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Long-term safety of glycopyrrolate: A randomized study in patients with moderate-to-severe COPD (GEM3)

Donald A. Mahler [a, f, *], Alex H. Gifford [a], Aditi Satti [b], Nicola Jessop [c], Joerg H. Eckert [c], Peter D'Andrea [d], Fernando Mota [c], Rudrani Banerjee [e]

[a] Geisel School of Medicine at Dartmouth, Hanover, NH 03755, USA
[b] Temple University College of Medicine, Philadelphia, PA, USA
[c] Novartis Pharma AG, Basel, Switzerland
[d] Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
[e] Novartis Healthcare Pvt. Ltd., Hyderabad, India
[f] Valley Regional Hospital, Claremont, NH 03743, USA

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death in the United States. Long-acting muscarinic antagonists (LAMAs) are a class of medications used as maintenance therapy for COPD. The GEM3 (**G**lycopyrrolate **E**ffect on sy**M**ptoms and lung function) study assessed the long-term safety and efficacy of a LAMA, glycopyrrolate (GLY) 15.6 μg twice daily (b.i.d.), compared with an approved long-acting β_2-agonist (LABA), indacaterol (IND) 75 μg once daily (q.d.) in patients with stable, symptomatic COPD with moderate-to-severe airflow limitation.

Methods: This 52-week, multicenter, double-blind, parallel-group study randomized patients (1:1) of the United States to receive GLY 15.6 μg b.i.d. or IND 75 μg q.d. both delivered via the Neohaler® device. The primary objective was to assess the safety and tolerability in terms of adverse event (AE) reporting rates over 52 weeks. Safety was also determined by evaluating multiple secondary endpoints, including vital signs, electrocardiograms (ECGs), and time to first moderate or severe exacerbation. Efficacy-related secondary endpoints included pre-dose forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC).

Results: Of the 511 randomized patients (GLY, n = 254; IND, n = 257), 81.6% completed the study. The overall incidences of AEs (GLY, 77.3%; IND, 77.0%) and serious AEs (GLY, 13.1%; IND, 13.3%) were comparable between the groups. The incidence of major adverse cardiovascular events was low and comparable between the groups. No clinically relevant differences for vital signs or ECG parameters were observed between the treatment groups. The three sudden deaths reported within 30 days of the treatment (GLY, n = 2; IND, n = 1) were adjudicated as unrelated to the study medication. In terms of efficacy, GLY 15.6 μg b.i.d. showed improvements in pre-dose FEV_1 and FVC from baseline, which was comparable to those with IND 75 μg q.d., with no statistically significant differences. No significant differences were observed between the treatment groups in the time to first moderate or severe COPD exacerbation.

Conclusion: GLY 15.6 μg b.i.d. showed a long-term safety profile comparable to that of IND 75 μg q.d. and provided rapid and sustained bronchodilation over 52 weeks in patients with COPD with moderate-to-severe airflow limitation.

Clinical trial registration number: NCT01697696.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease which remains one of the leading causes of death and economic burden in the United States (US) [1]. It is also associated

* Corresponding author. Geisel School of Medicine at Dartmouth, Hanover, NH 03755, USA.
E-mail addresses: mahlerdonald@gmail.com (D.A. Mahler), alex.h.gifford@hitchcock.org (A.H. Gifford), aditi.satti@tuhs.temple.edu (A. Satti), nicola.jessop@novartis.com (N. Jessop), joerg.eckert@novartis.com (J.H. Eckert), peter.dandrea@novartis.com (P. D'Andrea), fernando.mota@novartis.com (F. Mota), rudrani-1.banerjee@novartis.com (R. Banerjee).

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Abbreviations

AE	adverse event
b.i.d.	twice daily
CCV	cardiovascular and cerebrovascular
CI	confidence interval
COPD	chronic obstructive pulmonary disease
ECG	electrocardiogram
FAS	full analysis set
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GEM	**G**lycopyrrolate **E**ffect on sy**M**ptoms and lung function
GLY	glycopyrrolate
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	inhaled corticosteroid
IND	indacaterol
LABA	long-acting β_2-agonist
LAMA	long-acting muscarinic antagonist
LSM	least squares mean
MACE	major adverse cardiovascular events
mMRC	modified Medical Research Council
MMRM	mixed model repeated measures
OR	odds ratio
q.d.	once daily
SAE	serious adverse event;
SD	standard deviation

with specific comorbidities, which overall leads to an increase in healthcare utilization and costs [1,2]. Although there is no cure for this disease, several pharmacological therapies exist which can help relieve the associated symptoms [3]. The current Global Initiative for Chronic Obstructive Lung Disease (GOLD) [3] guidelines and the American Thoracic Society/European Respiratory Society guidelines [4] recommend treatment of COPD with long-acting bronchodilators such as long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs) alone or in a fixed dose combination or in combination with an inhaled corticosteroid (ICS).

