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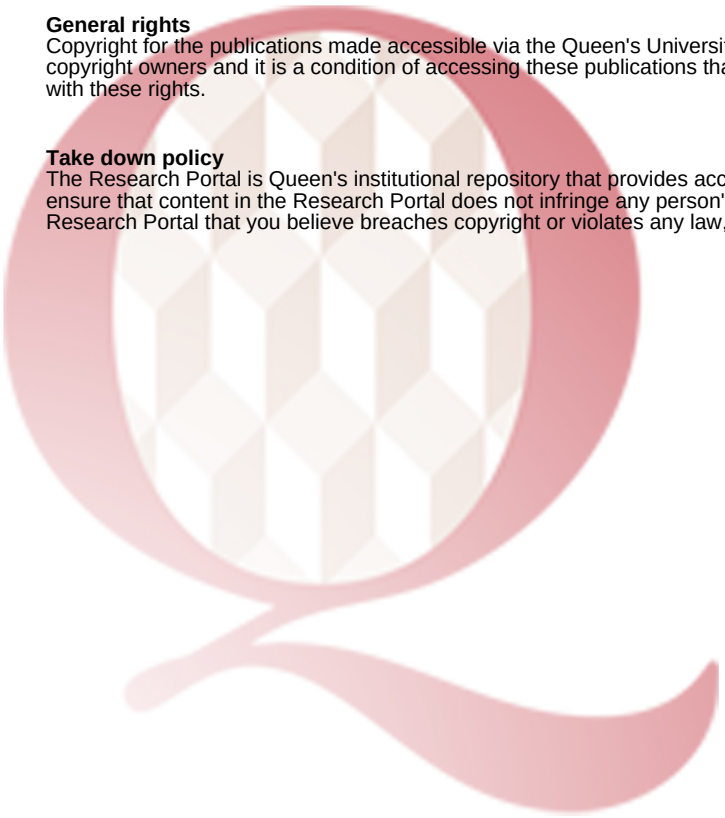

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Long-term general and cardiovascular safety of tiotropium/olodaterol in patients with moderate to very severe chronic obstructive pulmonary disease☆

Roland Buhl [a, *], Sheldon Magder [b], Ulrich Bothner [c], Kay Tetzlaff [c, d], Florian Voß [c], Lazaro Loaiza [c], Claus F. Vogelmeier [e], Lorcan McGarvey [f]

[a] Pulmonary Department, Mainz University Hospital, Mainz, Germany
[b] Royal Victoria Hospital, Montreal, Quebec, Canada
[c] Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
[d] Department of Sports Medicine, Medical Clinic V, University of Tübingen, Tübingen, Germany
[e] Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-University Marburg, Member of the German Center for Lung Research (DZL), Marburg, Germany
[f] Centre for Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK

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ABSTRACT

Background: Long-term safety, particularly cardiovascular safety, is of special interest in maintenance treatment of chronic obstructive pulmonary disease (COPD) with long-acting β_2-agonists and long-acting muscarinic antagonists, given potential cardiovascular effects.
Methods: Two 52-week Phase III trials (TONADO®) investigated tiotropium/olodaterol (5/5 and 2.5/5 μg) versus tiotropium 2.5, 5 μg and olodaterol 5 μg. In a pre-specified safety analysis, investigator-reported treatment-emergent adverse events (AEs), electrocardiogram and laboratory data were pooled. All serious AE (SAE) reports were reviewed by an independent Adjudication Committee, which assessed whether deaths, hospitalisations or intubations were respiratory, cardiovascular, cerebrovascular or other disease related. Subgroup analyses investigated cardiovascular safety including major cardiac events in patients with cardiovascular co-morbidities.
Results: This analysis comprised 3100 patients with moderate to very severe COPD, treated for ≤1 year, including 784 patients with cardiovascular co-morbidities. AEs were balanced across treatments in the total population as well as in patient subgroups with pre-existing cardiovascular co-morbidities. The incidence and nature of events were consistent with the disease under study and a 1-year trial duration. 494/3100 patients contributed to an adjudicated analysis of SAEs: 260 had respiratory-related, 53 had cardiovascular-related and 16 had cerebrovascular-related SAEs. Incidences of these SAEs were comparable between treatments. There was no evidence of any increased risk for the combination compared to the monotherapy groups.
Conclusions: These data provide confidence for clinicians that tiotropium/olodaterol 5/5 μg can be safely administered once-daily to patients with moderate to very severe COPD long-term, including those with significant cardiovascular co-morbidity.
Trial registry: ClinicalTrials.gov, Nos.: NCT01431274, NCT01431287.

Abbreviation list: AE, adverse event; COPD, chronic obstructive pulmonary disease; GOLD, Global initiative for chronic Obstructive Lung Disease; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

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* Corresponding author. Pulmonary Department, Mainz University Hospital, Langenbeckstraße 1, D-55131, Mainz, Germany.
E-mail address: r.buhl@3-med.klinik.uni-mainz.de (R. Buhl).

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1. Introduction

With the widespread use of long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs) in patients with moderate to very severe chronic obstructive pulmonary disease (COPD), it is important to evaluate their long-term safety, especially when given in combination. Cardiovascular safety is of particular interest, given the potential effects associated with both of these drug classes [1–3]. Cardiovascular diseases are among the most frequent serious co-morbid conditions in this patient population [4–7] and patients with COPD are at substantially greater risk of developing incident cardiac arrhythmia, thromboembolic disorders, myocardial infarction and stroke compared to healthy individuals [8,9]. Recent evidence from clinical studies of the safety and tolerability profile of LABAs supports their long-term use in COPD including those patients with a history, or increased risk, of cardiovascular disease, when given alone or as a fixed-dose combination with an inhaled corticosteroid [10,11].

