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Safety of inhaled glycopyrronium in patients with COPD: a comprehensive analysis of clinical studies and post-marketing data

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Background: Chronic use of inhaled anticholinergics by patients with chronic obstructive pulmonary disease (COPD) has raised long-term safety concerns, particularly cardiovascular. Glycopyrronium is a once-daily anticholinergic with greater receptor selectivity than previously available agents.

Methods: We assessed the safety of inhaled glycopyrronium using data pooled from two analysis sets, involving six clinical studies and over 4,000 patients with COPD who received one of the following treatments: glycopyrronium 50 µg, placebo (both delivered via the Breezhaler® device), or tiotropium 18 µg (delivered via the HandiHaler® device). Data were pooled from studies that varied in their duration and severity of COPD of the patients (ie, ≤12 weeks duration with patients having moderate or severe COPD; and >1 year duration with patients having severe and very severe COPD). Safety comparisons were made for glycopyrronium vs tiotropium or placebo. Poisson regression was used to assess the relative risk for either active drug or placebo (and between drugs where placebo was not available) for assessing the incidence of safety events. During post-marketing surveillance (PMS), safety was assessed by obtaining reports from various sources, and disproportionality scores were computed using EMPIRICA™. In particular, the cardiac safety of glycopyrronium during the post-marketing phase was evaluated.

Results: The overall incidence of adverse events and deaths was similar across groups, while the incidence of serious adverse events was numerically higher in placebo. Furthermore, glycopyrronium did not result in an increased risk of cerebro-cardiovascular events vs placebo. There were no new safety reports during the PMS phase that suggested an increased risk compared to results from the clinical studies. Moreover, the cardiac safety of glycopyrronium during the PMS phase was also consistent with the clinical data.

Conclusion: The overall safety profile of glycopyrronium was similar to its comparators indicating no increase in the overall risk for any of the investigated safety end points.

Keywords: COPD, drug safety, glycopyrronium, post-marketing surveillance

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not only progressive but also irreversible.[1] Inhaled bronchodilators are regarded as foundational pharmacologic agents in the management of patients with COPD, providing not only short-term symptom relief but also reducing the exacerbation frequency and improving the quality of life.[1] Long-acting muscarinic antagonists (LAMAs) (either alone or in combination with β-agonists) have been found to be effective bronchodilators for the treatment of patients with COPD.[1] LAMAs may produce typical anticholinergic side effects such as dry mouth, urinary retention, constipation, and nausea.[2] Inhaled tiotropium administered via soft mist inhaler at moderate and high dosages has been

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associated with the risk of increased mortality, in particular, cardiovascular mortality.[3] However, recent trials, such as the Tiotropium Safety and Performance in Respimat (TIOSPIR) study[4] and other more recent analyses show a mortality risk similar to that of tiotropium in dry powder (HandiHaler®) formulation.[5–9] Glycopyrronium (50 μg), delivered via the Breezhaler® device, is a once-daily (od) LAMA that is indicated for management of patients with COPD. Its efficacy and safety have been demonstrated in various clinical studies.[10] It is known to be safe and well tolerated while exhibiting sustained 24-hour bronchodilation in patients with moderate-to-severe COPD.[11] As compared to tiotropium, it has a greater selectivity for the M3 vs M2 receptor, a property that may reduce the risk of cardiovascular adverse events (AEs).[12] Additionally, it has been shown to exhibit a rapid onset of action as compared to tiotropium, thus allowing for rapid and sustained symptom relief.[11] To assess the safety of glycopyrronium, we have undertaken an analysis of pooled safety data from clinical trials involving glycopyrronium along with the available data from post-marketing surveillance (PMS) review periods. In this pooled analysis, the safety of glycopyrronium (delivered via the Breezhaler® device) and tiotropium (delivered via the HandiHaler® device) are compared with that of placebo. In the absence of placebo as a comparator, glycopyrronium is also compared with tiotropium.

Methods

All patients provided written informed consent. The comprehensive evaluation of the safety of glycopyrronium in the clinical studies was performed by using two distinct analysis sets that comprise the COPD core safety database (S-db) and the COPD long-term S-db. Studies with the recommended regimen of 50 μg glycopyrronium od, that were randomized double-blinded, placebo- and/or active-controlled, parallel design, with exposure duration of at least 12 weeks in patients with moderate or severe COPD (including following studies: CNVA237A2304 [GLOW1],[13] CNVA237A2303 [GLOW2],[14] CQVA149A2303 [SHINE],[15] CNVA237A2314 [GLOW5],[16] and CNVA237A2309 [GLOW7])[17] were included in the COPD core S-db. Within this database, data were pooled from all studies with similar disease severity, study design, and assessment methods utilized for evaluating AEs, deaths, and events of interest, with results adjusted for the length of exposure and reported as incidence (number of events per 100 patient treatment years [PTYs, sum of the duration of exposure over patients, in days/365.25 days]). The COPD long-term S-db included studies with an exposure duration of >1 year (CQVA149A2304 [SPARK],[18] a double-blinded, active-controlled, parallel design, and an exposure duration of at least 15 months in patients with severe and very severe COPD). The design of six individual studies included in the present analysis is summarized in Table 1. All the major adverse cardiovascular events and deaths were adjudicated by an external committee using predefined criteria. For the analysis of safety during the PMS review period, patient exposure to glycopyrronium was estimated based on the cumulative worldwide sales volume since its availability (September 28, 2012) for the approved 50 μg

Table 1 Details of studies included in the pooled analysis

Study name	Study design	Study duration	Patients randomized (N)	Patient population	Treatment groups	References
GLOW1 (CNVA237A2304)	R, DB, PC, PG	26 weeks	822	Moderate-to-severe COPD (Stage II and III, GOLD 2008)	GLY 50 μg od PBO od	13
GLOW2 (CNVA237A2303)	R, DB, and OL (TIO), PC, PG	52 weeks	1,066	Moderate-to-severe COPD (Stage II and III, GOLD 2008)	GLY 50 μg od PBO od OL-TIO 18 μg od	14
GLOW5 (CNVA237A2314)	R, DD, PG, BL (TIO)	12 weeks	657	Moderate-to-severe COPD (Stage II and III, GOLD 2010)	GLY 50 μg od Blinded TIO 18 μg od	16
GLOW7 (CNVA237A2309)	R, DB, PC, PG	26 weeks	459	Moderate-to-severe COPD (Stage II and III, GOLD 2010)	GLY 50 μg od PBO od	17
SHINE* (CQVA149A2303)	DB and OL (TIO), PG, R, PC, AC	26 weeks	2,144	Moderate-to-severe COPD (Stage II and III, GOLD 2008)	QVA149 110/50 μg od IND 150 μg od GLY 50 μg od OL-TIO 18 μg od PBO od	15
SPARK* (CQVA149A2304)	DB and OL (TIO), PG, R	64 weeks	2,224	Severe-to-very severe COPD (Stage III and IV, GOLD 2008)	QVA149 110/50 μg od GLY 50 μg od OL-TIO 18 μg od	18