Glycopyrrolate (GLY), also known as glycopyrronium bromide, administered as a 63 μg once-daily (q.d.) dose (equivalent to glycopyrronium 50 μg), is a fast-onset LAMA which provides a sustained 24-h bronchodilation in patients with moderate-to-severe COPD [5,6]. Inhaled glycopyrronium 50 μg q.d. (Seebri® Breezhaler®) has been approved as a maintenance bronchodilator for symptomatic treatment of patients with COPD in more than 80 countries, including countries within the EU and Latin America, Japan, Canada, Switzerland, and Australia [7]. Results from Phase III trials have shown that glycopyrronium 50 μg q.d. offers a substantial benefit to patients with moderate-to-severe COPD by improving lung function, decreasing dyspnea, improving health status, and decreasing rescue medication use, along with an overall acceptable safety profile [8]. Glycopyrronium 50 μg q.d. has also demonstrated an efficacy and safety profile comparable to that of tiotropium 18 μg q.d. [9,10]. Moreover, a comprehensive safety analysis using the pooled data from six clinical studies and a post-marketing surveillance exhibited a comparable safety profile for glycopyrronium 50 μg q.d. to those of tiotropium and placebo [11].

A dose-ranging study revealed that GLY 15.6 μg (equivalent to glycopyrronium 12.5 μg) twice daily (b.i.d.) resulted in statistically significant and clinically relevant improvements in trough forced expiratory volume in one second (FEV_1). Based on these data and discussions with the Food and Drug Administration, GLY 15.6 μg b.i.d. delivered via the low-resistance Neohaler® device was selected for the US Phase III clinical program [12]. This program included two replicate 12-week studies (GEM1, GEM2) and a 52-week long-term study, GEM3 (**G**lycopyrrolate **E**ffect on sy**M**ptoms and lung function). The GEM1 and GEM2 studies supported the efficacy and safety of GLY 15.6 μg b.i.d. showing improvements in lung function, COPD symptoms, health status, and rescue medication use, with a safety profile comparable to that of placebo [13,14]. GLY is now approved at a 15.6 μg b.i.d. dose (Seebri™ Neohaler®) in the US, for the long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema [15].

Here we report the results from the GEM3 study which evaluated the long-term safety and efficacy of GLY 15.6 μg b.i.d. over 52 weeks using an approved LABA, indacaterol (IND) 75 μg q.d., as a control, in a patient population in the US, with stable, symptomatic COPD with moderate-to-severe airflow limitation (according to the GOLD 2011 guidelines).

2. Methods

2.1. Study design and treatment

GEM3 was a 52-week, randomized, multicenter, double-blind, parallel-group study conducted at 65 centers in the US (ClinicalTrials.gov registration number: NCT01697696). The study comprised of a flexible screening period (between 1 and 7 days), a two-week run-in period, a 52-week randomized treatment period, and a 30-day safety follow-up period (Fig. 1). During the screening and run-in periods, several prohibited concomitant medications, such as LABAs, LAMAs and xanthines, had to be discontinued, and a stable background treatment with ICS was permitted to be continued throughout the study. During the study, patients were provided with albuterol as a rescue medication. At the start of the run-in period, patients were provided with an electronic patient diary (eDiary) to record symptoms and rescue medication usage twice daily. At the end of the run-in period, eligible patients were randomized (1:1) to receive GLY 15.6 μg b.i.d. (morning and evening dosing) or IND 75 μg q.d. (morning dosing), both delivered via a low-resistance, single-dose, dry powder inhaler (Neohaler™ device) for 52 weeks. The IND group received a matching placebo in the evening to maintain blinding. All randomized patients, regardless of whether they completed or discontinued the treatment before Week 52, were monitored throughout the treatment period and in the subsequent follow-up period (Fig. 1). The first patient was enrolled on October 26, 2012, and the last patient visit was completed on November 13, 2014. Additional details of the randomization and blinding procedures are included in the online supplementary material. This study was approved by the institutional review board for each center and was conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before participating in the study.

