ORIGINAL ARTICLE
ASTHMA

Tiotropium add-on therapy is safe and reduces seasonal worsening in paediatric asthma patients

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Once-daily tiotropium Respimat add-on therapy is safe in paediatric patients and reduces adverse events related to asthma exacerbations and symptoms, especially during seasonal peaks http://ow.ly/ujHw30of3xk

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ABSTRACT There remains an unmet need for effective, well-tolerated therapeutic options in paediatric patients with not fully controlled asthma, for whom safety is of paramount importance.

Data were pooled from five randomised, double-blind, placebo-controlled studies evaluating tiotropium 5 or 2.5 µg *versus* placebo add-on therapy in patients with symptomatic asthma aged 1–17 years. Analysis included adverse events (AEs) and serious AEs (SAEs) reported throughout and for 30 days following treatment.

Of 1691 patients treated, 1119 received tiotropium. Reporting of AEs was low and comparable across all groups: tiotropium 5 µg (51%), tiotropium 2.5 µg (51%) and placebo (54%). Reporting of drug-related AEs, those leading to discontinuation and SAEs was also low and balanced between treatment groups, irrespective of age, disease severity or sex. The number of AEs related to asthma symptoms and exacerbations was lower with tiotropium (5 µg) than with placebo, particularly during the seasonal peaks of these AEs.

This comprehensive analysis of a large safety database allowed subgroup analyses that are often impractical with individual trials and provides further support for the safety of once-daily tiotropium Respimat add-on therapy in paediatric patients with symptomatic asthma.

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Introduction

Asthma is one of the most prevalent chronic diseases in children and adolescents, affecting ∼10% of children and adolescents in the UK and USA [1–3]. Studies have shown that >50% of 4–18-year-old patients with asthma remain symptomatic despite treatment with at least an inhaled corticosteroid (ICS) [1, 2]. For these patients, the first intervention is to improve patient education and self-management. This involves ensuring adherence to the prescribed treatment and optimal use of the device, and, where possible, confirming the avoidance of allergens and exposure to environmental pollutants and tobacco smoke. Should symptoms persist, step-up treatments may be considered. Treatment options include addition of a long-acting β_2-agonist (LABA) and/or a leukotriene receptor antagonist (LTRA) to the maintenance treatment regimen and/or a further increase in the dose of ICS [4]. ICS therapy is shown to affect growth in children, particularly when administered in medium-to-high doses over an extended period of time; thus, an alternative to increasing the ICS dose would be attractive [5, 6]. Common side-effects associated with LABAs include increased heart rate, palpitations and tremor, although tremor commonly resolves after the first few doses [7]. The LTRA montelukast has generally been regarded as safe for use in children, although inferior to ICS in terms of efficacy [8]. Conversely, a study utilising the Swedish database for adverse drug reactions, SWEDIS, which investigated drug groups commonly used in children, has shown that montelukast was the drug with the most frequent adverse drug reactions in 2005. The majority of these were in children <5 years old and were predominately psychiatric in nature [9]. Another study has also highlighted some specific neuropsychiatric adverse events (AEs), of which users should be cognisant [10]. Therefore, there is an unmet need for more well-tolerated and efficacious therapeutic options for the treatment of paediatric patients with symptomatic asthma.

Tiotropium Respimat (Boehringer Ingelheim, Ingelheim am Rhein, Germany) (hereafter referred to as "tiotropium") is a long-acting muscarinic antagonist. It has been evaluated as an add-on therapy in a comprehensive phase 2 and 3 clinical trial programme including more than 6000 adult and paediatric patients with symptomatic asthma [11–24]. Based on the evidence from these trials, tiotropium is an efficacious add-on therapy, with safety and tolerability comparable with placebo in the individual studies. Tiotropium is indicated for once-daily use in the European Union (two inhalations of 2.5 µg) and USA (two inhalations of 1.25 µg) as maintenance treatment in patients with severe asthma aged ⩾6 years [25, 26]. In addition to the safety reports of tiotropium add-on therapy from the individual clinical trials, and an in-depth, systematic assessment of safety and tolerability in adult patients [27, 28], the analysis presented here, involving a large sample of paediatric patients, can provide greater power to detect any as-yet unidentified safety signals, and allows the analysis of safety in subgroups that is impractical with individual trials.

