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ORIGINAL ARTICLE

TIOtropium Safety and Performance In Respimat® (TIOSPIR™): Analysis of Asian cohort of COPD patients

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ABSTRACT

Background and objective: **The TIOtropium Safety and Performance In Respimat (TIOSPIR) trial showed similar safety and exacerbation efficacy profiles for tiotropium Respimat and HandiHaler in patients with COPD. The TIOSPIR results for patients in Asia are presented here.**

Methods: **TIOSPIR evaluated once-daily tiotropium Respimat 5 and 2.5 μg with HandiHaler 18 μg in patients with COPD. Primary endpoints included time to death and time to first COPD exacerbation. Safety and exacerbation efficacy profiles were determined for the Asian region, and for Asia (all treatment arms pooled) versus the rest of the world (RoW).**

Results: **In Asia (n = 2356), time to death was similar for Respimat 5 and 2.5 μg versus HandiHaler 18 μg (hazard ratio (HR) (95% CI): 0.96 (0.67, 1.38) and 1.23 (0.87, 1.73)). Risk of COPD exacerbation was similar for Respimat 5 μg, but increased for 2.5 μg versus HandiHaler 18 μg (HR (95% CI): 0.99 (0.85, 1.15) and 1.17 (1.00, 1.35)). Time to death in Asia and RoW was similar (HR (95% CI): 1.15 (0.99, 1.35)). Time to first COPD exacerbation was longer (HR (95% CI): 0.84 (0.78, 0.89)) and exacerbation rates were lower in Asia, but severe exacerbations were more frequent than in the RoW. Risk of major adverse cardiovascular events was similar for both regions.**

Conclusion: **Similar safety and exacerbation efficacy profiles were observed for tiotropium Respimat 5 μg and HandiHaler 18 μg in patients with COPD from Asia, analogous to the global analysis. Asian patients had lower risk of, and fewer exacerbations overall, but a higher proportion of severe exacerbations than in the RoW.**

SUMMARY AT A GLANCE

Asian cohort analysis in TIOtropium Safety and Performance In Respimat® (TIOSPIR™) COPD trial demonstrates that, analogous to the global analysis, tiotropium Respimat 5 μg and HandiHaler 18 μg have similar safety and exacerbation efficacy. However, patients in Asia had fewer, but more severe, exacerbations than patients from the rest of the world.

Clinical trial registration: NCT01126437 at ClinicalTrials.gov

Key words: chronic obstructive pulmonary disease, clinical respiratory medicine, clinical trials.

Abbreviations: APSR, Asian Pacific Society of Respirology; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; IHD, ischaemic heart disease; LABA, long-acting β_2-agonists; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; MMRC, Modified Medical Research Council; Q1, 25% percentile; Q3, 75% percentile; RoW, rest of the world; RR, rate ratio; SAE, serious adverse event; SOC, system organ class; TIOSPIR, TIOtropium Safety and Performance In Respimat; TORCH, Towards a Revolution in COPD Health; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.

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INTRODUCTION

Tiotropium is an inhaled, once-daily, long-acting, anticholinergic bronchodilator maintenance therapy for patients with COPD.[1] It improves lung function as well as health-related quality of life (HRQoL), dyspnoea and exercise tolerance,[2–6] and reduces the number and risk of exacerbations.[5,7–11] Tiotropium is available via HandiHaler 18 μg (dry powder; Boehringer Ingelheim, Ingelheim am Rhein, Germany) and Respimat 5 μg Mist Inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany),[12,13] both displaying similar bronchodilating efficacy and pharmacokinetics.[14,15]

The Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial demonstrated fewer deaths in patients with tiotropium HandiHaler compared with placebo.[5] However, a post hoc pooled analysis showed that tiotropium Respimat 5 μg was associated with a non-significant numerical increase in mortality versus placebo, particularly in patients with known cardiac rhythm disorders at baseline, although no relationship between tiotropium Respimat and mortality risk could be established.[13] The TIOtropium Safety and Performance In Respimat (TIOSPIR) trial was designed and powered to directly compare the safety and efficacy of tiotropium Respimat 2.5 or 5 μg versus HandiHaler 18 μg, in patients with COPD,[16,17] and showed that, in patients with COPD, tiotropium Respimat 5 μg and HandiHaler 18 μg display similar safety and exacerbation efficacy profiles.[16,17]

In Asia, the prevalence of tobacco smoking and indoor pollution contribute to a rise in the incidence of COPD, thereby causing significant societal burden.[18,19] The COPD burden in Asia was estimated to be higher than in Western countries, particularly in terms of mortality, years of life lost and time spent living with disability.[18] The Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1] does not differentiate treatment options according to potential racial or cultural differences; however, the local management of COPD may vary between different geographical regions.