2.2. Patients

The study population included male and female patients aged ≥40 years with stable COPD (GOLD 2011 levels 2 and 3), who were current or ex-smokers with a smoking history of at least 10 pack-

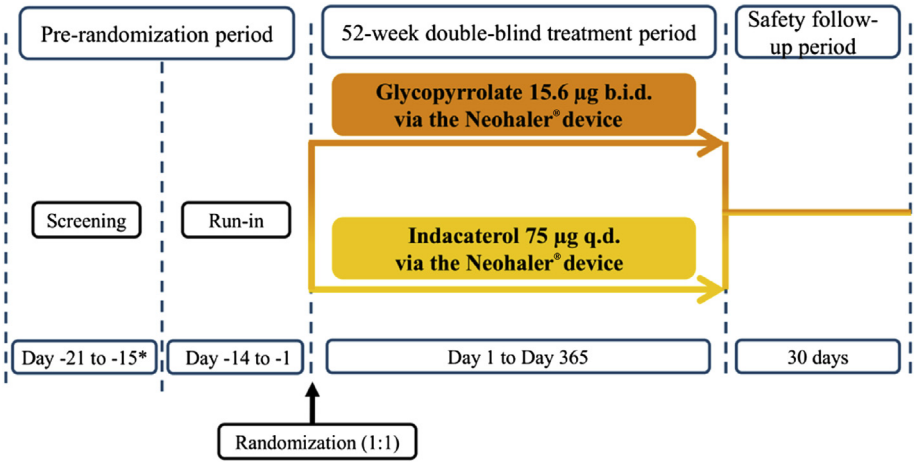

Fig. 1. Study design. *Screening epoch was kept flexible between 1 and 7 days. b.i.d., twice daily; q.d., once daily.

years, who presented with post-bronchodilator FEV_1 ≥30% and <80% of the predicted normal, and a post-bronchodilator FEV_1/forced vital capacity (FVC) < 0.70, and with a modified Medical Research Council (mMRC) Dyspnea Scale grade of at least 2 at the run-in visit. Key exclusion criteria included history of long QT syndrome or patients whose Fridericia corrected QT interval (QTcF) measured at the run-in visit was prolonged (>450 ms), clinically significant electrocardiogram (ECG) abnormality before randomization or at the run-in visit, clinically significant cardiovascular disease including significant arrhythmia, renal abnormalities, history of asthma, and COPD exacerbations that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization within the six weeks before the screening or during the screening and run-in periods. Detailed inclusion and exclusion criteria are provided in the online supplementary material.

2.3. Study objectives

The primary objective was to assess the safety and tolerability of GLY 15.6 µg b.i.d. over the 52-week treatment period versus IND 75 µg q.d. in terms of the adverse event (AE) reporting rates. Safety-related secondary endpoints included time to first moderate or severe COPD exacerbations, measurement of vital signs, ECG, and laboratory evaluations over 52 weeks. Efficacy-related secondary endpoints included pre-dose trough FEV_1 at Week 52 (mean of FEV_1 values at −45 and −15 min before the morning dose), FEV_1 and FVC measurements at all post-baseline time-points, and rescue medication use over 52 weeks of treatment period.

2.4. Statistical analyses

All statistical analyses described in this and subsequent sections were performed using the Statistical Analysis Software (SAS) Version 9.3 (Cary, NC). The primary analysis was the comparison of the overall AE rates between the treatment groups in terms of absolute and relative frequencies of treatment emergent AEs by primary system organ class and preferred term. It was performed on the safety set, which included all patients who received at least one dose of the study drug and had at least one post-baseline safety assessment. Treatment emergent AEs were defined as AEs starting on or after the time of the first administration of the study drug but not later than 7 days (30 days in case of a serious adverse event [SAE]) after the last administration. No statistical testing of the hypothesis was performed.

In addition, AEs adjusted for exposure and by major adverse cardiovascular events (MACE) outcomes were summarized.

The rate of moderate-to-severe COPD exacerbations was analyzed using a generalized linear model assuming a negative binomial distribution. The log (exposure time) was used as an offset variable in the model. The model included treatment, baseline total symptom score, history of baseline COPD exacerbation (i.e., the number of COPD exacerbations during the 12 months prior to study), smoking status at baseline, history of ICS use, and COPD disease severity as fixed effects. The time to first moderate or severe COPD exacerbation was analyzed using Cox regression model for the full analysis set (FAS), which included all randomized patients who received at least one dose of the study drug. The model included treatment, baseline total symptom score, history of baseline COPD exacerbation (i.e., the number of COPD exacerbations during 12 months prior to study), smoking status at baseline, history of ICS use, and COPD disease severity as fixed effects. All safety assessments were performed on the safety set.