The efficacy of tiotropium [12–19] and the novel LABA olodaterol [20–23] has been widely studied in patients with COPD. Two large-scale, Phase III, 1-year studies (TONADO®) have shown superior effects of tiotropium/olodaterol 5/5 μg on lung function and health-related quality of life compared to either of its monocomponents [24]. Here we report on a comprehensive, prespecified safety assessment of tiotropium/olodaterol maintenance treatment from this large population of patients with moderate to very severe COPD, a substantial proportion of whom had cardiovascular co-morbidities at baseline.

2. Materials and methods

2.1. Study design

These were two replicate, randomised, double-blind, five-arm, parallel-group, multicentre trials (TONADO®: Study 1237.5, NCT01431274; Study 1237.6, NCT01431287) (Fig. 1). Patients were randomised to tiotropium/olodaterol 2.5/5 μg or 5/5 μg, tiotropium 2.5 μg or 5 μg, or olodaterol 5 μg. All study drugs were delivered once daily in the morning via two actuations of the blinded Respimat® inhaler. This manuscript reports the data for the worldwide approved dose of tiotropium/olodaterol 5/5 μg and its monocomponents, tiotropium 5 μg and olodaterol 5 μg. Results for all treatment groups are reported in Appendices 1–7.

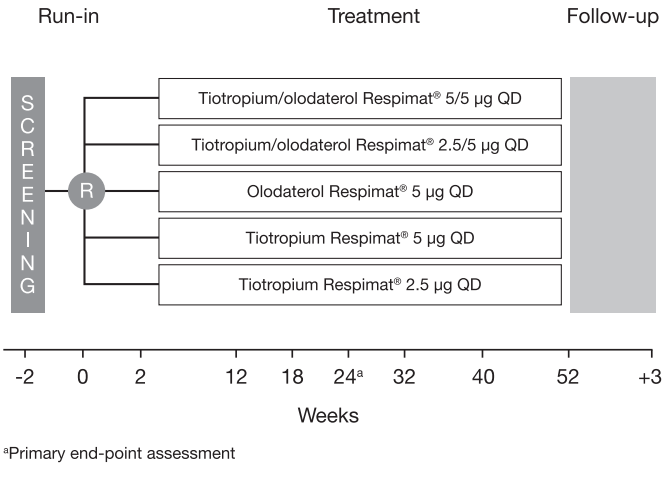

Fig. 1. Trial design. QD = once daily; R = randomisation. Reproduced with permission of the European Respiratory Society©: European Respiratory Journal Apr 2015, 45 (4) 969–979; http://dx.doi.org/10.1183/09031936.00136014.

The studies included patients aged ≥40 years with moderate to very severe COPD (Global initiative for chronic Obstructive Lung Disease [GOLD] 2–4). Further details can be found in Appendix 9.

The studies were conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and local regulations. Signed, informed consent was obtained from all patients. Institutional Review Board approval is described in Appendix 9.

2.2. Evaluations and outcome measures

Full details of the primary efficacy end points of these studies have previously been described [24]. The present analysis focuses on a pre-specified safety evaluation of pooled data from the two studies to maximise the available safety data.

Treatment-emergent adverse events (AEs) were recorded throughout the 52-week trial, regardless of causality. Vital signs were recorded at screening, baseline and after 12, 24 and 52 weeks of treatment, and measured before pre-dose pulmonary function tests and the 60-min post-dose pulmonary function tests. Twelve-lead electrocardiogram recordings were performed at screening and study withdrawal. In addition, 12-lead electrocardiogram recordings were performed pre-dose and 40 min post-dose at baseline and weeks 12, 24 and 52. A follow-up visit was performed 21 days after the 52 weeks of study treatment during which AEs, concomitant therapies and salbutamol use (rescue medication) were reviewed and recorded. At selected sites, 24-h Holter monitoring was performed in a subset of patients (150 per treatment group) before randomisation and after week 12.

2.3. Adjudicated safety evaluation

An independent external expert Adjudication Committee that was blinded to treatment independently assessed all serious adverse events (SAEs) to determine if any of the deaths, hospitalisations or intubations were respiratory, cardiovascular, cerebrovascular or other disease related. When an SAE was adjudicated as respiratory related, further determination was made to assess if it was related to COPD or pneumonia. When an SAE was adjudicated as cerebrovascular related, further determination was made to assess if it was related to stroke or other cerebrovascular disease.

2.4. Analysis

2.4.1. Overall AEs

All randomised patients who received at least one dose of treatment were included in the safety analysis set (treated set). Frequencies of investigator-reported AEs (coded using the Medical Dictionary for Regulatory Activities [MedDRA]) were analysed descriptively. The analysis was based on treatment-emergent AEs and included those AEs that occurred after the first dose of trial medication and within 21 days after the last dose of trial medication.

2.4.2. Aggregated end points

Aggregated safety end points reflecting cardiovascular safety (using Standardised MedDRA Queries and Boehringer Ingelheim-defined pharmacovigilance end points) as well as major adverse cardiovascular events (MACE) were compared across all treatment groups and in subgroups of patients with a history of cardiac disease including cardiac arrhythmia and ischaemic heart disease.