The aim of the current analysis, therefore, was to further assess the safety and tolerability of tiotropium from a pooled population of paediatric (1–17 years) patients with symptomatic asthma at different Global Initiative for Asthma (GINA) treatment steps, and to investigate the seasonality of AEs relating to asthma exacerbations and symptoms in the pooled populations.

Methods

This pooled analysis included all phase 3 parallel-group studies in children (6–11 years) and adolescents (12–17 years), as well as a phase 2/3 study in children aged 1–5 years, included in the clinical development programme of tiotropium in asthma. All trials were of randomised, double-blind, placebo-controlled design, and between 12 weeks and 1 year in duration (table 1) [18, 19, 21–23]. The treatment history (treatment step on enrolment) specified in each trial differed and reflected the severity of the patient population (table 1).

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TABLE 1 Overview of study designs and key inclusion/exclusion criteria

	NinoTinA-asthma [23]	CanoTinA-asthma [21]	VivaTinA-asthma [20]	RubaTinA-asthma [17]	PensieTinA-asthma [18]
ClinicalTrials.gov identifier	NCT01634113	NCT01634139	NCT01634152	NCT01257230	NCT01277523
Phase and design[#]	Phase 2/3	Phase 3, randomised, double-blind, placebo-controlled, parallel-group	Phase 3, randomised, double-blind, placebo-controlled, parallel-group	Phase 3, randomised, double-blind, placebo-controlled, parallel-group	Phase 3, randomised, double-blind, placebo-controlled, parallel-group
Objectives	Efficacy and safety	Efficacy and safety	Efficacy and safety	Efficacy and safety	Efficacy and safety
Patient population	1–5-year-olds with persistent asthmatic symptoms	6–11-year-olds with symptomatic moderate asthma	6–11-year-olds with symptomatic severe asthma	12–17-year-olds with symptomatic moderate asthma	12–17-year-olds with symptomatic severe asthma
History of asthma	NA	⩾6 months	⩾6 months	⩾3 months	⩾3 months
Symptomatic asthma	Daytime symptoms more than twice a week; any limitation of activities; any nocturnal symptoms/awakenings; need for rescue medication >2 days·week^{-1}	ACQ-IA ⩾1.5	ACQ-IA ⩾1.5	ACQ ⩾1.5	ACQ ⩾1.5
Minimum asthma controller medication	Stable ICS, with or without another controller, for ⩾4 weeks before screening	Medium-dose ICS (200–400 μg·day^{-1} budesonide or equivalent dose), with or without another controller, for ⩾4 weeks before screening; LABA had to be discontinued ⩾24 h prior to screening	High-dose ICS (>400 μg·day^{-1} budesonide or equivalent dose) plus ⩾1 controller or medium-dose ICS (200–400 μg·day^{-1} budesonide or equivalent dose) plus ⩾2 controllers for ⩾4 weeks before screening	Medium-dose ICS (400–800 μg·day^{-1} budesonide or equivalent dose), with or without LTRA, for ⩾4 weeks before screening; LABA had to be discontinued ⩾72 h prior to screening	High-dose ICS (800–1600 μg·day^{-1} budesonide or equivalent dose) plus ⩾1 controller or medium-dose ICS (400–800 μg·day^{-1} budesonide or equivalent dose) plus ⩾2 controllers for ⩾4 weeks before screening
Pre-bronchodilator FEV_1 % pred at screening	⩽90% for 5-year-olds	60–90%	60–90%	60–90%	60–90%
FEV_1 reversibility at screening		⩾12%, 15–30 min after 200 μg salbutamol	⩾12%, 15–30 min after 200 μg salbutamol	⩾12% and ⩾200 mL, 15–30 min after 400 μg salbutamol (age >14 years) or ⩾12% only (age 12–14 years)	⩾12% and ⩾200 mL, 15–30 min after 400 μg salbutamol (age >14 years) or ⩾12% only (age 12–14 years)
Variability of absolute FEV_1 from screening to randomisation[¶]		±30%	±30%	±30%	±30%
Smoking history				Nonsmoker or ex-smoker who stopped smoking ⩾1 year prior to enrolment	Nonsmoker or ex-smoker who stopped smoking ⩾1 year prior to enrolment
Exclusion criteria	Significant disease other than asthma	Significant disease other than asthma	Significant disease other than asthma	Significant disease other than asthma	Significant disease other than asthma
Treatment	Once-daily tiotropium (5 or 2.5 μg) or placebo[+]	Once-daily tiotropium (5 or 2.5 μg) or placebo	Once-daily tiotropium (5 or 2.5 μg) or placebo	Once-daily tiotropium (5 or 2.5 μg) or placebo	Once-daily tiotropium (5 or 2.5 μg) or placebo
Treatment duration	12 weeks	48 weeks	12 weeks	48 weeks	12 weeks
Sample size	102 randomised patients (101 treated, 102 planned); 101 completed patients	403 randomised patients (401 treated, 385 planned); 384 completed patients	401 randomised patients (400 treated, 375 planned); 392 completed patients	398 randomised patients (397 treated, 127 planned per group); 376 completed patients	392 randomised patients (392 treated, 375 planned); 388 completed patients