Efficacy endpoints were evaluated as secondary parameters on the FAS. The change from baseline in the pre-dose trough FEV_1 (L) (average of the two FEV_1 (L) measurements 45 and 15 min pre-dose) at all post-baseline visits was analyzed using a mixed-model repeated-measures (MMRM) analysis on the FAS. The model contained treatment, baseline FEV_1, visit, treatment by visit interaction, visit by baseline FEV_1 interaction, smoking status at baseline, history of ICS use, and COPD disease severity as fixed effects with an unstructured variance-covariance error matrix. The number of puffs of rescue medication was recorded twice daily by the patient in an electronic diary (eDiary) provided at the start of run-in period. Patient classification and sample size calculation are provided in the online supplementary material.

3. Results

3.1. Patient disposition and baseline characteristics

Of the 1296 screened patients, 511 were randomized to either the GLY (n = 254) or the IND (n = 257) group. A total of 417 (81.6%) (GLY, n = 207; IND, n = 210) patients completed the 52-week planned treatment period (Fig. 2); this included patients who completed the 52-week treatment period (66.1%) as well as those who discontinued the study treatment but continued study visits as part of the planned treatment period (15.5% of the total population). The most common reason for discontinuation was patient

decision, with similar rates between both the treatment groups (Fig. 2).

The safety set included 507 patients. Of these, 33.9% of patients permanently discontinued the study treatment before the end of the planned treatment period, with discontinuation rates comparable between both treatment groups (Table A.1). The mean (standard deviation [SD]) duration of exposure was comparable between both the treatment groups (GLY, 290.3 [119.05] days; IND, 285.0 [126.18] days).

Patient demographics and baseline characteristics were comparable between both treatment groups (Table 1). A majority of the patients were Caucasian (90.9%) and with moderate airflow limitation (54.0%). Most of the patients belonged to GOLD 2011 Group B (51.5%), followed by Group D (45.0%), and a majority (74.2%) did not have COPD exacerbations in the year prior to the study entry (Table 1).

3.2. Safety

3.2.1. Adverse events

Overall, the incidence of AEs was comparable between the GLY (77.3%) and IND (77.0%) groups (Table 2). A majority of AEs reported in both the treatment groups were mild (20.3%) or moderate (43.4%) in severity and occurred at comparable rates. AEs by preferred term were predominantly respiratory-related, with COPD (exacerbation) as the most commonly reported AE, which occurred at comparable rates between the treatment groups (GLY, 36.3%; IND, 37.1%). Moreover, COPD (exacerbations) was the primary reason of study drug discontinuation (GLY, 3.6%; IND, 2.0%). Severe AEs were reported in 13.9% of patients in the GLY group compared with 12.9% in the IND group. The incidence of suspected drug-related AEs was low and comparable between both the groups (GLY, 12.4%; IND, 9.0%). The rate of AEs reported to have led to permanent discontinuation from the study was low in both the treatment groups (GLY, 8.8%; IND, 9.8%).

3.2.2. Serious adverse events (SAEs) and deaths

Overall, the incidence of SAEs was balanced between the groups (GLY, 13.1%; IND, 13.3%). Most of the SAEs were respiratory-related, and the incidence rate was comparable between the treatments (GLY, 4.8%; IND, 5.5%). COPD exacerbation was the most frequently reported SAE, with similar rates between GLY (4.4%) and IND (4.7%). The rate of discontinuations of the study medication due to SAEs was low and comparable between the treatments (GLY, 4.0%; IND, 4.7%). Three deaths due to AEs were reported while on the study medication or within 30 days of the last study medication intake (GLY, n = 2; IND, n = 1).The adjudicated cause of deaths in both the groups was sudden death. None of the patients had a history of atrial fibrillation/flutter or cardiac arrhythmia and all patients had baseline cardiovascular risk factors. Moreover, no death was considered related to the study medication by the investigator.

3.2.3. Cardiovascular and cerebrovascular events

The incidence of serious cardiovascular and cerebrovascular (CCV) AEs was similar between the treatments (GLY, 3.2%; IND, 3.1%). Serious CCV events were evaluated by an independent adjudication committee and were adjudicated for MACE or non-MACE outcome. Similarly, all cases of atrial fibrillation/atrial flutter that occurred between randomization and the end of the follow-up period were adjudicated as new-onset or recurrent events. Adjudicated serious CCV AEs were comparable, with similar incidence rates of MACE and non-MACE in the two treatment groups (Table 3). The time to first serious CCV events adjudicated by MACE outcome was similar in the treatment groups. No discernible pattern was observed in subgroup analyses of serious CCV AEs adjudicated by MACE outcome (Table A.2).