The purpose of this post hoc analysis was to compare the safety and efficacy of tiotropium Respimat 2.5 and 5 μg with HandiHaler 18 μg for the Asian (region) cohort of TIOSPIR (pre-specified analysis for primary endpoints), and to determine differences between Asia and the rest of the world (RoW) (post hoc analysis).

METHODS

Study design

Design

TIOSPIR (NCT01126437), a large (n = 17 135), long-term (2–3 years), randomized, parallel-group, double-blind, double-dummy, event-driven trial in patients with COPD compared the safety and efficacy of once-daily tiotropium Respimat 2.5 and 5 μg (Boehringer Ingelheim) with HandiHaler 18 μg (Boehringer Ingelheim). The primary results as well as the study design have been published previously.[16,17] The trial was performed in accordance with the provisions of the Declaration of Helsinki; trial protocol and procedures were approved by relevant institutional review boards and ethics committees, and all patients provided written informed consent. An independent mortality adjudication committee attributed the cause of each death.

Study population

Patients in the TIOSPIR trial had a clinical diagnosis of COPD (more specifically, had post-bronchodilator forced expiratory volume in 1 s (FEV_1) ≤70% predicted, FEV_1/forced vital capacity (FVC) ≤0.70), were ≥40 years of age and had ≥10 pack-years of smoking history.[16,17] Patients with concomitant cardiac disease were included, except those who had a myocardial infarction (MI) within the previous 6 months, were hospitalized for New York Heart Association class III/IV heart failure, had unstable or life-threatening arrhythmia that required new treatment within the previous year or had known moderate or severe renal impairment. All COPD medications, except other inhaled anticholinergics, were allowed.[16,17]

Procedures

Patients were randomized to tiotropium Respimat 2.5 μg (two inhalations of 1.25 μg), tiotropium Respimat 5 μg (two inhalations of 2.5 μg) or tiotropium HandiHaler 18 μg.

Outcome measures

Primary endpoints were time to (all-cause) death and time to first COPD exacerbation. Secondary outcomes included number of COPD exacerbations, time to first moderate or severe exacerbation and time to first overall and fatal major adverse cardiovascular (CV) event (MACE).[16,17] COPD exacerbations were defined as the worsening of ≥2 major respiratory symptoms for ≥3 days requiring treatment changes (mild, new maintenance bronchodilator prescription; moderate, prescription for antibiotics and/or systemic glucocorticoids; severe, hospitalization).[16,17]

Assessments and statistical analysis

Patients were recruited to 105 centres in Asia (China, India, Korea, Malaysia, Philippines, Taiwan and Thailand). Outcomes were compared between treatment arms (Respimat 2.5 and 5 μg vs HandiHaler 18 μg). For the comparison between regions, treatment arms were pooled.

All patients (including those who prematurely discontinued) were followed up for vital status till the end of the trial.[17] The vital status and on-treatment analysis sets have been previously described.[17]

Hazard ratio (HR) and 95% CI were calculated using Cox proportional hazards regression model (without covariate adjustment) and demonstrated via Kaplan–Meier plots. Rate ratios (RRs) and 95% CI were used to compare incidence rates. Negative binomial regression models were used to compare event rates.

