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Tiotropium in asthmatic adolescents symptomatic despite inhaled corticosteroids: A randomised dose-ranging study

Christian Vogelberg [a,*], Michael Engel [b], Petra Moroni-Zentgraf [b], Migle Leonaviciute-Klimantaviciene [c], Ralf Sigmund [d], John Downie [e], Katja Nething [d], Viktorija Vevere [f], Mark Vandewalker [g]

[a] Technische Universität Dresden, University Hospital Carl Gustav Carus, Department of Pediatric Pneumology and Allergology, Fetscherstraße 74, 01307 Dresden, Germany
[b] Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Straße 173, 55218 Ingelheim am Rhein, Germany
[c] Vilnius University Hospital, Santariskiu 7, Vilnius LT-08406, Lithuania
[d] Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Straße 65, 88400 Biberach an der Riss, Germany
[e] Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Rd, Ridgefield, CT 06877, USA
[f] Private Practice, 18th Street November 21, Rēzekne LV4601, Latvia
[g] Clinical Research of the Ozarks, 601 W Nifong Blvd, Suite 2A, Columbia, MO 65203, USA

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Summary
Introduction: Tiotropium, a once-daily long-acting anticholinergic agent, has been shown to be an efficacious and safe add-on treatment for adults with symptomatic asthma, despite treatment with inhaled corticosteroids (ICS). A large proportion of asthmatic adolescents have symptomatic disease despite a wide range of therapeutic options. We investigated the efficacy and safety of three doses of tiotropium, administered in the evening (via Respimat® SoftMist™ inhaler), versus placebo in asthmatic adolescents symptomatic despite ICS treatment.
Methods: This randomised, double-blind, placebo-controlled, incomplete crossover study evaluated once-daily tiotropium 5 µg, 2.5 µg and 1.25 µg versus placebo in three 4-week treatment periods. Primary efficacy end point was change in peak forced expiratory volume in 1 s within 3 h post-dose from baseline (peak $FEV_{1(0-3h)}$).

* Corresponding author. Tel.: +49 (0) 351 458 5699; fax: +49 (0) 351 458 4334.
E-mail address: christian.vogelberg@uniklinikum-dresden.de (C.Vogelberg).

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Results: From 139 enrolled patients, 105 were randomised to receive one of four treatment sequences. Peak $FEV_{1(0-3h)}$ response for tiotropium 5 μg was significantly greater versus placebo ($p = 0.0043$). Trough FEV_1 responses were significantly greater for tiotropium 5 μg ($p < 0.00001$) and 1.25 μg ($p = 0.0134$) versus placebo, but not for 2.5 μg ($p = 0.0975$), while FEV_1 area under the $curve_{(0-3h)}$ responses were significant for all doses ($p = 0.00001$—0.0398). Overall incidence of adverse events was balanced across treatment groups, with no dose-dependent observations. The majority of adverse events were mild to moderate in intensity.
Conclusion: This first study of tiotropium in adolescents with symptomatic asthma demonstrates that tiotropium is well tolerated and efficacious as add-on to maintenance treatment with ICS.

ClinicalTrials.gov identifier; NCT01122680.

Introduction

Asthma affects 1—18% of the global population [1] and is linked to approximately one in every 250,000 deaths worldwide, many of which are preventable [1]. It is one of the leading causes of childhood morbidity in developed countries [2]. In the USA, it has been estimated that 10% of children aged 12—18 years have asthma, with over half of these patients having symptomatic disease [3]. There are various reasons for this, including: poor adherence to treatment, regarded as most relevant within this specific age group; lack of responsiveness to treatment; genetic components; and misdiagnoses [4,5]. Therefore, a need remains for alternative and potentially improved treatment options that may help to overcome some of these limitations [4].

At least 40% of patients with asthma remain symptomatic despite treatment with inhaled corticosteroids (ICS) as monotherapy or in combination with long-acting β_2-agonists (LABAs) [6—8]. The common treatment approach for these patients is a dose increase of ICS, with additional medications such as LABAs, leukotriene modifiers, sustained-release methylxanthines, oral glucocorticosteroids or anti-immunoglobulin E prescribed according to individual needs, as outlined in the National Asthma Education and Prevention Program guidelines [9]. However, the high proportion of asthmatic patients who do not achieve control with these medications suggests there is a need for alternative additional treatments, such as bronchodilator maintenance therapy added to ICS.

A meta-analysis of 10 randomised, double-blind, controlled studies of asthmatic patients with severe exacerbations demonstrated that the short-acting anticholinergic bronchodilator ipratropium bromide, as add-on therapy to short-acting β_2-agonists, improves lung function and reduces hospital admissions [10]. The long-term management of asthma by ipratropium bromide has not been fully elucidated, but global guidelines recommend short-acting anticholinergic bronchodilators, in combination with short-acting β_2-agonists, as reliever medication for asthmatic patients [1].