The incidences of cardiac arrhythmias (GLY, 1.6%; IND, 3.1%), cardiac failure (GLY, 0.0%; IND, 0.8%) and cerebrovascular events

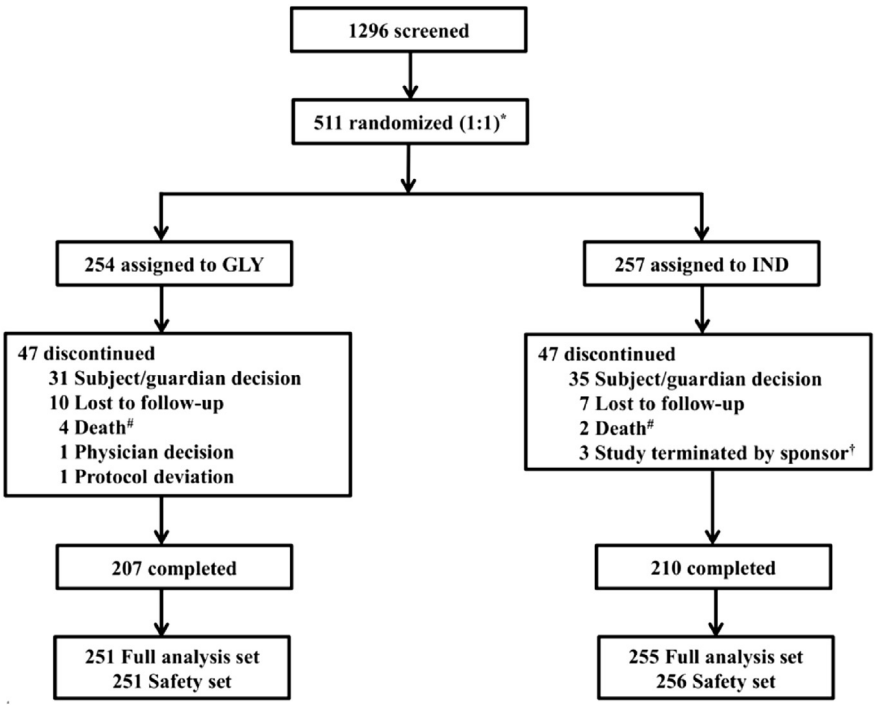

Fig. 2. Patient disposition. *One patient was erroneously randomized to IND group. #Two deaths in the GLY 15.6 μg b.i.d. group and one death in the IND 75 μg q.d. group occurred ≥30 days after the last dose of study medication. †One site was prematurely closed due to critical GCP non-compliance issues. b.i.d., twice daily; GCP, Good Clinical Practice; GLY, glycopyrrolate; IND, indacaterol; q.d., once daily.

Table 1
Patient demographics and baseline characteristics (Safety set).

Parameters	GLY 15.6 μg b.i.d. n = 251	IND 75 μg q.d. n = 256
Age (years)	63.3 (9.15)	63.2 (8.91)
Male, n (%)	141 (56.2)	149 (58.2)
Female, n (%)	110 (43.8)	107 (41.8)
Race, n (%)		
Caucasian	230 (91.6)	231 (90.2)
Black	17 (6.8)	19 (7.4)
Others	4 (1.6)	6 (2.34)
Duration of COPD (years)	7.0 (5.65)	6.6 (5.97)
Smoking history, n (%)		
Ex-smoker	115 (45.8)	114 (44.5)
Current smoker	136 (54.2)	142 (55.5)
Number of pack-years	48.6 (25.92)	54.2 (26.38)
Severity of COPD, airflow limitation, n (%)		
Moderate (GOLD 2)	133 (53.0)	141 (55.1)
Severe (GOLD 3)	110 (43.8)	104 (40.6)
Very severe (GOLD 4)	0	1 (0.4)
Missing	8 (3.2)	10 (3.9)
Severity of COPD, combined assessment, n (%)		
Group B	126 (50.2)	135 (52.7)
Group C	0	1 (0.4)
Group D	117 (46.6)	111 (43.4)
Missing	8 (3.2)	9 (3.5)
COPD exacerbation history, n (%)		
0	192 (76.5)	184 (71.9)
1	43 (17.1)	59 (23.0)
≥2	16 (6.4)	13 (5.1)
ICS use at baseline, n (%)	93 (37.1)	92 (35.9)
mMRC dyspnea scale, n (%)		
Grade 1	0	1 (0.4)
Grade 2	158 (62.9)	151 (59.0)
Grade 3	79 (31.5)	91 (35.5)
Grade 4	14 (5.6)	13 (5.1)
COPD assessment test (CAT) score	18.3 (7.53)	18.2 (7.61)
Pre-bronchodilator FEV_1 (L)	1.24 (0.50)	1.25 (0.46)
Post-bronchodilator FEV_1 (L)	1.46 (0.53)	1.47 (0.49)
Post-bronchodilator FEV_1, % predicted	53.1 (14.01)	53.1 (12.94)
Post-bronchodilator FEV_1 reversibility, %[a]	21.2 (16.51)	21.1 (15.30)
Cardiovascular risk factors		
CCV history/condition	66 (26.3)	48 (18.8)
Hypertension	142 (56.6)	150 (58.6)
Diabetes mellitus	51 (20.3)	30 (11.7)
Atrial fibrillation/flutter	4 (1.6)	2 (0.8)
Hyperlipidemia	145 (57.8)	146 (57.0)