Note: *Safety data for IND and QVA149 arms from the SHINE study, and the QVA149 arm from the SPARK study was not included in the current analysis.
Abbreviations: AC, active controlled; BL, blinded; COPD, chronic obstructive pulmonary disease; DB, double-blind; DD, double-dummy; GLOW, GLycopyrronium bromide in COPD airWays clinical study; GLY, glycopyrronium; IND, indacaterol; od, once daily; OL, open-label; PBO, placebo; PC, placebo-controlled; PG, parallel-group; R, randomized; TIO, tiotropium.

dose delivered via the Breezhaler® device, until the cut-off date of March 28, 2014.

Patients

The protocols for all studies were approved by institutional review boards and ethics committees at participating centers, and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent. Overall, the inclusion and exclusion criteria for patients were similar across the studies. The study population in all the trials comprised patients who were at least 40 years of age, had a smoking history of at least 10 pack-years, with post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio of <0.70 at screening, and diagnosed with moderate-to-severe COPD (Stage II or III according to the GOLD 2005 and 2008 criteria; post-bronchodilator FEV_1 of $\geq 30\%$ and $<80\%$ of the predicted normal) with the exception of the SPARK study that enrolled patients with severe-to-very severe COPD (Stage IV according to GOLD 2008; post-bronchodilator $FEV_1 \leq 50\%$ predicted).[18] Additionally, the clinical trial population also comprised patients with a medical history of stable cardiovascular disease.

Safety assessment

All analyses were based on the safety population, defined as all patients who received at least one dose of study medication. Common AEs were summarized according to the Medical Dictionary for Regulatory Activities (MedDRA, version 16.0) hierarchy, including primary system organ class and preferred term. Only those events regarded as identified risks (narrow-angle glaucoma, bladder outflow obstruction and urinary retention, and use in patients with severe renal impairment) and potential risks (cerebrovascular events, cardiovascular events including myocardial infarction and cardiac arrhythmias, atrial fibrillation, paradoxical bronchospasm, and medication errors) in the glycopyrronium (Seebri® Breezhaler®) risk management plan were searched through Standardized MedDRA Queries (SMQs) and Novartis MedDRA queries (NMQs). SMQs are collections of MedDRA (preferred) terms that relate to a defined medical condition, and allow identification of safety concerns, whereas NMQs are a customized group of search terms that define a medical concept for which there is no SMQ available.

The safety profile of glycopyrronium during the PMS review period was assessed by deriving AEs obtained from individual case study reports from health care professionals, consumers, scientific literature, spontaneous reports, competent authorities, noninterventional studies, and solicited sources such as compassionate use programs.

Furthermore, the safety of glycopyrronium during the PMS review period was also assessed by recording spontaneous voluntary reports of AEs. The EMPIRICA™ Signal System was used to calculate the disproportionality scores of the reported AEs using the Multi-item Gamma Poisson Shrinker (MGPS) algorithm. EMPIRICA™ is an advanced data mining tool used for automated detection and quantification of safety signals, applied to ARGUS™ (a Novartis global S-db that provides a comprehensive AE management system to support the Novartis pharmacovigilance program). The safety data coded by MedDRA (version 16.0) against events marked as "diagnosis" in ARGUS™ (leading events only) were retrieved by EMPIRICA™, after which all the AEs were assigned a statistical score.

Statistical analysis

For each event of interest from the clinical data, an estimate of the risk ratio (RR) of incidence density (each respective active treatment vs placebo or active control), together with the 95% confidence interval (CI), was produced through a Poisson regression with treatment and study as class effects in the model.

For the assessment of safety during the PMS review period, the statistical scores (represented as Empirical Bayes Geometric Mean [EBGM]) were calculated using the MGPS algorithm. The assignment of EBGM scores was based on the association of glycopyrronium and AEs together (drug–event combination) with a disproportionately high occurrence of reports, as compared to the proportion of reports in the entire ARGUS™ database for glycopyrronium and AEs independently. The lower 90% CI limit of EBGM (denoted as EB05) was used.

EB05 values <2 were considered as no technical signal and EMPIRICA™ alerted the reviewers if the reporting proportions of AEs were above the threshold value.[19] EMPIRICA™ calculates the disproportionality scores afresh each time to account for reconciliation of historic safety data. The disproportionality scores presented in this analysis were calculated on July 15, 2014.

Results

Patients and duration of their exposure to treatment

The analysis of the COPD core S-db included data from 4,178 patients. The length of time for which the patients were exposed to the study drugs is tabulated in Table 2.

Table 2 Duration of exposure to study drug after randomization (COPD core S-db)

Duration of exposure	GLY 50 µg N=2,180	TIO 18 µg N=1,077	PBO N=921
Total PTYs	1,138.642	534.234	508.216
PTYs exposure, % of patients (Total PTYs)			
1 day	0.41 (0.025)	0.37 (0.011)	0.54 (0.014)
2 days–<2 weeks	1.38 (0.605)	1.11 (0.162)	2.39 (0.408)
2 weeks–<1 month	1.83 (2.502)	1.67 (1.112)	4.13 (2.042)
1 month–<3 months	18.62 (86.439)	30.64 (74.209)	6.51 (9.785)
3 months–<6 months	12.25 (115.269)	10.68 (49.109)	12.49 (51.425)
6 months–<12 months	52.34 (645.478)	41.13 (253.741)	58.09 (297.736)
≥12 months	13.17 (288.323)	14.39 (155.890)	15.85 (146.806)

Abbreviations: COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; N, patients randomized; PBO, placebo; PTYs, patient treatment years; S-db, safety database; TIO, tiotropium.

The majority of PTYs occurred in patients treated from 3–>12 months on these studies. The characteristics of the pooled patient population along with other clinical characteristics were comparable across all the treatment groups (Table 3). There were a few noteworthy differences in the glycopyrronium group vs the other treatment groups: 1) by virtue of the way the studies were designed, the glycopyrronium group exhibited approximately twofold higher patient exposure and enrollment than the tiotropium and placebo groups (Table 2); 2) more patients were ≥85 years (0.41%, 0.19%, and 0.22%, for glycopyrronium, tiotropium, and placebo groups, respectively) (Table 3).

