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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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## Safety and tolerability of once-daily tiotropium Respimat<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> (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, 4.9%; tiotropium 2.5 µg, 2.0%; placebo 2.5 µg pool, 3.3%.

**Conclusion:** Tiotropium Respimat<sup>®</sup> 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<sup>®</sup> Soft Mist<sup>™</sup> 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<sup>®</sup> (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 β<sub>2</sub>-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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> in asthma. Studies of tiotropium Handi-Haler<sup>®</sup> 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.

Seventy 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<sup>®</sup>: NCT01316380) [12]; two replicate 24-week trials of once-daily tiotropium 5 µg and 2.5 µg and twice-daily salmeterol 50 µg in patients receiving ICS (MezzoTinA-asthma<sup>®</sup>: NCT01172808/NCT01172821) [10]; two replicate 48-week trials of once-daily tiotropium 5 µg in patients receiving ICS plus a LABA (PrimoTinA-asthma<sup>®</sup>: 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<sup>®</sup>: 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 (FEV<sub>1</sub>) increase of ≥12% and ≥200 mL (15–30 min after 400 µg salbutamol), except in PrimoTinA-asthma<sup>®</sup> where patients were required to have a positive hyper-responsiveness test or a positive trial of glucocorticosteroids or bronchodilator reversibility defined as either an FEV<sub>1</sub> 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<sup>®</sup> trials, and ≥3 months in the MezzoTinA-asthma<sup>®</sup>, GraziaTinA-asthma<sup>®</sup> and CadenTinA-asthma<sup>®</sup> 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<sup>®</sup>: ICS (≥800 µg budesonide or equivalent) plus a LABA; MezzoTinA-asthma<sup>®</sup>: ICS (400–800 µg budesonide or equivalent) alone or in fixed combination with a LABA or short-acting β<sub>2</sub>-agonist (SABA); GraziaTinA-asthma<sup>®</sup>: ICS (200–400 µg budesonide or equivalent) alone or in fixed combination with a SABA; CadenTinA-asthma<sup>®</sup>: 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 β<sub>2</sub>-adrenergic receptor and to have a documented history of asthma and bronchodilator reversibility resulting in an FEV<sub>1</sub> 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<sup>®</sup>, each as add-on therapy to pre-trial maintenance ICS (with a LABA in PrimoTinA-asthma<sup>®</sup>, and

**Table 1**  
Summary of study designs for the Phase II and III trials included in the pooled safety analysis.

| Authors; study identification number; study number/name                                    | Phase | Baseline maintenance therapy                             | Duration of treatment (weeks) | n <sup>a</sup> | Randomisation | Treatment arms, as add-on to baseline maintenance therapy  | Primary end points <sup>b</sup>   |
|--|-------|--|-------------------------------|----------------|---------------|--|---|
| Bateman et al., 2011 [6]<br>NCT00350207<br>Study 205.342                                   | II    | ICS (400–1000 µg budesonide or equivalent per day)       | 16                            | 388            | 1:1:1         | Once-daily tiotropium Respimat <sup>®</sup> 5 µg (n = 128);<br>twice-daily salmeterol 50 µg (n = 134);<br>placebo Respimat <sup>®</sup> (n = 126)  | Mean weekly morning PEF response at Week 16   |
| Paggiaro et al., 2016 [12]<br>NCT01316380<br>GraziaTinA-asthma <sup>®</sup>                | III   | ICS (200–400 µg budesonide or equivalent per day)        | 12                            | 464            | 1:1:1         | Once-daily tiotropium Respimat <sup>®</sup> 5 µg (n = 155);<br>once-daily tiotropium Respimat <sup>®</sup> 2.5 µg (n = 154);<br>placebo Respimat <sup>®</sup> (n = 155)                      | Peak FEV <sub>1(0–3h)</sub> response at Week 12   |
| Kerstjens et al., 2015 [10]<br>NCT01172808<br>NCT01172821<br>MezzoTinA-asthma <sup>®</sup> | III   | ICS (400–800 µg budesonide or equivalent per day)        | 24                            | 2100           | 1:1:1:1       | Once-daily tiotropium Respimat <sup>®</sup> 5 µg (n = 517);<br>once-daily tiotropium Respimat <sup>®</sup> 2.5 µg (n = 519);<br>twice-daily salmeterol 50 µg (n = 541);<br>placebo (n = 523) | Co-primary end points: peak FEV <sub>1(0–3h)</sub> and trough FEV <sub>1</sub> responses and ACQ-7 responder rate (pooled) at Week 24   |
| Kerstjens et al., 2012 [9]<br>NCT00772538<br>NCT00776984<br>PrimoTinA-asthma <sup>®</sup>  | III   | ICS (≥800 µg budesonide or equivalent per day) + LABA    | 48                            | 912            | 1:1           | Once-daily tiotropium Respimat <sup>®</sup> 5 µg (n = 456);<br>placebo Respimat <sup>®</sup> (n = 456)   | Co-primary end points: peak FEV <sub>1(0–3h)</sub> and trough FEV <sub>1</sub> responses at Week 24, and time to first severe asthma exacerbation during the 48-week treatment period (pooled)  |
| Ohta et al., 2015 [11]<br>NCT01340209<br>CadenTinA-asthma <sup>®</sup>                     | III   | ICS (400–800 µg budesonide or equivalent per day) ± LABA | 52                            | 285            | 2:2:1         | Once-daily tiotropium Respimat <sup>®</sup> 5 µg (n = 114);<br>once-daily tiotropium Respimat <sup>®</sup> 2.5 µg (n = 114);<br>placebo Respimat <sup>®</sup> (n = 57)                       | Primary objective: to evaluate long-term safety; therefore, no primary efficacy end points were defined<br>Secondary efficacy end points included trough FEV <sub>1</sub> and trough FVC responses, in-clinic trough PEF rate response and ACQ-7 responder rate |