The long-acting anticholinergic bronchodilator tiotropium bromide has demonstrated efficacy and tolerability as a once-daily dose in adult patients with chronic obstructive pulmonary disease [11,12]. More recently in two proof-of-concept studies, treatment with once-daily tiotropium 5 μg (via the Respimat® SoftMist™ inhaler [Boehringer Ingelheim, Ingelheim am Rhein, Germany], hereinafter referred to as tiotropium Respimat®) for 8—16 weeks improved lung function in patients with symptomatic asthma despite receiving ICS with or without LABAs [13,14]. Furthermore, in two replicate placebo-controlled, Phase III studies, once-daily tiotropium Respimat® 5 μg has been shown to reduce the risk of exacerbations and improve lung function in adult patients with symptomatic asthma despite the use of ICS plus LABAs [15].

To date, no study data have been published describing the pharmacology, efficacy or safety of tiotropium Respimat® add-on to at least ICS maintenance therapy in children or adolescents with asthma. Lung function and safety findings are presented here from the first study of tiotropium Respimat® add-on therapy to ICS with or without leukotriene modifiers in adolescents with symptomatic asthma.

Methods

Study design

This randomised, double-blind, placebo-controlled, dose-ranging, Phase II, incomplete crossover study was conducted at 19 centres in five countries (Germany, Latvia, Lithuania, Slovenia and the USA) from June 2010 to April 2011. After a 4-week run-in period, patients aged 12—17 years with moderate persistent asthma on medium-dose ICS were randomised in a 1:1:1:1 ratio to receive once-daily placebo or tiotropium 5 μg, 2.5 μg or 1.25 μg, all delivered via the Respimat® SoftMist™ inhaler, every evening during each of the three 4-week treatment periods (for a total of 12 weeks, without washout between treatment periods) according to an incomplete crossover design (Fig. 1). Clinic visits were scheduled at screening (Visit 0), prior to the 4-week run-in period (Visit 1), every 4 weeks during the 12-week treatment period (Visits 2—5) and at the end of the 3-week follow-up period (Visit 6). Background medium-dose ICS with or without leukotriene receptor antagonists were taken throughout the study with no change in dose. Patients receiving ICS plus LABA discontinued the LABA prior to the run-in period. Open-label short-acting β_2-agonist salbutamol

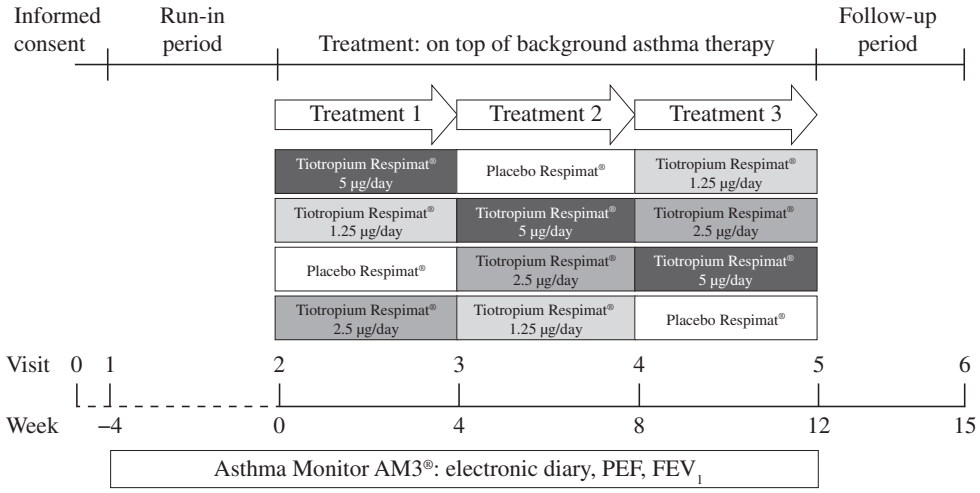

Figure 1 Study design. FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow.

(albuterol) hydrofluoroalkane metered-dose inhaler (100 µg per puff) was provided as rescue medication for use during the study. Patients receiving placebo Respimat® continued with background ICS with or without leukotriene receptor antagonists throughout the study, and salbutamol was provided as rescue medication. At both screening and randomisation, patients were trained in the correct use of the Respimat® SoftMist™ inhaler using placebo inhalation solution, and on all lung function test days, trial medication was administered under the supervision of a clinician.