Patient exposure during PMS review period

The cumulative worldwide sale of glycopyrronium (at its approved dosage of 50 µg) during the PMS review period is estimated to be approximately 3,332 g of the active pharmaceutical ingredient. Consequently, patient exposure to glycopyrronium (since its first availability and until the cut-off date) is estimated to be approximately 182,562 PTYs.

AEs during clinical studies

The five most common AEs in the glycopyrronium group were COPD worsening, nasopharyngitis, upper respiratory tract infection, cough, and headache (Table 4). Across all groups, COPD worsening was the most common AE that exhibited the least incidence in the glycopyrronium group. Generally, AEs were well balanced and the rates of occurrence of events for both glycopyrronium and tiotropium treatment arms were similar to that of placebo. The only AEs (among the five most common AEs) observed in >2% of patients and that numerically increased with glycopyrronium were nasopharyngitis and headache, which occurred with an incidence similar to that of placebo and tiotropium.

Overall, the cardiovascular AE rate was similar for glycopyrronium and placebo although atrial fibrillation was seen more often with glycopyrronium. The most commonly occurring LAMA-specific AEs were dizziness, dry mouth, constipation, nausea, and pyrexia. In general, these events

Table 3 Characteristics of pooled clinical trial study population (COPD core S-db)

Patient characteristics	GLY 50 µg N=2,180	TIO 18 µg N=1,077	PBO N=921
Age			
<65 years	1,128 (51.74)	575 (53.39)	455 (49.40)
65–<75 years	792 (36.33)	387 (35.93)	350 (38.00)
75–<85 years	251 (11.51)	113 (10.49)	114 (12.38)
≥85 years	9 (0.41)	2 (0.19)	2 (0.22)
Sex			
Male	1,689 (77.48)	776 (72.05)	702 (76.22)
Female	491 (22.52)	301 (27.95)	219 (23.78)
Race			
Caucasian	1,345 (61.70)	786 (72.98)	557 (60.48)
Black	28 (1.28)	17 (1.58)	15 (1.63)
Asian	758 (34.77)	241 (22.38)	331 (35.94)
Other	49 (2.25)	33 (3.06)	18 (1.95)
Number of CCV risk factors at baseline			
0	217 (9.95)	79 (7.34)	90 (9.77)
1	571 (26.19)	255 (23.68)	236 (25.62)
2	570 (26.15)	286 (26.56)	243 (26.38)
≥3	822 (37.71)	457 (42.43)	352 (38.22)
COPD severity			
Mild	2 (0.09)	1 (0.09)	0 (0)
Moderate	1,302 (59.72)	661 (61.37)	579 (62.87)
Severe	868 (39.82)	414 (38.44)	338 (36.70)
Very severe	8 (0.37)	0 (0)	4 (0.43)
Steroid use			
None	948 (43.49)	481 (44.66)	427 (46.36)
ICS	1,220 (55.96)	588 (54.60)	491 (53.31)
OCS	3 (0.14)	2 (0.19)	1 (0.11)
ICS and OCS	9 (0.41)	6 (0.56)	2 (0.22)
Baseline diabetes condition	274 (12.57)	141 (13.09)	119 (12.92)

Note: Values are n (%).
Abbreviations: CCV, cerebrovascular and cardiovascular; COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; ICS, inhaled corticosteroids; N, patients randomized; OCS, oral corticosteroids; PBO, placebo; S-db, safety database; TIO, tiotropium.

Table 4 Incidence of most common AEs (per 100 PTYs) in clinical studies sorted by primary system organ class and preferred term (>10 events/100 PTYs for GLY) (COPD core S-db)

Primary system organ class, preferred term	GLY 50 μg N=2,180	TIO 18 μg N=1,077	PBO N=921
Patients with ≥1 AE, (%)	1,274 (58.44)	607 (56.36)	586 (63.63)
Number of AEs/100 PTYs	342.952	371.373	393.927
Respiratory, thoracic, and mediastinal disorders			
Total	1,221 (107.233)	682 (127.659)	709 (139.508)
COPD worsening	868 (76.231)	510 (95.464)	538 (105.860)
Cough	87 (7.641)	39 (7.300)	39 (7.674)
Dyspnea	53 (4.655)	19 (3.556)	29 (5.706)
Oropharyngeal pain	27 (2.371)	14 (2.621)	16 (3.148)
Sinus congestion	16 (1.405)	5 (0.936)	2 (0.394)
Dysphonia	14 (1.230)	7 (1.310)	5 (0.984)
Nasal congestion	12 (1.054)	8 (1.497)	8 (1.574)
Epistaxis	11 (0.966)	5 (0.936)	2 (0.394)
Infections and infestations			
Total	1,029 (90.371)	546 (102.202)	537 (105.664)
Nasopharyngitis	209 (18.355)	79 (14.788)	93 (18.299)
Upper RTI	170 (14.930)	73 (13.664)	100 (19.677)
Lower RTI	55 (4.830)	34 (6.364)	28 (5.509)
Bronchitis	43 (3.776)	29 (5.428)	24 (4.722)
Sinusitis	42 (3.689)	22 (4.118)	20 (3.935)
Urinary tract infection	42 (3.689)	23 (4.305)	13 (2.558)
Viral upper RTI	42 (3.689)	35 (6.551)	38 (7.477)
Influenza	34 (2.986)	18 (3.369)	13 (2.558)
Pneumonia	31 (2.723)	16 (2.995)	22 (4.329)
Pharyngitis	20 (1.756)	17 (3.182)	8 (1.574)
Rhinitis	19 (1.669)	7 (1.310)	4 (0.787)
Cellulitis	12 (1.054)	6 (1.123)	6 (1.181)
Oral candidiasis	12 (1.054)	7 (1.310)	6 (1.181)
Gastroenteritis	11 (0.966)	3 (0.562)	6 (1.181)
Gastroenteritis viral	10 (0.878)	4 (0.749)	3 (0.590)
RTI	10 (0.878)	5 (0.936)	3 (0.590)
Nervous system disorders			
Total	205 (18.004)	82 (15.349)	83 (16.332)
Headache	82 (7.202)	38 (7.113)	33 (6.493)
Syncope	14 (1.230)	0	4 (0.787)
Cardiac disorders			
Total	104 (9.134)	34 (6.364)	55 (10.822)
Atrial fibrillation	15 (1.317)	4 (0.749)	2 (0.394)
Angina pectoris	10 (0.878)	5 (0.936)	10 (1.968)
Eye disorders			
Total	43 (3.776)	23 (4.305)	19 (3.739)
Cataract	10 (0.878)	7 (1.310)	2 (0.394)
Gastrointestinal disorders			
Total	263 (23.098)	140 (26.206)	138 (27.154)
Diarrhea	29 (2.547)	10 (1.872)	18 (3.542)
Toothache	16 (1.405)	5 (0.936)	4 (0.787)
Dyspepsia	15 (1.317)	6 (1.123)	4 (0.787)
Abdominal pain	13 (1.142)	8 (1.497)	5 (0.984)
Vomiting	13 (1.142)	10 (1.872)	11 (2.164)
Gastroesophageal reflux disease	12 (1.054)	9 (1.685)	10 (1.968)

