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ORIGINAL RESEARCH

Early bronchodilator action of glycopyrronium versus tiotropium in moderate-to-severe COPD patients: a cross-over blinded randomized study (Symptoms and Pulmonary function in the moRnING)

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Background: Morning symptoms associated with COPD have a negative impact on patients' quality of life. Long-acting bronchodilators with rapid onset may relieve patients' symptoms. In the Symptoms and Pulmonary function in the moRnING study, we prospectively compared the rapid onset bronchodilator profile of glycopyrronium (GLY) and tiotropium (TIO) during the first few hours after dosing in patients with moderate-to-severe COPD.

Methods: Patients were randomized (1:1) to receive either once-daily GLY (50 µg) or TIO (18 µg) and corresponding placebos in a cross-over design for 28 days. The primary objective was to demonstrate the superiority of GLY versus TIO in area under the curve from 0 to 4 hours ($AUC_{0\text{-}4h}$) forced expiratory volume in 1 second (FEV_1) after the first dose. The secondary objective was to compare GLY versus TIO using the patient reported outcomes Morning COPD Symptoms Questionnaire 3 hours post-inhalation.

Results: One-hundred and twenty-six patients were randomized (male 70.2%; mean age 65.7 years) and 108 patients completed the study. On Day 1, GLY resulted in significantly higher FEV_1 $AUC_{0\text{-}4h}$ after the first dose versus TIO (treatment difference [Δ], 0.030 L, 95% confidence interval 0.004–0.056, P=0.025). Improvements in morning COPD symptoms from baseline at Days 1 and 28 were similar between GLY and TIO. Post hoc analysis of the FEV_1 $AUC_{0\text{-}4h}$ by time point on Day 1 showed significant improvements in patients receiving GLY versus TIO at 5 minutes (Δ=0.029 L, P=0.015), 15 minutes (Δ=0.033 L, P=0.026), and 1 hour (Δ=0.044 L, P=0.014). Safety results were comparable between both treatments.

Conclusion: The SPRING study demonstrates the superiority of GLY versus TIO in terms of superior bronchodilation in the first 4 hours after administration, thus extending the clinical data that support a faster onset of action of GLY versus TIO.

Keywords: LAMA, glycopyrronium, tiotropium, lung function, fast onset, rapid onset, patient reported outcome, COPD

Introduction

COPD is a progressive disease which impairs lung function resulting in breathlessness and ultimately affecting the quality of life.[1,2] These symptoms can be more severe in the morning, compromising the ability to perform even simple tasks and may be associated with an increased frequency of exacerbations.[2–4] Long-acting bronchodilators with a fast onset of

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action may relieve these morning symptoms and thus improve treatment compliance while decreasing dosing frequency.[5,6]

Inhaled bronchodilators like the long-acting muscarinic antagonist (LAMA) are central to the management of symptomatic patients with COPD as they improve lung function, reduce hyperinflation (both at rest and during exercise), and improve exercise performance.[1] Glycopyrronium (GLY) and tiotropium (TIO) are both once-daily LAMAs approved for the maintenance treatment of patients with COPD.[7] In previous studies, GLY has been shown to provide statistically significant improvements in trough forced expiratory volume in 1 second (FEV_1) versus placebo,[8,9] immediate and significant improvement in exercise tolerance,[10] and in a secondary endpoint analysis, a faster onset of action with greater levels of bronchodilation in the initial 4 hours following inhalation versus open label TIO.[9,11]

The "Symptoms and Pulmonary function in the moRnING" (SPRING) study aimed to compare prospectively and adequately powered, the bronchodilator efficacy profile of GLY and TIO during the first few hours after dosing. Additionally the impact on morning symptoms in patients with moderate-to-severe COPD was assessed.

Methods

Patients

Male and female patients aged ≥40 years, who were either current or ex-smokers with a smoking history of ≥10 pack-years, a clinical diagnosis of COPD confirmed by a post-bronchodilator FEV_1/forced vital capacity (FVC) ratio <0.70 and a FEV_1 between <80% and ≥40% of the predicted value, and a COPD Assessment Test score of ≥10 at baseline, were enrolled in this study.

Patients were excluded from this study, if they had a respiratory tract infection or exacerbation within 6 weeks before screening, were contraindicated to LAMA treatment, had a history of asthma, unstable cardiovascular disease/arrhythmias (including atrial fibrillation/flutter), or were concomitantly using agents known to prolong QT intervals (unless these were permanently discontinued during treatment).

Study design and treatments

This was a prospective, multicenter, randomized, blinded, two-period cross-over study in patients with moderate-to-severe COPD (ClinicalTrials.gov identifier: NCT01959516).