A fixed block randomisation was used to ensure that the number of patients allocated to each treatment was balanced. The order of assignment of patients to treatment sequences at Visit 2 was also randomised. The randomisation list was generated by Boehringer Ingelheim using a validated system with a pseudo-random number generator and a supplied seed number.

The study met all local legal and regulatory requirements, followed the Declaration of Helsinki and conformed to Good Clinical Practice guidelines. All patients and their parents/legal guardians gave written, informed consent prior to enrolment into the study. The protocol was approved by an independent ethics committee at each study centre. The study was registered at www.clinicaltrials.gov (NCT01122680).

Study population

Male and female outpatients aged 12—17 years with a documented minimum 3-month history of asthma were eligible for enrolment into this study. All patients were symptomatic as defined by a seven-question Asthma Control Questionnaire (ACQ-7) mean score of $\geq$1.5 at screening (Visit 1) and prior to randomisation (Visit 2), had a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) >60% and $\leq$90% of the predicted normal [16], and had an FEV_1 increase of at least 12% and 200 mL from baseline 15—30 min after 400 µg salbutamol at Visit 1. In patients aged 12—14 years, who are likely to have a smaller forced vital capacity, positive reversibility testing could be based solely on the relative ($\geq$12%) post-bronchodilator response. Eligible patients were non-smokers or had not smoked in the year before enrolment. Key exclusion criteria were: a significant respiratory medical condition, other than asthma (eg cystic fibrosis), or congenital heart disease; an exacerbation or acute respiratory tract infection in the 4 weeks prior to screening or during the run-in period; and treatment with a long-acting anticholinergic or systemic (oral or intravenous) corticosteroid within 4 weeks prior to screening.

Study end points and assessments

The primary efficacy end point was peak FEV_1 response within 3 h after administration of the maintenance and study drugs (peak $FEV_{1(0-3h)}$) as a change from baseline FEV_1 at the end of each of the three 4-week treatment periods. Secondary end points included: trough FEV_1 response as a change from baseline pre-dose FEV_1 at the end of each of the three 4-week treatment periods (measured just prior to the last administration of the randomisation treatment); FEV_1 area under the curve $(AUC)_{(0-3h)}$ response; and pre-dose morning and evening peak expiratory flow (PEF). As an additional exploratory end point, control of asthma was assessed by ACQ-7 at the end of each 4-week treatment period.

Lung function assessments were performed at 30 min, 1 h, 2 h and 3 h after inhalation of the study medication during clinic visits at screening, at the end of the 4-week run-in period and at the end of each 4-week treatment period. At each time point, FEV_1 was measured from a series of at least three spirometric manoeuvres that included an acceptable test start and were free from artefacts such as coughing, and the highest FEV_1 from an acceptable manoeuvre was recorded. Spirometers and their use, including daily calibration, were required to meet American Thoracic Society criteria. FEV_1 and PEF were measured using the Asthma Monitor® (AM3®; eResearch Technology GmbH, Estenfeld, Germany), which was also used by patients as an e-diary. PEF means were determined in the last week of each treatment period to avoid carry-over of previous treatment effects. Patients completed ACQ-7 at Visit 1 and then at every visit during the treatment period. It comprised six questions for the patient and one question on FEV_1 for the clinic personnel [17].

Treatment compliance was assessed throughout the study based on the recorded information in the AM3® device and calculated as the number of AM3® entries indicating study medication uptake divided by the number of non-clinic days on treatment then multiplied by 100%.

The analysis of safety and tolerability was descriptive in nature, and measured based on the incidence and intensity of adverse events (AEs) and changes in 12-lead electrocardiogram (assessed during screening and at the end of the treatment period), physical examination and vital signs, including pulse rate and seated blood pressure.

Statistical analysis

Assuming a standard deviation of 228 mL, based on adult data for within-patient difference in peak $FEV_{1(0-3h)}$ [14], a sample size of 44 completed patients was required in order to detect a treatment difference of 100 mL for the peak $FEV_{1(0-3h)}$ response with 80% power. Using the equation $n = 3*m/2$, it was determined that 66 patients would be needed for the incomplete block design used in this study [18]. It was estimated that approximately 92 patients would be required to be randomised in order to obtain 66 completer patients, allowing for a drop-out rate of almost 30%.

The primary efficacy analysis was performed using the full analysis set, defined as all randomised patients who were treated with at least one dose of study medication, had baseline data and had at least one on-treatment efficacy measurement after a 4-week treatment period. The number of patients varied between treatment groups as some patients had no evaluable data for ≥1 treatments due to premature discontinuation of the study. The primary analysis was a mixed model repeated measures analysis that included 'treatment' and 'period' as fixed effects ('period' as repeated) and 'patient' as a random effect. Study baseline was included as a covariate. Adjusted mean values were calculated, in addition to treatment contrasts, with 95% confidence intervals and *p* values.

