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A pooled safety analysis

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Safety and tolerability of once-daily tiotropium Respimat® as add-on to at least inhaled corticosteroids in adult patients with symptomatic asthma: A pooled safety analysis

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ABSTRACT

Background: Tiotropium, a long-acting anticholinergic bronchodilator, has demonstrated efficacy and safety as add-on therapy to inhaled corticosteroids (ICS), with or without other maintenance therapies, in patients with symptomatic asthma.

Objective: To evaluate safety and tolerability of tiotropium delivered via the Respimat® device, compared with placebo, each as add-on to at least ICS therapy, in a pooled sample of adults with symptomatic asthma at different treatment steps.

Methods: Data were pooled from seven Phase II and III, randomised, double-blind, parallel-group trials of 12–52 weeks' treatment duration, which investigated once-daily tiotropium Respimat® (5 μg, 2.5 μg) versus placebo as add-on to different background maintenance therapy including at least ICS. Adverse events (AEs) including serious AEs were assessed throughout treatment + 30 days after the last dose of trial medication.

Results: Of 3474 patients analysed, 2157 received tiotropium. The percentage of patients with AEs was comparable between treatment groups: tiotropium 5 μg, 60.8%; placebo 5 μg pool, 62.5%; tiotropium 2.5 μg, 57.1%; placebo 2.5 μg pool, 55.1%. Consistent with the disease profile, the most frequent AEs overall were asthma, decreased peak expiratory flow rate (both less frequent with tiotropium) and nasopharyngitis. Overall incidence of dry mouth, commonly associated with use of anticholinergics, was low: tiotropium 5 μg, 1.0%; placebo 5 μg pool, 0.5%; tiotropium 2.5 μg, 0.4%; placebo 2.5 μg pool, 0.5%. The percentage of cardiac disorder AEs was comparable between tiotropium and placebo: tiotropium 5 μg, 1.4%; placebo 5 μg pool, 1.4%; tiotropium 2.5 μg, 1.4%; placebo 2.5 μg pool, 1.1%. The proportions of patients with serious AEs were balanced across groups: tiotropium 5 μg, 4.0%; placebo 5 μg pool, 4.3%; tiotropium 2.5 μg, 2.0%; placebo 2.5 μg pool, 3.3%.

Conclusion: Tiotropium Respimat® demonstrated safety and tolerability comparable with those of placebo, as add-on to at least ICS therapy, at different treatment steps in adults with symptomatic asthma.

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1. Introduction

Asthma affects approximately 300 million people worldwide; it is a heterogeneous condition with various underlying disease processes and is usually characterised by chronic airway inflammation [1]. The Global Initiative for Asthma recommends a stepwise approach to achieving and maintaining control of asthma symptoms [1]. Despite treatment according to current recommendations, at least 40% of patients with asthma remain symptomatic [2–4]. There is therefore a need for additional treatment options.

A large and comprehensive Phase II and III clinical trial programme, performed in more than 5000 adult patients with symptomatic asthma, has investigated tiotropium delivered by the Respimat® Soft Mist™ inhaler (Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany) as add-on therapy to inhaled corticosteroids (ICS) with or without other maintenance therapies. This programme has confirmed that tiotropium Respimat® (hereafter referred to as ‘tiotropium’) is an efficacious add-on therapy, with safety and tolerability comparable with those of placebo, across treatment steps [5–13]. Based on the published evidence from the above programme, the 5 μg dose was approved for use in the European Union in 2014 as add-on therapy to maintenance ICS (≥800 μg budesonide or equivalent) plus a long-acting β2-agonist (LABA), in patients aged ≥18 years who experienced ≥1 severe asthma exacerbations in the previous year. The 2015 update of the Global Initiative for Asthma guidelines included tiotropium, delivered by the Respimat® inhaler, as an add-on therapy option at steps 4 and 5 in patients aged ≥18 years with a history of exacerbations [1]. The 2.5 μg tiotropium Respimat® dose has since been approved by the US Food and Drug Administration for once-daily maintenance treatment of asthma in patients aged ≥12 years; other countries that have approval include Australia, Canada and Japan.

In addition to the safety reports of tiotropium add-on therapy in individual clinical trials, an in-depth assessment of safety and tolerability in a much larger patient sample can provide greater power to detect any as yet unidentified safety signals. The objective of the analysis described here was to evaluate the safety and tolerability of once-daily tiotropium 5 μg and 2.5 μg (two puffs, irrespective of dose) compared with placebo, each as add-on to at least ICS therapy, in a large sample of adult patients with symptomatic asthma at different treatment steps. To achieve this, data were pooled across seven Phase II and III parallel-group trials of tiotropium of 12–52 weeks’ duration.