The study consisted of two cross-over 28-day treatment periods with a 14-day wash-out period in between and a 30-day post-treatment safety follow-up period (Figure 1). After screening, eligible patients were randomized (1:1) to receive either GLY (50 µg once-daily, delivered via the Breezhaler® device) or TIO (18 µg once-daily, delivered via the HandiHaler® device) and their corresponding placebos in a cross-over design for 28 days. The treatments were administered in the morning between 8 am and 11 am by a third party (un-blinded study nurse/center personnel) and the investigator remained blinded to both treatments. Patients were provided with a salbutamol inhaler to be used as rescue medication during the study.

The study was approved by institutional review boards and ethics committees at the participating centers: Ethik-Kommission bei der Landesärztekammer Hessen; Comitate Etico Area Vasta Centro; Comitato Etico Centrale

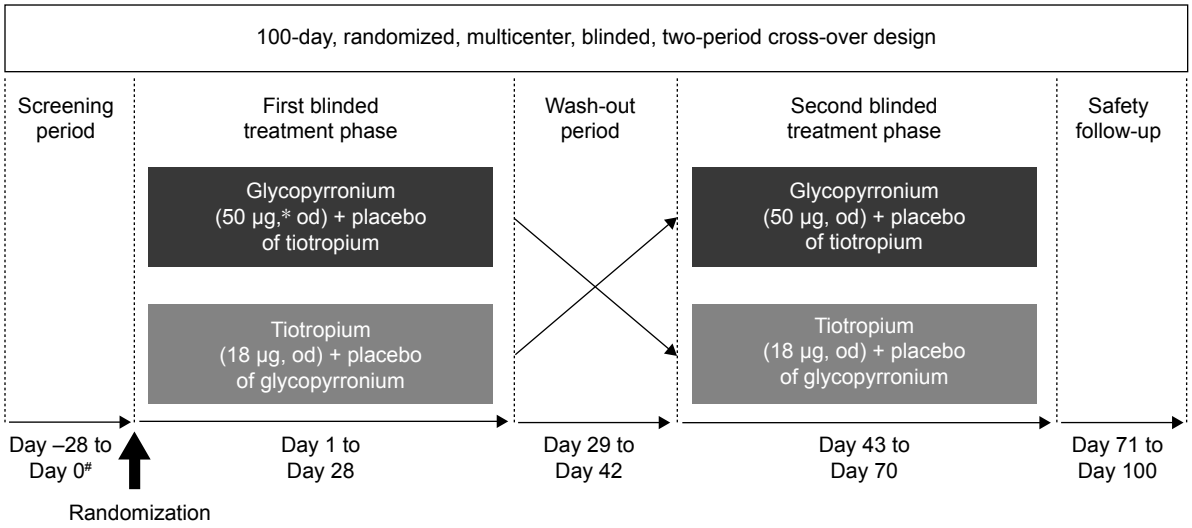

Figure 1 SPRING study design.
Notes: *50 µg refers to the quantity of glycopyrronium moiety present in the capsule, which corresponds to a delivered dose of 44 µg. #Patients on parenteral or oral corticosteroids therapy who may enter the study after 28-day wash-out period.
Abbreviations: od, once-daily; SPRING, Symptoms and Pulmonary function in the moRnING.

deii'IRCCS Fondazione Salvatore Maugeri (IRCCS) di Pavia; Cei dell'Azienda Ospedaliera Universitaria S. Luigi Gonzaga di Orbassano; CEIC Aragon (CEICA); and NRES Committee Yorkshire & The Humber – Leeds West, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. In order to participate in the study, all patients were required to provide written informed consent.

Assessments

The primary objective of the study was to demonstrate the superiority of GLY versus TIO in terms of least squares mean area under the curve from 0 to 4 hours (AUC_{0-4h}) of the FEV_1. A key secondary objective was to compare GLY versus TIO in terms of symptoms through patient reported outcomes (PRO)-Morning COPD Symptoms Questionnaire measurement, 3 hours after inhalation on Day 1 and Day 28 of treatment.

A post hoc analysis was carried out to compare the mean FEV_1 values of GLY versus TIO, after the first dose and after the dose given at Day 28 of treatment by time point, to support positive conclusions from the primary efficacy endpoint (FEV_1 AUC_{0-4h}). Additionally, the PRO-Morning COPD Symptoms Questionnaire total score pre-dose values were compared from Day 1 to Day 28 for each treatment.