All secondary end points were analysed using the full analysis set, unless otherwise stated, and a mixed model repeated measures analysis. All calculated *p* values were exploratory. Data are presented as adjusted mean change from baseline after 4 weeks of treatment, unless noted otherwise.

The treated set was used for safety evaluation and was defined as all randomised patients who took at least one dose of study medication.

Results

Overall, 139 adolescent patients were enrolled (see Supplementary Fig. 1). Of these patients, 105 were randomised to receive once-daily tiotropium Respimat® 5 μg ($n = 80$), 2.5 μg ($n = 75$) or 1.25 μg ($n = 75$), or placebo Respimat® ($n = 75$). The treated set therefore included all randomised patients who received at least one dose of study medication ($n = 105$). Due to premature discontinuation during either the treatment period or the study, the number of evaluable patients within the analysis sets varied between treatments.

A total of 97 patients completed all three treatment periods. Of the eight patients who prematurely discontinued study medication, two discontinued due to AEs, two due to non-compliance, one due to withdrawal of consent, one due to randomisation error, one due to an ACQ-7 score of <1.5 at Visit 2 and one as a result of patient decision. Three patients discontinued study medication while receiving tiotropium Respimat® 5 μg, one while receiving tiotropium Respimat® 2.5 μg, three while receiving tiotropium Respimat® 1.25 μg and one while receiving placebo Respimat®. Overall, median compliance ranged from 85% to 87% across the treatment groups.

Baseline demographics and disease characteristics

The baseline characteristics of all randomised patients at screening are shown in Table 1. The study population was predominantly male and white, and the mean age overall

Table 1 Baseline demographics and clinical characteristics at screening (treated set).

Characteristic	All treated patients ($n = 105$)
Gender, *n* (%)	
Male	67 (63.8)
Female	38 (36.2)
Race, *n* (%)	
White	102 (97.1)
Black/African-American	2 (1.9)
Asian	1 (1.0)
Ethnicity, *n* (%)	
Not Hispanic/Latino	104 (99.0)
Hispanic/Latino	1 (1.0)
Mean age, years (SD)[a]	14.0 (1.5)
BMI, kg/m^2 (SD)	21.0 (5.3)
Smoking history, *n* (%)	
Never smoked	104 (99.0)
Ex-smoker	1 (1.0)
Duration of asthma, *n* (%)	
<1 year	6 (5.7)
1–<3 years	24 (22.9)
3–<10 years	39 (37.1)
10–17 years	36 (34.3)
Concomitant pulmonary therapies, *n* (%)[b]	
Glucocorticoids	105 (100)
Inhaled	105 (100)
Intranasal	29 (27.6)
Oral	2 (1.9)
β_2-adrenoceptor agonists	53 (50.5)
Long-acting	46 (43.8)
Short-acting	22 (21.0)
Leukotriene modifiers	24 (22.9)
Systemic antihistamines	21 (20.0)
Anti-allergic agents (excluding corticosteroids)	11 (10.5)
Short-acting anticholinergics	2 (1.9)

BMI, body mass index; SD, standard deviation.
[a] Age range was 12–17 years.
[b] Received within the last 3 months before Visit 1.

Table 2 Disease characteristics measured during reversibility testing and at study site (treated set; $n = 105$).

	Reversibility testing (Visit 1)		Study baseline (Visit 2)
	Pre-bronchodilator[a]	Post-bronchodilator[b]	Pre-dose[c]
	Mean (SD)	Mean (SD)	Mean (SD)
FEV_1			
Predicted normal, mL	3397 (784)	–	–
Actual, mL	2642 (608)	3276 (714)	2742 (697)
Actual, % predicted normal	77.5 (6.6)	97.2 (10.5)	80.9 (10.3)
Reversibility, mL[d]	–	653 (261)	–
Reversibility, % of pre-bronchodilator[e]	–	25.6 (11.2)	–
Variation, %[f]	–	–	4.8 (13.5)
Mean PEF, L/min			
Morning	–	–	346.5 (89.5)
Evening	–	–	370.3 (91.9)
Asthma Control Questionnaire	–	–	2.1 (0.4)

FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; SD, standard deviation.
[a] Measured 10 min prior to inhalation of four puffs of salbutamol (100 µg per puff) at Visit 1.
[b] Measured 15–30 min after inhalation of four puffs of salbutamol (100 µg per puff) at Visit 1.
[c] Measured 10 min prior to inhalation of study medication at Visit 2.
[d] Calculated as: FEV_1 post-bronchodilator − FEV_1 pre-bronchodilator.
[e] Calculated as: 100 × ([FEV_1 post-bronchodilator/FEV_1 pre-bronchodilator] − 1).
[f] Calculated as: 100 × ([FEV_1 at Visit 2/post-bronchodilator FEV_1 at Visit 1] − 1).