ACQ-7 = seven-question Asthma Control Questionnaire. FEV<sub>1</sub> = forced expiratory volume in 1 s. FVC = forced vital capacity; ICS = inhaled corticosteroids. LABA = long-acting β<sub>2</sub>-agonist. Peak FEV<sub>1(0–3h)</sub> = peak forced expiratory volume in 1 s within 3 h post-dose. PEF = peak expiratory flow.

<sup>a</sup> Treated set.

<sup>b</sup> Response defined as change from baseline at study end point.

with or without a LABA in CadenTinA-asthma<sup>®</sup> (Table 1). In MezzoTinA-asthma<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup>. 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 2**

Main inclusion and exclusion criteria for all included trials.

| Authors; study identification number; study number/name | Bateman et al., 2011 [6]<br>NCT00350207<br>Study 205.342  | Paggiaro et al., 2016 [12]<br>NCT01316380<br>GraziaTinA-asthma®   | Kerstjens et al., 2015 [10]<br>NCT01172808<br>NCT01172821<br>MezzoTinA-asthma® | Kerstjens et al., 2012 [9]<br>NCT00772538<br>NCT00776984<br>PrimoTinA-asthma® | Ohta et al., 2015 [11]<br>NCT01340209<br>CadenTinA-asthma®      |
|---|---|---|--|---|---|
| Population  | 18–65 years of age; homozygous for B16-Arg  | 18–75 years of age  | 18–75 years of age   | 18–75 years of age  | 18–75 years of age  |
| Severity of persistent asthma                           | Moderate  | Mild  | Moderate   | Severe, $\geq 1$ exacerbations in the past year                               | Moderate to severe  |
| History of asthma                                       | Yes, duration not defined   | $\geq 3$ months   | $\geq 3$ months  | $\geq 5$ years  | $\geq 12$ weeks   |
| Symptomatic asthma                                      | Not defined   | ACQ $\geq 1.5^a$  | ACQ $\geq 1.5^a$   | ACQ $\geq 1.5^a$  | ACQ $\geq 1.5^a$  |
| Minimum asthma controller medication                    | ICS (400–1000 $\mu\text{g}$ budesonide or equivalent) <sup>b</sup>  | ICS (200–400 $\mu\text{g}$ budesonide or equivalent) <sup>c</sup> | ICS (400–800 $\mu\text{g}$ budesonide or equivalent) <sup>b</sup>              | ICS ( $\geq 800$ $\mu\text{g}$ budesonide or equivalent) + LABA               | ICS (400–800 $\mu\text{g}$ budesonide or equivalent) $\pm$ LABA |
| FEV <sub>1</sub> % predicted at screening               | Pre-bronchodilator: On LABA: $\leq 90\%$<br>Not on LABA: $\leq 80\%$  | Pre-bronchodilator: 60–90%  | Pre-bronchodilator: 60–90%   | Post-bronchodilator: $\leq 80\%$ , FEV <sub>1</sub> /FVC $\leq 70\%$          | Pre-bronchodilator: 60–90%                                      |
| Reversibility at screening                              | Yes <sup>d</sup>  | Yes <sup>e</sup>  | Yes <sup>e</sup>   | Not required <sup>f</sup>   | Yes <sup>e</sup>  |
| Smoking history   | Lifelong non-smoker or ex-smoker (<10 pack-years) with no smoking for at least 1 year before study entry  |   |  |   |   |
| Exclusion criteria                                      | Chronic obstructive pulmonary disease or significant lung disease other than asthma<br>Recent history (within the past 6 months) of myocardial infarction; hospitalised for cardiac failure during past year; unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy within past year |   |  |   |   |