2. Methods

2.1. Study design

The pooled analysis included all parallel-group Phase II or III adult studies in the Boehringer Ingelheim programme of tiotropium Respimat® in asthma. Studies of tiotropium Handi-Haler® were not included. All trials were of randomised, double-blind, placebo-controlled design of at least 12 weeks’ duration, in adult patients (aged 18–75 years) with symptomatic asthma. Tiotropium or placebo were each administered as add-on therapy to ICS maintenance treatment with or without other background therapies. Placebo was therefore equivalent to patients’ background maintenance therapy.

Several trials were included in this pooled safety analysis (Table 1). One of these was a Phase II, 16-week trial of tiotropium 5 μg and twice-daily salmeterol 50 μg in patients receiving ICS (study 205.342; NCT00350207) [6]. The remainder were Phase III studies: one 12-week trial of tiotropium 5 μg and 2.5 μg in patients receiving ICS (GraziaTinA-asthma®: NCT01316380) [12]; two replicate 24-week trials of once-daily tiotropium 5 μg in patients receiving ICS plus a LABA (PrimoTinA-asthma®: NCT00772538/NCT00776984) [9]; and one 52-week trial of tiotropium 5 μg and 2.5 μg in patients receiving ICS with or without a LABA (CadenTinA-asthma®: NCT01340209) [11]. Further details regarding the background therapy, treatment arms and primary endpoints of each trial are provided in Table 1; inclusion and exclusion criteria are provided in Table 2.

2.2. Analysis population

In all seven trials, patients were lifelong non-smokers or ex-smokers (<10 pack-years) with no smoking for at least 1 year before study entry. Patients with chronic obstructive pulmonary disease (COPD), a significant lung disease other than asthma or a recent history of certain cardiac diseases (myocardial infarction; hospitalisation for cardiac failure; unstable or life-threatening cardiac arrhythmia; or cardiac arrhythmia requiring intervention or a change in drug therapy) were excluded (Table 2). In all the Phase III trials, patients were required to have symptomatic asthma (as defined by a seven-question Asthma Control Questionnaire mean score of ≥1.5) and a diagnosis of asthma before the age of 40 years. Patients were required to have bronchodilator reversibility resulting in a forced expiratory volume in 1 s (FEV1) increase of ≥12% and ≥200 mL (15–30 min after 400 μg salbutamol), except in PrimoTinA-asthma® where patients were required to have a positive hyper-responsiveness test or a positive trial of glucocorticosteroids or bronchodilator reversibility defined as either an FEV1 increase of ≥12% and ≥200 mL or a peak expiratory flow increase of ≥20% after use of salbutamol/albuterol from a pressurised metered-dose inhaler. Different degrees of lung function impairment were specified in the different trial protocols (Table 2). A documented history of asthma of ≥5 years was required in the PrimoTinA-asthma® trials, and ≥3 months in the MezzoTinA-asthma®, GraziaTinA-asthma® and CadenTinA-asthma® trials [9–12].

The treatment history (treatment step on enrolment) specified in each trial differed and reflected the severity of the patient population (Table 2). Background treatment was required to be stable for ≥4 weeks before enrolment, as follows: PrimoTinA-asthma®: ICS (≥800 μg budesonide or equivalent) plus a LABA; MezzoTinA-asthma®: ICS (400–800 μg budesonide or equivalent) alone or in fixed combination with a LABA or short-acting β2-agonist (SABA); GraziaTinA-asthma®: ICS (200–400 μg budesonide or equivalent) alone or in fixed combination with a SABA; CadenTinA-asthma®: ICS (400–800 μg budesonide or equivalent) alone or in fixed combination with a LABA.

In the Phase II study 205.342, patients were required to be homozygous for arginine at the 16th amino acid position of the β2-adrenergic receptor and to have a documented history of asthma and bronchodilator reversibility resulting in an FEV1 increase of ≥12% and ≥200 mL (30 min after 400 μg salbutamol and 80 μg ipratropium). Patients also received stable treatment with ICS (400–1000 μg budesonide or equivalent) alone or in fixed combination with a LABA or SABA for ≥3 weeks before enrolment [6].

