keeling JE, et al. Pharmacological characterization of the muscarinic receptor antagonist, glycopyrrolate, in human and guinea-pig airways. *Br J Pharmacol*. 1999;127(2):413-20. doi:http://dx.doi.org/10.1038/sj.bjp.0702573
7. D'Urzo A, Kerwin E, Overend T, et al. Once daily glycopyrronium for the treatment of COPD: pooled analysis of the GLOW1 and GLOW2 studies. *Curr Med Res Opin*. 2014;30(3):493-508. doi:http://dx.doi.org/10.1185/03007995.2013.858618
8. Arievich H, Overend T, Renard D, et al. A novel model-based approach for dose determination of glycopyrronium bromide in COPD. *BMC Pulm Med*. 2012;12:74. doi: http://dx.doi.org/10.1186/1471-2466-12-74
9. Mysovskikh IP. Trapezium formula. Encyclopedia of Mathematics website. http://www.encyclopediaofmath.org/index.php?title=Trapezium_formula&oldid=12696. Updated February 7, 2011. Accessed January 2016.
10. Cazzola M, MacNee W, Martinez FJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J*. 2008;31(2):416-469. doi: http://dx.doi.org/10.1183/09031936.00099306
11. Rennard SI, Scanlon PD, Ferguson GT, et al. ACCORD COPD II: a randomized clinical trial to evaluate the 12-week efficacy and safety of twice-daily aclidinium bromide in chronic obstructive pulmonary disease patients. *Clin Drug Invest*. 2013;33(12):893-904. doi: http://dx.doi.org/10.1007/s40261-013-0138-1
12. Westwood M, Bourbeau J, Jones PW, et al. Relationship between FEV_1 change and patient-reported outcomes in randomised trials of inhaled bronchodilators for stable COPD: a systematic review. *Respir Res*. 2011;12:40. doi:http://dx.doi.org/10.1186/1465-9921-12-40
13. Glaab T, Vogelmeier C, Buhl R. Outcome measures in chronic obstructive pulmonary disease (COPD): strengths and limitations. *Respir Res*. 2010;11:79. doi: http://dx.doi.org/10.1186/1465-9921-11-79
14. Global initiative for chronic Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2014. GOLD website. www.goldcopd.com. Published 2014. Accessed January 2016.
15. Ulrik CS. Once-daily glycopyrronium bromide, a long-acting muscarinic antagonist, for chronic obstructive pulmonary disease: a systematic review of clinical benefit. *Int J Obstruct Pulmon Dis*. 2012;7:673-678. doi: http://dx.doi.org/10.2147/COPD.S35990
16. Jones PW, Beeh KM, Chapman KR, et al. Minimal clinically important differences in pharmacological trials. *Am J Respir Crit Care Med*. 2014;189(3):250-255. doi: http://dx.doi.org/10.1164/rccm.201310-1863PP
17. Vogelmeier C, Verkindre C, Cheung D, et al. Safety and tolerability of NVA237, a once-daily long-acting muscarinic antagonist, in COPD patients. *Pulm Pharmacol Ther*. 2010; 23(5):438-444. doi: http://dx.doi.org/10.1016/j.pupt.2010.04.005
18. Verkindre C, Fukuchi Y, Flemale A, et al. Sustained 24-h efficacy of NVA237, a once-daily long-acting muscarinic antagonist, in COPD patients. *Respir Med*. 2010; 104(10):1482-1489. doi: http://dx.doi.org/10.1016/j.rmed.2010.04.006
19. Manickam R, Asija A, Aronow WS. Umeclidinium for treating COPD: an evaluation of pharmacologic properties, safety and clinical use. *Expert Opin Drug Saf*. 2014;13(11):1555-1561. doi: http://dx.doi.org/10.1517/14740338.2014.968550