Efficacy assessments

Spirometry (FEV_1 and FVC) was done in accordance with American Thoracic Society/European Respiratory Society standards.[12] Spirometry measurements were performed prior to the run-in period to determine eligibility. Thereafter, spirometry was performed during the treatment periods from Day 1 to Day 28 (first treatment sequence), Day 43 to Day 70 (second treatment sequence), and during premature discontinuation.

FEV_1 and FVC were recorded at the following time points relative to the morning dose: −15/10 minutes pre-dose, 5, 15, and 30 minutes, 1 hour, 2 hours, and 4 hours post-dose on Days 1, and 28; −15/10 minutes pre-dose, 5, 15, and 30 minutes, 1 hour and 4 hours post-dose on Days 43, and 70 after dosing.

PRO-Morning COPD Symptoms Questionnaire total score

The PRO-Morning COPD Symptoms Questionnaire is a paper-based self-administered PRO instrument developed by Novartis to evaluate patients' experience of early morning symptoms of COPD (see Table S1). This questionnaire represents the morning assessment of the COPD e-Diary that has been previously validated in patients with COPD.[13]

Briefly, the PRO-Morning COPD Symptoms Questionnaire comprised two parts ranging in scores from 0–60 with 0 representing no symptoms and 60 representing the worst severity of COPD morning symptoms. Part 1 of the questionnaire was completed by each patient at home, at the time of waking-up before inhalation and part 2 was completed on site, 3 hours after inhalation of the investigational medication. The questionnaire was completed by each patient on Days 1, 28, 43, and 70.

Safety assessments

Safety was assessed by recording all adverse events (AEs), serious AEs, and vital signs over the treatment period and during the 30-day follow-up period, after discontinuation of the study drug. AEs were coded using the Medical Dictionary of Regulatory Activities and summarized by preferred term, maximum severity, and relationship to the study drug.

Determination of sample size

A sample size of 120 patients (assuming a 10% dropout) was needed to provide the power (80%) to detect a 55 mL difference between GLY and TIO in FEV_1 AUC_{0-4h}. The superiority margin of 55 mL was considered based on earlier studies where GLY had been shown to be about 50–60 mL better than TIO[9,14] for FEV_1 AUC_{0-4h} at Day 1.

Statistical analysis

Three populations (intention-to-treat [ITT]; per protocol [PP]; and safety population) were defined for the purpose of analysis. The ITT population comprised of all randomized patients who received at least one dose of study medication and had at least one post-dose FEV_1 measurement. The PP population included all patients in the ITT population without any major protocol deviations. The safety population comprised of all patients who received at least one dose of study medication and were analyzed according to the treatment they received.

Efficacy analyses were performed based on the ITT and PP populations (primary endpoint only for the latter). All safety data were displayed for the safety population. The primary efficacy analysis was performed in both the ITT and PP populations (robustness check). The primary objective, superiority in terms of FEV_1 AUC_{0-4h} after the first dose would be demonstrated by a rejection of the null hypothesis at the two-sided 0.05 level.

The comparison between treatments for FEV_1 AUC_{0-4h} after the first dose of treatment was made using an analysis of covariance mixed model for cross-over designs, using period, and treatment as fixed effects, and patient as a random

effect. To adjust for the cross-level bias in the subject random effect model,[15] the model included subject average baseline FEV_1 AUC_{0-4h} and period-adjusted baseline correction FEV_1 AUC_{0-4h}. The spirometry data were summarized by treatment, time point, and visit. The secondary efficacy variable, ie, the PRO-Morning COPD Symptoms Questionnaire was analyzed using a similar mixed model in a 2×2 cross-over design and the total score and changes from baseline were summarized by treatments.

The post hoc analysis was performed using a mixed model for FEV_1 and PRO-Morning COPD Symptoms Questionnaire total score pre-dose. The model included period, treatment, and time point as fixed effects, subject as a random effect, and the interactions of time point with treatment and period-adjusted baseline. All statistical hypotheses were two-sided and were performed using a 5% significance level; SAS (version 9.4) was used to determine all efficacy variables.

Results

Patient disposition and baseline characteristics

The study was undertaken at 21 centers across four countries (Germany, Italy, Spain, and the United Kingdom). The first patient was enrolled on February 13, 2014; the last patient completed the study on October 27, 2014. A total of 166 patients were enrolled in this study, of whom 126 were randomized and 108 completed the study. Two randomized patients did not receive at least one dose of any study medication, thus resulting in 124 (98.4%) patients in the ITT and the safety follow-up population (Figure 2). Information on complete follow-up was available for all 124 patients, who received both treatments in the cross-over design (ie, GLY and TIO).