2.3. Trial medication

During the treatment period, all trials investigated tiotropium and placebo, delivered by the Respimat inhaler®, each as add-on therapy to pre-trial maintenance ICS (with a LABA in PrimoTinA-asthma®, and
with or without a LABA in CadenTinA-asthma® (Table 1). In MezzoTinA-asthma® and study 205.342, patients were to be on medium-dose ICS (400–800 μg and 400–1000 μg budesonide or equivalent, respectively). An additional placebo in MezzoTinA-asthma® and study 205.342 was a hydrofluoroalkane metered-dose inhaler, to match the salmeterol pressurised metered-dose inhaler arm in these studies. In GraziaTinA-asthma®, patients were to be on low-dose ICS (200–400 μg budesonide or equivalent). Salbutamol was allowed as rescue medication as necessary during each of the seven studies; a washout period of >8 h was required before lung function tests.

2.4. End points

A descriptive assessment of safety over 52 weeks was the primary objective in CadenTinA-asthma®. Safety was a secondary end point in all other trials.

All adverse events (AEs), including serious AEs (SAEs), occurring during the clinical trials (ie from signing informed consent until 30 days after the last dose of trial medication) were collected, documented and reported to the sponsor by the investigator on the appropriate reporting forms. All events with an onset after the first dose of trial medication up to 30 days after the last dose of trial medication were assigned to the treatment period; others were assigned to either the screening period or the post-trial period, as appropriate. AEs were coded using the Medical Dictionary for Regulatory Activities (version 16.1). For each AE, the investigator was to provide the onset and end dates, intensity, treatment required, outcome, seriousness and action taken with the investigational drug, and to determine the relationship of the investigational drug to the AE. All AEs were followed up until resolved or sufficiently characterised.

Standard definitions of AEs and SAEs were applied. An AE was defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient who received the trial medication; the event did not necessarily have a causal relationship with the trial medication. An SAE was defined as any AE which: resulted in death; was immediately life-threatening; resulted in persistent or significant disability or incapacity; required or prolonged patient hospitalisation; was a congenital anomaly or birth defect; or was to be deemed serious for any other reason, if it was an important medical event when based on appropriate medical judgement, which may have jeopardised the patient and required medical or surgical intervention to prevent one of the outcomes listed above. A treatment-related AE was defined as an AE for which there was a reasonable causal relationship between the randomised trial medication (tiotropium or placebo) and the AE. The medical judgement of the investigator was used to determine the causal relationship, considering all relevant factors such as the temporal relationship between treatment administration and the AE, and confounding factors such as concomitant medication and concomitant diseases.

Laboratory parameters, vital signs and a 12-lead electrocardiogram were recorded in the individual studies; these assessments

<table>
<thead>
<tr>
<th>Authors; study identification number; study number/name</th>
<th>Phase Baseline maintenance therapy</th>
<th>Duration of treatment (weeks)</th>
<th>n</th>
<th>Randomisation</th>
<th>Treatment arms, as add-on to baseline maintenance therapy</th>
<th>Primary end point(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bateman et al., 2011 [6] NCT00350207 Study 205.342</td>
<td>II ICS (400–1000 μg budesonide or equivalent per day)</td>
<td>16</td>
<td>388</td>
<td>1:1:1</td>
<td>Once-daily tiotropium Respimat® 5 μg (n = 128); twice-daily salmeterol 50 μg (n = 134); placebo Respimat® (n = 126)</td>
<td>Mean weekly morning PEF response at Week 16</td>
</tr>
<tr>
<td>Paggiaro et al., 2016 [12] NCT01316380 GraziaTinA-asthma®</td>
<td>III ICS (200–400 μg budesonide or equivalent per day)</td>
<td>12</td>
<td>464</td>
<td>1:1:1</td>
<td>Once-daily tiotropium Respimat® 5 μg (n = 155); once-daily tiotropium Respimat® 2.5 μg (n = 154); placebo Respimat® (n = 155)</td>
<td>Peak PEF(3h–16h) response at Week 12</td>
</tr>
<tr>
<td>Kerstjens et al., 2015 [10] NCT0172808 NCT0172821 MezzoTinA-asthma®</td>
<td>III ICS (400–800 μg budesonide or equivalent per day)</td>
<td>24</td>
<td>2100</td>
<td>1:1:1:1</td>
<td>Once-daily tiotropium Respimat® 5 μg (n = 517); once-daily tiotropium Respimat® 2.5 μg (n = 519); twice-daily salmeterol 50 μg (n = 541); placebo (n = 523)</td>
<td>Co-primary end points: peak PEF(1–3h) and trough PEF response and ACQ-7 responder rate (pooled) at Week 24</td>
</tr>
<tr>
<td>Kerstjens et al., 2012 [9] NCT00772538 NCT00776984 PrimoTinA-asthma®</td>
<td>III ICS (&gt;800 μg budesonide or equivalent per day) + LABA</td>
<td>48</td>
<td>912</td>
<td>1:1</td>
<td>Once-daily tiotropium Respimat® 5 μg (n = 456); placebo Respimat® (n = 456)</td>
<td>Co-primary end points: peak PEF(1–3h) and trough PEF responses at Week 24, and time to first severe asthma exacerbation during the 48-week treatment period (pooled)</td>
</tr>
<tr>
<td>Ohta et al., 2015 [11] NCT01340209 CadenTinA-asthma®</td>
<td>III ICS (400–800 μg budesonide or equivalent per day) ± LABA</td>
<td>52</td>
<td>285</td>
<td>2:2:1</td>
<td>Once-daily tiotropium Respimat® 5 μg (n = 114); once-daily tiotropium Respimat® 2.5 μg (n = 114); placebo Respimat® (n = 57)</td>
<td>Primary objective: to evaluate long-term safety; therefore, no primary efficacy end points were defined</td>
</tr>
</tbody>
</table>