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Table 1 Patient baseline characteristics (treated set)

Characteristics	Asia			Asia, total (n = 2356)	RoW, total (n = 14 760)	Asia versus RoW P-value
	Tiotropium Respimat 2.5 μg (n = 788)	Tiotropium Respimat 5 μg (n = 774)	Tiotropium HandiHaler 18 μg (n = 794)			
Male gender, n (%)	748 (94.9)	729 (94.2)	751 (94.6)	2228 (94.6)	10 009 (67.8)	<0.0001
Age, mean years (SD)	66.4 (8.7)	65.8 (8.4)	65.9 (9.2)	66.1 (8.8)	64.8 (9.1)	<0.0001
BMI, mean kg/m^2 (SD)	22.1 (3.9)	21.9 (3.9)	22.1 (3.9)	22.0 (3.9)	26.9 (5.6)	<0.0001
Duration of COPD, mean years (SD)	7.2 (6.6)	7.3 (6.7)	6.9 (6.3)	7.1 (6.5)	7.5 (6.1)	<0.0001
Smoking history, mean pack-years (SD)	38.7 (22.2)	39.1 (24.1)	37.8 (23.5)	38.5 (23.3)	44.6 (24.9)	<0.0001
Current smokers, n (%)	165 (20.9)	173 (22.4)	162 (20.4)	500 (21.2)	6019 (40.8)	<0.0001
Post-bronchodilator FEV_1, mean, L (SD)	1.123 (0.414)	1.113 (0.394)	1.119 (0.402)	1.118 (0.403)	1.374 (0.480)	<0.0001
Post-bronchodilator FEV_1, % of predicted value, mean (SD)	43.9 (14.4)	43.7 (14.1)	44.1 (14.4)	43.9 (14.3)	49.0 (13.7)	<0.0001
Post-broncholidator FVC, mean, L (SD)	2.450 (0.767)	2.420 (0.765)	2.417 (0.751)	2.429 (0.761)	2.758 (0.848)	<0.0001
Post-bronchodilator FEV_1/FVC, mean (SD)	0.464 (0.113)	0.468 (0.113)	0.470 (0.113)	0.467 (0.113)	0.504 (0.114)	<0.0001
GOLD Stage, n (%)						<0.0001
I + II	281 (35.7)	274 (35.4)	298 (37.5)	853 (36.2)	7339 (49.7)	
III	361 (45.8)	349 (45.1)	342 (43.1)	1052 (44.7)	5794 (39.3)	
IV	143 (18.1)	144 (18.6)	151 (19.0)	438 (18.6)	1404 (9.5)	
History of cardiac arrhythmia, n (%)	34 (4.3)	36 (4.7)	48 (6.0)	118 (5.0)	1707 (11.6)	<0.0001
History of CAD/IHD, n (%)	51 (6.5)	33 (4.3)	53 (6.7)	137 (5.8)	2457 (16.7)	<0.0001
Cardiac history, n (%)	88 (11.2)	78 (10.1)	100 (12.6)	266 (11.3)	4203 (28.5)	<0.0001
Number of COPD episodes treated in last year, n (%)						0.0005
0	382 (48.5)	373 (48.2)	377 (47.5)	1132 (48.0)	7687 (52.1)	
1	228 (28.9)	236 (30.5)	244 (30.7)	708 (30.1)	4168 (28.2)	
>1	178 (22.6)	165 (21.3)	173 (21.8)	516 (21.9)	2893 (19.6)	
MMRC scale, n (%)						<0.0001
0	25 (3.3)	28 (3.8)	32 (4.2)	85 (3.8)	776 (5.4)	
1	309 (41.3)	313 (42.2)	318 (42.2)	940 (41.9)	5434 (38.0)	
>1	415 (52.7)	401 (51.8)	404 (50.9)	1220 (51.8)	8095 (54.8)	
Ever breathless = no	36 (4.6)	29 (3.7)	37 (4.7)	102 (4.3)	442 (3.0)	
Sputum-producing cough (>3 months for two consecutive years)	446 (56.6)	433 (55.9)	455 (57.3)	1334 (56.6)	9552 (64.8)	<0.0001
Any respiratory medication, n (%)	661 (83.9)	627 (81.0)	638 (80.4)	1926 (81.7)	13 574 (92.0)	<0.0001
LABA (but not ICS)	31 (3.9)	35 (4.5)	36 (4.5)	102 (4.3)	1604 (10.9)	
ICS (but not LABA)	57 (7.2)	50 (6.5)	60 (7.6)	167 (7.1)	1064 (7.2)	
LABA and ICS	411 (52.2)	398 (51.4)	386 (48.6)	1195 (50.7)	7677 (52.0)	
Neither LABA nor ICS	289 (36.7)	291 (37.6)	312 (39.3)	892 (37.9)	4415 (29.9)	
Any CV medication	234 (29.7)	193 (24.9)	205 (25.8)	632 (26.8)	8121 (55.0)	<0.0001