The mean time since COPD diagnosis was 7.6 years and a majority of patients had moderate COPD (71.0%). Twenty-nine percent (29.0%) of patients had a history of at least one exacerbation (mainly of moderate severity, 81.0%) in the previous year. A total of 117 (94.4%) of patients received at least one prior medication (LAMA [54.7%], long-acting β_2-agonist [32.5%] or inhaled corticosteroid [44.4%; either alone or as long-acting β_2-agonist/inhaled corticosteroid fixed-dose combination]) (Table 1).

Efficacy assessments

The least squares mean FEV_1 AUC_{0-4h} after the first dose of treatment was significantly higher in patients receiving GLY compared with patients receiving TIO, both in the ITT (treatment difference [Δ]=0.030 L, 95% confidence interval [CI]: 0.004–0.056, P=0.025) and in the PP analysis (Δ=0.029 L, 95% CI: 0.002–0.058, P=0.039) (Figure 3).

Post hoc analysis of FEV_1 AUC_{0-4h} after the first dose of treatment by time point further revealed a significantly higher improvement in patients receiving GLY versus TIO at 5 minutes

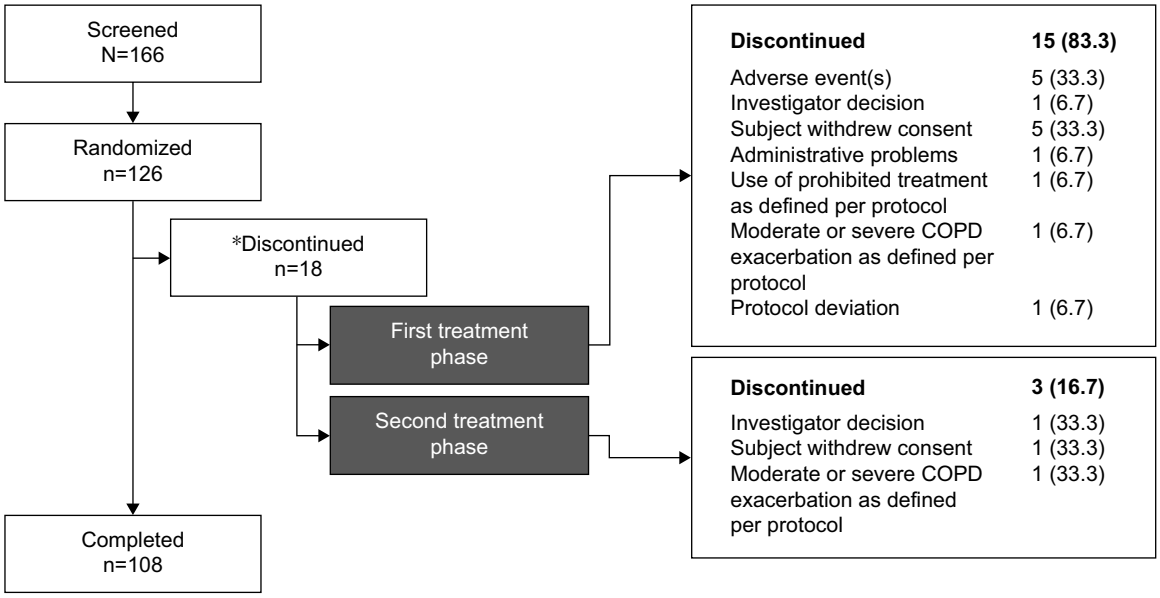

Figure 2 Disposition of patients during the study.
Notes: Values are n (%) unless otherwise stated. *Two randomized patients did not receive at least one dose of any study medication, thus resulting in 124 (98.4%) patients in the ITT and the safety follow-up population.
Abbreviation: ITT, intention-to-treat.

Table 1 Baseline characteristics (ITT population)

	n=124
Mean (SD) age (years)	65.7 (8.1)
Male, n (%)	87 (70.2)
Race, n (%)	
Caucasian	124 (100.0)
Mean BMI (SD) (kg/m^2)	27.9 (5.1)
Smoking history, n (%)	
Ex-smoker	64 (51.6)
Current smoker	60 (48.4)
Mean (SD) duration of smoking, pack-years	47.7 (23.6)
Mean (SD) duration of COPD, years	7.6 (5.9)
Severity of COPD (GOLD 2013), n (%)	
Moderate	88 (71.0)
Severe	19 (15.3)
Unknown*	17 (13.7)
Number of COPD exacerbations in the previous year, n (%)	
0	88 (71.0)
1	24 (19.4)
≥2	12 (9.7)
ICS use at baseline, n (%)**	52 (44.4)
Prior COPD medication use, n (%)	117 (94.4)
Mean (SD) post-bronchodilator FEV_1 (L)	1.7 (0.5)
Mean (SD) post-bronchodilator FEV_1 (% predicted)	60.6 (10.6)
Mean (SD) post-bronchodilator FEV_1 reversibility (%)	13.9 (12.7)
Mean (SD) post-bronchodilator FEV_1/FVC (%)	50.4 (8.9)

Notes: *Patients with unacceptable forced spirometry measurement; **n=117 patients (patients who received at least one prior COPD medication).
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; ITT, intention-to-treat; SD, standard deviation.

