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Early View

Original article

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Tiotropium add-on therapy is safe and reduces seasonal worsenings 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

Plain Language Summary

Tiotropium is an option for maintenance treatment of children and adolescents with asthma. We looked at the safety of tiotropium in almost 1700 children and adolescents with asthma. We found that patients who added tiotropium to their usual asthma treatments reported fewer side effects than those who did not. This was true for patients in different gender, age, or disease severity groups. We noted that patients who were adding tiotropium to their other asthma treatments had fewer asthma-related events, especially in spring and autumn.

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 randomized, 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%), 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 gender. 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.

Clinical Trial Registration

NinoTinA-asthma® (NCT01634113), CanoTinA-asthma® (NCT01634139), VivaTinA-asthma® (NCT01634152), RubaTinA-asthma® (NCT01257230), PensieTinA-asthma® (NCT01277523).

Introduction

Asthma is one of the most prevalent chronic diseases in children and adolescents, affecting approximately 10% of children and adolescents in the UK and USA [1–3]. Studies have shown that over 50% of 4–18-year-old patients with asthma remain symptomatic despite treatment with at least 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, 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 under 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 cognizant [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 program 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 Respimat® is indicated for once-daily use in the EU (two inhalations of 2.5 μg) and the US (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 and efficacy 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 program of tiotropium in asthma. All trials were of randomized, 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).

Trial medication

During the treatment period in all trials, patients received tiotropium (5 µg or 2.5 µg) or placebo (delivered by Respimat® 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 (Trudell Medical International, Ontario, 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 mouth piece, depending on preference.

Endpoints

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 endpoint was improvement in forced expiratory volume in 1 second, 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 endpoint, 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 Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. See the online supplement for further details and definitions of AEs and serious AEs (SAEs).

A composite endpoint, 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 Table E1 in the online supplement.

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

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 randomized 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 was 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 and 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 and five patients receiving placebo) and appendicitis (two patients receiving tiotropium 5 µg, two patients receiving tiotropium 2.5 µg and 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 and viral respiratory tract infection (Table 3; AEs reported by ≥2% of patients shown in Table E2 in the online supplement). 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 endpoint, 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 [RR] over placebo 0.76 [95% confidence interval (CI) 0.63–0.93]; tiotropium 2.5 µg: 195 patients with event [34.9%], RR over placebo 0.87 [95% CI 0.72–1.05]). Description of safety topics of interest is available in the online supplement.

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 Table E3 in the online supplement). 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 Table E4 in the online supplement.

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 vs. 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 randomization 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 gender

In an analysis of AEs by gender, 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 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 Figure E1 in the online supplement.

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 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 (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 with tiotropium added to ICS/LABA has been observed with other interventions, including ICS/LABA combinations [30] and biologics [31]. As long-term asthma exacerbation trials in paediatric patients remain ethically challenging, this analysis highlights an alternative endpoint 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, gender 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 longer than 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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Author contributions: M. Engel and P. Moroni-Zentgraf are employees of Boehringer Ingelheim, and were involved in the study design, data analysis and its interpretation. G. El Azzi was an employee of Boehringer Ingelheim during the time of the study and manuscript development and was involved in the data analysis and interpretation. GEA is currently an employee of AstraZeneca. S. Vulcu is an employee of Boehringer Ingelheim and was involved in the data analysis and interpretation. All authors were involved in the writing of the manuscript and the decision to submit the manuscript for publication.

Conflict of interest: C. Vogelberg reports study-related payments to their institution from Boehringer Ingelheim, during the conduct of the study, and personal fees for advisory boards and lectures from Boehringer Ingelheim and Novartis, outside the submitted work. S. Szefler has consulted for Aerocrine, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo,

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Table 1. Overview of study designs and key inclusion/exclusion criteria