ACQ = Asthma Control Questionnaire. FEV<sub>1</sub> = forced expiratory volume in 1 s. FVC = forced vital capacity; ICS = inhaled corticosteroids. LABA = long-acting  $\beta_2$ -agonist. SABA = short-acting  $\beta_2$ -agonist.

<sup>a</sup> At screening (Visit 1) and randomisation (Visit 2).

<sup>b</sup> Alone or in a fixed combination with a LABA or a SABA.

<sup>c</sup> Alone or in a fixed combination with a SABA.

<sup>d</sup> An FEV<sub>1</sub> increase of  $\geq 12\%$  and  $\geq 200$  mL either 45 min after 80  $\mu\text{g}$  ipratropium or 30 min after subsequent inhalation of 400  $\mu\text{g}$  salbutamol.

<sup>e</sup> An FEV<sub>1</sub> increase of  $\geq 12\%$  and  $\geq 200$  mL 15–30 min after 400  $\mu\text{g}$  salbutamol/albuterol.

<sup>f</sup> Used for patient characterisation only.

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  $\leq 50$  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  $\mu\text{g}$  and 2.5  $\mu\text{g}$ ; 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  $\mu\text{g}$  dose was assessed in seven trials, and the 2.5  $\mu\text{g}$  dose in four trials. All seven trials included in the analysis included a tiotropium 5  $\mu\text{g}$  arm, but only four included a tiotropium 2.5  $\mu\text{g}$  arm. Thus, when comparing the pooled tiotropium 2.5  $\mu\text{g}$  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  $\mu\text{g}$  pool for comparison with tiotropium 5  $\mu\text{g}$  (placebo patients pooled from all seven trials) and a placebo 2.5  $\mu\text{g}$  pool for comparison with tiotropium 2.5  $\mu\text{g}$  (placebo patients pooled from the four trials that included a tiotropium 2.5  $\mu\text{g}$  arm: MezzoTinA-asthma® [two replicate trials], GraziaTinA-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  $\mu\text{g}$  and 1317 patients who received placebo were compared (tiotropium 5  $\mu\text{g}$  pool), as were data from 787 patients receiving tiotropium 2.5  $\mu\text{g}$  and 735 patients receiving placebo (tiotropium 2.5  $\mu\text{g}$  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 ( $\pm$  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 ( $\pm$  SD) ranged from 20.3 (13.6) to 23.8 (14.7) years.

