*Online Supplementary Data*

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

## Methods

### Inclusion and Exclusion Criteria

*Inclusion Criteria*

- Male or female adults aged ≥ 40 years, who had signed an informed consent form before initiation of any study-related procedure

- Patients with stable, symptomatic COPD with airflow obstruction of level 2 and 3 according to the current Global initiative for chronic Obstructive Lung Disease (GOLD) strategy (GOLD 2011)

- Current or ex-smokers with a smoking history of at least 10 pack years (10 pack years was defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years). An ex-smoker was defined as a patient who had not smoked for ≥ 6 months at screening.

- Patients with a post-bronchodilator forced expiratory volume in 1 second ($FEV_1$) ≥30% and < 80% of the predicted normal, and a post-bronchodilator $FEV_1$/forced vital capacity (FVC) < 0.70 at run-in visit. Post-bronchodilator referred to 45 minutes after inhalation of 84 μg ipratropium bromide (or equivalent dose)

*Exclusion Criteria*

- Patients with Type I or uncontrolled Type II diabetes
- Patients with a history of long QT syndrome or whose corrected QT (QTc) measured at run-in visit (Fridericia method) was prolonged (> 450 ms for males and females) and confirmed by a central assessor. These patients were not to be re-screened

- Patients who had a clinically significant electrocardiogram (ECG) abnormality at run-in or baseline visits. These patients were not be re-screened

- Patients with a history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years regardless of whether there is evidence of local recurrence or metastasis

- Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive β-hCG laboratory test

- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using effective methods of contraception during dosing of study treatment. Women were considered post-menopausal and not of child bearing potential if they had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks before. In the case of oophorectomy alone, only when the reproductive status of the woman was confirmed by follow up hormone level assessment, was she considered not of child-bearing potential

- Patients who in the judgment of the investigator, would be at potential risk if enrolled into the study
- Patients who had a clinically significant laboratory abnormality at run-in visit
- Patients with a body mass index (BMI) of more than 40 $kg/m^2$

- Patients with clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, New York Health Authority (NYHA) Class III/IV left ventricular failure, myocardial infarction), arrhythmia, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities that could interfere with the assessment of the efficacy and safety of the study treatment

- Patients with paroxysmal (e.g. intermittent) atrial fibrillation. Patients with persistent atrial fibrillation defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (e.g., beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months could be considered for inclusion. In such patients, atrial fibrillation had to be present at run-in and baseline visits, with a resting ventricular rate of < 100/min

- Patients contraindicated for treatment with, or having a history of reactions/hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof: anticholinergics, long-/short-acting $\beta_2$-agonists, sympathomimetic amines, lactose, or any of the other excipients

- Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction, severe renal impairment or urinary retention (Benign prostatic hyperplasia patients who were stable on treatment could be considered)

- Patients who had not achieved acceptable spirometry results at screening (run-in visit) in

accordance with American Thoracic Society and European Respiratory Society Task Force: Standardization of Lung Function Testing (ATS/ERS) criteria for acceptability and repeatability and spirometry guidance

- Patients who had a COPD exacerbation that required treatment with antibiotics, systemic steroids and/or hospitalization in the 6 weeks before pre-screening. Patients could be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation;

- Patients who had a COPD exacerbation between the pre-screening and randomization visits were not eligible but were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation;

- Patients who had a respiratory tract infection within 4 weeks prior to pre-screening. Patients who developed a respiratory tract infection between screening period and treatment were not eligible, but were permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection;

- Patients requiring long-term oxygen therapy prescribed for >12 hours per day;

- Patients with any history of asthma;

- Patients with a blood eosinophil count of >600/$mm^3$ (during run-in visit);

- Patients with an onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years;

- Patients with allergic rhinitis who were using an H1 antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose or regimen was permitted);

- Patients with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension);

- Patients with clinically significant bronchiectasis;

- Patients with a diagnosis of alpha-1 antitrypsin deficiency;

- Patients with active pulmonary tuberculosis, unless confirmed by imaging to be no longer active;

- Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation;

- Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study. Participation in a maintenance program was permitted;

- Patients receiving any medications in the classes listed in the study protocol;

- Use of other investigational drugs/devices (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever was longer, or previous participation in the GEM1 replicate study

- Patients unable to use an e-diary;

- Patients unable to use a dry powder inhaler device or a pressurized metered-dose inhaler (pMDI) (rescue medication) or comply with the study regimen. Spacer devices were not permitted;

- Investigational site staff, their immediate family, or sponsor staff connected with this study, were to be excluded from participation in this trial;

**Randomization and Blinding**

All eligible patients were randomized via the Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate contacted the IRT after confirming that the patient fulfilled all inclusion / exclusion criteria. Randomization was stratified by smoking status (current smoker, ex-smoker). A randomization ratio of 1:1 was used and the balance was maintained at the country level (USA). Patients, investigator staff, persons performing the assessments and data analysts remained blinded to the identity of the treatment that a patient had been randomized to from the time of randomization until database lock.