	NinoTinA-asthma®[23] **NCT01634113**	**CanoTinA-asthma®[21] NCT01634139**	**VivaTinA-asthma®[20] NCT01634152**	**RubaTinA-asthma®[17] NCT01257230**	**PensieTinA-asthma®[18] NCT01277523**
Phase and design*	**Phase 2/3**	**Phase 3, randomized, double-blind, placebo-controlled, parallel group**			
Objectives	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	**N/A**	**≥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	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 budesonide or equivalent dose), with or without another controller, for ≥4 weeks before screening; LABA had to be discontinued ≥24 hours prior to screening	High-dose ICS (>400 µg/day budesonide or equivalent dose) plus ≥1 controller or medium-dose ICS (200–400 µg/day budesonide or equivalent dose) plus ≥2 controllers for ≥4 weeks before screening	Medium-dose ICS (400–800 µg/day budesonide or equivalent dose), with or without LTRA, for ≥4 weeks before screening; LABA had to be discontinued ≥72 hours prior to screening	High-dose ICS (800–1600 µg/day budesonide or equivalent dose) plus ≥1 controller or medium-dose ICS (400–800 µg/day budesonide or equivalent dose) plus ≥2 controllers for ≥4 weeks before screening
Pre-bronchodilator FEV_1 percent predicted normal at screening	≤90% for 5-year-olds	60–90%	60–90%	60–90%	60–90%
FEV_1 reversibility at screening	–	≥12%, 15–30 minutes after 200 µg salbutamol		≥12% and ≥200 mL, 15–30 minutes after 400 µg salbutamol (age >14 years) or ≥12% only (age 12–14 years)	
Variability of absolute FEV_1 from screening to randomization[†]	–	±30%	±30%	±30%	±30%

Smoking history	–	–	–	Non-smoker or ex-smoker who stopped smoking ≥1 year prior to enrolment	
Exclusion criteria	**Significant disease other than asthma**				
Treatment	Once-daily tiotropium Respimat® (5 µg or 2.5 µg) or placebo Respimat®‡	Once-daily tiotropium Respimat® (5 µg or 2.5 µg) or placebo Respimat®	Once-daily tiotropium Respimat® (5 µg or 2.5 µg) or placebo Respimat®	Once-daily tiotropium Respimat® (5 µg or 2.5 µg) or placebo Respimat®	Once-daily tiotropium Respimat® (5 µg or 2.5 µg) or placebo Respimat®
Treatment duration	12 weeks	48 weeks	12 weeks	48 weeks	12 weeks
Sample size	102 randomized patients (101 treated, 102 planned); 101 completed patients	403 randomized patients (401 treated, 385 planned); 384 completed patients	401 randomized patients (400 treated, 375 planned); 392 completed patients	398 randomized patients (397 treated, 127 planned per group); 376 completed patients	392 randomized patients (392 treated, 375 planned); 388 completed patients

*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 [23], patients aged 1–4 years at Visit 1 were required to use an Aerochamber Plus® Flow-Vu® valved holding chamber (Trudell Medical International, London, Ontario, Canada), commonly referred to as a spacer, with a face mask for the inhalation of trial medication to reduce variability and ensure standardized dosing. Children aged 5 years at Visit 1 were permitted to use the Respimat® without a spacer. Overall, three patients did not use a spacer.

Definition of abbreviations: ACQ = Asthma Control Questionnaire; ACQ-IA = interviewer-administered Asthma Control Questionnaire; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LTRA = leukotriene receptor antagonists; N/A = not applicable.

Table 2. Overview of baseline demographics and disease characteristics

Demographic/characteristic	**NinoTinA-asthma® (N=101)**	**CanoTinA-asthma® (N=401)**	**VivaTinA-asthma® (N=400)**	**RubaTinA-asthma® (N=397)**	**PensieTinA-asthma® (N=392)**
Male, n (%)	61 (60.4)	264 (65.8)	279 (69.8)	258 (65.0)	242 (61.7)
Age, years, median (range)	3.0 (1–5)	9.0 (6–11)	9.0 (6–11)	14.0 (11–17)	14.0 (12–17)
Race, n (%)					
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 Isle	0	0	0	0	0
Ethnicity, n (%)					
Hispanic/Latino	0	55 (13.7)	72 (18.0)	42 (10.6)	68 (17.3)
Never smoked, n (%)	–	–	–	396 (99.7)	392 (100)
No exposure to second-hand smoke, n (%)	92 (91.1)	372 (92.8)	369 (92.3)	353 (88.9)	367 (93.6)
Age at onset of asthma, years, mean ± SD	1.5 ± 1.2	4.7 ± 2.4	4.1 ± 2.4	6.5 ± 4.1	6.5 ± 3.9
Duration of asthma, years, median (range)	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, n (%)					
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 percent predicted, mean ± SD	–	84.06 ± 10.79	81.64 ± 11.45	82.79 ± 10.56	79.52 ± 11.49
FEV_1 percent reversibility, mean ± SD	–	26.48 ± 12.41	27.43 ± 13.43	26.80 ± 12.86	29.19 ± 14.26
ACQ score, mean ± SD*	—	1.868 ± 0.31	1.966 ± 0.36	2.03 ± 0.43	2.13 ± 0.43
Concomitant therapies at baseline, n (%)				33 (8.3)	
LTRAs	41 (40.6)	107 (26.7)	339 (84.8)	1 (0.3)	315 (80.4)
LABAs	8 (7.9)	1 (0.2)	313 (78.3)		324 (82.7)
ICS dose of stable maintenance treatment (µg; budesonide or equivalent dose), mean ± SD	255.2 ± 187.4	310.0 ± 112.0	457.4 ± 236.0	539.4 ± 292.7	747.0 ± 357.7

Treated set.