Note: Values are total number of AEs (AEs/100 PTYs) unless otherwise stated.
Abbreviations: AEs, adverse events; COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; N, patients randomized; PBO, placebo; PTYs, patient treatment years; RTI, respiratory tract infection; S-db, safety database; TIO, tiotropium.

occurred most commonly in the placebo group, with only dry mouth, constipation, and throat irritation modestly increasing with glycopyrronium (Table 5).

Adjudicated deaths and serious AEs reported during clinical phase

The incidence of deaths and serious AEs (SAEs) adjusted per PTYs is listed in Table 6. The occurrence of deaths (exposure adjusted) was comparable across groups. Respiratory cause was the leading reason for deaths among the treatment groups, and was lowest in the glycopyrronium group. Furthermore, the RR for respiratory deaths relative to placebo was slightly lower for glycopyrronium (RR: 1.059 vs placebo; 95% CI – 0.368, 3.047) than for tiotropium (RR: 1.928 vs placebo; 95% CI – 0.471, 7.892) (Table 6). The overall incidence of SAEs (exposure adjusted) in glycopyrronium and tiotropium

Table 5 Incidence of AEs most commonly associated with LAMAs, classified according to primary system organ class and preferred term (COPD core S-db)

Primary system organ class, preferred term	GLY 50 µg N=2,180	TIO 18 µg N=1,077	PBO N=921
Total PTYs	1,138.642	534.234	508.216
Nervous system disorders			
Dizziness	25 (2.196)	9 (1.685)	13 (2.558)
Renal and urinary disorders			
Urinary retention	4 (0.351)	2 (0.374)	0
Gastrointestinal disorders			
Dry mouth	33 (2.898)	14 (2.621)	10 (1.968)
Constipation	22 (1.932)	5 (0.936)	9 (1.771)
Nausea	16 (1.405)	11 (2.059)	11 (2.164)
General disorders			
Pyrexia	35 (3.074)	9 (1.685)	25 (4.919)
Eye disorders			
Vision blurred	5 (0.439)	1 (0.187)	3 (0.590)
Dry eye	3 (0.263)	2 (0.374)	1 (0.197)
Respiratory disorders			
Throat irritation	11 (0.966)	3 (0.562)	4 (0.787)
Rhinorrhea	5 (0.439)	6 (1.123)	10 (1.968)
Cardiac disorders			
Tachycardia	2 (0.176)	1 (0.187)	4 (0.787)
Palpitations	5 (0.439)	2 (0.374)	4 (0.787)

Note: Values are total number of AEs (AEs/100 PTYs).
Abbreviations: AEs, adverse events; COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; LAMAs, long-acting muscarinic antagonists; N, patients randomized; PBO, placebo; PTYs, patient treatment years; S-db, safety database; TIO, tiotropium.

groups was lower than that in the placebo group. The most commonly occurring SAE was COPD worsening, which was the lowest in the glycopyrronium group.

The incidence of SAEs by preferred term for gastrointestinal, vascular, and renal/urinary disorders was lower than the threshold (>0.2 events/100 PTYs for glycopyrronium). The overall frequency of occurrence (events/100 PTYs) of SAEs in the various treatment arms was as follows: glycopyrronium (gastrointestinal, 1.317; vascular, 0.790; renal/urinary, 0.439); tiotropium (gastrointestinal, 1.872; vascular, 0; renal/urinary, 0.187); and placebo (gastrointestinal, 2.558; vascular, 0.394; renal/urinary, 0.787).

Cerebrovascular and cardiovascular events during clinical phase

The frequency of occurrence of cerebrovascular and cardiovascular (CCV) events are shown in Table 7 (also refer Supplementary materials, Tables S1–S4). Glycopyrronium did not result in any increased risk for cardiovascular events in patients in comparison with placebo. Cumulative assessment of the clinical data did not establish any underlying association of cardiovascular events and glycopyrronium. Compared to placebo, both actives, glycopyrronium (RR: 3.805 vs placebo; 95% CI – 0.875, 16.550) and tiotropium (RR: 1.550, 95% CI – 0.253, 9.495), exhibited an increase in the exposure-adjusted incidence of atrial fibrillation, although these were not statistically significant (Tables 7, S1 and S2). The RR for cerebrovascular events for glycopyrronium (RR: 1.95 vs placebo; 95% CI – 0.553, 6.870) (95% CI of 0.553, 6.870) was lower than that for tiotropium (RR: 2.62

Table 6 Adjudicated deaths, and SAEs (>0.2 events/100 PTYs for GLY) (COPD core S-db)