ACQ-7 = seven-question Asthma Control Questionnaire. FEV1 = forced expiratory volume in 1 s. FVC = forced vital capacity. ICS = inhaled corticosteroids. LABA = long-acting β2-agonist. Peak PEF(1–3h) = peak forced expiratory volume in 1 s within 3 h post-dose. PEF = peak expiratory flow.

a Treated set.

b Response defined as change from baseline at study end point.
are not described here because clinically relevant changes were also recorded as AEs. In all trials, patients with known moderate or severe renal impairment (defined as creatinine clearance ≤50 mL/min) were monitored closely but were not excluded.

2.5. Statistical analyses

Analyses of safety data were based on the treated set, defined as all randomised patients who received at least one dose of trial medication, and were evaluated using descriptive analyses. No inferential statistical analyses of safety outcomes were pre-specified.

All seven trials except CadenTinA-asthma® were powered for analyses of efficacy end points. The primary objective of CadenTinA-asthma® was to descriptively evaluate the safety of tiotropium 5 μg, and 2.5 μg; the study was not powered to detect a difference in safety profile between either tiotropium dose and placebo, but to numerically compare the incidence of specific AEs and AEs overall.

The tiotropium 5 μg dose was assessed in seven trials, and the 2.5 μg dose in four trials. All seven trials included in the analysis included a tiotropium 5 μg arm, but only four included a tiotropium 2.5 μg arm. Thus, when comparing the pooled tiotropium 2.5 μg data set with that of placebo, it is not accurate to compare it with the pooled placebo arms from all seven trials. Therefore, we present two placebo groups: a placebo 5 μg pool for comparison with tiotropium 5 μg (placebo patients pooled from all seven trials) and a placebo 2.5 μg pool for comparison with tiotropium 2.5 μg (placebo patients pooled from the four trials that included a tiotropium 2.5 μg arm: MezzoTinA-asthma® [two replicate trials], GraziTinA-asthma® and CadenTinA-asthma®). In this analysis, which is focused only on tiotropium compared with placebo, we do not report data from the salmeterol arms of study 205.342 or MezzoTinA-asthma® [6,10].

3. Results

In this pooled analysis of seven randomised, placebo-controlled, parallel-group trials in adult patients with symptomatic asthma, data from 1370 patients who received tiotropium 5 μg and 1317 patients who received placebo were compared (tiotropium 5 μg pool), as were data from 787 patients receiving tiotropium 2.5 μg and 735 patients receiving placebo (tiotropium 2.5 μg pool).

3.1. Baseline demographics and disease characteristics

Baseline patient demographics and disease characteristics in both pools were similar between tiotropium and placebo groups (Table 3). All patients were adults: the mean age (± standard deviation [SD]) in each treatment group ranged from 43.2 (12.9) to 46.9 (13.5) years. Approximately 60% of patients were female and the majority were white or Asian. Most patients had never smoked (77.2–84.5%), and the mean duration of asthma (± SD) ranged from 20.3 (13.6) to 23.8 (14.7) years.