Data is presented as mean (standard deviation) unless otherwise stated. [a]FEV_1 reversibility is calculated as percentage increase of FEV_1 value after inhalation of bronchodilator relative to FEV_1 value before inhalation. COPD severity is based on the GOLD 2011 criteria. b.i.d., twice daily; q.d., once daily; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GLY, glycopyrrolate; IND, indacaterol; ICS, inhaled corticosteroid; mMRC, modified Medical Research Council; CCV, cardiovascular and cerebrovascular; pack-years, total years of smoking × cigarette packs smoked/day.

(GLY, 0.8%; IND, 1.6%) were lower in the GLY group than in the IND group. Atrial fibrillation/flutter events occurred in four (1.6%) and five (2.0%) patients in the GLY and IND groups, respectively, of whom, one patient in the GLY group and two in the IND group had new onset of events.

3.2.4. Additional safety parameters

There were no clinically meaningful differences between the two treatment groups for any of the vital signs (pulse rate and, systolic and diastolic blood pressure), and hematology, biochemistry, or urinalysis parameters. The proportion of patients with newly occurring or worsening clinically notable QTcF values was comparable in both the treatment groups. The number of patients who showed an increase from baseline in QTcF of 30–60 ms was low and comparable between both the treatment groups (GLY, n = 28 [11.2%]; IND, n = 23 patients [9.0%]). None of these clinically notable values or increases from baseline was associated with an AE.

Table 2
Frequent AEs (≥3% of patients in either treatment group) by preferred term (Safety set).

Preferred term	GLY 15.6 μg b.i.d. n = 251	IND 75 μg q.d. n = 256
Patients with at least one AE	194 (77.3)	197 (77.0)
COPD*	91 (36.3)	95 (37.1)
Nasopharyngitis	20 (8.0)	27 (10.5)
Cough	18 (7.2)	20 (7.8)
Dyspnea	14 (5.6)	9 (3.5)
Upper respiratory tract infection	14 (5.6)	16 (6.3)
Viral upper respiratory tract infection	12 (4.8)	12 (4.7)
Bronchitis	11 (4.4)	10 (3.9)
Fatigue	11 (4.4)	3 (1.2)
Oropharyngeal pain	11 (4.4)	11 (4.3)
Sinusitis	10 (4.0)	12 (4.7)
Diarrhea	9 (3.6)	5 (2.0)
Nasal congestion	9 (3.6)	9 (3.5)
Nausea	9 (3.6)	6 (2.3)
Back pain	8 (3.2)	4 (1.6)
Urinary tract infection	8 (3.2)	6 (2.3)
Headache	4 (1.6)	8 (3.1)
Hypertension	3 (1.2)	8 (3.1)
Lower respiratory tract infection	3 (1.2)	10 (3.9)

All values presented as n (%). *worsening of COPD which includes COPD exacerbation. b.i.d., twice daily; COPD, chronic obstructive pulmonary disease; AE, adverse event; GLY, glycopyrrolate; IND, indacaterol; q.d., once daily.