*ACQ-IA in CanoTinA-asthma® and VivaTinA-asthma®.

Definition of abbreviations: ACQ = Asthma Control Questionnaire; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LTRA = leukotriene receptor antagonists; SD = standard deviation.

Table 3. Overview of patients reporting AEs in the pooled population

	Tiotropium Respimat® 5 µg	**Tiotropium Respimat® 2.5 µg**	**Placebo Respimat®**
n (%)	**n=560**	**n=559**	**n=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)
SAEs	10 (1.8)	8 (1.4)	13 (2.3)
AEs reported in ≥5% of 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)

Treated set. Treatment + 30 days. Percentages are calculated using total number of patients per treatment as the denominator. *In at least one treatment group.
Definition of abbreviations: AE = adverse event; SAE = serious AE.

Table 4. Overview of patients reporting AEs by age subgroups

	Tiotropium Respimat® 5 µg	**Tiotropium Respimat® 2.5 µg**	**Placebo Respimat®**
1–5 years [23]**, n (%)**	**n=31**	**n=36**	**n=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
SAEs	0	0	3 (8.8)
AEs reported in ≥5% and ≥10 patients[†]			
Asthma exacerbation/worsening	2 (6.5)	5 (13.9)	10 (29.4)
6–11 years [21, 22]**, n (%)**	**n=265**	**n=271**	**n=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)
SAEs	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)
12–17 years [18, 19]**, n (%)**	**n=264**	**n=252**	**n=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)
SAEs	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)

Treated set. Treatment + 30 days. Percentages are calculated using total number of patients per treatment as the denominator.

[*] In at least one treatment group.

Definition of abbreviations: AE = adverse event; SAE = serious AE.

Table 5. Overview of patients reporting AEs in subgroups by asthma severity

	Tiotropium Respimat® 5 µg	**Tiotropium Respimat® 2.5 µg**	**Placebo Respimat®**
Moderate asthma [18, 22]**, n (%)**	**n=269**	**n=260**	**n=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)
SAEs	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], **n (%)**	**n=260**	**n=263**	**n=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)
SAEs	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	20 (7.7)	24 (9.1)	33 (12.3)

rate			
Nasopharyngitis/rhinopharyngitis	11 (4.2)	11 (4.2)	14 (5.2)

Treated set. Treatment + 30 days. Percentages are calculated using total number of patients per treatment as the denominator. [*]In at least one treatment group.
Definition of abbreviations: AE = adverse event; SAE = serious AE.

Table 6. Overview of patients reporting AEs in subgroups by gender

	Tiotropium Respimat® 5 µg	**Tiotropium Respimat® 2.5 µg**	**Placebo Respimat®**
Male, n (%)	**n=365**	**n=373**	**n=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)
SAEs	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)
Female, n (%)	**n=195**	**n=186**	**n=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)
SAEs	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	17 (8.7)	15 (8.1)	24 (11.7)

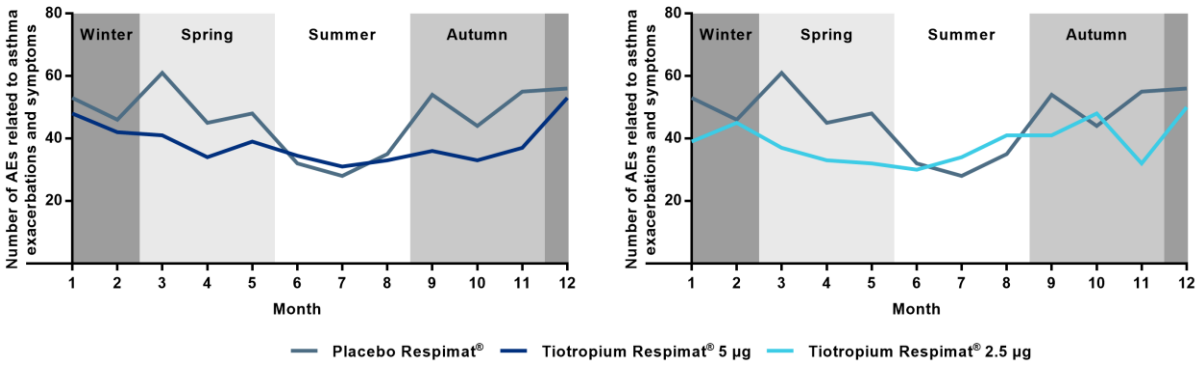
rate			
Nasopharyngitis/rhinopharyngitis	15 (7.7)	12 (6.5)	15 (7.3)
Viral respiratory tract infection	11 (5.6)	10 (5.4)	8 (3.9)