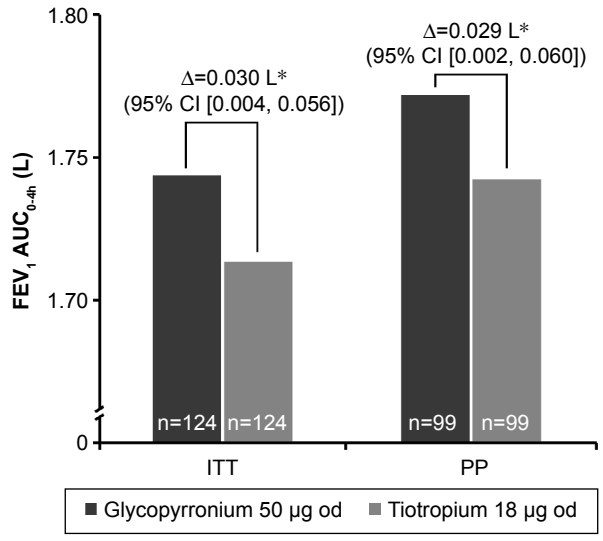

Figure 3 FEV_1 AUC_{0-4h} treatment differences between glycopyrronium and tiotropium post-first treatment dose on Day 1 (ITT and PP population).
Notes: *$P<0.05$; data are least squares means; Δ, treatment difference between glycopyrronium and tiotropium.
Abbreviations: FEV_1, forced expiratory volume in 1 second; AUC_{0-4h}, area under the curve from 0 to 4 hours; CI, confidence interval; ITT, intention-to-treat; od, once-daily; PP, per protocol.

(Δ=0.029 L, 95% CI: 0.006–0.052, P=0.015), 15 minutes (Δ=0.033 L, 95% CI: 0.004–0.062, P=0.026), and 1 hour (Δ=0.044 L, 95% CI: 0.009–0.079, P=0.014) (Figure 4).

No statistically significant difference in the least squares mean of FEV_1 AUC_{0-4h} was observed between GLY and TIO on Day 28 (see Figures S1 and S2).

PRO-Morning COPD Symptoms Questionnaire total score

The PRO-Morning COPD Symptoms Questionnaire scores from baseline to 3 hours after the first dose were similar between GLY and TIO on Day 1 (Δ=−0.69, 95% CI: −1.62 to 0.24, P=0.144) and Day 28 (Δ=0.15, 95% CI: −1.05 to 1.34, P=0.81).

Data were further analyzed using a post hoc analysis based on the change in PRO-Morning COPD Symptoms Questionnaire total scores from pre-dose values on Day 28 versus Day 1 for each treatment. A statistically significant effect on symptoms on Day 28 versus Day 1 was observed with GLY but not with TIO (Table 2). Similar scores were seen in the 3-hour post-dose evaluation of the PRO-Morning COPD Symptoms Questionnaire at Day 28 and Day 1 (GLY: 10.4 [standard deviation (SD) =8.8]; 9.6 [SD =8.8] and TIO: 10.3 [SD =9.3]; 10.6 [8.1]), respectively.

Safety assessments

The overall incidences of treatment emergent AEs (TEAEs) (GLY, 18 [14.5%]; TIO, 13 [10.5%]) and serious TEAEs