3.3. Efficacy

3.3.1. Lung function

The change from baseline in the pre-dose trough FEV_1 (an average of the two FEV_1 measurements 45 and 15 min pre-dose) was analyzed at all post-baseline visits; no statistically significant differences were observed between the two treatments at any visit (Fig. 3, additional data in Table A.4). Similar profiles of the least squares mean (LSM) change from baseline in the pre-dose trough FEV_1 (L) was seen over all visits for both the treatment groups throughout the entire treatment period (Fig. 3, Additional data in Table A.4). At the end of the treatment period, the change from baseline in the pre-dose FEV_1 was also comparable between the groups (GLY, 0.056 L; IND, 0.060 L; treatment difference, −0.004 L, p = 0.902). Moreover, no statistically significant treatment differences were observed between the treatment groups for pre-dose trough FVC (change from baseline) at any visit, with the exception of Week 12, which showed a difference in favor of GLY (LSM treatment difference, 0.071 L; p = 0.049).

3.3.2. COPD exacerbations

Over 52 weeks of treatment, no statistically significant differences were found between the treatment groups for the incidence of moderate or severe COPD exacerbations (incidence rate ratio, 0.92; 95% CI: 0.65, 1.29; p = 0.625). The number of moderate or severe COPD exacerbations over the treatment period is given in the Table A.3. Moreover, the time to first moderate or severe COPD exacerbation was also comparable across both the treatment groups (hazard ratio, 0.92; 95% CI: 0.64, 1.31; p = 0.636).

3.3.3. Rescue medication use

There were no statistically significant difference between GLY and IND treatments for the mean nighttime number of puffs of the rescue medication (treatment difference, 0.21 puffs; p = 0.071) or the number of days with no rescue medication use (treatment

Table 3
Serious CCV events adjudicated by MACE outcome (Safety set).

Adjudicated MACE outcome	GLY 15.6 μg b.i.d. n = 251	IND 75 μg q.d. n = 256
Patients with at least one adjudicated serious CCV AE	8 (3.2)	9 (3.5)
MACE*	4 (1.6)	5 (2.0)
Non-fatal myocardial infarction	2 (0.8)	3 (1.2)
Non-fatal unstable angina	0	0
Non-fatal stroke	0	0
Heart failure requiring hospitalization	0	0
Coronary re-vascularization (CABG or PCI)	4 (1.6)	3 (1.2)
Non-MACE serious CCV AE*	5 (2.0)	6 (2.3)

All values are presented as n (%); table includes events that occurred on or after the time of the first administration of the study drug but not later than 30 days after the last administration. A patient with multiple events was included for each event. *Patients may have had both MACE and non-MACE, therefore the values may not be additive.
CCV AE, cardiovascular and cerebrovascular adverse events; MACE, major adverse cardiovascular events; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; GLY, glycopyrrolate; IND, indacaterol; b.i.d., twice daily; q.d., once daily.

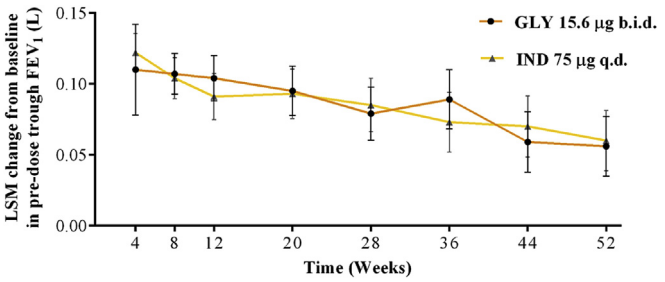

Fig. 3. Change in pre-dose trough FEV_1 from baseline, over post-baseline visits (FAS). MMRM: Change from baseline in pre-dose trough FEV_1 = treatment + baseline FEV_1 + smoking status at baseline + baseline ICS use + visit + treatment by visit interaction + visit by baseline FEV_1 interaction + COPD disease severity; Pre-dose trough FEV_1 is defined as the mean of FEV_1 at −45 and −15 min before the morning dose. The number of patients included in the analysis, GLY (n = 229) and IND (n = 227) at all the assessed time-points. MMRM, mixed model repeated measures; LSM, least squares mean; FAS, full analysis set; GLY, glycopyrrolate; IND, indacaterol, b.i.d., twice daily; q.d., once daily; FEV_1, forced expiratory volume in one second.

difference, −5.7 days; p = 0.057). However, the change from baseline in the use of the rescue medication was numerically lower in daily (treatment difference, 0.63 puffs; p = 0.014), and daytime (treatment difference, 0.34 puffs; p = 0.014) number of puffs with IND versus that with GLY.