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

**Table 3**  
Baseline patient demographics and disease characteristics in the pooled safety analysis.

|   | Tiotropium Respimat <sup>®</sup><br>5 µg pool (N = 1370) | Placebo Respimat <sup>®</sup> (tiotropium<br>Respimat <sup>®</sup> 5 µg pool) <sup>a</sup> (N = 1317) | Tiotropium Respimat <sup>®</sup><br>2.5 µg pool (N = 787) | Placebo Respimat <sup>®</sup> (tiotropium<br>Respimat <sup>®</sup> 2.5 µg pool) <sup>a</sup> (N = 735) |
|---|--|---|---|--|
| Female, n (%)   | 817 (59.6)   | 805 (61.1)  | 470 (59.7)  | 452 (61.5)   |
| Race, n (%)   |  |   |   |  |
| White   | 857 (62.6)   | 864 (65.6)  | 374 (47.5)  | 365 (49.7)   |
| Asian   | 427 (31.2)   | 357 (27.1)  | 360 (45.7)  | 306 (41.6)   |
| Black/African-American  | 50 (3.6)   | 59 (4.5)  | 17 (2.2)  | 28 (3.8)   |
| American Indian/Alaska Native                                     | 35 (2.6)   | 35 (2.7)  | 34 (4.3)  | 35 (4.8)   |
| Hawaiian/Pacific Isle   | 1 (0.1)  | 2 (0.2)   | 2 (0.3)   | 1 (0.1)  |
| Ethnicity, n (%) <sup>b</sup>                                     |  |   |   |  |
| Not Hispanic/Latino   | 1045 (76.3)  | 1054 (80.0)   | 602 (76.5)  | 613 (83.4)   |
| Hispanic/Latino   | 83 (6.1)   | 80 (6.1)  | 71 (9.0)  | 65 (8.8)   |
| Age, mean ± SD  | 46.5 ± 13.3  | 46.9 ± 13.5   | 43.7 ± 13.0   | 43.2 ± 12.9  |
| Age group, n (%)  |  |   |   |  |
| <65 years   | 1250 (91.2)  | 1186 (90.1)   | 746 (94.8)  | 699 (95.1)   |
| ≥65 years   | 120 (8.8)  | 131 (9.9)   | 41 (5.2)  | 36 (4.9)   |
| BMI, mean ± SD  | 27.3 ± 5.9   | 27.3 ± 6.0  | 26.3 ± 5.9  | 26.6 ± 6.0   |
| Smoking status, n (%)   |  |   |   |  |
| Never smoked  | 1058 (77.2)  | 1060 (80.5)   | 656 (83.4)  | 621 (84.5)   |
| Ex-smoker   | 312 (22.8)   | 256 (19.4)  | 131 (16.6)  | 113 (15.4)   |
| Current smoker  | 0  | 1 (0.1)   | 0   | 1 (0.1)  |
| Smoking history, mean pack-<br>years ± SD                         | 4.81 ± 2.9   | 4.74 ± 2.9  | 4.08 ± 2.8  | 4.64 ± 3.0   |
| B16-Arg/Arg genotype, n (%)                                       | 171 (12.5)   | 164 (12.5)  | NA  | NA   |
| Duration of asthma, mean<br>years ± SD                            | 23.7 ± 14.5  | 23.8 ± 14.7   | 21.1 ± 14.2   | 20.3 ± 13.6  |
| Patients with cardiac history,<br>n (%) <sup>c</sup>              | 27 (2.0)   | 31 (2.4)  | 11 (1.4)  | 8 (1.1)  |
| Concomitant allergic rhinitis,<br>n (%)                           | 381 (27.8)   | 366 (27.8)  | 275 (34.9)  | 250 (34.0)   |
| Concomitant therapies at baseline, n (%)                          |  |   |   |  |
| LTRAs   | 166 (12.1)   | 166 (12.6)  | 84 (10.7)   | 58 (7.9)   |
| LABAs   | 512 (37.4)   | 488 (37.1)  | 62 (7.9)  | 36 (4.9)   |
| ICS dose of stable maintenance<br>therapy, µg, mean ± SD          | 841.7 ± 466.7  | 834.0 ± 472.0   | 640.3 ± 288.8   | 619.8 ± 248.7  |
| FEV <sub>1</sub> % predicted at screening,<br>pre-bronchodilator  | 66.4 ± 13.4  | 66.4 ± 13.7   | 73.0 ± 8.4  | 73.3 ± 8.4   |
| FEV <sub>1</sub> % predicted at screening,<br>post-bronchodilator | 79.4 ± 17.8  | 79.5 ± 17.6   | 90.0 ± 11.5   | 89.8 ± 10.8  |
| FEV <sub>1</sub> % reversibility, mean ± SD                       | 19.9 ± 13.5  | 20.1 ± 13.7   | 23.6 ± 11.7   | 22.8 ± 10.4  |
| Allergic/inflammatory asthma, n (%)                               |  |   |   |  |
| Clinician judgement 'yes'   | 796 (58.1)   | 770 (58.5)  | 526 (66.8)  | 487 (66.3)   |
| Total serum IgE >430 µg/L   | 679 (49.6)   | 627 (47.6)  | 470 (59.7)  | 443 (60.3)   |
| Blood eosinophil count<br>>0.6 × 10 <sup>9</sup> /L               | 281 (20.5)   | 262 (19.9)  | 170 (21.6)  | 154 (21.0)   |

Treated set.