was 14 years. One patient was an ex-smoker, but no patient smoked at randomisation. In 37.1% of patients, the duration of asthma was between 3 and 10 years. A slightly lower percentage (34.3%) of patients had an asthma duration of 10–17 years, with the remainder (28.6%) having an asthma duration of <3 years. Within 3 months before Visit 1, almost half of the study population had received LABAs, almost a quarter had received leukotriene modifiers and a fifth had received systemic antihistamines.

Following salbutamol inhalation, an overall improvement in FEV_1 values was observed from the baseline pre-bronchodilator FEV_1 value of <90% after a 4-week run-in period (Table 2). A post-bronchodilator FEV_1 >90% of the predicted normal [16] was recorded in 77.1% of patients, and 20% of patients had FEV_1 >80% but ≤90% of the predicted normal. The average reversibility, change in pre- to post-bronchodilation, was 653 mL (25.6%). At Visit 2, FEV_1 >90% of the predicted normal was reported in 18.1% of patients, 38.1% of patients had FEV_1 >80% but ≤90% of the predicted normal, 41.0% of patients had FEV_1 ≥60% but ≤80% of the predicted normal, and only 2.9% of patients had FEV_1 <60%.

Efficacy

Efficacy end points were assessed in the 104 patients included in the full analysis set. Efficacy data were not available for one patient who discontinued study medication during the first treatment period.

Primary end point

Overall, mean FEV_1 at baseline was 2746 mL. The largest adjusted mean peak $FEV_{1(0-3h)}$ response from baseline was reported with tiotropium Respimat® 5 µg (602 mL) (Fig. 2); this difference was significant compared with placebo Respimat® (113 mL; $p = 0.004$). Smaller responses in the adjusted mean peak $FEV_{1(0-3h)}$ response were associated with tiotropium Respimat® 2.5 µg and 1.25 µg (546 mL and 556 mL, respectively) compared with placebo Respimat® (489 mL). Treatment differences between tiotropium Respimat® 2.5 µg and 1.25 µg and placebo Respimat® did not reach statistical significance (57 mL [$p = 0.1484$] and 67 mL [$p = 0.0664$], respectively).

Secondary end points

Trough FEV_1 response with tiotropium Respimat® was also greater than with placebo Respimat® (adjusted mean: 5 µg, 442 mL; 2.5 µg, 353 mL; 1.25 µg, 384 mL; placebo, 292 mL) (Fig. 2). The largest response in trough FEV_1 over placebo Respimat® was observed with tiotropium Respimat® 5 µg and was statistically significant (adjusted mean of difference: 151 mL; $p < 0.0001$). Lower treatment differences were observed between tiotropium Respimat® 2.5 µg and 1.25 µg and placebo Respimat® (62 mL [$p = 0.0975$] and 92 mL [$p = 0.0134$], respectively).

The adjusted mean FEV_1 $AUC_{(0-3h)}$ response was greater for all three tiotropium Respimat® groups (5 µg, 497 mL; 2.5 µg, 434 mL; 1.25 µg, 455 mL) compared with placebo Respimat® (363 mL) (Fig. 3). The adjusted mean of difference in FEV_1 $AUC_{(0-3h)}$ response over placebo Respimat® was highest with tiotropium Respimat® 5 µg and statistically significant (133 mL; $p = 0.001$).

The maximum FEV_1 response (505 mL) was observed 1 h after tiotropium Respimat® 5 µg inhalation (Fig. 4). At 2 or 3 h after inhalation, the maximum FEV_1 response was reached in the tiotropium Respimat® 2.5 µg and 1.25 µg and placebo Respimat® groups (2.5 µg, 489 mL; 1.25 µg, 467 mL; placebo, 396 mL). FEV_1 responses following tiotropium Respimat® 5 µg were superior to placebo Respimat® at all