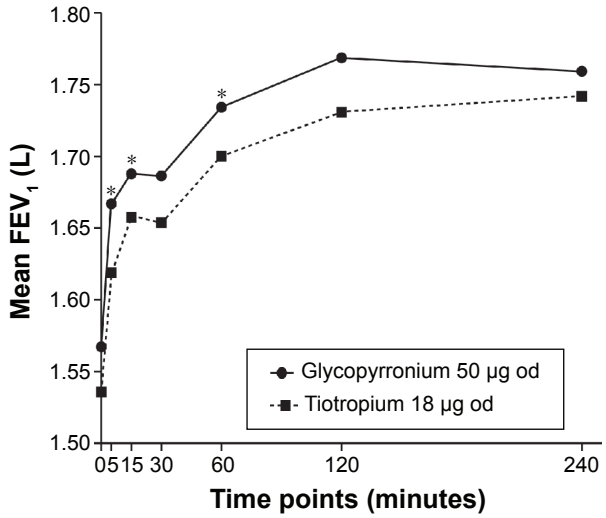

Figure 4 FEV_1 AUC_{0-4h} treatment differences between glycopyrronium and tiotropium by time point post-first treatment dose on Day 1 (ITT population).
Note: *$P<0.05$ versus tiotropium at the relative time points.
Abbreviations: FEV_1, forced expiratory volume in 1 second; AUC_{0-4h}, area under the curve from 0 to 4 hours; ITT, intention-to-treat; od, once-daily.

Table 2 PRO-Morning COPD Symptoms Questionnaire total score comparison between Day 1 versus Day 28 for each treatment, separately (ITT population)

	Glycopyrronium (n=124)	Tiotropium (n=124)
PRO-Morning COPD Symptoms Questionnaire score on Day 1 (pre-dose)	16.7 (11.1)	16.6 (10.0)
PRO-Morning COPD Symptoms Questionnaire score on Day 28 (pre-dose)	14.5 (10.7)	15.2 (11.6)
Improvement in PRO-Morning COPD Symptoms Questionnaire score from Day 1 versus Day 28 (pre-dose)	1.9 (7.8)	1.2 (7.9)
P-value	0.002	0.063

Note: Values are least squares mean (SD).
Abbreviations: PRO, patient reported outcomes; ITT, intention-to-treat; SD, standard deviation.

(GLY, 2 [1.6%]; TIO 2 [1.6%]) were similar in both treatment groups (Table 3). However, none of the serious TEAEs were related to the treatment medication according to the investigators. Nasopharyngitis and cough were the most common (>1%) TEAE.

No deaths were reported during treatment or during the 30-day post-treatment safety follow-up period. The percentage of patients with post-baseline notable Fridericia-corrected QT interval (QTc) values was similar and low across both treatment groups (GLY 4.0% for QTc >450 ms and 0% for >480 ms; TIO 2.4% for >450 ms and 1.6% for >480 ms).

Discussion

In this prospective adequately powered cross-over study, GLY demonstrated for the first time, superiority in terms of improvement in FEV_1 $AUC_{0\text{-}4h}$ when compared with TIO after the initial drug administration on Day 1, confirmed both in the ITT and the PP analysis. These results further validate the secondary endpoint results of the GLOW2[9] and GLOW5 studies.[11] To better understand the performance of GLY versus TIO in serial spirometries in these first 4 hours, a post hoc analysis of the data was carried out by point-by-point differences in FEV_1 after the first dose of study drug. A statistically significant increase in FEV_1 at 5 minutes, 15 minutes, and 1 hour after the first dose was observed with GLY versus TIO, thereby supporting the comparative fast onset of action of GLY versus TIO. No statistically significant difference in FEV_1 $AUC_{0\text{-}4h}$ was observed between GLY and TIO on Day 28.

In addition to the spirometric onset of action, the impact of GLY and TIO on symptoms was recorded using a self-administered PRO-Morning COPD Symptoms Questionnaire, as it was hypothesized that a faster onset of bronchodilator action would lead to a different perception of clinically relevant symptoms after dosing. Both GLY and TIO demonstrated comparable improvements in terms of PRO-Morning COPD Symptoms Questionnaire scores in the morning at 3 hours post-dose on Day 1 and after 4 weeks of treatment. In this context it is of note, that the PRO-Morning COPD Symptoms Questionnaire measurement is a newly developed tool, containing symptoms that may (eg, breathlessness) or may not (eg, cough, sputum production) be responsive to treatment in the short term (0–4 hours). Most of the patients in this analysis were only mildly symptomatic (mean symptom score of 17 of a total of 60), which may have prevented the demonstration of a clinically significant difference in improvement in the PRO-Morning COPD Symptoms

Table 3 Summary of safety findings (safety population)

	Glycopyrronium n=124	Tiotropium n=124
Number of patients with at least one TEAE	18 (14.5)	13 (10.5)
Discontinuations due to TEAE	2 (1.6)	1 (0.8)
Lower respiratory tract infection	0 (0.0)	1 (0.8)
Pneumonia	1 (0.8)	0 (0.0)
Dyspnea	1 (0.8)*	0 (0.0)
Serious TEAE(s)	2 (1.6)	2 (1.6)
Dyspnea	1 (0.8)*	0 (0.0)
Pleurisy	0 (0.0)	1 (0.8)
Pneumonia	1 (0.8)	0 (0.0)
Lumbar vertebral fracture	0 (0.0)	1 (0.8)

Notes: Values are n (%); *viral infection.
Abbreviation: TEAE, treatment emergent adverse event.