Treated set. Treatment + 30 days. Percentages are calculated using total number of patients per treatment as the denominator. [*]In at least one treatment group.
Definition of abbreviations: AE = adverse event; SAE = serious AE.

Figure legends

Figure 1. Number of reported adverse events related to asthma exacerbations and symptoms over 12 months in the pooled population – tiotropium 5 µg and placebo group (left), tiotropium 2.5 µg and placebo group (right)

Data from the Southern hemisphere shifted by 6 months to align the seasons (Northern hemisphere: June = Month 6; Southern hemisphere: December = Month 6).



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

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Supplementary Material

Supplementary Methods

Definition of an adverse event

An adverse event (AE) was defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition; the event did not necessarily have to have a causal relationship with this treatment. For each AE, the investigator was asked to provide the start 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 characterized. A drug-related AE was defined as an AE for which there was a reasonable causal relationship between the randomized 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, concomitant diseases and relevant history). A serious AE (SAE) was defined as any AE that resulted in death, was immediately life-threatening, resulted in persistent or significant disability/incapacity, required or prolonged patient hospitalization, was a congenital anomaly/birth defect, or was to be deemed serious for any other reason that might have jeopardized the patient and

might have required medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Supplementary Results

Safety topics of interest

The incidence of patients with dry mouth – a common side effect associated with anticholinergic therapies – was low and comparable between treatment groups, including placebo: dry mouth was reported in one patient receiving tiotropium 5 µg, one patient receiving tiotropium 2.5 µg and two patients receiving placebo. Dry mouth did not lead to treatment discontinuation in any of these cases.

Cough was also reported infrequently, and the number of patients reporting was comparable between the tiotropium and placebo groups (five patients receiving tiotropium 5 µg, ten patients receiving tiotropium 2.5 µg and 13 patients receiving placebo). Cough did not lead to treatment discontinuation in any of the cases in the tiotropium treatment groups.

Urinary retention was not reported in any patients, and constipation, another potential class effect event, was only reported by one patient in the placebo group. Cardiac events (metabolic cardiomyopathy and palpitations) were reported by two patients in the placebo group. Eye disorders (allergic conjunctivitis, eye/eyelid pruritus and myopia), another potential class effect, were infrequent and only reported by three patients receiving tiotropium 5 µg, two patients receiving tiotropium 2.5 µg and four patients receiving placebo. Eye disorders did not lead to treatment discontinuation in any of these cases.

Supplementary tables

Table E1. MedDRA-preferred terms included in composite endpoint analysis for patients reported with adverse events related to asthma exacerbations and asthma symptoms