Comparison between the 5 μg and 2.5 μg pools was not an objective of this analysis. The differences in baseline characteristics between the 5 μg and 2.5 μg pools reflect the differences in inclusion criteria of the trials included in each pool; there was comparatively less severe disease in the 2.5 μg pool. Study 205.342 and PrimoTinA-asthma® included patients at higher treatment steps than in the other trials, and contained no tiotropium 2.5 μg arm (Table 3). Consequently, baseline values for lung function were higher and mean dose of ICS was lower in the 2.5 μg pool versus the 5 μg pool.
between treatment arms (Supplementary Table 1).

duration. Within each trial, mean exposure was comparable differences in mean treatment exposure between trials of different
tion in treatment exposure between pools is due to the marked
pool versus 162.1 (68.8) days in corresponding placebo. The varia-

<table>
<thead>
<tr>
<th>B16-Arg/Arg genotype, n (%)</th>
<th>171 (12.5)</th>
<th>164 (12.5)</th>
<th>NA</th>
<th>NA</th>
</tr>
</thead>
</table>

3.2. Exposure to trial medication

Mean (± SD) exposure to trial medication was 217.2 (105.9) days in the tiotropium 5 μg pool versus 211.4 (103.2) days in corre-

3.3. Safety

3.3.1. AEs, treatment-related AEs and SAEs

The frequency of patients reporting any type of AE was com-
parable between the tiotropium 5 μg pool (n = 833, 60.8%) and corresponding placebo pool (n = 823, 62.5%), and between the
tiotropium 2.5 μg pool (n = 449, 57.1%) and corresponding placebo pool (n = 405, 55.1%) (Table 4). Treatment-related AEs were re-
ported in a similar percentage of patients between the tiotropium 5 μg pool and corresponding placebo pool, and between the tiotropium 2.5 μg pool and corresponding placebo pool (Table 4). The distribution of patients with AEs leading to discontinuation of trial medication was balanced between active treatment and placebo groups, in both the 5 μg and 2.5 μg pools (Table 4): tiotropium 5 μg (n = 25, 1.8%); placebo 5 μg (n = 30, 2.3%); tiotropium 2.5 μg (n = 9, 1.1%); placebo 2.5 μg (n = 14, 1.9%).

The most commonly reported AEs, occurring in ≥2% of patients in any treatment group, are presented in Table 5. Asthma wors-
ning/exacerbation, decreased peak expiratory flow rate and upper respiratory tract infection occurred less frequently with tiotropium compared with placebo, in both the 5 μg and 2.5 μg pools. Commonly reported AEs occurring more frequently with tiotropium compared with placebo in both the 5 μg and 2.5 μg pools.
Dry mouth, a common side effect associated with anticholinergic therapies [14], was reported with a slightly higher frequency in the tiotropium 5 μg pool versus placebo included dysphonia, dry throat, dry mouth, thirst, headache and palpitations in the tiotropium 5 μg pool, and oropharyngeal discomfort, nausea, headache, elevated gamma-glutamyltransferase and palpitations in the 2.5 μg pool. The largest difference in frequency of treatment-related AEs between tiotropium and placebo was 0.5% points.

The frequency of patients reporting SAES was comparable between treatment groups in each pool: tiotropium 5 μg (n = 55, 4.0%); placebo 5 μg (n = 65, 4.8%); tiotropium 2.5 μg (n = 16, 2.0%); placebo 2.5 μg (n = 24, 3.3%) (Table 7). The most common SAE was asthma worsening/exacerbation, which was reported at a similar frequency with tiotropium and placebo in each pool: tiotropium 5 μg (n = 18, 14%); placebo 5 μg (n = 27, 2.1%); tiotropium 2.5 μg (n = 2, 0.3%); placebo 2.5 μg (n = 5, 0.7%). Drug-related SAES occurred in two patients: one patient in the tiotropium 5 μg pool and one patient in the placebo group (in both the placebo 5 μg pool and the placebo 2.5 μg pool) reported an asthma exacerbation; both of these required hospitalisation, but treatment was not discontinued.