Cardiac history is defined as history of at least one of myocardial infarction, cardiac arrhythmia, New York Heart Association heart failure classes I–IV or IHD/CAD. Any CV medication includes beta blockers, calcium channel blockers, cardiac glycosides (digoxin), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nitrates, anti-arrhythmics class I or III (sodium or potassium channel blockers), acetylsalicylic acid, anticoagulants (vitamin K antagonists, direct thrombin inhibitors and factor Xa inhibitors) and antiplatelets. Only relevant categories are displayed in the table. To compare geographical subgroups, Wilcoxon rank-sum test was used for continuous variables and chi-square test for categorical variables. P-values are based on the categories as collected in the study and used in analysis. MMRC was collected only for patients with breathlessness (ever breathless = yes).

CAD, coronary artery disease; CV, cardiovascular; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; IHD, ischaemic heart disease; LABA, long-acting β_2-agonists; MMRC, Modified Medical Research Council; RoW, rest of the world; SD, standard deviation.

RESULTS

Study population

In total, 2356 patients (n = 788, n = 774 and n = 794 for tiotropium Respimat 2.5 and 5 μg and HandiHaler 18 μg, respectively) within Asia were treated for a mean duration of 691 days (Table 1). This represented 14% of the total TIOSPIR population; 43% of the Asian cohort were from China. The remaining 14 760 treated patients from TIOSPIR were classified to the RoW region. A total of 476 (20.2%) and 3441 (23.3%) patients discontinued treatment in Asia and the RoW, respectively. Total exposure to tiotropium was 4459 patient-years for patients in Asia and 29 626 patient-years in the RoW (vital status follow-up: 99.9% (Asia), 99.7% (RoW)).

Patient baseline demographics and characteristics were similar across tiotropium groups in Asia (Table 1). Despite similar baseline age, duration of COPD and number of COPD exacerbations treated in the last year, patients in Asia included a higher proportion of males, had a lower BMI and included a lower proportion of current smokers compared with those from the RoW. Patients in Asia also had a lower FEV_1 % predicted value, that is more severe COPD than in the RoW. On the other hand, a lower proportion of patients in Asia had a history of cardiac arrhythmia, coronary artery disease (CAD) or ischaemic heart disease (IHD), or were receiving CV or respiratory medication at baseline than patients in the RoW (Table 1).

Mortality

Across treatment groups, there was similar risk of death due to any cause (time to death) for patients in Asia (vital status analysis; similar results obtained for the on-treatment analysis) (Table 2; Table S1, Fig. S1, Supplementary Information).

Overall mortality and adjudicated causes of death were similar across treatment arms in Asia, with a majority of deaths due to COPD exacerbations (Table S1, Supplementary Information).

Time to death was also similar between Asia and the RoW (pooled treatment arms) (HR (95% CI): 1.15 (0.99, 1.35) (vital status follow-up; Table 3; Fig. S1, Supplementary Information) and 1.08 (0.90, 1.28) (on-treatment analysis)).

Although all-cause mortality was similar for Asia and the RoW, deaths due to cardiac disorders (Medical Dictionary for Regulatory Activities System Organ Classes (MedDRA SOC)) occurred numerically less frequently (RR (95% CI): 0.44 (0.16, 1.20)) and those due to respiratory, thoracic and mediastinal disorders occurred more frequently in Asia (RR (95% CI): 1.81 (1.41, 2.32)). The majority of respiratory deaths were due to fatal COPD exacerbations for both regions (Table 3).