Primary system organ class, preferred term	GLY 50 µg N=2,180	TIO 18 µg N=1,077	PBO N=921
Total deaths, n (%)	11 (0.23)	5 (0.46)	5 (0.54)
Risk ratio	1.059	1.928	
95% CI (lower, upper limit)	0.368, 3.047	0.471, 7.892	
P-value	0.9160	0.3610	
Deaths/100 PTYs	0.966	0.936	0.984
Cardiovascular	0.263	0.187	0.197
Respiratory	0.351	0.562	0.590
Cancer	0.176	0.187	0
Unknown	0	0	0.197
Other causes	0.176	0	0
Patients with ≥1 SAE	163	72	94
Number of SAEs/100 PTYs	25.205	20.965	35.615
Respiratory, thoracic, and mediastinal disorders			
Total	84 (7.377)	37 (6.926)	61 (12.003)
COPD worsening	54 (4.742)	28 (5.241)	48 (9.445)
Respiratory failure	7 (0.615)	2 (0.374)	5 (0.984)
Dyspnea	3 (0.263)	0	2 (0.394)
Pneumothorax	3 (0.263)	2 (0.374)	0
Acute respiratory failure	2 (0.176)	2 (0.374)	0
Infections and infestations			
Total	54 (4.742)	25 (4.680)	35 (6.887)
Pneumonia	19 (1.669)	9 (1.685)	15 (2.951)
Bronchitis	6 (0.527)	2 (0.374)	1 (0.197)
Upper respiratory tract infection bacterial	5 (0.439)	2 (0.374)	5 (0.984)
Lower respiratory tract infection	3 (0.263)	1 (0.187)	3 (0.590)
Cellulitis	3 (0.263)	1 (0.187)	1 (0.197)
Cardiac disorders			
Total	34 (2.986)	5 (0.936)	16 (3.148)
Atrial fibrillation	8 (0.703)	0	0
Acute coronary syndrome	3 (0.263)	0	0
Cardiac failure congestive	3 (0.263)	1 (0.187)	1 (0.197)
Myocardial infarction	3 (0.263)	1 (0.187)	1 (0.197)
Angina pectoris	2 (0.176)	1 (0.187)	3 (0.590)
Nervous system disorders			
Total	16 (1.405)	8 (1.497)	6 (1.181)
Syncope	6 (0.527)	0	1 (0.197)
Transient ischemic attack	4 (0.351)	0	1 (0.197)

Notes: Values are total number of events (events/100 PTYs) unless otherwise stated. Risk ratio values are represented as active vs placebo.
Abbreviations: COPD, chronic obstructive pulmonary disease; CI, confidence interval; GLY, glycopyrronium; N, patients randomized; PBO, placebo; PTYs, patient treatment years; SAEs, serious adverse events; S-db, safety database; TIO, tiotropium.

Table 7 Incidence of CCV-related AEs and FAEs (defined by SMQ) adjusted for exposure with risk ratio and 95% CI (COPD core S-db)

Preferred term	GLY 50 µg N=2,180	TIO 18 µg N=1,077	PBO N=921
Cardiac arrhythmias			
Number (episodes/100 PTYs)	51 (4.48)	24 (4.49)	25 (4.92)
Relative risk	0.909	0.770	
95% CI (lower, upper limit)	0.562, 1.472	0.431, 1.374	
P-value	0.6990	0.3758	
Myocardial infarction or ischemic heart disease			
Number (episodes/100 PTYs)	24 (2.11)	7 (1.31)	19 (3.74)
Relative risk	0.585	0.352	
95% CI (lower, upper limit)	0.320, 1.071	0.144, 0.863	
P-value	0.0824	0.0225	
Atrial fibrillation			
Number (episodes/100 PTYs)	16 (1.41)	3 (0.56)	2 (0.39)
Relative risk	3.805	1.550	
95% CI (lower, upper limit)	0.875, 16.550	0.253, 9.495	
P-value	0.0748	0.6354	
Cardiac failure			
Number (episodes/100 PTYs)	11 (0.97)	2 (0.37)	8 (1.57)
Relative risk	0.618	0.264	
95% CI (lower, upper limit)	0.246, 1.550	0.052, 1.335	
P-value	0.3045	0.1073	
Cerebrovascular events			
Number (episodes/100 PTYs)	13 (1.14)	7 (1.31)	3 (0.59)
Relative risk	1.950	2.620	
95% CI (lower, upper limit)	0.553, 6.870	0.626, 10.976	
P-value	0.2986	0.1875	
Patients with ≥1 CCV-related FAEs	1	1	1
Number of CCV-related FAEs/100 PTYs	0.088	0.187	0.197
Cardiopulmonary failure	0	0	1 (0.197)
Thalamus hemorrhage	1 (0.088)	0	0
Myocardial infarction	0	1 (0.187)	0

Notes: CCV condition determined based on the following predefined search criteria: Cerebrovascular disorders (SMQ) (narrow); Cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias) (SMQ) (broad); Myocardial infarction (SMQ) (narrow); Other ischemic heart disease (SMQ) (narrow); Cardiac failure (SMQ) (narrow); Sudden death (PT); Sudden cardiac death (PT). Risk ratio values are represented as active vs placebo; Episodes/100 PTYs =100× (n/total PTYs). Values are number of AEs/100 PTYs (n/total PTYs) ×100.

Abbreviations: AEs, adverse events; CCV, cerebrovascular and cardiovascular; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FAEs, fatal AEs; GLY, glycopyrronium; N, patients randomized; PBO, placebo; PTYs, patient treatment years; RR, risk ratio; S-db, safety database; SMQ, Standardized MedDRA Query; TIO, tiotropium.

vs placebo; 95% CI – 0.626, 10.976) (although at wide CI). The glycopyrronium arm exhibited the least incidence of CCV-related fatal AEs (exposure-adjusted). The incidence of angioedema (exposure-adjusted and defined as Standard MedDRA Query narrow search) for glycopyrronium was similar to that for placebo and tiotropium albeit with numerically lower RR for glycopyrronium: (RR: 1.183 vs placebo; 95% CI – 0.371, 3.773) compared with tiotropium (RR: 1.474 vs placebo; 95% CI – 0.394, 5.519) (Table S4). Overall, the cardiovascular AE rate was similar for glycopyrronium and placebo, although atrial fibrillation events were seen more often with glycopyrronium, although not statistically significant.

Long-term CCV safety (in patients with severe-to-very severe airflow limitation)

The long-term clinical study enrolled patients at risk for exacerbations (defined as patients with severe-to-very severe airflow limitation, Stage III or IV according to GOLD 2008 criteria) and a documented history of at least one exacerbation in the previous 12 months requiring treatment with systemic corticosteroids or antibiotics, or both.

The exposure-adjusted incidence of events related to myocardial infarction, ischemic heart disease, and cardiac arrhythmia was numerically slightly higher for glycopyrronium as compared with tiotropium (Table 8); however, wide CIs preclude any clinical or statistical significance. The low number of observed cases did not allow meaningful comparison. The RR for the occurrence of cardiac failure was low for glycopyrronium (RR: 0.504 vs tiotropium; 95% CI – 0.227, 1.122). The incidence of cerebrovascular events (exposure-adjusted) during the long-term period was low compared to that of cardiovascular events, and also similar for tiotropium and glycopyrronium.