NA: not applicable; ACQ: Asthma Control Questionnaire; IA: interviewer-administered; ICS: inhaled corticosteroid; LTRA: leukotriene receptor antagonist; LABA: long-acting β_2-agonist; FEV_1: forced expiratory volume in 1 s; % pred: % predicted. [#]: note that NinoTinA-asthma was a phase 2/3 trial; [¶]: the study allowed variation of absolute FEV_1 values for visit 1 (pre-bronchodilator) compared with visit 2 (pre-dose) within ±30%; [+]: in the NinoTinA-asthma study, patients aged 1–4 years at visit 1 were required to use an Aerochamber Plus Flow-Vu valved holding chamber (commonly referred to as a spacer) with a face mask for the inhalation of trial medication to reduce variability and ensure standardised dosing, whereas children aged 5 years at visit 1 were permitted to use the Respimat without a spacer (overall three patients did not use a spacer).

Trial medication

During the treatment period in all trials, patients received tiotropium (5 or 2.5 μg) or placebo (delivered by a Respimat inhaler as two puffs) once daily. Tiotropium was administered as add-on therapy to ICS maintenance treatment with or without other controller therapies. In the NinoTinA-asthma study [23], patients aged 1–4 years at screening were required to use an Aerochamber Plus Flow-Vu valved holding chamber (commonly referred to as a spacer; Trudell Medical International, London, ON, Canada) with a face mask for the inhalation of trial medication. Children aged 5 years at screening were permitted to use the Respimat with or without a spacer and mouthpiece, depending on preference.

End-points

The assessment of safety (together with efficacy) was a primary objective in all five trials. In the four trials in children aged 6–17 years, the primary efficacy end-point was improvement in forced expiratory volume in 1 s and this is what the power calculations were based on. In the trial involving children aged <6 years, there was no formal power calculation related to an end-point, but the recruitment was considered sufficient for the descriptive evaluation of efficacy and safety. This analysis is based on AEs occurring between first drug inhalation and until 30 days after the last dose of trial medication, coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 (www.meddra.org). Further details and definitions of AEs and serious AEs (SAEs) can be found in the supplementary material.

A composite end-point, grouping all AEs relating to the MedDRA-preferred term group "asthma exacerbations and asthma-related symptoms", from all studies in the pooled analysis was also analysed. Preferred terms included in this analysis are listed in supplementary table E1.

TABLE 2 Overview of baseline demographics and disease characteristics: treated set