Table 2 Key mortality, exacerbation and safety results by treatment arms

	Asia				
n (%)	Tiotropium Respimat 2.5 μg (*n* = 788)	Tiotropium Respimat 5 μg (*n* = 774)	Tiotropium HandiHaler 18 μg (*n* = 794)	Respimat 2.5 μg versus HandiHaler HR (95% CI)	Respimat 5 μg versus HandiHaler HR (95% CI)
Patients with death	72 (9.1)	56 (7.2)	60 (7.6)	1.23 (0.87, 1.73)	0.96 (0.67, 1.38)
Patients with fatal MACE	18 (2.3)	13 (1.7)	13 (1.6)	1.42 (0.70, 2.90)	1.03 (0.48, 2.22)
Patients with COPD exacerbations, *n* (%)	363 (46.1)	314 (40.6)	333 (41.9)	1.17 (1.00, 1.35)	0.99 (0.85, 1.15)
Patients with MACE	30 (3.8)	25 (3.2)	26 (3.3)	1.20 (0.71, 2.02)	1.02 (0.59, 1.76)

MACE includes stroke, transient ischaemic attack, myocardial infarction, sudden death, cardiac death, sudden cardiac death or fatal event in SOCs for cardiac and vascular disorders. SOCs were defined according to MedDRA. On-treatment analysis, time to event comparison shown as HR.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; RR, rate ratio; SOC, system organ class.

Table 3 Risk of mortality by region (vital status analysis)

n (%)	Asia, total (*n* = 2356)	RoW, total (*n* = 14 779)	Asia versus RoW, HR or RR (95% CI)
Patients with death[†]	188 (8.0)	1114 (7.5)	1.15 (0.99, 1.35)
Patients with fatal MACE[†]	44 (1.9)	289 (2.0)	1.04 (0.76, 1.43)
Adjudicated causes of death[‡]			
Respiratory, thoracic and mediastinal disorders	78 (3.3)	291 (2.0)	1.81 (1.41, 2.32)
COPD	75 (3.2)	267 (1.8)	1.90 (1.47, 2.45)
General disorders	47 (2.0)	273 (1.9)	1.16 (0.85, 1.59)
Sudden death	19 (0.8)	110 (0.7)	1.17 (0.72, 1.90)
Sudden cardiac death	17 (0.7)	71 (0.5)	1.62 (0.95, 2.75)
Neoplasms benign, malignant and unspecified	29 (1.2)	276 (1.9)	0.71 (0.48, 1.04)
Cardiac disorders	4 (0.2)	62 (0.4)	0.44 (0.16, 1.20)
Vascular disorders	0 (0.0)	13 (0.1)	—

MACE includes stroke, transient ischaemic attack, myocardial infarction, sudden death, cardiac death, sudden cardiac death or fatal event in SOCs for cardiac and vascular disorders. SOCs were defined according to MedDRA.

[†]Time to event analysis, comparisons are shown as HR.

[‡]Adjudicated causes of death comparisons are shown as RR.

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; RoW, rest of the world; RR, rate ratio; SOC, system organ class.

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The risk of death was similar for Asia and the RoW in most subgroups (age, smoking status, GOLD Stage and pulmonary concomitant medication) (Fig. S2, Supplementary Information). There was a trend for a lower risk of death in patients with a history of cardiac arrhythmia or cardiac history at baseline in Asia compared with the RoW (Fig. S2, Supplementary Information).

Exacerbations

There was no difference in the risk of exacerbation (time to first exacerbation) between Respimat 5 μg and HandiHaler 18 μg in Asia (HR (95% CI): 0.99 (0.85, 1.15), $P = 0.85$) (Table 2; Table S2, Fig. S1, Supplementary Information). Similar results were obtained for the subgroup analyses, including baseline pulmonary medication and history of cardiac arrhythmia (data not shown). However, the risk of exacerbation was significantly higher with Respimat 2.5 μg versus Respimat 5 μg or HandiHaler 18 μg (HR (95% CI): 1.18 (1.02, 1.38), $P = 0.03$ and 1.17 (1.00, 1.35), $P = 0.04$, respectively) (Table S2 and Fig. S1, Supplementary Information). The annual exacerbation rate was similar across treatment arms in Asia, including severe exacerbations (Table S2 and Fig. S1, Supplementary Information).

The risk of exacerbation (time to first exacerbation) was lower in Asia compared with the RoW (pooled treatment arms) (HR (95% CI): 0.84 (0.78, 0.89); $P < 0.0001$), including most subgroups (Table 4; Figs S1, S2, Supplementary Information). Accordingly, the annual exacerbation rate was lower in Asia versus the RoW (RR (95% CI): 0.83 (0.77, 0.89); $P < 0.0001$) (Table 4). However, severe exacerbations occurred more frequently in patients from Asia (RR (95% CI): 1.62 (1.43, 1.83); $P < 0.0001$) (Table 4; Fig. S1, Supplementary Information).