Safety during PMS review period

Table 9 summarizes the incidence of SAEs and non-SAEs during the PMS review phase (ie, from September 28, 2012 to March 28, 2014). By system organ class, the three most commonly occurring events during the PMS phase (in the order of decreasing frequency) were respiratory disorders, followed by gastrointestinal disorders and nervous system disorders. Cough was the most commonly occurring event across all organ system classes during the PMS review period; compared with data from clinical studies, glycopyrronium did not increase the risk of AEs and SAEs in patients during PMS.

Table 8 Incidence of cerebrovascular and cardiovascular AEs (defined by SMQ) during long-term (≥1 year) period and adjusted for exposure with risk ratio and 95% CI (COPD long-term S-db)

Preferred term	GLY 50 µg N=740	TIO 18 µg N=737
Cardiac arrhythmias		
Number (episodes/100 PTYs)	29 (3.45)	16 (1.89)
Relative risk	1.828	
95% CI (lower, upper limit)	0.993, 3.365	
P-value	0.0528	
Myocardial infarction or ischemic heart disease		
Number (episodes/100 PTYs)	26 (3.09)	19 (2.24)
Relative risk	1.380	
95% CI (lower, upper limit)	0.764, 2.493	
P-value	0.2859	
Atrial fibrillation		
Number (episodes/100 PTYs)	14 (1.66)	9 (1.06)
Relative risk	1.569	
95% CI (lower, upper limit)	0.679, 3.624	
P-value	0.2919	
Cardiac failure		
Number (episodes/100 PTYs)	9 (1.07)	18 (2.12)
Relative risk	0.504	
95% CI (lower, upper limit)	0.227, 1.122	
P-value	0.0935	
Cerebrovascular events		
Number (episodes/100 PTYs)	9 (1.07)	10 (1.18)
Relative risk	0.908	
95% CI (lower, upper limit)	0.369, 2.234	
P-value	0.8329	

Notes: CCV condition determined based on the following predefined SMQ search criteria: Angioedema (narrow scope); Cerebrovascular disorders (narrow); Cardiac arrhythmia (including bradyarrhythmias and tachyarrhythmias) (broad); Myocardial infarction (narrow); Other ischemic heart disease (narrow). Risk ratio values are represented as glycopyrronium vs tiotropium.
Abbreviations: AEs, adverse events; CCV, cerebrovascular and cardiovascular; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; N, patients randomized; PTYs, patient treatment years; RR, risk ratio; S-db, safety database; SMQ, Standardized MedDRA Query; TIO, tiotropium.

The cardiovascular safety profile of glycopyrronium was found to be consistent with the approved label as supported by data from the clinical development program. Furthermore, there was no increase in the severity or incidence of reports related to atrial fibrillation with identification of no new safety concern compared with safety information on the package insert of Seebri® Breezhaler®.

Safety analysis during PMS review period using EMPIRICA™

Based on the safety data retrieved using EMPIRICA™, EB05 disproportionality scores for all AEs were less than the threshold value (EB05 <2) except for urinary retention and cardiac arrhythmia, which are well-known side effects of anticholinergic compounds (Table 10).

Table 9 Summary of serious and nonserious adverse reactions during PMS sorted by primary system organ class and preferred term

Primary system organ class, preferred term	Total reports[a]	Reporting frequency[b]
Respiratory, thoracic, and mediastinal disorders		
Total	263	0.144
Cough	59	0.032
Dyspnea	55	0.030
Epistaxis	25	0.014
Dysphonia	17	0.009
Throat irritation	17	0.009
Oropharyngeal pain	16	0.009
Gastrointestinal disorders		
Total	223	0.122
Dry mouth	38	0.021
Diarrhea	32	0.018
Nausea	24	0.013
Upper abdominal pain	16	0.009
Constipation	12	0.007
Nervous system disorders		
Total	106	0.058
Headache	43	0.024
Dizziness	13	0.007
Dysgeusia	12	0.007
Skin and subcutaneous tissue disorders		
Total	81	0.044
Rash	22	0.012
Pruritus	11	0.006
Cardiac disorders		
Total	74	0.041
Palpitations	23	0.013
Tachycardia	13	0.007
Renal and urinary disorders		
Total	72	0.039
Urinary retention	18	0.010
Dysuria	16	0.009
Pollakiuria	11	0.006
Musculoskeletal disorders		
Total	71	0.039
Myalgia	17	0.009
Pain in extremity	14	0.008
Eye disorders		
Total	66	0.036
Visual impairment	12	0.007
Psychiatric disorders		
Total	44	0.024
Insomnia	16	0.009

Notes: [a]Includes serious and nonserious adverse reactions. [b]Incidence is reported only for events that occurred with a frequency of 0.007/100 PTYs.
Abbreviations: PMS, post-marketing surveillance; PTYs, patient treatment years.

Discussion

Analyzing the pooled data from clinical studies and the PMS review period of glycopyrronium offers the first opportunity for a comprehensive assessment of AEs and SAEs related to its use in COPD. The importance of this relates to the possible adverse consequences of LAMA use in this setting.

Table 10 Statistical scores for AEs of clinical interest during the PMS phase

Preferred term (leading event)	EB05 disproportionality scores
Angioedema (SMQ-narrow)	0.787
Angioedema (SMQ-broad)	0.739
Atrial fibrillation	1.768
Cardiac arrhythmia (nonspecific SMQ-broad)	0.777
Cardiac arrhythmia terms* (SMQ-broad)	1.398
Cardiac failure (SMQ-narrow)	0.598
Cardiac failure (SMQ-broad)	0.417
Glaucoma (SMQ-narrow)	0.99
Glaucoma (SMQ-broad)	0.443
Myocardial infarction (SMQ-narrow)	0.223
Myocardial infarction (SMQ-broad)	0.277
Urinary retention	5.699
Urinary tract disorder	0.264

Notes: *Including bradyarrhythmias and tachyarrhythmias. EB05 disproportionality scores represent the lower 90% CI limit of Empirical Bayes Geometric Mean.
Abbreviations: AEs, adverse events; PMS, post-marketing surveillance; SMQ, Standardized MedDRA Query.