	NinoTinA-asthma [23]	CanoTinA-asthma [21]	VivaTinA-asthma [20]	RubaTinA-asthma [17]	PensieTinA-asthma [18]
Subjects	101	401	400	397	392
Male	61 (60.4)	264 (65.8)	279 (69.8)	258 (65.0)	242 (61.7)
Age years	3.0 (1–5)	9.0 (6–11)	9.0 (6–11)	14.0 (11–17)	14.0 (12–17)
Race					
White	77 (76.2)	339 (84.5)	358 (89.5)	368 (92.7)	371 (94.6)
Asian	17 (16.8)	10 (2.5)	2 (0.5)	13 (3.3)	10 (2.6)
Black/African-American	7 (6.9)	7 (1.7)	5 (1.3)	14 (3.5)	8 (2.0)
American Indian/Alaska Native	0	45 (11.2)	35 (8.8)	2 (0.5)	3 (0.8)
Hawaiian/Pacific Islander	0	0	0	0	0
Ethnicity					
Hispanic/Latino	0	55 (13.7)	72 (18.0)	42 (10.6)	68 (17.3)
Never-smoker				396 (99.7)	392 (100)
No exposure to second-hand smoke	92 (91.1)	372 (92.8)	369 (92.3)	353 (88.9)	367 (93.6)
Age at onset of asthma years	1.5±1.2	4.7±2.4	4.1±2.4	6.5±4.1	6.5±3.9
Duration of asthma years	1.3 (0.5–5.0)	4.0 (0.5–11.0)	4.8 (0.6–11.0)	8.0 (0.3–16.3)	8.0 (0.3–16.5)
Concomitant diagnoses					
Allergic rhinitis	20 (19.8)	230 (57.4)	238 (59.5)	219 (55.2)	225 (57.4)
Atopic dermatitis	17 (16.8)	55 (13.7)	38 (9.5)	37 (9.3)	38 (9.7)
FEV_1 % pred		84.06±10.79	81.64±11.45	82.79±10.56	79.52±11.49
FEV_1 % reversibility		26.48±12.41	27.43±13.43	26.80±12.86	29.19±14.26
ACQ score#		1.868±0.31	1.966±0.36	2.03±0.43	2.13±0.43
Concomitant therapies at baseline					
LTRAs	41 (40.6)	107 (26.7)	339 (84.8)	33 (8.3)	315 (80.4)
LABAs	8 (7.9)	1 (0.2)	313 (78.3)	1 (0.3)	324 (82.7)
ICS dose of stable maintenance treatment μg·day^{-1} budesonide or equivalent	255.2±187.4	310.0±112.0	457.4±236.0	539.4±292.7	747.0±357.7

Data are presented as n, n (%), median (range) or mean±SD. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; ACQ: Asthma Control Questionnaire; LTRA: leukotriene receptor antagonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid. #: interviewer-administered ACQ in CanoTinA-asthma and VivaTinA-asthma.

Pooled safety data are presented for the following analysis groups: all patients, and subgroups by age, asthma severity and sex.

Additionally, the number of AEs related to asthma exacerbations and symptoms in the pooled data were plotted by month, with data from the Southern hemisphere shifted by 6 months to align the seasons (Northern hemisphere: June=month 6; Southern hemisphere: December=month 6).

Analyses were performed on the treated set, defined as all randomised patients who received at least one dose of trial medication. Analyses were evaluated descriptively and no inferential statistics were performed. Analysis of AEs related to asthma exacerbations and symptoms in the pooled data were plotted by month as a *post hoc* analysis and therefore considered exploratory only.

As has been reported, each study was conducted in accordance with the amended Declaration of Helsinki. The ethics research boards of the respective institutions approved the protocols, and signed, informed consent was obtained from all patients and/or their parents. See original publications for further details [18, 19, 21–23].

Results

A total of 1691 patients comprised the treated set (table 2): 560 patients received tiotropium 5 µg, 559 patients received tiotropium 2.5 µg and 572 patients received placebo. Overall, the mean exposure to study medication was 314, 304 and 314 patient-years with tiotropium 5 µg, tiotropium 2.5 µg and placebo, respectively.

Safety

The overall number of patients with AEs was generally comparable between treatment groups, including placebo (table 3). Approximately half of the patients (n=879 (52%)) experienced at least one AE (n=283 (51%) receiving tiotropium 5 µg; n=286 (51%) receiving tiotropium 2.5 µg; n=310 (54%) receiving placebo). Very few AEs led to treatment discontinuation: two in patients receiving tiotropium 5 µg and five in patients receiving placebo. The only AE leading to discontinuation reported for more than one patient was asthma exacerbation/worsening (two patients receiving tiotropium 5 µg and two patients receiving placebo). The incidence of patients with investigator-defined drug-related AEs was low and comparable between treatment groups, including placebo. None of the drug-related AEs in the tiotropium treatment groups were serious or led to treatment discontinuation. The only AE assessed as drug related that was reported in more than two patients was cough (one patient receiving tiotropium 5 µg; one patient receiving tiotropium 2.5 µg; four patients receiving placebo). The overall frequency of patients that experienced SAEs was low and comparable between treatment groups. No SAEs were considered drug related or led to treatment discontinuation. The only SAEs reported for more than two patients were asthma exacerbation/worsening/crisis (five patients receiving tiotropium 5 µg; three patients receiving tiotropium 2.5 µg; five patients receiving placebo) and appendicitis (two patients receiving tiotropium 5 µg; two patients receiving tiotropium 2.5 µg; one patient receiving placebo). No deaths occurred during any of the trials.