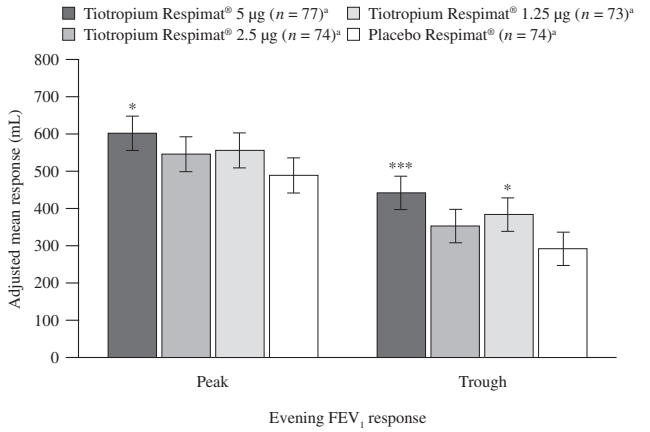

Figure 2 Evening peak FEV_1 within 3 h post-dose from baseline and trough FEV_1 responses to tiotropium Respimat® and placebo Respimat® (full analysis set). $*p < 0.05$; $***p < 0.001$ versus placebo Respimat®. [a]The number of patients within the full analysis set for whom the end point measurement is available. FEV1, forced expiratory volume in 1 s.

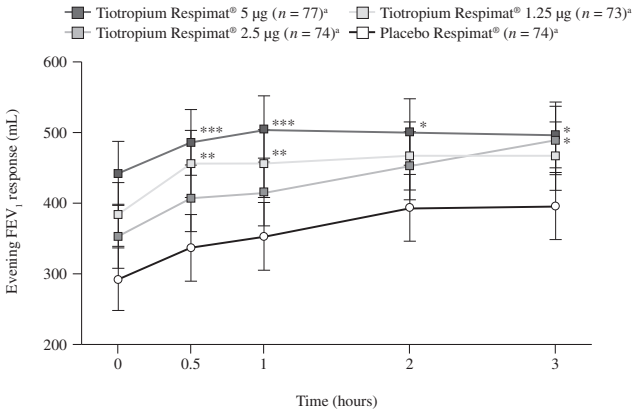

Figure 4 Evening FEV_1 response to tiotropium Respimat® and placebo Respimat® over time (full analysis set). $*p < 0.05$; $**p < 0.01$; $***p < 0.001$ versus placebo Respimat®. [a]The number of patients within the full analysis set for whom the end point measurement is available. FEV_1, forced expiratory volume in 1 s.

time points (1, 2 and 3 h after tiotropium Respimat® 5 µg inhalation; $p \leq 0.014$). There was a significant difference between tiotropium Respimat® 5 µg and 2.5 µg in adjusted mean FEV_1 response up to 1 h after study drug inhalation in favour of the higher dose (890 mL; 95% confidence interval: 22−157 mL).

In the overall study population, morning and evening mean PEF at baseline (Visit 2) were 346 L/min and 370 L/min, respectively. After 4 weeks of randomised treatment, the adjusted mean PEF response for placebo was 7.3 L/min in the morning and −0.552 L/min in the evening (Fig. 5). Morning PEF response for all three tiotropium Respimat® groups was superior to placebo Respimat® (adjusted mean of difference: 5 µg, 13.2 L/min; 2.5 µg, 15.9 L/min; 1.25 µg, 11.3 L/min; $p < 0.05$), with no dose ordering. The evening PEF response in the tiotropium Respimat® 5 µg and 2.5 µg groups was also superior compared with the placebo Respimat® group (adjusted mean of difference: 5 µg, 17.1 L/min; $p = 0.0031$; 2.5 µg, 19.5 L/min; $p = 0.0009$). A smaller difference in evening PEF response was reported between the tiotropium Respimat® 1.25 µg and placebo Respimat® groups (6.537 L/min; $p = 0.2220$).

Exploratory end point mean ACQ-7 score at randomisation (Visit 2) was 2.1. At the end of the 4-week treatment periods, adjusted mean ACQ-7 scores improved similarly in all treatment groups (5 µg, 1.3; 2.5 µg, 1.4; 1.25 µg, 1.2; placebo, 1.4).

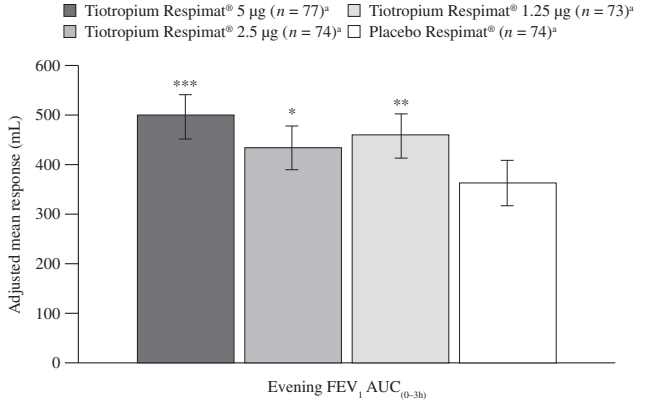

Figure 3 Evening FEV_1 AUC responses to tiotropium Respimat® and placebo Respimat® (full analysis set). $*p < 0.05$; $**p < 0.01$; $***p < 0.001$ versus placebo Respimat®. [a]The number of patients within the full analysis set for whom the end point measurement is available. AUC, area under the curve; FEV_1, forced expiratory volume in 1 s.