B16-Arg/Arg = homozygous for arginine at the 16th amino acid position of the β<sub>2</sub>-adrenergic receptor. BMI = body mass index. FEV<sub>1</sub> = forced expiratory volume in 1 s. ICS = inhaled corticosteroids. IgE = immunoglobulin E. LABA = long-acting β<sub>2</sub>-agonist. LTRA = leukotriene receptor antagonist. NA = not applicable. SD = standard deviation.

<sup>a</sup> Placebo Respimat<sup>®</sup> 5 µg pool: all seven trials; placebo Respimat<sup>®</sup> 2.5 µg pool: MezzoTinA-asthma<sup>®</sup>, GraziaTinA-asthma<sup>®</sup> and CadenTinA-asthma<sup>®</sup>.

<sup>b</sup> Ethnicity missing for patients in study 205.342 because it was not collected on the case report form.

<sup>c</sup> A patient with cardiac history was defined as a patient who responded 'yes' to 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.

### 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 corresponding placebo, and 177.3 (84.2) days in the tiotropium 2.5 µg pool versus 162.1 (68.8) days in corresponding placebo. The variation in treatment exposure between pools is due to the marked differences in mean treatment exposure between trials of different duration. Within each trial, mean exposure was comparable between treatment arms (Supplementary Table 1).

### 3.3. Safety

#### 3.3.1. AEs, treatment-related AEs and SAEs

The frequency of patients reporting any type of AE was comparable 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 reported 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 worsening/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

**Table 4**

Overall summary of adverse events in the pooled safety analysis.

| n (%)  | Tiotropium Respimat®<br>5 µg pool (N = 1370) | Placebo Respimat® (tiotropium<br>Respimat® 5 µg pool) <sup>a</sup> (N = 1317) | Tiotropium Respimat®<br>2.5 µg pool (N = 787) | Placebo Respimat® (tiotropium<br>Respimat® 2.5 µg pool) <sup>a</sup> (N = 735) |
|--|--|---|---|--|
| Patients with any AE   | 833 (60.8)                                   | 823 (62.5)  | 449 (57.1)                                    | 405 (55.1)   |
| Patients with investigator-defined<br>treatment-related AEs            | 82 (6.0)                                     | 58 (4.4)  | 44 (5.6)                                      | 33 (4.5)   |
| Patients with AEs leading to<br>discontinuation of trial<br>medication | 25 (1.8)                                     | 30 (2.3)  | 9 (1.1)                                       | 14 (1.9)   |
| Patients with serious AEs <sup>b</sup>                                 | 55 (4.0)                                     | 65 (4.9)  | 16 (2.0)                                      | 24 (3.3)   |
| Fatal  | 0  | 0   | 0   | 0  |
| Immediately life-threatening   | 5 (0.4)                                      | 1 (0.1)   | 1 (0.1)                                       | 1 (0.1)  |
| Disabling/incapacitating   | 2 (0.1)                                      | 0   | 0   | 0  |
| Requiring hospitalisation  | 50 (3.6)                                     | 60 (4.6)  | 16 (2.0)                                      | 20 (2.7)   |
| Prolonged hospitalisation  | 3 (0.2)                                      | 3 (0.2)   | 1 (0.1)                                       | 2 (0.3)  |
| Other  | 6 (0.4)                                      | 3 (0.2)   | 0   | 3 (0.4)  |

Treated set.

AE = adverse event.

<sup>a</sup> Placebo Respimat® 5 µg pool: all seven trials; placebo Respimat® 2.5 µg pool: MezzoTinA-asthma®, GraziaTinA-asthma® and CadenTinA-asthma®.<sup>b</sup> A patient may be counted in more than one seriousness criterion. Percentages calculated using total number of patients per treatment as the denominator.**Table 5**

Adverse events occurring in ≥2% of patients in any treatment group (by preferred term).