Consistent with the disease profile, the most frequently reported AEs, reported by ⩾5% of patients, were asthma exacerbation/worsening, decreased peak expiratory flow (PEF) rate, nasopharyngitis/rhinopharyngitis

TABLE 3 Overview of patients reporting adverse events (AEs) in the pooled population: treated set (treatment plus 30 days following treatment)

	Tiotropium 5 µg	Tiotropium 2.5 µg	Placebo
Subjects	560	559	572
Any AEs	283 (50.5)	286 (51.2)	310 (54.2)
Drug-related AEs	7 (1.3)	1 (0.2)	8 (1.4)
AEs leading to discontinuation	2 (0.4)	0	5 (0.9)
Serious AEs	10 (1.8)	8 (1.4)	13 (2.3)
AEs reported in ⩾5% and ⩾10 patients#			
Asthma exacerbation/worsening	110 (19.6)	115 (20.6)	143 (25.0)
Decreased peak expiratory flow rate	55 (9.8)	64 (11.4)	68 (11.9)
Nasopharyngitis/rhinopharyngitis	44 (7.9)	46 (8.2)	49 (8.6)
Viral respiratory tract infection	27 (4.8)	24 (4.3)	30 (5.2)

Data are presented as n or n (%). Percentages are calculated using total number of patients per treatment as the denominator. #: in at least one treatment group.

and viral respiratory tract infection (table 3; AEs reported by ⩾2% of patients are shown in supplementary table E2). These were reported by a similar proportion of patients in the tiotropium and placebo groups, except asthma exacerbation/worsening, which was reported by fewer patients in the tiotropium treatment groups.

The frequency of patients reporting a composite end-point, grouping all AEs related to asthma exacerbations and asthma symptoms, was lower in the tiotropium treatment groups than with placebo (placebo: 217 patients with event (37.9%); tiotropium 5 µg: 177 patients with event (31.6%), rate ratio over placebo 0.76 (95% CI 0.63–0.93); tiotropium 2.5 µg: 195 patients with event (34.9%), rate ratio over placebo 0.87 (95% CI 0.72–1.05)). A description of safety topics of interest is available in the supplementary material.

Subgroups by age

Safety in the different age categories was generally comparable with the pooled population (table 4). The lower proportion of patients with asthma exacerbation/worsening as an AE in the tiotropium groups compared with the placebo group was most prominently observed in patients aged 1–5 years (6.5% for tiotropium 5 µg; 13.9% for tiotropium 2.5 µg; 29.4% for placebo), with similar trends in patients aged 6–11 years (26.4% for tiotropium 5 µg; 25.5% for tiotropium 2.5 µg; 32.8% for placebo) and 12–17 years (14.4% for tiotropium 5 µg; 16.3% for tiotropium 2.5 µg; 16.8% for placebo).

No SAEs were reported in patients treated with tiotropium in the 1–5-year-old group and no AEs in this age group led to discontinuation in any treatment group (table 4; SAEs by age are shown in supplementary table E3). Asthma was the only AE preferred term reported in ⩾5%, or in 10 or more patients, in any of the treatment groups.

An analysis of pooled data from studies with patients aged ⩾6 years is detailed in supplementary table E4.

TABLE 4 Overview of patients reporting adverse events (AEs) by age subgroups: treated set (treatment plus 30 days following treatment)