MACE and serious adverse events

In Asia, the risk of MACE (time to first MACE) was similar for Respimat 2.5 and 5 μg versus HandiHaler 18 μg. The risk of fatal MACE was also similar across treatment arms (Table 2; Tables S1, S3 and Fig. S1, Supplementary Information). There was no difference between Respimat 2.5 μg or Respimat 5 μg versus HandiHaler 18 μg when risk of MACE was analysed by subgroup (data not shown).

The risk of MACE or fatal MACE was also similar for Asia and the RoW (Table 3; Table S3, Figs S1, S2, Supplementary Information).

Serious adverse event (SAE) frequency was similar across treatment arms in Asia (Table S4, Supplementary Information). The risk of an SAE was, however, slightly higher in Asia versus the RoW (HR (95% CI): 1.08 (1.00, 1.16)), particularly for respiratory, thoracic or mediastinal disorders (HR (95% CI): 1.48 (1.35, 1.63)) and infections or infestations (HR (95% CI): 1.16 (1.01, 1.34)) (Table S3, Supplementary Information). Patients in Asia also reported a higher risk of pneumonia compared with the RoW (HR (95% CI): 1.32 (1.12, 1.56); Table S3, Supplementary Information).

DISCUSSION

This sub-analysis from TIOSPIR showed that, analogous to the global TIOSPIR analysis,[17] tiotropium Respimat 5 μg and tiotropium HandiHaler 18 μg display similar safety and exacerbation efficacy profiles in patients with COPD who were enrolled in Asia. Although exhibiting similar safety profiles, exacerbation risk might be increased with the lower Respimat dose (2.5 μg), consistent with reduced bronchodilator efficacy found with lower doses.[20–22] Patients enrolled in Asia included proportionally more males and had more severe COPD than those in the RoW. Despite a similar total mortality rate for both Asia and the RoW, the causes of death were different, with numerically fewer cardiac, and more respiratory causes in Asia. Deaths attributed to MACE were similar in both regions. However, patients in Asia were at lower risk of exacerbations and experienced fewer exacerbations overall, but a higher risk of severe exacerbations than in the RoW.

Table 4 Risk of COPD exacerbations by region (treated set)

	Asia, total (n = 2356)	RoW, total (n = 14 760)	Asia versus RoW, HR or RR (95% CI); P-value
Patients with COPD exacerbations, n (%)	1010 (42.9)	7332 (49.7)	
Median time to first exacerbation, days (Q1 and Q3)	922 (251, —)	693 (188, —)	HR: 0.84 (0.78, 0.89); $P < 0.0001$
Exacerbation events			
Total number of any COPD exacerbation event, n (%)	2139 (11.0)	17 355 (89.0)	
Adjusted annual rate of any COPD exacerbation event[†] (95% CI)	0.50 (0.47, 0.53)	0.60 (0.59, 0.62)	RR: 0.83 (0.77, 0.89); $P < 0.0001$
Total number of severe exacerbation events	737 (19.3)	3079 (80.7)	
Adjusted annual rate of severe COPD exacerbation[†] (95% CI)	0.18 (0.16, 0.20)	0.11 (0.10, 0.12)	RR: 1.62 (1.43, 1.83); $P < 0.0001$

On-treatment analysis (from randomization to drug stop date + 1 day).

[†]Per patient-year.

—, time exceeding trial duration; CI, confidence interval; HR, hazard ratio; Q1, 25% percentile; Q3, 75% percentile; RoW, rest of the world; RR, rate ratio.