4. Discussion

The overall results of the GEM3 study demonstrate that the safety and efficacy of GLY b.i.d. were comparable to safety and efficacy of an approved LABA, IND, in patients with moderate-to-severe COPD over the 52-week treatment period. IND was chosen as the active comparator in this study for ethical reasons regarding a placebo group in a long-term study in COPD patients [12]. The safety of IND 75 μg q.d. has already been evaluated in 12-week duration studies, showing an AE rate similar to that of placebo [17].

In this study, GLY was well tolerated over 52 weeks of treatment with an overall incidence of AEs similar to that of IND. Most of the reported AEs were of mild to moderate severity, which further supported the safety of GLY b.i.d. A higher incidence of respiratory-related AEs as observed in this study is expected for long-term studies which evaluate safety in COPD population [18]. AE reporting rates in the previous GEM studies (referred to as GEM1 and GEM2) were comparable between glycopyrrolate 15.6 μg b.i.d. treatment and placebo.

The incidence of SAEs reported in this study was low and comparable between the treatment groups, with a majority being related to the respiratory, thoracic, and mediastinal disorders system organ class in both treatment groups. Moreover, the nature/type of SAEs seen in this study was similar to that in a one-year safety study with tiotropium [20]. It should be noted that the association of cardiovascular morbidity and mortality in COPD populations is well known; thus, CCV events in this study investigating an elderly patient population were to be expected [21]. The incidence of adjudicated serious CCV AEs, including MACE and non-MACE outcomes, in GEM3 was comparable between both treatment groups. However, due to the low number of patients with MACE, caution should be exercised when interpreting results between the treatment groups. The rate of adjudicated atrial fibrillation/flutter events was low and balanced between the treatment groups (GLY, one patient [0.4%] versus IND, two patients [0.8%]). Notably, there were no thromboembolic outcomes associated with the events of atrial fibrillation/flutter events. The incidence of atrial fibrillation was generally similar to that of other marketed LAMAs [22,23].

The GEM3 study illustrates the relevant concerns regarding the cardiovascular safety of LAMAs in general; e.g., cardiovascular safety concerns which were raised for tiotropium since its launch in 2004 [24]. Those concerns were largely addressed with the results of the Tiotropium Safety and Performance in Respimat (TIOSPIR) trial which specifically included patients with a medical history of cardiac disorders such as arrhythmias, myocardial infarction, or cardiac failure, where tiotropium showed an acceptable safety profile [25]. A comprehensive safety analysis from the GLOW (**GL**ycopyrronium bromide in C**O**PD air**W**ays) clinical studies showed that glycopyrronium 50 μg q.d. had an acceptable safety profile, with low frequencies of cardiac and typical anti-muscarinic adverse effects [8,10]. Moreover, the SHINE and SPARK studies showed that glycopyrronium, used in combination with indacaterol, did not lead to any associated risks towards the cardiovascular safety, and had a safety profile similar to that of tiotropium, in patients with COPD [26,27].

Lung function parameters, such as pre-dose trough FEV_1, trough FVC, and the number of exacerbation rates, were evaluated as secondary objectives. No statistically significant and clinically relevant differences were observed for these parameters between both treatment groups. At the end of the treatment period, the change from baseline in pre-dose trough FEV_1 was comparable between the groups. However, a decline in pre-dose trough FEV_1 was observed across the treatment groups over time (Fig. 3). This lung function decline has been reported to be consistent with the underlying progressive nature of COPD [28]. Due to the lack of a placebo comparator in this study, the actual treatment effect of GLY must be interpreted with caution as, without placebo adjustment,

the improvements in trough FEV_1 could not take into account the decline which is expected without treatment [28]. Considering the fact that the patients selected in this study had no or a very low risk of exacerbations, the incidences of COPD exacerbations observed during the treatment period were low, too. Overall, a similar lung function improvement was achieved with GLY as compared to IND, an approved bronchodilator in the United States with an established efficacy profile.

5. Conclusion

This long-term study shows that GLY 15.6 μg b.i.d. has a favorable safety and tolerability profile, similar to that of an approved LABA, IND 75 μg q.d., in COPD patients. Low incidences of SAEs, MACE, atrial fibrillation, and deaths indicate that treatment with GLY 15.6 μg b.i.d. poses a low risk including cardiovascular risk in COPD patients, comparable to indacaterol. Moreover, treatment with GLY led to an improvement in lung function over 52 weeks, which was comparable to that with IND. Overall, the safety and efficacy results of the GEM3 study show that GLY 15.6 μg b.i.d. is a treatment option for patients with stable, symptomatic COPD with moderate-to-severe airflow limitation.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2016.03.015.

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