	Tiotropium 5 µg	Tiotropium 2.5 µg	Placebo
Age 1–5 years [23]			
Subjects	31	36	34
Any AEs	18 (58.1)	20 (55.6)	25 (73.5)
Drug-related AEs	2 (6.5)	0	2 (5.9)
AEs leading to discontinuation	0	0	0
Serious AEs	0	0	3 (8.8)
AEs reported in ⩾5% and ⩾10 patients[#]			
Asthma exacerbation/worsening	2 (6.5)	5 (13.9)	10 (29.4)
Age 6–11 years [21, 22]			
Subjects	265	271	265
Any AEs	138 (52.1)	145 (53.5)	155 (58.5)
Drug-related AEs	1 (0.4)	0	4 (1.5)
AEs leading to discontinuation	2 (0.8)	0	2 (0.8)
Serious AEs	5 (1.9)	5 (1.8)	8 (3.0)
AEs reported in ⩾5% and ⩾10 patients[#]			
Asthma exacerbation/worsening	70 (26.4)	69 (25.5)	87 (32.8)
Decreased peak expiratory flow rate	44 (16.6)	46 (17.0)	47 (17.7)
Nasopharyngitis/rhinopharyngitis	18 (6.8)	21 (7.7)	24 (9.1)
Age 12–17 years [18, 19]			
Subjects	264	252	273
Any AEs	127 (48.1)	121 (48.0)	130 (47.6)
Drug-related AEs	4 (1.5)	1 (0.4)	2 (0.7)
AEs leading to discontinuation	0	0	3 (1.1)
Serious AEs	5 (1.9)	3 (1.2)	2 (0.7)
AEs reported in ⩾5% and ⩾10 patients[#]			
Asthma exacerbation/worsening	38 (14.4)	41 (16.3)	46 (16.8)
Nasopharyngitis/rhinopharyngitis	24 (9.1)	18 (7.1)	20 (7.3)
Decreased peak expiratory flow rate	11 (4.2)	18 (7.1)	21 (7.7)
Viral respiratory tract infection	11 (4.2)	11 (4.4)	14 (5.1)

Data are presented as n or n (%). Percentages are calculated using total number of patients per treatment as the denominator. [#]: in at least one treatment group.

TABLE 5 Overview of patients reporting adverse events (AEs) in subgroups by asthma severity: treated set (treatment plus 30 days following treatment)

	Tiotropium 5 µg	Tiotropium 2.5 µg	Placebo
Moderate asthma [18, 22]			
Subjects	269	260	269
Any AEs	166 (61.7)	165 (63.5)	171 (63.6)
Drug-related AEs	4 (1.5)	1 (0.4)	3 (1.1)
AEs leading to discontinuation	0	0	2 (0.7)
Serious AEs	4 (1.5)	5 (1.9)	8 (3.0)
AEs reported in ⩾5% and ⩾10 patients[#]			
Asthma exacerbation/worsening	69 (25.7)	76 (29.2)	89 (33.1)
Decreased peak expiratory flow rate	35 (13.0)	40 (15.4)	35 (13.0)
Nasopharyngitis/rhinopharyngitis	31 (11.5)	28 (10.8)	30 (11.2)
Viral respiratory tract infection	18 (6.7)	19 (7.3)	19 (7.1)
Respiratory tract infection	15 (5.6)	16 (6.2)	21 (7.8)
Severe asthma [19, 21]			
Subjects	260	263	269
Any AEs	99 (38.1)	101 (38.4)	114 (42.4)
Drug-related AEs	1 (0.4)	0	3 (1.1)
AEs leading to discontinuation	2 (0.8)	0	3 (1.1)
Serious AEs	6 (2.3)	3 (1.1)	2 (0.7)
AEs reported in ⩾5% and ⩾10 patients[#]			
Asthma exacerbation/worsening	39 (15.0)	34 (12.9)	44 (16.4)
Decreased peak expiratory flow rate	20 (7.7)	24 (9.1)	33 (12.3)
Nasopharyngitis/rhinopharyngitis	11 (4.2)	11 (4.2)	14 (5.2)

Data are presented as n or n (%). Percentages are calculated using total number of patients per treatment as the denominator. [#]: in at least one treatment group.

Subgroups by asthma severity

The safety in the different asthma severity categories was generally comparable with the pooled population (table 5). However, compared with the pooled population, more patients with moderate asthma reported at least one AE and fewer patients with severe asthma reported at least one AE. This is most likely due to the longer duration of the studies in moderate asthma (48 weeks for moderate asthma *versus* 12 weeks for severe asthma). Of note, in patients with severe asthma, decreased PEF rate was reported by fewer patients in the tiotropium groups than in the placebo group.

Subgroup analyses of LABA and LTRA use at randomisation were also performed; as expected, the results were consistent with the subgroup analyses by severity, since LABAs/LTRAs were predominantly taken by patients with more severe asthma.

Subgroups by sex

In an analysis of AEs by sex, there were fewer females than males in each treatment group; proportionally, slightly fewer females reported AEs compared with males, particularly in the tiotropium 5 µg and placebo groups, with no notable differences in the proportion of patients with drug-related AEs or AEs leading to discontinuation (table 6). As in the overall analysis, the frequency of patients experiencing SAEs was low and comparable between treatment groups.