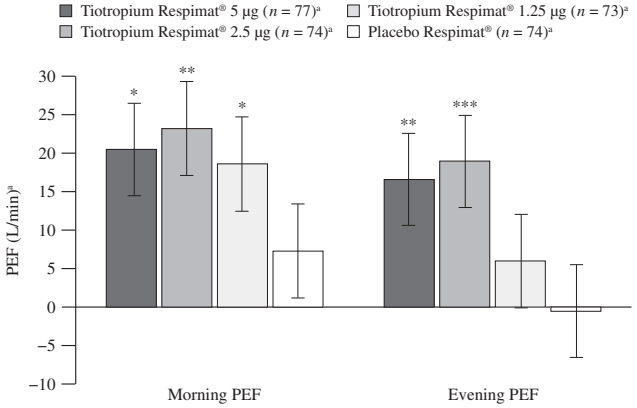

Figure 5 Morning and evening PEF response to tiotropium Respimat® and placebo Respimat® (full analysis set). $*p < 0.05$; $**p < 0.01$; $***p < 0.001$ versus placebo Respimat®. [a]Determined as a response from baseline on the weekly mean of the last week of treatment for each treatment period. [b]The number of patients within the full analysis set for whom the end point measurement is available. PEF, peak expiratory flow.

Safety and tolerability

Tiotropium Respimat® appeared well tolerated across all three doses. There was a slightly higher rate of AEs in the tiotropium Respimat® 5 µg group than in either the tiotropium Respimat® 2.5 µg group or the tiotropium Respimat® 1.25 µg group. This was due to a marginally increased number of patients reporting with asthma (3.8%), rhinitis (2.5%), sinusitis (2.5%) and gastroenteritis (2.5%) (Table 3). The most commonly experienced AEs were nasopharyngitis, asthma, bronchitis and pharyngitis, with the majority of these reported as mild to moderate in intensity. Four serious AEs were experienced by two patients during the study: pre-syncope was reported in a patient receiving tiotropium Respimat® 5 µg; asthma exacerbations, H1N1 influenza and mycoplasmal pneumonia were observed in a patient receiving tiotropium Respimat® 1.25 µg. The investigators did not consider any of these serious AEs to be related to the study medication. Both patients who experienced serious AEs prematurely discontinued study medication as a result. No life-threatening or fatal AEs were reported.

Overall, mean systolic and diastolic blood pressure and heart rate were comparable between the four treatment groups at Visit 1 and over 3 h post-dose. No dose-dependent trends were observed in the tiotropium Respimat® treatment groups.

Discussion

This is the first placebo-controlled clinical study of tiotropium Respimat® in adolescent patients with symptomatic asthma. The clinical findings demonstrate that once-daily tiotropium, administered via the Respimat® SoftMist™ inhaler, is an efficacious and well-tolerated bronchodilator as add-on therapy to ICS for this patient population.

From the efficacy analyses performed in this study, the preferred dose of once-daily tiotropium Respimat® appears to be 5 µg in adolescent patients with symptomatic asthma. Results from lung function analyses demonstrated that peak $FEV_{1(0-3h)}$ (the primary end point), trough FEV_1, FEV_1 $AUC_{(0-3h)}$ and morning/evening PEF responses for tiotropium Respimat® 5 µg were superior to those for placebo Respimat® and were greater than those observed with the two lower doses of tiotropium Respimat®. This study provided an opportunity to evaluate the morning reduction in PEF experienced by these patients before medication is taken. Our observations are in line with previous studies in adult patients with symptomatic asthma in whom significant improvements in peak and trough FEV_1 and PEF were reported following once-daily tiotropium Respimat® 5 µg treatment compared with placebo [14,15].

In this dose-ranging study in adolescent patients, all three doses of tiotropium Respimat® were generally well tolerated, with only a slightly higher incidence of AEs (asthma, rhinitis, sinusitis and gastroenteritis) reported in the tiotropium Respimat® 5 µg treatment group. There was no evidence of dose ordering in any preferred term observed at higher incidence in this treatment group. This study was designed (short-term and incomplete crossover) to investigate dose ranging but not safety. Any conclusions on safety are therefore limited, and long-term or parallel-group studies are required for further investigation. In the proof-of-concept Phase II study of tiotropium Respimat® 5 µg versus salmeterol or placebo as add-on to ICS for adult patients with moderate persistent asthma, AEs were well balanced across treatment groups [13]. Results from long-term, parallel-group, Phase III studies will be needed to provide further insight into the safety of tiotropium Respimat® in adolescent patients with asthma. Safety findings are already available from two Phase III studies of tiotropium Respimat® 5 µg versus placebo Respimat® in adult patients with symptomatic asthma despite ICS plus LABA [15]. In these studies, AEs were similarly well balanced across the two treatment groups.