2.4.3. Adjudicated safety analysis

A composite end point was defined as the incidence of death, hospitalisation and intubation for respiratory-, cardiovascular-,

cerebrovascular- or other disease-related events/causes. Incidences of the composite end point and its individual components were evaluated based on adjudicated SAEs.

For comparisons of tiotropium/olodaterol with the respective monotherapy components, time to first event (end point) analysis was conducted using stratified Cox regression, with study as a stratum and treatment as the only factor in the model. Hazard ratios with corresponding 95% confidence intervals were calculated based on this model. For hospitalisations and intubations, this was the time to onset of the event; for deaths, this was the time to death.

2.4.4. Subgroup analyses

Frequencies of AEs were compared in the following pre-defined subgroups: sex, age, race, COPD disease severity, inhaled corticosteroid use at baseline, medical history of diabetes mellitus, any cardiac history, cardiac arrhythmia and ischaemic heart disease at baseline. The definitions of the cardiovascular history disease subgroups at baseline can be found in Appendix 9.

3. Results

3.1. Patient population and treatment exposure

In the TONADO® studies, 6887 patients were screened and 5163 patients were randomised to treatment. In this analysis of the marketed doses, 3100 patients received at least one dose of study medication (Study 1237.5: 1577 patients; Study 1237.6: 1523 patients). Baseline demographics were similar across the treatment groups (Table 1). Results on the additional doses of tiotropium and olodaterol can be found in the Appendix. Most patients were male (72.6%) and classified as GOLD 2/3 (87.9%); GOLD 2 categorised as moderate COPD with 50% ≤ FEV_1 <80% predicted and GOLD 3 categorised as severe COPD with 30% ≤ FEV_1 <50% predicted. In addition, 37.0% were current smokers. Overall, 86.7% of patients had diagnosed co-morbidities at baseline: 666 (21.5%) had cardiac disorders and 1520 (49.0%) had vascular disorders including hypertension. Mean exposure to study medication was similar across treatment groups, ranging from 326 to 340 days (Table 1).

3.1.1. Overall incidence of AEs

Incidences of AEs, SAEs, investigator-reported treatment-related AEs and AEs leading to death are presented in Table 2. Incidence of AEs was generally balanced across all treatment groups; most events were mild to moderate in severity and 6.6% were considered treatment related by the investigator (most frequently, respiratory [2.0%] and gastrointestinal [1.5%] disorders). Incidences of SAEs and deaths were also similar across treatment groups.

The most frequently reported AEs were from the MedDRA System Organ Classes of “respiratory, thoracic and mediastinal disorders” and “infections and infestations” (Fig. 2), with COPD and nasopharyngitis being the most commonly reported. The incidence of these most common events was similar across treatment groups.

3.1.2. Cardiovascular AEs

Cardiovascular AEs were generally balanced across treatment groups (Table 3) and the frequencies of events for tiotropium/olodaterol were not statistically significantly different to those for the monotherapy components. Cardiac arrhythmias were reported in 129 patients (4.2%; range 3.9–4.5%) and ischaemic heart disease in 70 patients (2.3%; range 2.1–2.5%).

Incidence of MACE ranged from 1.8% in the tiotropium arm to 2.4% in the olodaterol arm (Table 4). The exposure-adjusted rate ratios for tiotropium/olodaterol vs the monotherapies were 0.94

Table 1
Demographic and baseline patient characteristics and extent of exposure.

	Olodaterol 5 μg(n = 1038)	Tiotropium 5 μg(n = 1033)	Tiotropium/olodaterol 5/5 μg(n = 1029)
Male, n (%)	764 (73.6)	755 (73.1)	733 (71.2)
Mean (SD) age, years	64.2 (8.2)	63.9 (8.6)	63.8 (8.3)
Smoking status, n (%)			
Ex-smoker	660 (63.6)	663 (64.2)	629 (61.1)
Current smoker	378 (36.4)	370 (35.8)	400 (38.9)
Co-morbidities,[a] n (%)	897 (86.4)	902 (87.3)	890 (86.5)
Cardiac history	281 (27.1)	247 (23.9)	256 (24.9)
Cardiac rhythm disorders	100 (9.6)	87 (8.4)	98 (9.5)
Ischaemic heart disease	149 (14.4)	124 (12.0)	120 (11.7)
Vascular disorders[b]	511 (49.2)	513 (49.7)	496 (48.2)
Diabetes mellitus	152 (14.6)	136 (13.2)	125 (12.1)
GOLD, n (%)			
1 (≥80%)	0 (0.0)	1 (0.1)	0 (0.0)
2 (50–<80%)	532 (51.3)	517 (50.0)	502 (48.8)
3 (30–<50%)	378 (36.4)	387 (37.5)	408 (39.7)
4 (<30%)	128 (12.3)	128 (12.4)	119 (11.6)
Baseline pulmonary medication, n (%)			
SAMA	134 (12.9)	131 (12.7)	125 (12.1)
LAMA	365 (35.2)	346 (33.5)	378 (36.7)
SABA	424 (40.8)	401 (38.8)	400 (38.9)
LABA	491 (47.3)	450 (43.6)	486 (47.2)
ICS	505 (48.7)	466 (45.1)	506 (49.2)
Xanthines	96 (9.2)	109 (10.6)	108 (10.5)
Baseline cardiovascular medication,[c] n (%)	620 (59.7)	596 (57.7)	581 (56.5)
β-blocker	102 (9.8)	109 (10.6)	110 (10.7)
Mean (SD) extent of exposure, days	326.3 (96.6)	331.8 (91.3)	340.0 (79.6)

GOLD = Global initiative for chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β_2-agonist; SAMA = short-acting muscarinic antagonist; SD = standard deviation.