Life-threatening SAES occurred in five patients in the tiotropium 5 μg pool (0.4%; cerebral infarction [n = 1]; hypotension, shock and renal failure following hospitalisation for a non-life-threatening asthma exacerbation [n = 1]; acute respiratory failure and asthma exacerbation [n = 1]; anaphylactic reaction [n = 1]; and chemical poisoning [n = 1]) and in one patient in the tiotropium 2.5 μg pool (0.1%; myocardial infarction); none of these life-threatening SAES was considered to be related to tiotropium treatment. One patient in the placebo group experienced a life-threatening SAE (0.1%; life-threatening asthma exacerbation; the patient was enrolled in a trial investigating both tiotropium 5 μg and 2.5 μg, and was therefore included in both the placebo 5 μg pool and the placebo 2.5 μg pool) (Supplementary Table 2).

No deaths occurred during any of the seven trials.

### 3.3.2. AEs of special interest

Dry mouth, a common side effect associated with anticholinergic therapies [14], was reported with a slightly higher frequency in the tiotropium 5 μg pool versus placebo: tiotropium 5 μg, n = 14 (1.0%); placebo 5 μg, n = 7 (0.5%); tiotropium 2.5 μg, n = 3 (0.4%); placebo 2.5 μg, n = 4 (0.5%). This was not classed as serious, nor did it lead to treatment discontinuation, in any of the patients. Treatment-related dry mouth AEs occurred with the following patient frequencies: tiotropium 5 μg, n = 11 (0.8%); placebo 5 μg, n = 5 (0.4%); tiotropium 2.5 μg, n = 3 (0.4%); placebo 2.5 μg, n = 3 (0.4%).
Table 6
Frequency of patients with treatment-related adverse events reported in ≥0.3% of patients in any treatment group (by primary system organ class and preferred term).

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Tiotropium Respimat® 5 µg pool (N = 1370)</th>
<th>Placebo Respimat® 5 µg pool (N = 1317)</th>
<th>Tiotropium Respimat® 2.5 µg pool (N = 787)</th>
<th>Placebo Respimat® 2.5 µg pool (N = 735)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any treatment-related AE</td>
<td>82 (6.0)</td>
<td>58 (4.4)</td>
<td>44 (5.6)</td>
<td>33 (4.5)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>32 (2.3)</td>
<td>28 (2.1)</td>
<td>11 (1.4)</td>
<td>13 (1.8)</td>
</tr>
<tr>
<td>Asthmaa</td>
<td>12 (0.9)</td>
<td>13 (1.0)</td>
<td>3 (0.4)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>9 (0.7)</td>
<td>3 (0.2)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (0.2)</td>
<td>7 (0.5)</td>
<td>2 (0.3)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Dry throat</td>
<td>5 (0.4)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Oropharyngeal discomfort</td>
<td>1 (0.1)</td>
<td>0</td>
<td>3 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>1 (0.1)</td>
<td>0</td>
<td>2 (0.2)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>15 (1.1)</td>
<td>7 (0.5)</td>
<td>11 (1.4)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>11 (0.8)</td>
<td>5 (0.4)</td>
<td>3 (0.4)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>2 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>11 (0.8)</td>
<td>3 (0.2)</td>
<td>6 (0.8)</td>
<td>3 (0.4)</td>
</tr>
</tbody>
</table>

Treated set.

AE = adverse event.
a Placebo Respimat® 5 µg pool: all seven trials; placebo Respimat® 2.5 µg pool: MezzoTinA-asthma, GraziaTinA-asthma and CadenTinA-asthma.
b Represents asthma worsening or exacerbation.

Table 7
Frequency of patients with serious adverse events occurring in ≥2 patients in any treatment group (by primary system organ class and preferred term).

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Tiotropium Respimat® 5 µg pool (N = 1370)</th>
<th>Placebo Respimat® 5 µg pool (N = 1317)</th>
<th>Tiotropium Respimat® 2.5 µg pool (N = 787)</th>
<th>Placebo Respimat® 2.5 µg pool (N = 735)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with SAEs</td>
<td>55 (4.0)</td>
<td>65 (4.9)</td>
<td>16 (2.0)</td>
<td>24 (3.3)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>23 (1.7)</td>
<td>28 (2.1)</td>
<td>4 (0.5)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Asthmaa</td>
<td>19 (1.4)</td>
<td>27 (2.1)</td>
<td>2 (0.3)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>7 (0.5)</td>
<td>12 (0.9)</td>
<td>5 (0.6)</td>
<td>6 (0.8)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (0.1)</td>
<td>2 (0.2)</td>
<td>2 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3 (0.2)</td>
<td>6 (0.5)</td>
<td>1 (0.1)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>0</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>4 (0.3)</td>
<td>4 (0.3)</td>
<td>2 (0.3)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Intervertebral disc protrusion</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>2 (0.1)</td>
<td>2 (0.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>2 (0.1)</td>
<td>3 (0.2)</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
<td>2 (0.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Treated set.