Regional and cultural factors may account for varied trial results in terms of different responses and mortality rates. Variations in the characteristics and symptoms of patients with COPD as well as their treatment outcomes may also exist between cities within Asia, given the differences in exposure to biomass fuels or dust and access to healthcare that translate into increased respiratory and related risks.[23,24] It is important to assess these factors in order to optimize patient management strategies. For example, due to regional differences in countries such as China, patients in rural areas may be reluctant to be hospitalized until their symptoms become very severe, due to insufficient reimbursement of medical expense by the government or social insurance. On the other hand, patients in some areas are more often admitted to hospital for a COPD exacerbation because they cannot have easy access to corticosteroids or antibiotics through a primary care system. Some exacerbations in Asia may therefore be classified as severe, where they would not have been in other regions or countries with a different infrastructure. Given the overlapping clinical symptoms of severe exacerbations and pneumonia, it is possible that these two events may be misreported (with severe exacerbations possibly representing pneumonia); patients in Asia reported significantly greater risks of severe exacerbations and pneumonia than those in the RoW. In the 4-year UPLIFT trial (n = 5992), a higher proportion of the Asian cohort were males (95% vs 75% in the total cohort), with lower FEV_1, lower BMI, a lower proportion of current smokers (13% vs 30%) and more severe lung function impairment.[23] Despite these demographic differences, tiotropium improved lung function and HRQoL, and reduced exacerbations in patients from Asia to the same extent as in patients in the overall global UPLIFT cohort.[23] Similar demographic differences between the Asian cohort and the RoW as seen in the UPLIFT trial were observed in the TIOSPIR analysis described here, with overall safety and exacerbation efficacy results in Asia showing no differences to the global TIOSPIR analysis.[17] Consistent with the global UPLIFT population,[5,25] tiotropium was shown to decrease mortality compared with placebo within the Asian UPLIFT population, with slightly higher overall mortality rates than the global cohort.[23] The Towards a Revolution in COPD Health (TORCH) study found geographical differences in HRQoL change.[26] Quality of life in patients receiving placebo was found to improve in the Asia-Pacific region, whereas it was worse or stabilized in other parts of the world.

Ethnic-specific differences have been previously reported, for example, a study of Mexican, Puerto Rican and African American patients with asthma treated with salbutamol (albuterol) revealed ethnic-specific differences in bronchodilator drug responsiveness.[27] Causes of death have been shown to vary by region, with more respiratory infections and non-communicable respiratory diseases leading to deaths in the Asia-Pacific and South-East Asian regions compared with the RoW, whereas Western Europe has a greater proportion of deaths due to CV diseases.[28] This is reflected in this study, where causes of death differed between Asia and the RoW, with numerically fewer cardiac and more respiratory causes in Asia.

Although the TIOSPIR trial lacked a placebo arm, tiotropium HandiHaler 18 μg, previously shown to reduce mortality compared with placebo,[5,25,29] was used as a control. A placebo arm was specifically not included in TIOSPIR, as it would have been difficult to obtain high adherence and follow-up without effective symptom relief. This study excluded patients with severe unstable CV conditions or with moderate to severe renal impairment; however, a large (n = 10 805) pooled safety analysis of tiotropium confirmed that worsening renal function did not increase incidence RRs of adverse events in patients treated with tiotropium.[30] The TIOSPIR trial exhibited several strengths. Notably, it was a large trial with over 34 000 patient-years' exposure to tiotropium (4459 patient-years in Asia), that was specifically powered to precisely estimate the rates of death and exacerbations. Vital status follow-up rates were very high (Asia: 99.9%; RoW: 99.7%), eliminating differential follow-up bias. Furthermore, the study design allowed the use of all respiratory medications, except for other inhaled anticholinergics. The trial results therefore reflect those likely to be seen in standard clinical practice.

In conclusion, similar safety and exacerbation efficacy profiles were shown for tiotropium Respimat 5 μg and tiotropium HandiHaler 18 μg in patients from Asia. Compared with the RoW, patients in Asia experienced fewer exacerbations overall, but with a higher risk of severe exacerbations. Geographical differences (and therefore environmental, ethnic and cultural differences) in patient recruitment and treatment practice may have an impact on the likelihood of particular outcomes in clinical trials of COPD treatment, and should be taken into consideration when designing trials and applying results to different world regions.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Figure S1 (a) Time to death. (b) First exacerbation (any). (c) First severe exacerbation. (d) First MACE.

Figure S2 Risk of death, exacerbation and MACE by region.

Table S1 Risk of mortality by treatment arm (vital status analysis).

Table S2 Risk of COPD exacerbations by treatment arm (treated set).

Table S3 Safety by region (on-treatment).

Table S4 Safety by treatment arm (on-treatment).