[a] Definitions of the cardiovascular disease subgroups at baseline can be found in Appendix 9.

[b] Most frequent vascular co-morbidities (>1%) were aortic aneurysm (1.1%), atherosclerosis (1.5%), hypertension (43.7%), peripheral arterial occlusive disease (1.1%), peripheral vascular disorder (1.5%) and varicose vein (2.1%).

[c] Anti-hypertensives, diuretics, anti-arrhythmics, nitrates, vasodilators, platelet aggregation inhibitors, anticoagulants, cardiac glycosides.

Table 2
Summary of general safety: incidence of total AEs, investigator reported as treatment-related AEs, AEs leading to discontinuations, SAEs and deaths.

	Olodaterol 5 μg	Tiotropium 5 μg	Tiotropium/ olodaterol 5/5 μg
Total patients, n	1038	1033	1029
All AEs, n (%)	795 (76.6)	757 (73.3)	761 (74.0)
Treatment-related AEs	69 (6.6)	63 (6.1)	73 (7.1)
Severe AEs[a]	162 (15.6)	145 (14.0)	157 (15.3)
AEs leading to discontinuation	103 (9.9)	93 (9.0)	76 (7.4)
SAEs	181 (17.4)	172 (16.7)	169 (16.4)
Fatal	14 (1.3)	17 (1.6)	18 (1.7)

AE = adverse event; SAE = serious adverse event.
[a] Defined as incapacitating or causing inability to work or perform usual activities.

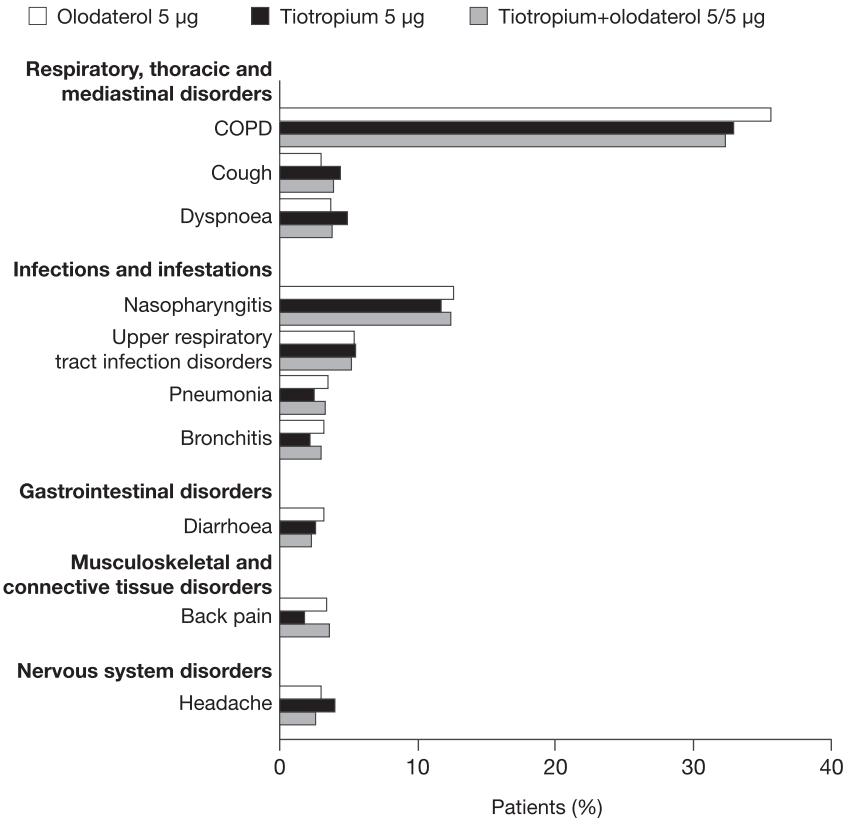

Fig. 2. Most frequently reported adverse events (>3% in any treatment group) by Medical Dictionary for Regulatory Activities System Organ Classes. COPD = chronic obstructive pulmonary disease.

Table 3
Summary of cardiovascular safety: cardiovascular AEs grouped by MedDRA SMQs.

MedDRA SMQ	Olodaterol 5 μg	Tiotropium 5 μg	Tiotropium/olodaterol 5/5 μg
Total patients, n	1038	1033	1029
Cardiac arrhythmias, n (%)	41 (3.9)	47 (4.5)	41 (4.0)
Torsades de pointes/QT prolongation,[a] n (%)	5 (0.5)	3 (0.3)	5 (0.5)
Ischaemic heart disease, n (%)	26 (2.5)	22 (2.1)	22 (2.1)
Cardiac failure, n (%)	12 (1.2)	8 (0.8)	5 (0.5)
Cerebrovascular disorders, n (%)	11 (1.1)	9 (0.9)	8 (0.8)
Hypertension, n (%)	53 (5.1)	35 (3.4)	36 (3.5)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Query.
[a] There was no occurrence of Torsades de Pointes arrhythmia; all cases were single QT prolongation reported as an AE in any of the repeated electrocardiogram measurements.