Questionnaire score. One also has to critically state that the study may have been underpowered to demonstrate statistical differences between active treatments for the PRO-morning score, and therefore in conclusion these results have to be seen as exploratory. However, and in order to understand the long-term effect of LAMA treatments on morning symptoms, a post hoc analysis was carried out to determine the statistical significance of the changes in the pre-dose PRO-Morning COPD Symptoms Questionnaire scores from baseline to Day 28. A significant improvement in the pre-dose PRO-Morning COPD Symptoms Questionnaire score versus baseline after 4 weeks of treatment was observed with GLY but not with TIO. The clinical meanings of these observations may be obscured by the fact that the SPRING study population was only mildly symptomatic, and they certainly require further research. In the SPRING study, no new safety signals were observed for GLY. Safety and tolerability of GLY were similar to TIO, with the overall incidence of AEs being low, and none of the AEs were suspected to be related to the study medication. Cardiac disorders were uncommon and no AE with fatal outcome was reported.

Study limitations

There were limitations in the study that must be acknowledged. These involved the cross-over study design, short study duration, limited patient population due to the clinical trial settings, as well as selection of patients due to COPD Assessment Test rather than the presence of morning symptoms. An additional limitation was that the PRO-Morning COPD Symptoms Questionnaire has not been previously validated, and findings are additionally obscured by the mildly symptomatic population included in this trial.

Conclusion

In conclusion, the SPRING study demonstrates the superiority of GLY versus TIO in improving lung function in the first 4 hours after administration, extending the existing clinical data that support a faster onset of action of GLY versus TIO. This study further builds on the good safety profile of GLY previously reported during the GLOW study program.[8–11] The study further provides evidence on the differences in the onset of action between LAMAs that may be of value in treatment choices in clinical practice.

Acknowledgments

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Author contributions

All authors have provided substantial contribution for the study conception and design, acquisition of data, or analysis and interpretation of data. All authors were involved in drafting/revising this manuscript for important intellectual content and have given final approval of the version to be published.

Disclosure

JMM participated in advisory meetings or as conference speaker for Boehringer Ingelheim, GlaxoSmithKline, and Novartis.

KMBs institution has received compensation for organizing or participating in advisory boards (from Almirall Hermal, Cytos, Chiesi, Boehringer Ingelheim, AstraZeneca, Mundipharma, Novartis, and TEVA), participated in scientific meetings or courses (supported by Almirall Hermal, AstraZeneca, Boehringer Ingelheim, Mundipharma, Novartis, Pfizer and TEVA) in the past 3 years, received consulting fees (from Ablynx, Apellis Pharmaceuticals, Sterna GmbH, Chiesi and Cytos), and received compensation for the design, performance or participation in single or multicenter clinical trials in the past 3 years (from Almirall, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Infinity, Mundipharma, Novartis, Pfizer, Revotar Biopharmaceuticals, Sterna GmbH, TEVA, and Zentiva).

LS conducted clinical studies sponsored by Novartis since 2013 at study site Studienpraxis Berlin-Brandenburg, and is one of the two owners of this study site; in addition he conducted several Novartis Studies as employee of a contract research organization and site management organization during the last 3 years. DS has spoken for Novartis. AC, KK, MA-M, and RC are full time employees of Novartis Pharma AG. AC is a shareholder of Novartis Pharma AG, KK has been an advisory board member (for AstraZeneca, Chiesi, ELPEN, Novartis and Takeda), has received honoraria (from AstraZeneca, Boehringer Ingelheim, Chiesi, ELPEN, GlaxoSmithKline, Merck Sharp & Dohme, Novartis and Takeda and UCB), and has availed accommodation/travel/meeting expenses (from AstraZeneca, Boehringer Ingelheim,

Chiesi, ELPEN, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Takeda and UCB). All authors conducted the trial at their respective study sites. WC and AG declare that they have no additional competing interests.