**Sample size calculation**

A difference of 100 mL between glycopyrrolate and placebo in terms of $FEV_1AUC_{0-12}$ at Week 12 was assumed for the sample size calculation. A standard deviation (SD) of 200 mL was assumed based on data from other Novartis sponsored COPD clinical studies, 86 completers per arm gave 90% power with a type I error of 0.05. In addition, 191 completers per arm gave 85% power to detect a treatment difference of 4 units between glycopyrrolate and placebo for the SGRQ total score at the level of 0.05, assuming a SD of 13 units. A drop-out of 10% was assumed therefore it was planned to randomize approximately 426 patients (or 213 randomized patients per arm) into the study.

**Supplementary Table 1: Treatment Differences Between Glycopyrrolate and Placebo for Other Secondary Efficacy Outcomes (FAS)**

| | Treatment difference GLY versus PBO (LSM [95% CI]) | |
|---|---|---|
| Parameters | Day 1 | Week 12 |
| Pre-dose trough $FEV_1$ (L) | --- | 0.061 (0.020, 0.102)** |
| Peak $FEV_1$ (L) | 0.137 (0.112, 0.162)*** | 0.148 (0.103, 0.193)*** |
| Peak FVC (L) | 0.223 (0.177, 0.268)*** | 0.201 (0.128, 0.274)*** |
| Trough FVC (L)[a] | 0.171 (0.110, 0.232)*** | 0.130 (0.055, 0.205)*** |
| $FEV_1$ AUC $_{0\text{-}4h}$ (L) | 0.141 (0.117, 0.164)*** | 0.149 (0.105, 0.193)*** |
| $FEV_1$ AUC $_{4\text{-}8h}$ (L) | 0.107 (0.078, 0.136)*** | 0.107 (0.064, 0.151)*** |
| $FEV_1$ AUC $_{8\text{-}12h}$ (L) | 0.106 (0.074, 0.138)*** | 0.108 (0.063, 0.152)*** |
| CAT score | --- | –1.5 (–2.7, –0.4)** |

[a]Day 2 and Day 86 data is given for trough FVC. **p<0.01, ***p<0.001 versus PBO; CAT=COPD assessment test; CI=confidence interval; FAS=full analysis set; $FEV_1$=forced expiratory volume in 1 second; FVC=forced vital capacity; LSM=least squares mean; GLY=glycopyrrolate; PBO=placebo

**Supplementary Table 2. Improvement in Symptom Scores and Reduction in Rescue Medication Use With Glycopyrrolate Versus Placebo Over the 12 Week Treatment Period**

| Parameters | Treatment difference GLY versus PBO (LSM [95% CI]) |
|---|---|
| **Symptom Scores (change from baseline)** | |
| Daily total symptom score | –0.29 (–0.57, –0.01)* |
| Daytime total symptom score | –0.25 (–0.51, 0.02) |
| Nighttime total symptom score | –0.27 (–0.54, 0.00) |
| Percentage of nights with no nighttime awakenings | 3.9 (–0.2, 8.0) |
| Percentage of days with no daytime symptoms | 1.0 (–2.1, 4.1) |
| Percentage of days able to perform usual daily activities | 4.2 (–0.1, 8.6) |
| **Rescue Medication Use (change from baseline)** | |
| Daily number of puffs | –0.53 (–0.96, –0.10)* |
| Daytime number of puffs | –0.30 (–0.54, –0.06)* |
| Nighttime number of puffs | –0.25 (–0.46, –0.04)* |
| Percentage of days with no rescue medication use | 4.4 (–0.8, 9.7) |

CI=confidence interval; LSM=least squares mean; GLY=glycopyrrolate; PBO=placebo; SE=standard error; *p<0.05 versus placebo