(95% confidence interval: 0.53, 1.64) for olodaterol and 1.24 (95% confidence interval: 0.68, 2.26) for tiotropium, indicating no statistically significant difference. The most common MACE end points included myocardial infarction (29 patients, 0.9% overall;

Table 4
Summary of cardiovascular safety MACE end points.

	Olodaterol 5 μg	Tiotropium 5 μg	Tiotropium/ olodaterol 5/5 μg
Total patients, n	1038	1033	1029
MACE, n (%)	25 (2.4)	19 (1.8)	24 (2.3)
Cardiac disorders – SOC (fatal)	4 (0.4)	3 (0.3)	3 (0.3)
Vascular disorders – SOC (fatal)	1 (0.1)	1 (0.1)	2 (0.2)
Myocardial infarction – SMQ (any)	10 (1.0)	8 (0.8)	11 (1.1)
Stroke – PV (any)	10 (1.0)	7 (0.7)	7 (0.7)
Sudden death – PT	0 (0.0)	1 (0.1)	1 (0.1)
Cardiac death – PT	0 (0.0)	0 (0.0)	0 (0.0)
Sudden cardiac death – PT	0 (0.0)	0 (0.0)	0 (0.0)

MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; PV = sponsor-defined pharmacovigilance end point; SOC = System Organ Class; SMQ = Standardised MedDRA Query.

range 0.8–1.1%), stroke (24 patients, 0.8% overall; range 0.7–1.0%) and fatal cardiac disorders (System Organ Class) (10 patients, 0.3% overall; range 0.3–0.4%).

3.1.3. Respiratory AEs

Respiratory events are presented in Appendices 6 and 10; MedDRA Preferred Terms searched in the end points are detailed in Appendix 11. Overall, there were no substantial differences in the incidence of respiratory AEs across treatment groups.

3.1.4. Adjudicated SAEs

A summary of the adjudicated SAEs is provided in Table 5. In total, 494 out of 3100 patients (15.9%; range 15.6–16.5% by treatment arm) had adjudicated events meeting the criteria of the composite end point (hospitalisation, intubation or death). The large majority of the adjudicated SAEs (470 patients; 15.2%) were hospitalisations, while there were 16 (0.5%) patients with intubation and 49 (1.6%) with fatal SAEs.

Fig. 3 provides a summary of the hazard ratios with 95% confidence intervals from the analysis of time to adjudicated SAEs. All hazard ratios were close to one and there were no statistically significant differences between treatments for the comparisons examined.

3.2. Subgroup analyses in pre-existing disease risk groups

The frequency of AEs tended to be higher in women, in patients with diabetes mellitus and in those using inhaled corticosteroids at baseline, and also with older age and severity of COPD (Table 6). However, across these patient subgroups, there were no notable differences between the treatment groups in overall incidence of AEs.

A total of 784 (25.3%) patients had cardiac history at baseline (Appendix 3). In general, the incidence of patients with at least one AE was slightly higher in this subgroup compared to patients without cardiac history (79.5% vs 73.0%); however, across the treatment groups, incidences of AEs were broadly similar. In the subset of patients with cardiac history, incidence of MACE was 2.7%, 4.5% and 3.6% in the tiotropium/olodaterol 5/5 μg, tiotropium 5 μg and olodaterol 5 μg groups, respectively. Although the incidences of AEs tended to be higher in the subgroups of patients with cardiac history or diabetes mellitus at baseline, there were no differences between treatment groups.

In particular, there were no relevant differences across treatment groups in cardiovascular AEs (defined by Standardised MedDRA Queries) in patients with or without pre-existing ischaemic heart disease or cardiac rhythm disorders at baseline (Tables 6 and 7).

3.3. Other safety parameters

No significant abnormalities in vital signs or laboratory parameters were observed. In addition, there were no clinically relevant changes in any electrocardiogram parameter and no dose- or time-related trends in QT interval (QTcF or QTcB) change across treatment groups. With the 24-h Holter monitoring conducted in a subset of 506 (16.3%) patients, there were no clinically relevant dose- or time-related trends or patterns observed in the magnitudes of mean changes in heart rate, supraventricular premature

Table 5
Summary of adjudicated SAEs composite analyses.

	Olodaterol 5 μg	Tiotropium 5 μg	Tiotropium/olodaterol 5/5 μg
Total patients, n	1038	1033	1029
Any adjudicated SAEs, n (%)	171 (16.5)	162 (15.7)	161 (15.6)
Any respiratory-related SAEs, n (%)	85 (8.2)	84 (8.1)	91 (8.8)
Key respiratory-related SAEs	78 (7.5)	70 (6.8)	83 (8.1)
COPD-related SAEs	67 (6.5)	65 (6.3)	71 (6.9)
Pneumonia-related SAEs	15 (1.4)	9 (0.9)	18 (1.7)
Other respiratory-related SAEs	7 (0.7)	17 (1.6)	11 (1.1)
Cardiovascular-related SAEs, n (%)	15 (1.4)	19 (1.8)	19 (1.8)
Any cerebrovascular SAEs, n (%)	6 (0.6)	5 (0.5)	5 (0.5)
Stroke-related SAEs	3 (0.3)	5 (0.5)	2 (0.2)
Other cerebrovascular-related SAEs	4 (0.4)	0 (0.0)	3 (0.3)
Non-respiratory, non-cardiovascular or non-cerebrovascular-related SAEs, n (%)	78 (7.5)	74 (7.2)	71 (6.9)

COPD = chronic obstructive pulmonary disease; SAE = serious adverse event.