Analysis of seasonal asthma worsening

When analysed by month, reports of AEs related to asthma exacerbations and symptoms were greatest in the placebo group in the spring, autumn and winter (figure 1), and lowest in the summer. With both doses of tiotropium, spring and autumn peaks were reduced. An analysis by month of reported AEs relating to asthma exacerbations and symptoms from studies with patients aged ⩾6 years is detailed in supplementary figure E1.

Discussion

In this comprehensive pooled analysis, tiotropium was well tolerated, with a safety profile comparable with placebo. Specifically, the incidence of patients reporting drug-related AEs, AEs leading to discontinuation, SAEs and AEs commonly associated with anticholinergic therapy was low and generally balanced between treatment groups, including placebo. Baseline demographics and disease characteristics were comparable between the treatment groups within each trial (table 2). Pharmacokinetic data from the 1–5-year-old

TABLE 6 Overview of patients reporting adverse events (AEs) in subgroups by sex: treated set (treatment plus 30 days following treatment)

	Tiotropium 5 µg	Tiotropium 2.5 µg	Placebo
Males			
Subjects	365	373	366
Any AEs	195 (53.4)	190 (50.9)	201 (54.9)
Drug-related AEs	5 (1.4)	0	5 (1.4)
AEs leading to discontinuation	2 (0.5)	0	3 (0.8)
Serious AEs	7 (1.9)	6 (1.6)	4 (1.1)
AEs reported in ⩾5% and ⩾10 patients[#]			
Asthma exacerbation/worsening	75 (20.5)	73 (19.6)	94 (25.7)
Decreased peak expiratory flow rate	38 (10.4)	49 (13.1)	44 (12.0)
Nasopharyngitis/rhinopharyngitis	29 (7.9)	34 (9.1)	34 (9.3)
Viral respiratory tract infection	16 (4.4)	14 (3.8)	22 (6.0)
Respiratory tract infection	14 (3.8)	11 (2.9)	20 (5.5)
Females			
Subjects	195	186	206
Any AEs	88 (45.1)	96 (51.6)	109 (52.9)
Drug-related AEs	2 (1.0)	1 (0.5)	3 (1.5)
AEs leading to discontinuation	0	0	2 (1.0)
Serious AEs	3 (1.5)	2 (1.1)	9 (4.4)
AEs reported in ⩾5% and ⩾10 patients[#]			
Asthma exacerbation/worsening	35 (17.9)	42 (22.6)	49 (23.8)
Decreased peak expiratory flow rate	17 (8.7)	15 (8.1)	24 (11.7)
Nasopharyngitis/rhinopharyngitis	15 (7.7)	12 (6.5)	15 (7.3)
Viral respiratory tract infection	11 (5.6)	10 (5.4)	8 (3.9)

Data are presented as n or n (%). Percentages are calculated using total number of patients per treatment as the denominator. [#]: in at least one treatment group.

group (including those using the valved holding chamber) have previously been shown to be comparable with results from 6–17-year-old groups when adjusted for body size, indicating adequacy of systemic exposure to tiotropium [29].

Efficacy data suggest that tiotropium is an effective add-on to ICS, with or without additional controller therapies, in children and adolescents with asthma [16–19, 22, 23]. The results of this pooled analysis provide additional evidence of the favourable safety profile of tiotropium in children and adolescents with symptomatic asthma (aged 1–17 years) [28, 29].

An important finding is that AEs related to asthma symptoms and exacerbations were reported by fewer patients in the tiotropium 5 µg treatment group compared with the placebo, with particular effect in reducing spring and autumn seasonal peaks. While reported as a safety parameter, this signal may also be considered in terms of efficacy, particularly in very young children with asthma, where validated tools for the assessment of efficacy in clinical trials are currently limited [23]. It is interesting to note that this effect