| n (%)                                  | Tiotropium Respimat® 5 µg<br>pool (N = 1370) | Placebo Respimat® (tiotropium Respimat®<br>5 µg pool) <sup>a</sup> (N = 1317) | Tiotropium Respimat® 2.5 µg<br>pool (N = 787) | Placebo Respimat® (tiotropium Respimat®<br>2.5 µg pool) <sup>a</sup> (N = 735) |
|--|--|---|---|--|
| Asthma <sup>b</sup>                    | 359 (26.2)                                   | 406 (30.8)  | 140 (17.8)                                    | 157 (21.4)   |
| Decreased peak<br>expiratory flow rate | 176 (12.8)                                   | 219 (16.6)  | 67 (8.5)                                      | 97 (13.2)  |
| Nasopharyngitis                        | 153 (11.2)                                   | 142 (10.8)  | 102 (13.0)                                    | 77 (10.5)  |
| Upper respiratory tract<br>infection   | 54 (3.9)                                     | 69 (5.2)  | 37 (4.7)                                      | 50 (6.8)   |
| Headache                               | 45 (3.3)                                     | 50 (3.8)  | 26 (3.3)                                      | 15 (2.0)   |
| Bronchitis                             | 54 (3.9)                                     | 31 (2.4)  | 24 (3.0)                                      | 10 (1.4)   |
| Sinusitis                              | 35 (2.6)                                     | 34 (2.6)  | 20 (2.5)                                      | 8 (1.1)  |
| Influenza                              | 34 (2.5)                                     | 27 (2.1)  | 8 (1.0)                                       | 10 (1.4)   |
| Pharyngitis                            | 28 (2.0)                                     | 17 (1.3)  | 26 (3.3)                                      | 10 (1.4)   |

Treated set.

<sup>a</sup> Placebo Respimat® 5 µg pool: all seven trials; placebo Respimat® 2.5 µg pool: MezzoTinA-asthma®, GraziaTinA-asthma® and CadenTinA-asthma®.<sup>b</sup> Represents asthma worsening or exacerbation.

were nasopharyngitis, bronchitis and pharyngitis. Of these, only bronchitis led to treatment discontinuation, in two patients in the tiotropium 5 µg pool (0.1%).

Treatment-related AEs reported in ≥0.3% of patients in any treatment group are presented in Table 6. The most common treatment-related AEs in the 5 µg pool were asthma, dry mouth, dysphonia and thirst, and in the 2.5 µg pool, asthma, cough, dry mouth, headache and thirst. Treatment-related AEs occurring with greater frequency with tiotropium versus placebo included dysphonia, dry throat, dry mouth, thirst, headache and palpitations in the 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, 4.9%); 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 = 19, 1.4%); 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  $\geq 0.3\%$  of patients in any treatment group (by primary system organ class and preferred term).

| n (%)   | Tiotropium Respimat <sup>®</sup><br>5 µg pool (N = 1370) | Placebo Respimat <sup>®</sup> (tiotropium<br>Respimat <sup>®</sup> 5 µg pool) <sup>a</sup> (N = 1317) | Tiotropium Respimat <sup>®</sup><br>2.5 µg pool (N = 787) | Placebo Respimat <sup>®</sup> (tiotropium<br>Respimat <sup>®</sup> 2.5 µg pool) <sup>a</sup> (N = 735) |
|---|--|---|---|--|
| Patients with any treatment-related AE                      | 82 (6.0)   | 58 (4.4)  | 44 (5.6)  | 33 (4.5)   |
| <b>Respiratory, thoracic and mediastinal disorders</b>      | 32 (2.3)   | 28 (2.1)  | 11 (1.4)  | 13 (1.8)   |
| Asthma <sup>b</sup>   | 12 (0.9)   | 13 (1.0)  | 3 (0.4)   | 5 (0.7)  |
| Dysphonia   | 9 (0.7)  | 3 (0.2)   | 1 (0.1)   | 1 (0.1)  |
| Cough   | 3 (0.2)  | 7 (0.5)   | 2 (0.3)   | 4 (0.5)  |
| Dry throat  | 5 (0.4)  | 1 (0.1)   | 1 (0.1)   | 1 (0.1)  |
| Oropharyngeal discomfort                                    | 1 (0.1)  | 0   | 3 (0.4)   | 0  |
| Oropharyngeal pain  | 1 (0.1)  | 2 (0.2)   | 0   | 2 (0.3)  |
| <b>Gastrointestinal disorders</b>                           | 15 (1.1)   | 7 (0.5)   | 11 (1.4)  | 4 (0.5)  |
| Dry mouth   | 11 (0.8)   | 5 (0.4)   | 3 (0.4)   | 3 (0.4)  |
| Nausea  | 0  | 0   | 2 (0.3)   | 0  |
| <b>General disorders and administration site conditions</b> | 11 (0.8)   | 3 (0.2)   | 6 (0.8)   | 3 (0.4)  |
| Thirst  | 9 (0.7)  | 3 (0.2)   | 3 (0.4)   | 3 (0.4)  |
| <b>Nervous system disorders</b>                             | 6 (0.4)  | 4 (0.3)   | 8 (1.0)   | 3 (0.4)  |
| Headache  | 4 (0.3)  | 2 (0.2)   | 5 (0.6)   | 1 (0.1)  |
| <b>Investigations</b>                                       | 9 (0.7)  | 6 (0.5)   | 5 (0.6)   | 4 (0.5)  |
| Blood glucose abnormal                                      | 1 (0.1)  | 2 (0.2)   | 0   | 2 (0.3)  |
| Gamma-glutamyltransferase increased                         | 3 (0.2)  | 0   | 2 (0.3)   | 0  |
| <b>Cardiac disorders</b>                                    | 5 (0.4)  | 3 (0.2)   | 3 (0.4)   | 2 (0.3)  |
| Palpitations  | 4 (0.3)  | 1 (0.1)   | 2 (0.3)   | 1 (0.1)  |