SAE = serious adverse event.
a Placebo Respimat® 5 µg pool: all seven trials; placebo Respimat® 2.5 µg pool: MezzoTinA-asthma, GraziaTinA-asthma and CadenTinA-asthma.
b Represents asthma worsening or exacerbation.

Constipation, a potential ‘class effect’ event, occurred less frequently with tiotropium versus placebo in both pools: tiotropium 5 µg, n = 4 (0.3%); placebo 5 µg, n = 8 (0.6%); tiotropium 2.5 µg, n = 1 (0.1%); placebo 2.5 µg, n = 4 (0.5%). Urinary retention AEs, also ‘class effect’ events, were not observed.

Ocular AEs were reported with similar frequency with tiotropium and placebo in both pools (tiotropium 5 µg, n = 28 [2.0%]; placebo 5 µg, n = 24 [1.8%]; tiotropium 2.5 µg, n = 11 [1.4%]; placebo 2.5 µg, n = 9 [1.2%]); the majority of ocular AEs were conjunctivitis. Ocular discomfort, eye pain, eye swelling, blurred vision or events related to glaucoma were each reported in ≤0.2% of patients.

The number of patients with cardiac disorder AEs was low and the frequency comparable in tiotropium and placebo groups in each pool: tiotropium 5 µg, n = 19 (1.4%); placebo 5 µg, n = 19 (1.4%); tiotropium 2.5 µg, n = 11 (1.4%); placebo 2.5 µg, n = 8 (1.1%). The frequency of patients with treatment-related cardiac disorder AEs was as follows: tiotropium 5 µg, n = 19 (1.4%); placebo 5 µg, n = 19 (1.4%); tiotropium 2.5 µg, n = 11 (1.4%); placebo 2.5 µg, n = 8 (1.1%). The proportion of patients with a cardiac history at baseline (defined as patients with at least one of the following medical histories: myocardial infarction; cerebrovascular accidents; cardiac arrhythmia; or heart failure New York Heart
Association class III or IV) was between 1.1% and 2.4% (Table 3); patients were not excluded if they developed cardiac AEs during the trial.

The most common cardiac disorder AEs overall were palpitations and tachycardia, and none was reported in more than 0.5% of patients in any treatment arm (Supplementary Table 3).

Serious cardiac disorder AEs occurred in two patients (0.1%) in the tiotropium 5 μg pool (supraventricular arrhythmia, coronary artery occlusion, coronary artery stenosis and ventricular tachycardia in one patient; atrial fibrillation in one patient) and in two patients (0.3%) in the tiotropium 2.5 μg pool (atrial fibrillation and myocardial infarction). One patient (0.1%) common to both placebo pools (the patient was enrolled in a trial investigating both tiotropium 5 and 2.5 μg) experienced two cardiac disorder AEs (acute myocardial infarction and coronary artery disease). None of the serious cardiac disorder AEs was considered treatment-related. There were no patients with fatal major adverse cardiovascular events (defined in Supplementary Table 4); non-fatal major adverse cardiovascular events were reported in nine patients overall: tiotropium 5 μg pool, n = 4 (0.3%); placebo 5 μg pool, n = 4 (0.3%); tiotropium 2.5 μg pool, n = 1 (0.1%); placebo 2.5 μg pool, n = 4 (0.5%).

### 3.3.3. Safety in population subgroups

Table 8 presents a summary of AE and SAE frequencies in patient subgroups across which the frequency of AEs is known to vary; for example, the incidence of AEs tends to be higher in elderly patients. Accordingly, we include findings from three subgroups of interest: age < 65 years; high versus low blood eosinophil count, and with and without leukotriene receptor antagonist (LTRA) use at baseline.

In the overall pooled analysis and in patients <65 years of age, the frequencies of patients with AEs and SAEs were generally comparable between treatment groups in the low eosinophil (<0.6 × 10^9/L) and high eosinophil (>0.6 × 10^9/L) subgroups in both pools (Table 8), although in the high eosinophil subgroup there was a slightly higher frequency of patients with AEs in the tiotropium 2.5 μg pool (64.7%) compared with the corresponding placebo pool (57.8%).