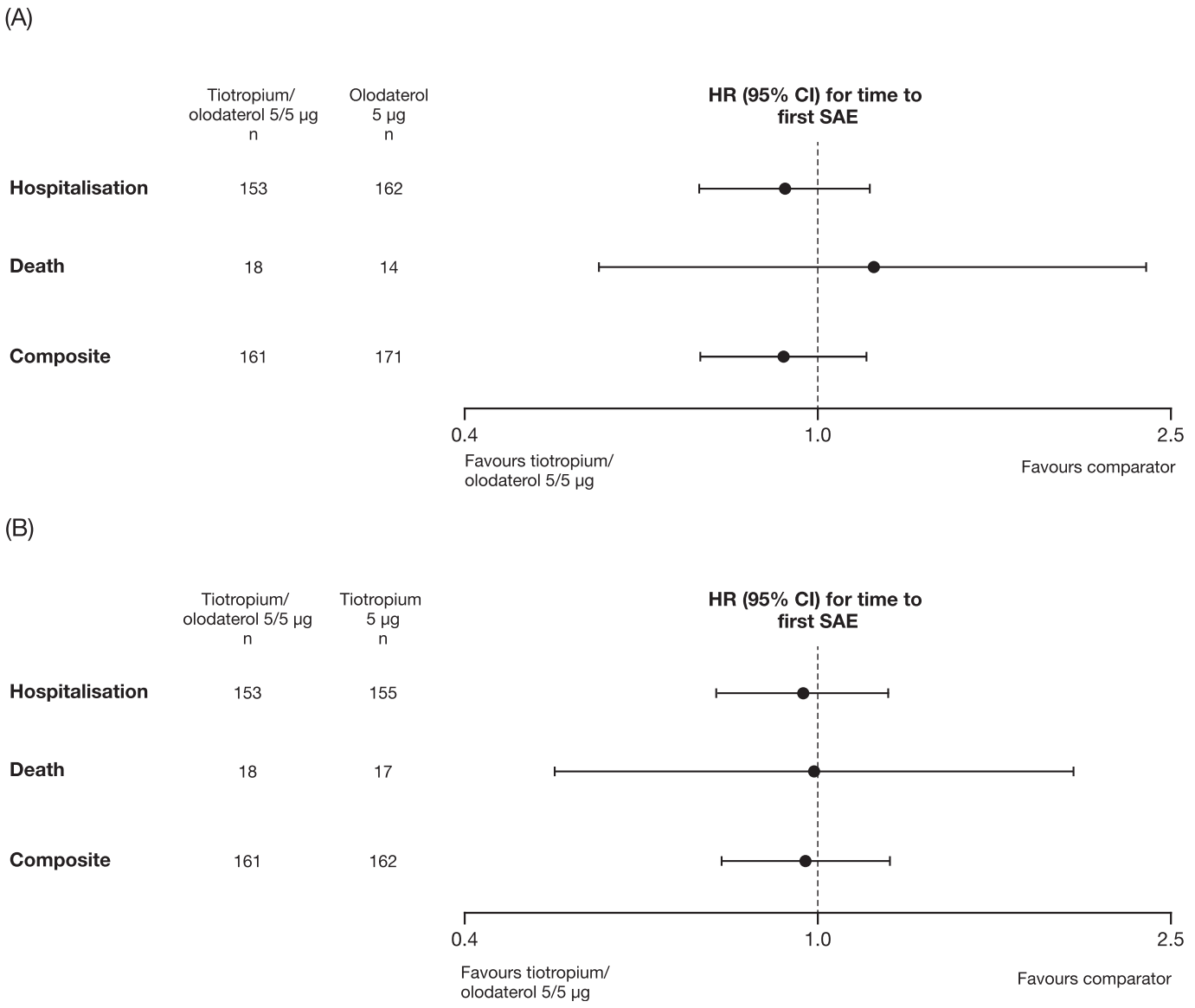

Fig. 3. Forest plot of HRs (95% CIs) from the analysis of the time to adjudicated SAEs: (A) tiotropium/olodaterol 5/5 µg vs olodaterol 5 µg; (B) tiotropium/olodaterol 5/5 µg vs tiotropium 5 µg. CI = confidence interval; HR = hazard ratio; SAE = serious adverse event.

Table 6
Clinically relevant cardiovascular AEs in patients with pre-existing cardiac rhythm disorder at baseline.