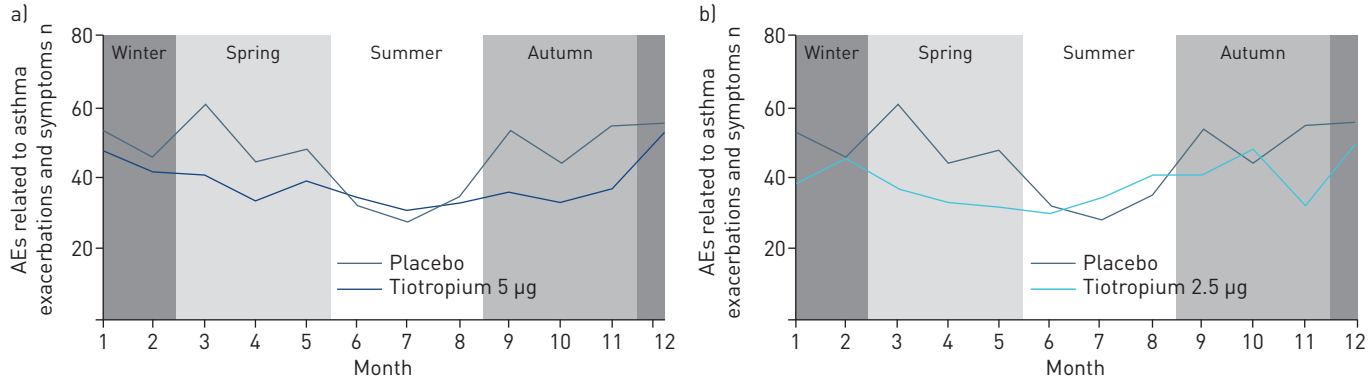

FIGURE 1 Number of reported adverse events (AEs) related to asthma exacerbations and symptoms over 12 months in the pooled population. a) Tiotropium 5 µg and placebo groups. b) Tiotropium 2.5 µg and placebo groups. Data from the Southern hemisphere shifted by 6 months to align the seasons (Northern hemisphere: June=month 6; Southern hemisphere: December=month 6).

with tiotropium added to ICS/LABA has been observed with other interventions, including ICS/LABA combinations [30] and biologicals [31]. As long-term asthma exacerbation trials in paediatric patients remain ethically challenging, this analysis highlights an alternative end-point to investigate such efficacy in children. These data also highlight the importance of trial timing to account for seasonal exacerbation peaks when a 12-month study length is not practical. However, since this finding is exploratory, it should be confirmed in a predefined study that could also investigate which age subgroup had the greatest benefit.

Reported class effects of anticholinergics include upper respiratory tract infections, tachycardia, dry mouth and other gastrointestinal complications, as well as urinary retention and urinary tract infections [32–35]. The incidence of patients reporting these AEs was low in the present analysis and, overall, the safety profile of tiotropium was comparable with placebo in all trials reported here [29]. Notably, cardiac events were reported by only two patients and they were both in the placebo group.

Within analyses of population subgroups defined by age, asthma severity, sex and LABA/LTRA use at baseline, the proportions of patients reporting AEs and SAEs were generally comparable between treatment groups, including placebo. This is further supported by a recent systematic review of the efficacy and safety of tiotropium in children aged 6–11 years with symptomatic moderate-to-severe asthma [36]. The authors concluded that none of the three studies included in the analysis (two of which are included in the analysis presented here) showed an increase in the rate of AEs or SAEs reported in the tiotropium group compared with placebo [36].

A major strength of this analysis is that all the trials were placebo controlled with comparable design and therefore provide the most valid comparison for assessing AEs. Furthermore, all patients continued to receive their usual maintenance therapies (except for LABA in patients with moderate asthma), allowing investigation of tiotropium in varied settings of concurrent medications and thereby making it as representative of treatment in a real-world setting as is achievable in a clinical trial setting. The patient sample was very large and covered a wide age range; patients were recruited from various populations and geographical locations, including a high proportion of Latin American patients (a population noted to have a high incidence and a higher severity of childhood asthma). Limitations of our pooled analysis included the difference in duration of the five included trials (two at 48 weeks and three at 12 weeks) and that none were >48 weeks.

Conclusions

Once-daily tiotropium as add-on to at least ICS maintenance treatment in patients aged 1–17 years with symptomatic asthma at different GINA treatment steps is an addition to current treatment options, with a safety and tolerability profile comparable with that of placebo. No new safety signals were identified in this comprehensive analysis, which supports the favourable risk–benefit profile of once-daily tiotropium as add-on to maintenance ICS with or without additional controllers in paediatric patients with symptomatic asthma. Moreover, a reduction in patients reporting AEs related to asthma exacerbations and asthma symptoms was observed with tiotropium 5 μg, especially related to seasonal peaks in exacerbations.

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