In the subgroups with and without LTRA use at baseline, the frequencies of patients with AEs and SAEs were generally comparable between treatment groups, as in the overall analysis (Table 8). An exception to this was the higher frequency of patients with AEs in the tiotropium 2.5 μg pool compared with the corresponding placebo pool in the LTRA use subgroup.

Patients with a history of renal or urinary tract diseases formed a small proportion of the pooled analysis data set (tiotropium 5 μg, n = 25, 1.8%; placebo 5 μg, n = 27, 2.1%; tiotropium 2.5 μg, n = 20, 2.5%; placebo 2.5 μg, n = 13, 1.8%). Renal and urinary disorder AEs were reported in similar proportions of patients across treatment groups in each pool: tiotropium 5 μg, n = 7, 0.5%; placebo 5 μg, n = 10, 0.8%; tiotropium 2.5 μg, n = 4, 0.5%; placebo 2.5 μg, n = 2, 0.3%. Renal failure or acute renal failure was reported as an SAE in one patient in the tiotropium 5 μg pool and in one patient in the placebo 5 μg pool.

### 4. Discussion

In this pooled analysis of data from 3474 patients with symptomatic asthma who received tiotropium or placebo as add-on to at least ICS maintenance therapy, the frequencies of patients reporting AEs, SAEs and treatment-related AEs were comparable between tiotropium and placebo treatment groups, and there were no deaths. Dry mouth, an AE of special interest because of its known association with anticholinergic therapies, was reported at a slightly higher frequency with tiotropium than with placebo, but was less frequent than that reported in studies of patients with COPD [15]. Importantly, dry mouth was not described as serious, nor did it lead to discontinuation of the study medication, in any of the asthma patients in the analysis.

The frequencies of patients with cardiac disorder AEs and SAEs were low overall and balanced between tiotropium and placebo
treatment groups in the respective 5 µg and 2.5 µg pools. Within population subgroups defined by age (< and ≥65 years), blood eosinophil count and LTRA use at baseline, the frequencies of patients with AEs and SAEs were generally comparable between treatment groups.

Our findings in patients with symptomatic asthma are consistent with the safety signals observed with tiotropium in patients with COPD [15,16]. In 2014, previous concerns in COPD (based on pooled post hoc analyses and meta-analyses) that there may have been an increased risk of death with tiotropium Respimat® were convincingly disproven in the large-scale [17,135 patients] TIOSPIR study [15]. It is evident that tiotropium is well tolerated in both conditions, and, indeed, as we have highlighted, there have been no deaths in any of the trials that have investigated tiotropium Respimat® for the treatment of asthma. The fact that patients with asthma tend to be younger and have fewer co-morbidities than patients with COPD may explain the lower overall rate of AEs and SAEs in the current analysis.

A limitation of our pooled analysis includes the different durations of the seven included trials and that none was longer than 52 weeks. Although the pool included three trials of between 48 and 52 weeks’ duration, these contributed a relatively small proportion to the overall analysis, as the remaining trials were between 12 and 24 weeks’ duration. While the primary objective of CadenTina-asthma® was to evaluate the safety of tiotropium over 52 weeks, none of the trials was powered individually to assess safety as a primary end point. There is also a degree of limitation in our findings in that all participants were screened for, and treated in, randomised controlled trials, rather than in a ‘real-life’ setting. Nevertheless, in all of the trials included in our analysis all patients were required to have symptomatic asthma at entry, and tiotropium or placebo were administered on top of a wide range of patients’ normal background therapy (ICS with or without other controller medication). We therefore believe that our pooled trial population presented here is as representative of the ‘true’ asthma population as can be achieved in a randomised clinical trial setting.

The major advantage of this analysis is that all trials included in the pool were placebo-controlled and therefore provide the most valid comparison for assessing adverse reactions associated with tiotropium use. An additional strength is that all pooled trials were sourced from one clinical trial programme, offering a high degree of consistency in study design while also including a relatively wide variety of asthma severities through differences in inclusion and exclusion criteria. Furthermore, because of their add-on design, all patients continued to receive their usual background therapies, allowing investigation of tiotropium therapy in varied settings of concurrent medications. A further strength is that the patient sample was recruited from various populations and geographic regions, and includes a high proportion of Asian patients.

5. Conclusions

In summary, once-daily tiotropium Respimat® as add-on to maintenance treatment in adult patients with symptomatic asthma at different treatment steps, including ICS, demonstrated a safety and tolerability profile comparable with that of placebo.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2016.07.001.

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