	Cardiac rhythm disorder at baseline NO			Cardiac rhythm disorder at baseline YES		
MedDRA SMQ	Olodaterol 5 µg	Tiotropium 5 µg	Tiotropium/olodaterol 5/5 µg	Olodaterol 5 µg	Tiotropium 5 µg	Tiotropium/olodaterol 5/5 µg
Total patients, n	938	946	931	100	87	98
Any AEs, n (%)	723 (77.1)	685 (72.4)	686 (73.7)	72 (72.0)	72 (82.8)	75 (76.5)
Tachyarrhythmias, n (%)	11 (1.2)	11 (1.2)	8 (0.9)	2 (2.0)	1 (1.1)	6 (6.1)
Supraventricular tachyarrhythmias (incl. atrial fibrillation/flutter)	5 (0.5)	7 (0.7)	1 (0.1)	1 (1.0)	1 (1.1)	4 (4.1)
Ventricular tachyarrhythmias	5 (0.5)	2 (0.2)	4 (0.4)	1 (1.0)	0 (0.0)	2 (2.0)
Ischaemic heart disease, n (%)	23 (2.5)	18 (1.9)	21 (2.3)	3 (3.0)	4 (4.6)	1 (1.0)
Myocardial infarction	8 (0.9)	6 (0.6)	10 (1.1)	2 (2.0)	2 (2.3)	1 (1.0)
Other ischaemic heart disease (non-infarction)	16 (1.7)	14 (1.5)	12 (1.3)	3 (3.0)	2 (2.3)	0 (0.0)
Cardiac failure, n (%)	8 (0.9)	5 (0.5)	5 (0.5)	4 (4.0)	3 (3.4)	0 (0.0)
Cerebrovascular disorders, n (%)	10 (1.1)	9 (1.0)	8 (0.9)	1 (1.0)	0 (0.0)	0 (0.0)
Haemorrhagic	6 (0.6)	4 (0.4)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemic	6 (0.6)	7 (0.7)	7 (0.8)	1 (1.0)	0 (0.0)	0 (0.0)
Hypertension, n (%)	47 (5.0)	28 (3.0)	34 (3.7)	6 (6.0)	7 (8.0)	2 (2.0)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Query.

Table 7
Clinically relevant cardiovascular AEs in patients with pre-existing ischaemic heart disease at baseline.

	Ischaemic heart disease at baseline NO			Ischaemic heart disease at baseline YES		
MedDRA SMQ	Olodaterol 5 μg	Tiotropium 5 μg	Tiotropium/olodaterol 5/5 μg	Olodaterol 5 μg	Tiotropium 5 μg	Tiotropium/olodaterol 5/5 μg
Total patients, n	889	909	909	149	124	120
Any AEs, n (%)	680 (76.5)	656 (72.2)	668 (73.5)	115 (77.2)	101 (81.5)	93 (77.5)
Tachyarrhythmias, n (%)	12 (1.3)	10 (1.1)	9 (1.0)	1 (0.7)	2 (1.6)	5 (4.2)
Supraventricular tachyarrhythmias (incl. atrial fibrillation/flutter)	6 (0.7)	7 (0.8)	4 (0.4)	0 (0.0)	1 (0.8)	1 (0.8)
Ventricular tachyarrhythmias	5 (0.6)	1 (0.1)	2 (0.2)	1 (0.7)	1 (0.8)	4 (3.3)
Ischaemic heart disease, n (%)	20 (2.2)	14 (1.5)	12 (1.3)	6 (4.0)	8 (6.5)	10 (8.3)
Myocardial infarction	8 (0.9)	6 (0.7)	9 (1.0)	2 (1.3)	2 (1.6)	2 (1.7)
Other ischaemic heart disease (non-infarction)	13 (1.5)	9 (1.0)	4 (0.4)	6 (4.0)	7 (5.6)	8 (6.7)
Cardiac failure, n (%)	5 (0.6)	4 (0.4)	5 (0.6)	7 (4.7)	4 (3.2)	0 (0.0)
Cerebrovascular disorders, n (%)	9 (1.0)	7 (0.8)	6 (0.7)	2 (1.3)	2 (1.6)	2 (1.7)
Haemorrhagic	5 (0.6)	3 (0.3)	2 (0.2)	1 (0.7)	1 (0.8)	1 (0.8)
Ischaemic	7 (0.8)	5 (0.6)	5 (0.6)	0 (0.0)	2 (1.6)	2 (1.7)
Hypertension, n (%)	44 (4.9)	32 (3.5)	32 (3.5)	9 (6.0)	3 (2.4)	4 (3.3)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Query.

beat indices or ventricular premature beat indices.

4. Discussion

This predefined pooled analysis of data from two large registration trials demonstrated that tiotropium/olodaterol 5/5 μg had acceptable long-term safety and tolerability across a spectrum of patients with moderate to very severe COPD.

Pooled long-term safety data for new therapies provide comprehensive information to practising clinicians beyond what is available from individual studies. With this in mind, the studies included in our analysis were designed to provide long-term data over 1 year from a large patient population representative of clinical practice (including very severe COPD). In addition, the use of an independent Adjudication Committee that was blinded to the treatment arms provided robust validation and standardised analysis of the SAEs, hence minimising variation between study sites in how they are reported. The analysis was based on a large pooled database, with a high proportion of patients having reported pre-existing cardiac history (~25%) or vascular (~50%) co-morbidities. This allowed the assessment of safety across a broad range of patient subtypes including those with histories of cardiovascular disease and diabetes mellitus, both of which are prevalent in patients with COPD.