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Supplementary materials

Table S1 PRO-Morning COPD Symptoms Questionnaire

PRO-Morning COPD Symptoms Questionnaire: pre-morning dose assessment	
Please rate the severity of your shortness of breath when you woke up today	0–10 Numeric Rating Scale (0= no shortness of breath to 10= shortness of breath as bad as you can imagine)
Please rate the difficulty you had clearing the phlegm/mucus from your lungs when you woke up today	0–10 Numeric Rating Scale (0= no phlegm/mucus to 10= as difficult as you can imagine)
Please rate the severity of your chest tightness when you woke up today	0–10 Numeric Rating Scale (0= no chest tightness to 10= chest tightness as bad as you can imagine)
Please rate the severity of your wheezing when you woke up today	0–10 Numeric Rating Scale (0= no wheezing to 10= wheezing as bad as you can imagine)
Please rate the severity of your coughing when you woke up today	0–10 Numeric Rating Scale (0= no coughing to 10= coughing as bad as you can imagine)
Please rate how bothered you were by your COPD symptoms when you woke up today	0–10 Numeric Rating Scale (0= no bother to 10= bothered as bad as you can imagine)
PRO-Morning COPD Symptoms Questionnaire: post-morning dose assessment: to be answered approximately 3 hours after morning medication	
Please rate the severity of your shortness of breath as you feel now	0–10 Numeric Rating Scale (0= no shortness of breath to 10= shortness of breath as bad as you can imagine)
Please rate the difficulty you had clearing the phlegm/mucus as you feel now	0–10 Numeric Rating Scale (0= no phlegm/mucus to 10= as difficult as you can imagine)
Please rate the severity of your chest tightness as you feel now	0–10 Numeric Rating Scale (0= no chest tightness to 10= chest tightness as bad as you can imagine)
Please rate the severity of your wheezing as you feel now	0–10 Numeric Rating Scale (0= no wheezing to 10= wheezing as bad as you can imagine)
Please rate the severity of your coughing as you feel now	0–10 Numeric Rating Scale (0= no coughing to 10= coughing as bad as you can imagine)
Please rate how bothered you feel now by your COPD symptoms	0–10 Numeric Rating Scale (0= no bother to 10= bothered as bad as you can imagine)

Abbreviations: COPD, chronic obstructive pulmonary disease; PRO, patient reported outcome.

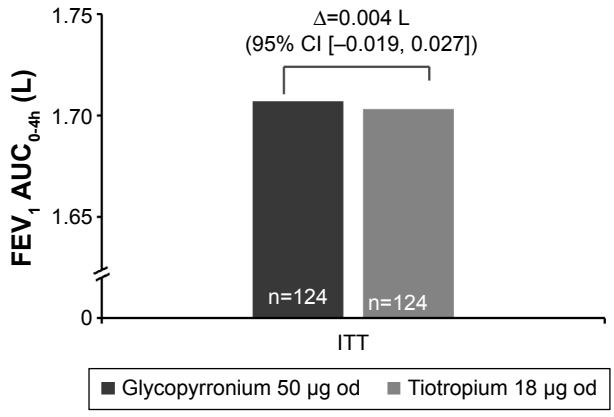

Figure S1 FEV_1 $AUC_{0\text{-}4h}$ treatment differences between glycopyrronium and tiotropium post-first treatment dose on Day 28 (ITT).
Notes: *P*=0.7293; data are least squares means; Δ, treatment difference between glycopyrronium and tiotropium.
Abbreviations: $AUC_{0\text{-}4h}$, area under the curve from 0 to 4 hours; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ITT, intention-to-treat; od, once-daily.

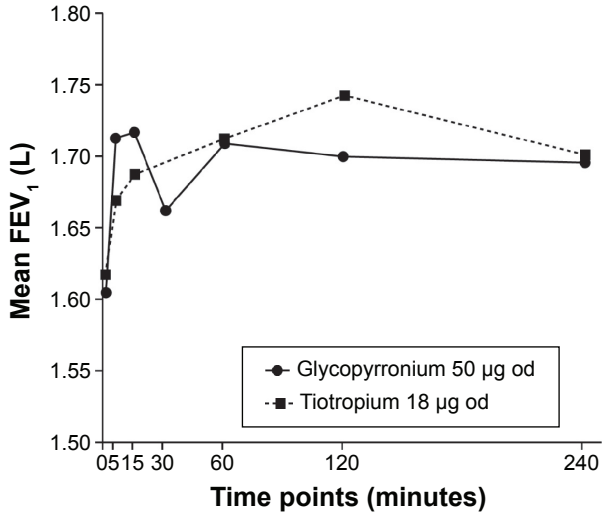

Figure S2 FEV_1 $AUC_{0\text{-}4h}$ treatment differences between glycopyrronium and tiotropium by time point post-first treatment dose on Day 28 (ITT population).
Abbreviations: $AUC_{0\text{-}4h}$, area under the curve from 0 to 4 hours; FEV_1, forced expiratory volume in 1 second; ITT, intention-to-treat; od, once-daily.