Allergic bronchitis	Pneumocystis jirovecii pneumonia
Allergic cough	Pneumonia
Allergic respiratory symptom	Pneumonia adenoviral
Asthma	Pneumonia anthrax
Asthma exercise induced	Pneumonia bacterial
Asthma prophylaxis	Pneumonia blastomyces
Asthma–chronic obstructive pulmonary disease overlap syndrome	Pneumonia bordetella
	Pneumonia chlamydial
Asthmatic crisis	Pneumonia cryptococcal
Atypical mycobacterial pneumonia	Pneumonia cytomegaloviral
Atypical pneumonia	Pneumonia escherichia
Breathing-related sleep disorder	Pneumonia fungal
Bronchitis	Pneumonia haemophilus
Bronchitis bacterial	Pneumonia helminthic
Bronchitis chronic	Pneumonia herpes viral
Bronchitis fungal	Pneumonia influenzal
Bronchitis haemophilus	Pneumonia klebsiella
Bronchitis moraxella	Pneumonia legionella
Bronchitis pneumococcal	Pneumonia measles
Bronchitis viral	Pneumonia moraxella
Bronchospasm	Pneumonia mycoplasmal
Bronchospasm paradoxical	Pneumonia necrotizing
Chest discomfort	Pneumonia parainfluenzae viral
Chest pain	Pneumonia pneumococcal
Congenital pneumonia	Pneumonia pseudomonal
Cough	Pneumonia respiratory syncytial viral
Dyspnoea	Pneumonia salmonella
Dyspnoea at rest	Pneumonia staphylococcal
Dyspnoea exertional	Pneumonia streptococcal
Dyspnoea paroxysmal nocturnal	Pneumonia toxoplasmal
Dyssomnia	Pneumonia tularaemia
Embolic pneumonia	Pneumonia viral
Enterobacter pneumonia	Poor quality sleep
Fatigue	Post procedural pneumonia
Fibrinous bronchitis	Productive cough
Herpes simplex pneumonia	Prolonged expiration
Hyposomnia	Psychogenic respiratory distress
Hypoventilation	Reactive airways dysfunction

Increased bronchial secretion	syndrome
Increased viscosity of bronchial secretion	Respiration abnormal
Infective exacerbation of chronic obstructive airways disease	Respiratory depth increased
	Respiratory distress
Initial insomnia	Respiratory fatigue
Insomnia	Respiratory tract infection
Lethargy	Respiratory tract infection viral
Lower respiratory tract infection	Sinobronchitis
Lung hypoinflation	Sluggishness
Lung infection	Sputum discoloured
Lung infection pseudomonal	Sputum purulent
Middle insomnia	Status asthmaticus
Miliary pneumonia	Tachypnoea
Neonatal pneumonia	Terminal insomnia
Nocturnal dyspnoea	Tracheobronchitis
Noninfective bronchitis	Upper-airway cough syndrome
Obstructive airways disorder	Varicella zoster pneumonia
Orthopnoea	Wheezing
Peak expiratory flow rate	
Peak expiratory flow rate abnormal	
Peak expiratory flow rate decreased	

AEs were coded using MedDRA version 18.1**.**

Definition of abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Table E2. AEs reported by ≥2% patients by preferred term in patients aged 1–17 years

	Tiotropium Respimat® 5 µg	**Tiotropium Respimat® 2.5 µg**	**Placebo Respimat®**
Total with AEs, n (%)	**283 (50.5)**	**286 (51.2)**	**310 (54.2)**
Asthma	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 (viral)	27 (4.8)	24 (4.3)	30 (5.2)
Headache	14 (2.5)	18 (3.2)	10 (1.7)
Allergic rhinitis	10 (1.8)	14 (2.5)	16 (2.8)
Pharyngitis	8 (1.4)	14 (2.5)	14 (2.4)
Bronchitis	8 (1.4)	13 (2.3)	8 (1.4)
Cough	5 (0.9)	10 (1.8)	13 (2.3)

Definition of abbreviations: AE = adverse event.

Table E3. Patients reporting SAEs by preferred term in subgroups by age

	Tiotropium Respimat® 5 µg	**Tiotropium Respimat® 2.5 µg**	**Placebo Respimat®**
1–5 years, n (%) [1]	**n = 31**	**n = 36**	**n = 34**
Appendicitis	0	0	1 (2.9)
Upper respiratory tract infection	0	0	1 (2.9)
Bronchopneumonia	0	0	1 (2.9)
6–11 years [2,3]	**n = 265**	**n = 271**	**n = 265**
Appendicitis	1 (0.4)	1	0
Appendicitis and paralytic ileus	1 (0.4)	0	0
Asthma	3 (1.1)	3 (1.1)	3 (1.1)
Asthmatic crisis	0	0	1 (0.4)
Gastroenteritis	0	0	1 (0.4)
Renal abscess	0	0	1 (0.4)
Concussion, fall, haematoma and skull fracture	0	0	1 (0.4)
Anaphylactic reaction	0	0	1 (0.4)
Epilepsy	0	1	0
12–17 years [4,5]	**n = 264**	**n = 252**	**n = 273**
Appendicitis	0	1 (0.4)	0

Asthma	2 (0.8)	0	0
Allergy to plants/anaphylactic reaction	1 (0.4)	0	0
Abdominal pain	1 (0.4)	0	0
Atopic dermatitis and pyoderma	0	1 (0.4)	0
Ligament sprain	1 (0.4)	0	0
Multiple injuries	0	1 (0.4)	0
Gastroenteritis	0	0	1 (0.4)
Teratoma	0	0	1 (0.4)

Treated set. Treatment + 30 days. Percentages are calculated using total number of patients per treatment as the denominator.
Definition of abbreviations: SAE = serious adverse event.