Treated set.

AE = adverse event.

<sup>a</sup> Placebo Respimat<sup>®</sup> 5 µg pool: all seven trials; placebo Respimat<sup>®</sup> 2.5 µg pool: MezzoTinA-asthma<sup>®</sup>, GraziaTinA-asthma<sup>®</sup> and CadenTinA-asthma<sup>®</sup>.

<sup>b</sup> Represents asthma worsening or exacerbation.

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

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

Treated set.

SAE = serious adverse event.

<sup>a</sup> Placebo Respimat<sup>®</sup> 5 µg pool: all seven trials; placebo Respimat<sup>®</sup> 2.5 µg pool: MezzoTinA-asthma<sup>®</sup>, GraziaTinA-asthma<sup>®</sup> and CadenTinA-asthma<sup>®</sup>.

<sup>b</sup> 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  $\leq 0.2\%$  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 = 5 (0.4%); placebo 5 µg pool, n = 3 (0.2%); tiotropium 2.5 µg, n = 3 (0.4%); placebo 2.5 µg pool, n = 2 (0.3%). 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



**Table 8**  
Summary of the frequency of patients with adverse events and serious adverse events, overall and in specific population subgroups.

| n (%)                         | Tiotropium Respimat® 5 µg pool (N = 1370) |                                   | Placebo Respimat® (tiotropium Respimat® 5 µg pool) <sup>a</sup> (N = 1317) |                                   | Tiotropium Respimat® 2.5 µg pool (N = 787) |                                   | Placebo Respimat® (tiotropium Respimat® 2.5 µg pool) <sup>a</sup> (N = 735) |                                   |
|-------------------------------|---|-----------------------------------|--|-----------------------------------|--|-----------------------------------|---|-----------------------------------|
| <b>Overall</b>                |   |                                   |  |                                   |  |                                   |   |                                   |
| Any AE                        | 833 (60.8)                                |                                   | 823 (62.5)   |                                   | 449 (57.1)                                 |                                   | 405 (55.1)  |                                   |
| SAEs                          | 55 (4.0)                                  |                                   | 65 (4.9)   |                                   | 16 (2.0)                                   |                                   | 24 (3.3)  |                                   |
| <b>Age group</b>              | <b>&lt;65 years</b>                       | <b>≥65 years</b>                  | <b>&lt;65 years</b>  | <b>≥65 years</b>                  | <b>&lt;65 years</b>                        | <b>≥65 years</b>                  | <b>&lt;65 years</b>   | <b>≥65 years</b>                  |
| n (% of N) <sup>b</sup>       | 1250 (91.2)                               | 120 (8.8)                         | 1186 (90.1)  | 131 (9.9)                         | 746 (94.8)                                 | 41 (5.2)                          | 699 (95.1)  | 36 (4.9)                          |
| Any AE <sup>c</sup>           | 751 (60.1)                                | 82 (68.3)                         | 723 (61.0)   | 100 (76.3)                        | 427 (57.2)                                 | 22 (53.7)                         | 381 (54.5)  | 24 (66.7)                         |
| SAEs <sup>c</sup>             | 45 (3.6)                                  | 10 (8.3)                          | 51 (4.3)   | 14 (10.7)                         | 16 (2.1)                                   | 0                                 | 21 (3.0)  | 3 (8.3)                           |
| <b>Blood eosinophil count</b> | <b>≤0.6 × 10<sup>9</sup>/L</b>            | <b>&gt;0.6 × 10<sup>9</sup>/L</b> | <b>≤0.6 × 10<sup>9</sup>/L</b>   | <b>&gt;0.6 × 10<sup>9</sup>/L</b> | <b>≤0.6 × 10<sup>9</sup>/L</b>             | <b>&gt;0.6 × 10<sup>9</sup>/L</b> | <b>≤0.6 × 10<sup>9</sup>/L</b>  | <b>&gt;0.6 × 10<sup>9</sup>/L</b> |