For example, cardiovascular safety concerns had been raised with the use of tiotropium in widespread usage since its launch in January 2004, evident primarily when used via the Respimat® device.[3,20] A comprehensive examination of drug safety often continues beyond the clinical phase leading up to the PMS period, thus providing an opportunity to not only capture the occurrence of expected safety concerns but also those that are infrequent or may be unexpected. The analysis of the data from various clinical studies and the PMS review period showed that glycopyrronium did not increase the risk for any investigated safety points in comparison to placebo, although the incidence of atrial fibrillation was numerically higher with glycopyrronium vs placebo. Anticholinergics are known to be associated with cardiovascular AEs, such as arrhythmias.[2] The analysis also indicates that safety profile of glycopyrronium was similar to that of tiotropium. COPD worsening was the most common AE and SAE reported in clinical trials, and occurred least frequently with glycopyrronium vs comparators. The long-term safety of glycopyrronium was also very similar to that of tiotropium.

There are some limitations to our analysis. In particular, clinical trials have predefined criteria for inclusion and exclusion of patients that may not always replicate the real-life setting or may not represent clinical characteristics of patients with COPD who receive the approved treatment. In addition, our reliance on incidence rates may have confounded our analysis. The incidence rate of AEs is calculated as the total number of episodes divided by the total patient years. Although this method can account for differences in exposure and appears appropriate for use when the data from patient population is pooled from studies with different exposure duration, there is an implicit assumption that each AE does not increase or decrease in frequency and/or severity over time. This may not be a valid assumption in all the cases. Additionally, the hygroscopic nature of tiotropium makes it challenging to remove the powder from the capsule (marked with manufacturer's logo) to a placebo capsule. In the GLOW2, SHINE (both from COPD core S-db), and SPARK (COPD long-term S-db) studies, tiotropium was dosed open-label, which may have influenced patient expectations. It is possible that in open-label studies, patients receiving the unblinded treatment may over report more favorable outcomes or, under report unfavorable safety signals. Finally, there could also be potential under reporting of AEs available in the ARGUS™ database, which are used as background incidence for calculation.

The comprehensive analysis of safety of glycopyrronium presented here has numerous strengths since it pools data from five randomized clinical trials (from the COPD core S-db) representing more than 4,000 patients with moderate-to-severe COPD. Our analysis also presents long-term safety (>1 year) of glycopyrronium, specifically in patients with severe-to-very severe COPD (from the COPD long-term S-db), who are at an increased risk of exacerbation.[1]

Furthermore, the inclusion and exclusion criteria across all studies were similar and so were the clinical characteristics of recruited patients (with the exception of the SPARK study to assess long-term safety). The pooled studies also exhibit an almost identical method of collection of AE reports and allow for the analysis of cardiovascular safety in patients with COPD with different exposure duration. Along with the pooled data from clinical studies, the safety of glycopyrronium was also evaluated during the PMS review period, particularly its cardiac safety. This provides a complete picture of the safety profile of glycopyrronium. Finally, the EMPIRICA™ data mining tool allows using an innovative approach for assessing drug safety for detection of statistics of disproportionate reporting for recognizing emerging trends in spontaneous AE reports for effective pharmacovigilance.

Conclusion

The analysis of pooled data from various clinical studies did not reveal any increase in the overall risk for any of the investigated safety end points. Glycopyrronium exhibited a comparable safety profile to tiotropium and placebo. Furthermore, the safety of glycopyrronium during the PMS review period was consistent with its approved label and did not indicate any clinically important safety findings, indicating a favorable overall benefit–risk balance.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

ADD has received research, consulting, and lecturing fees from GlaxoSmithKline, Sepracor, Schering-Plough, Altana, Methapharm, AstraZeneca, ONO Pharma, Merck Canada, Forest Laboratories, Novartis Canada/USA, Boehringer Ingelheim (Canada) Ltd., Pfizer Canada, SkyePharma, and KOS Pharmaceuticals.

EMK has served on advisory boards, speaker panels, or received travel reimbursement for Amphastar, AstraZeneca (Pearl Pharma), Boehringer-Ingelheim, Forest, GlaxoSmithKline, Merck (Schering-Plough), Mylan, Novartis, Sanofi Aventis, Sunovion, Teva and Theravance. He has conducted multicenter clinical research trials for approximately forty pharmaceutical companies.

KRC in the past 3 years has received compensation for consulting with Boehringer Ingelheim, CSL Behring, GlaxoSmithKline, Merck Frosst, Novartis, Takeda, Pfizer, Roche, Schering-Plough, and Grifols; has undertaken research funded by AstraZeneca, Boehringer Ingelheim, CSL Behring, Forest Laboratories, GlaxoSmithKline, Novartis, Parangenix, Roche, Takeda, and Grifols; and has participated in continuing medical education activities sponsored in whole or in part by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, Merck Frosst, Novartis, Takeda, and Pfizer. He is participating in research funded by the Canadian Institutes of Health Research operating grant entitled: Canadian Cohort Obstructive Lung Disease (http://clinicaltrials.gov - NCT00920348). Professor Chapman holds the GSK-CIHR Research Chair in Respiratory Health Care Delivery at the University Health Network, Toronto, Canada.

MD has been part of the Advisory Board for Boehringer-Pfizer, GSK, Nycomed, and Altana. He has performed consulting work for Boehringer-Pfizer, GSK, AstraZeneca, and Dompé. He also received lecture fees from these companies. All of the above amounted to less than 10,000 euro/year. He received a research grant of 45,000 euro/year from AstraZeneca. PDA, HH, and PA are employees of Novartis Pharmaceuticals Corporation. RDG and PG are employees of Novartis Pharma AG. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 Number of patients with atrial fibrillation and flutter (adjudicated) adjusted for exposure (COPD core S-db)

	GLY 50 µg	TIO 18 µg	PBO
Overall			
Total population	2,180	1,077	921
Patients with ≥1 event	44	23	14
Total patient years	1,138.642	534.234	508.216
Patients/100 PTYs	3.864	4.305	2.755
New onset			
Total population	2,124	1,049	900
Patients with ≥1 event	10	5	1
Total patient years	1,111.373	519.661	498.042
Patients/100 PTYs	0.900	0.962	0.201
Recurrent			
Total population	56	28	21
Patients with ≥1 event	34	18	13
Total patient years	27.269	14.574	10.174
Patients/100 PTYs	124.684	123.511	127.779

Abbreviations: COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; PBO, placebo; PTYs, patient treatment years; S-db, safety database; TIO, tiotropium.