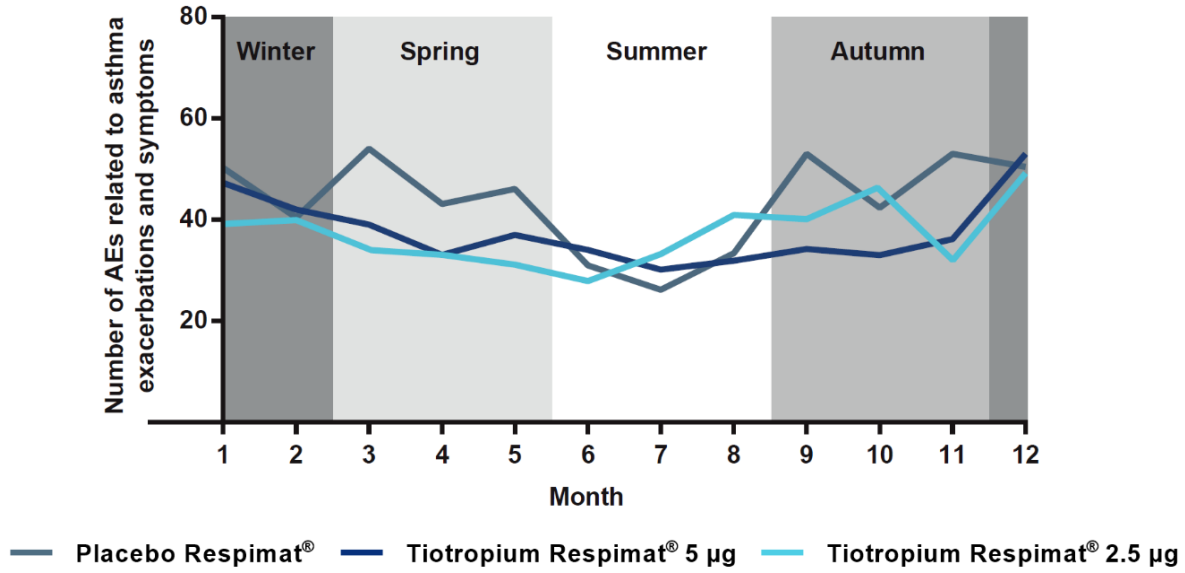
Table E4. Overview of patients reporting AEs by preferred term in the pooled population aged 6–17 years (excluding patients aged 1–5 years)

	Tiotropium Respimat® 5 µg	**Tiotropium Respimat® 2.5 µg**	**Placebo Respimat®**
n (%)	**n = 529**	**n = 523**	**n = 538**
Any AEs	265 (50.1)	266 (50.9)	285 (53.0)
Drug-related AEs	5 (0.9)	1 (0.2)	6 (1.1)
AEs leading to discontinuation	2 (0.4)	0	5 (0.9)
SAEs	10 (1.9)	8 (1.5)	10 (1.9)
AEs reported in ≥5% of patients[*]			
Asthma exacerbation/worsening	108 (20.4)	110 (21.0)	133 (24.7)
Decreased peak expiratory flow rate	55 (10.4)	64 (12.2)	68 (12.6)
Respiratory tract infection	19 (3.6)	17 (3.3)	28 (5.2)

Treated set. Treatment + 30 days. Percentages are calculated using total number of patients per treatment as the denominator. [*]In at least one treatment group
Definition of abbreviations: AE = adverse event; SAE = serious AE.

Supplementary Figures

Figure E1. Number of reported AEs related to asthma exacerbations and symptoms over 12 months in the pooled population aged 6–17 years, (excluding patients aged 1–5 years)



Data from the Southern hemisphere shifted by 6 months to align the seasons (Northern hemisphere: June = Month 6; Southern hemisphere: December = Month 6).

Supplementary references

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3. Vogelberg C, Engel M, Laki I, Bernstein JA, Schmidt O, El Azzi G, Moroni-Zentgraf P, Sigmund R, Hamelmann E. Tiotropium add-on therapy improves lung function in children with symptomatic moderate asthma. *J Allergy Clin Immunol Pract* 2018; [Epub ahead of print].

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