The important finding from this safety analysis was that the AE profile of a combination LAMA/LABA was comparable to that of its monocomponents, ie, there was no additive adverse safety effect by combining the two different mechanisms of action. In particular, the incidence of cardiovascular events was not different across the treatment groups and there was a low incidence of cardiovascular AEs in those patients with cardiovascular co-morbidities at baseline. The incidence of respiratory-related AEs was also similar across the treatment groups. A strength of the current analysis was the data from a pre-planned adjudicated analysis of all SAEs demonstrating that the risk of having an event (composite end point of hospitalisations, intubations and death) was similar for tiotropium/olodaterol 5/5 μg compared to the monotherapy components (tiotropium 5 μg and olodaterol 5 μg). These results provide comprehensive and robust evidence for the acceptable long-term safety of the tiotropium/olodaterol 5/5 μg dose and the monocomponents with regards to cardiovascular and respiratory safety. Incidences of AEs, SAEs and fatal AEs were shown to be comparable between treatment groups with no unexpected safety findings. In addition, there were no differences in the risk of MACE or cardiac disorders System Organ Class across treatment groups in the study population, including subgroups with pre-existing cardiovascular disease. The numbers of first severe exacerbation were in the range (~6%) of reported SAEs for COPD and in line with our published exacerbation analyses [25].

In the TONADO® studies, the 5/5 μg dose was shown to provide benefits across efficacy end points, including patients' health status (as determined by St George's Respiratory Questionnaire total scores) [24]. This supports the favourable benefit-risk profile of the 5/5 μg dose of tiotropium/olodaterol.

In contrast to other LAMAs, tiotropium has been marketed for a long time and consequently has the largest safety database available for any long-acting bronchodilator. A recent analysis of a very large database of patients with COPD showed that tiotropium does not increase the overall risks of AEs, SAEs, fatal AEs or cardiovascular events compared to placebo [26]. Olodaterol has also been compared to placebo: in four 1-year studies of once-daily olodaterol (5 or 10 μg), the AE profile was similar to that of placebo [27].

Further support for the safety of LAMA/LABA combinations has been provided in a pooled analysis of safety data from the clinical programmes of indacaterol, glycopyrronium and indacaterol/glycopyrronium [28]. Although based on 14 studies with differing designs and durations, this analysis also demonstrated no increased risk with this combination compared to the monotherapy components. The safety of umeclidinium/vilanterol was recently assessed in a 52-week, placebo-controlled study [29]. While the incidence of AEs was shown to be similar between placebo and umeclidinium/vilanterol, no such comparison can be made from our studies because it was considered unethical to allocate patients with severe to very serve COPD to placebo alone over a 1-year period. However, in a shorter-term, 12-week study of tiotropium/olodaterol, both doses (2.5/5 and 5/5 μg) were well tolerated, with an overall incidence of AEs similar to placebo [30]. In addition, data from a pooled analysis from three 6-week crossover studies showed that the incidence of AEs was similar with tiotropium/olodaterol, the monocomponents and placebo (Appendix 12). Although the overall incidence of AEs and SAEs was generally lower in the umeclidinium/vilanterol study, the patient population had less severe COPD (all GOLD 1–3) than in our analysis, which comprised >10% of patients with GOLD 4 disease. In addition, our analysis was based on a longer follow-up period (21 days after discontinuation of study treatment vs 1 day post-treatment in the umeclidinium/vilanterol study) [31].

When interpreting these results, some additional factors should

be considered. The current analysis of a large database, with >1000 patients per treatment arm, adds to the evidence base with respect to the safety of the Respimat® device. It should be noted that there is no placebo group in this study as it was deemed inappropriate to include patients with symptomatic COPD in a placebo arm, without the use of any long-acting bronchodilator, in a study lasting 1 year [24]. In line with standard practice, unstable patients, who were unlikely to reach the end of the study period, were excluded from this Phase III trial. Additionally, this study does not inform on the safety of tiotropium/olodaterol in the small fraction of COPD patients with very severe recent or unstable pre-existing cardiac comorbidities. Overall, no imbalances in mortality were seen over 1 year and the nature and frequencies of fatal events were as expected given the study duration and COPD population under investigation [13,32].

5. Conclusions

These data, taken together with those from the wider Phase III clinical programme, provide evidence for the long-term safety and tolerability of once-daily tiotropium/olodaterol 5/5 μg, as validated by an independent external Adjudication Committee, in patients with moderate to very severe COPD.

Importantly, there was no evidence of increased cardiovascular risk with tiotropium/olodaterol 5/5 μg in comparison to its monocomponents.

Conflict of interest

R.B. reports personal fees and grants from Boehringer Ingelheim, Novartis and Roche, and personal fees from AstraZeneca, Chiesi, GlaxoSmithKline, Takeda and Teva. S.M. reports personal fees from Boehringer Ingelheim during the conduct of the study and personal fees from GlaxoSmithKline outside of the submitted work. C.V. reports personal fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cytos, GlaxoSmithKline, Mundipharma, Novartis, Takeda and Janssen, and grants and personal fees from Grifols outside of the submitted work. L.M. reports personal fees from Applied Clinical Intelligence during the conduct of the study, grants from Asthma UK, NI Chest Heart & Stroke, NC3Rs, British Heart Foundation and Chiesi, travel and subsistence for attendance at scientific meetings from Boehringer Ingelheim, GlaxoSmithKline and Chiesi, and advisory board/consultancy fees from Almirall, NAPP, GlaxoSmithKline and Boehringer Ingelheim outside the submitted work. U.B., K.T., F.V. and L.L. are employees of Boehringer Ingelheim.

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All authors were involved in the hypothesis development for this *post hoc* study. R.B. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects.

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The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. They take full responsibility for the scope, direction, content of, and editorial decisions relating to, the manuscript, were involved at all stages of development and have approved the submitted manuscript. The authors received no compensation related to the development of the manuscript. Medical writing assistance was provided by Rob Kite, on behalf of Complete HealthVizion.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2016.11.011.

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