Table S2 Number of patients with atrial fibrillation and flutter (adjudicated) adjusted for exposure for long-term safety assessment (COPD long-term S-db)

	GLY 50 µg	TIO 18 µg
Overall		
Total population	740	737
Patients with ≥1 event	21	24
Total patient years	841.645	848.780
Patients/100 PTYs	2.495	2.828
New onset		
Total population	717	714
Patients with ≥1 event	6	8
Total patient years	817.615	825.944
Patients/100 PTYs	0.734	0.969
Recurrent		
Total population	23	23
Patients with ≥1 event	15	16
Total patient years	24.030	22.836
Patients/100 PTYs	62.422	70.064

Abbreviations: COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; PTYs, patient treatment years; S-db, safety database; TIO, tiotropium.

Table S3 Incidence of CCV-related AEs (per 100 patient years) in clinical studies sorted by primary system organ class and preferred term (>10 events for GLY) (COPD core S-db)

Primary system organ class, preferred term	GLY 50 µg N=2,180	TIO 18 µg N=1,077	PBO N=921
Patients with ≥1 AE	83	31	37
Number of AEs/100 PTYs	8.695	7.487	10.822
Cardiac disorders			
Total	83 (7.289)	27 (5.054)	44 (8.658)
Atrial fibrillation	15 (1.317)	4 (0.749)	2 (0.394)
Angina pectoris	10 (0.878)	5 (0.936)	10 (1.968)
Cardiac failure congestive	6 (0.527)	1 (0.187)	2 (0.394)
Ventricular extrasystoles	6 (0.527)	4 (0.749)	2 (0.394)

(*Continued*)

Table S3 (*Continued*)

	GLY 50 µg N=2,180	TIO 18 µg N=1,077	PBO N=921
Atrioventricular block first-degree	4 (0.351)	1 (0.187)	2 (0.394)
Acute coronary syndrome	3 (0.263)	0	0
Cardiac failure	3 (0.263)	1 (0.187)	0
Coronary artery disease	3 (0.263)	0	2 (0.394)
Myocardial infarction	3 (0.263)	1 (0.187)	2 (0.394)
Myocardial ischemia	3 (0.263)	0	1 (0.197)
Supraventricular extrasystoles	3 (0.263)	3 (0.562)	3 (0.590)
Supraventricular tachycardia	3 (0.263)	1 (0.187)	4 (0.787)
Atrial flutter	2 (0.176)	0	4 (0.787)
Bundle branch block left	2 (0.176)	2 (0.374)	0
Bundle branch block right	2 (0.176)	0	0
Sinus tachycardia	2 (0.176)	2 (0.374)	2 (0.394)
Acute myocardial infarction	1 (0.088)	0	1 (0.197)
Arteriosclerosis coronary artery	1 (0.088)	0	1 (0.197)
Atrial tachycardia	1 (0.088)	0	0
Atrioventricular block	1 (0.088)	0	0
Atrioventricular dissociation	1 (0.088)	0	0
Cor pulmonale	1 (0.088)	0	2 (0.394)
Cor pulmonale chronic	1 (0.088)	0	0
Long QT syndrome	1 (0.088)	0	0
Nodal arrhythmia	1 (0.088)	0	0
Sick sinus syndrome	1 (0.088)	0	0
Sinus bradycardia	1 (0.088)	0	1 (0.197)
Tachyarrhythmia	1 (0.088)	0	1 (0.197)
Wandering pacemaker	1 (0.088)	0	0
Angina unstable	0	0	1 (0.197)
Arrhythmia	0	1 (0.187)	0
Cardiac failure acute	0	0	1 (0.197)
Cardiopulmonary failure	0	0	1 (0.197)
Coronary artery insufficiency	0	1 (0.187)	0
Right ventricular failure	0	0	1 (0.197)
Ventricular tachycardia	0	0	0
Nervous system disorders			
Total	13 (1.142)	6 (1.123)	3 (0.590)
Transient ischemic attack	5 (0.439)	0	2 (0.394)
Carotid artery stenosis	2 (0.176)	0	0
Carotid artery disease	1 (0.088)	0	0
Cerebral arteriosclerosis	1 (0.088)	0	0
Cerebral infarction	1 (0.088)	0	0
Cerebrovascular accident	1 (0.088)	2 (0.374)	0
Thalamus hemorrhage	1 (0.088)	0	0
Vertebrobasilar insufficiency	1 (0.088)	0	1 (0.197)
Hemorrhagic stroke	0	1 (0.187)	0
Ischemic stroke	0	2 (0.374)	0
Spinal hematoma	0	1 (0.187)	0
Respiratory, thoracic, and mediastinal disorders			
Total	0	0	1 (0.197)
Pulmonary edema	0	0	1 (0.197)
Injury, poisoning, and procedural complications			
Total	0	1 (0.187)	0
Extradural hematoma	0	1 (0.187)	0
Investigations			
Total	3 (0.263)	6 (1.123)	7 (1.377)
Heart rate irregular	2 (0.176)	0	0
Electrocardiogram QT prolonged	1 (0.088)	6 (1.123)	7 (1.377)

Note: Values in parentheses are total number of AEs per 100 PTYs.

Abbreviations: AEs, adverse events; CCV, cerebrovascular and cardiovascular; COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; N, patients randomized; PBO, placebo; PTYs, patient treatment years; S-db, safety database; TIO, tiotropium.

Table S4 Incidence of angioedema (defined by SMQ)-narrow AE episodes adjusted for exposure by primary system organ class and preferred term with RR and 95% CI (COPD core S-db)

	GLY 50 µg N=2,180	TIO 18 µg N=1,077	PBO N=921
Patients with ≥1 event	9	4	4
Episodes/100 PTYs	0.878	1.123	0.787
Risk ratio	1.183	1.474	
95% CI (lower, upper limit)	0.371, 3.773	0.394, 5.519	
P-value	0.7762	0.5643	
Eye disorders			
Total	1 (0.088)	0	1 (0.197)
Periorbital edema	1 (0.088)	0	0
Eye swelling	0	0	1 (0.197)
Gastrointestinal disorders			
Total	0	2 (0.374)	1 (0.197)
Lip edema	0	2 (0.374)	0
Palatal edema	0	0	1 (0.197)
Skin and subcutaneous tissue disorders			
Total	9 (0.790)	4 (0.749)	2 (0.394)
Urticaria	9 (0.790)	3 (0.562)	2 (0.394)
Angioedema	0	1 (0.187)	0

Notes: Risk ratio values are represented as active vs placebo. Values in parentheses are total number of AEs per 100 PTYs.
Abbreviations: AE, adverse event; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; N, patients randomized; PBO, placebo; PTYs, patient treatment years; RR, risk ratio; S-db, safety database; SMQ, Standardized MedDRA Query; TIO, tiotropium.