| n (% of N) <sup>b</sup>       | 1072 (78.2)                               | 281 (20.5)                        | 1038 (78.8)  | 262 (19.9)                        | 615 (78.1)                                 | 170 (21.6)                        | 580 (78.9)  | 154 (21.0)                        |
| Any AE <sup>c</sup>           | 641 (59.8)                                | 181 (64.4)                        | 635 (61.2)   | 175 (66.8)                        | 338 (55.0)                                 | 110 (64.7)                        | 316 (54.5)  | 89 (57.8)                         |
| SAEs <sup>c</sup>             | 41 (3.8)                                  | 12 (4.3)                          | 50 (4.8)   | 14 (5.3)                          | 12 (2.0)                                   | 4 (2.4)                           | 18 (3.1)  | 6 (3.9)                           |
| <b>LTRA use at baseline</b>   | <b>+ LTRA</b>                             | <b>– LTRA</b>                     | <b>+ LTRA</b>  | <b>– LTRA</b>                     | <b>+ LTRA</b>                              | <b>– LTRA</b>                     | <b>+ LTRA</b>   | <b>– LTRA</b>                     |
| n (% of N) <sup>b</sup>       | 166 (12.1)                                | 1204 (87.9)                       | 166 (12.6)   | 1151 (87.4)                       | 84 (10.7)                                  | 703 (89.3)                        | 58 (7.9)  | 677 (92.1)                        |
| Any AE <sup>c</sup>           | 126 (75.9)                                | 707 (58.7)                        | 131 (78.9)   | 692 (60.1)                        | 62 (73.8)                                  | 387 (55.0)                        | 36 (62.1)   | 369 (54.5)                        |
| SAEs <sup>c</sup>             | 12 (7.2)                                  | 43 (3.6)                          | 15 (9.0)   | 50 (4.3)                          | 2 (2.4)                                    | 14 (2.0)                          | 3 (5.2)   | 21 (3.1)                          |

Treated set.

AE = adverse event. LTRA = leukotriene receptor antagonist.

<sup>a</sup> Placebo Respimat® 5 µg pool: all seven trials; placebo Respimat® 2.5 µg pool: MezzoTinA-asthma®, GraziaTinA-asthma® and CadenTinA-asthma®.

<sup>b</sup> Percentages calculated using total number of patients per treatment pool as the denominator.

<sup>c</sup> Percentages calculated using total number of patients per subgroup per treatment as the denominator.

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 µg and 2.5 µg) experienced two cardiac disorder SAEs (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 < and ≥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 comparable between treatment groups, while in patients ≥65 years of age these frequencies were higher with placebo than with tiotropium in both pools (Table 8). Such differences should be treated with some caution because of the small number of patients in the older age group (n = 36–131).

As in the overall analysis, the frequencies of patients with AEs

and SAEs were generally comparable between treatment groups in the low eosinophil (≤0.6 × 10<sup>9</sup>/L) and high eosinophil (>0.6 × 10<sup>9</sup>/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<sup>®</sup> 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<sup>®</sup> 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 of patients to the overall pool, and the remaining trials were between 12 and 24 weeks' duration. While the primary objective of CadenTina-asthma<sup>®</sup> 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<sup>®</sup> 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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