With regard to patient-reported outcomes, ACQ-7 scores in this study improved during treatment with all three

Table 3 Overview of adverse events (treated set).

n (%)	Tiotropium Respimat®			Placebo Respimat® (*n* = 75)
	5 µg (*n* = 80)	2.5 µg (*n* = 75)	1.25 µg (*n* = 75)	
Any AE	18 (22.5)	10 (13.3)	13 (17.3)	10 (13.3)
Type of AE[a,b]				
Nasopharyngitis	2 (2.5)	3 (4.0)	3 (4.0)	1 (1.3)
Asthma	3 (3.8)	0	2 (2.7)	3 (4.0)
Bronchitis	2 (2.5)	2 (2.7)	1 (1.3)	0
Pharyngitis	1 (1.3)	0	2 (2.7)	0
Rhinitis	2 (2.5)	1 (1.3)	0	0
Sinusitis	2 (2.5)	0	0	0
Gastroenteritis	2 (2.5)	0	0	0
Viral infection	0	0	0	2 (2.7)
Any drug-related AEs	0	0	0	0
Serious AEs	1 (1.3)	0	1 (1.3)	0
AEs resulting in discontinuation of study drug	1 (1.3)	0	1 (1.3)	0

AE, adverse event.
[a] Medical Dictionary for Drug Regulatory Affairs coding system (V 14.0) preferred term classification.
[b] Occurring in ≥2% of patients in any treatment group.

tiotropium Respimat® doses and placebo Respimat® to almost the same degree. ACQ-7 is an exploratory tool, and evaluation of findings may be limited by the observed large placebo effect due to trial procedures leading to improved compliance, which reduces the possibility of achieving a clinically significant treatment effect in a short-term duration study. In addition, the crossover design of this study with no washout periods impairs the discriminating ability of the study. Further long-term studies are required to more fully understand the patient-reported outcomes associated with tiotropium Respimat® in adolescents as well as in adults.

The decision to use an incomplete crossover design for this study was driven by the wish to reduce the treatment burden on patients compared with a full crossover study. Although slightly more patients are required in an incomplete crossover study, the sample size is still relatively small compared with a parallel-group study. By assigning an equal number of patients to each treatment group, the period effect (the order in which the study drug was administered) was minimised. Washout periods were not included between treatment periods as these can destabilise patients. A 4-week treatment period was used, as steady-state tiotropium is reached after at least 3 weeks [19]. It is important to note that there were no safety concerns during the placebo treatment period as patients continued receiving background ICS and were supplied with short-acting β_2-agonist rescue medication. Lastly, patients must have received a stable maintenance ICS dose for at least 4 weeks prior to screening and during the 4-week run-in period, facilitating a steady state that was equally likely to improve compliance in all arms during the treatment period.

Based on efficacy and safety evaluations from this randomised, placebo-controlled, dose-ranging study, the preferred dose of tiotropium Respimat® add-on therapy to maintenance treatment with ICS in adolescents with moderate persistent asthma appears to be once-daily 5 μg, which is consistent with findings from studies of tiotropium Respimat® therapy for adult asthma patients. However, the study population was rather limited with regard to safety recording and, due to the study design, long-term safety and tolerability could not be investigated.

Based on the results from this study, further investigation of the tiotropium Respimat® 5 μg dose added on to ICS maintenance therapy is justified in a larger adolescent population, and evaluation of tiotropium Respimat® in children younger than 12 years should be considered, as a therapeutic benefit is anticipated in this patient population. Two long-term, randomised, double-blind, placebo-controlled, parallel-group, Phase III studies of tiotropium Respimat® add-on to ICS maintenance therapy in adult patients with moderate persistent asthma have been conducted (NCT01172808 and NCT01172821). These studies investigated tiotropium (once-daily 5 μg and 2.5 μg via the Respimat® SoftMist™ inhaler) versus placebo Respimat®, and exploratory comparisons with an active comparator (salmeterol), with the aim of providing further information on long-term safety and efficacy, including clinical outcomes, relevant for both adult and adolescent patients. In addition, a 1-year, randomised, double-blind, placebo-controlled, parallel-group, Phase III study (NCT01257230) in adolescent patients with moderate persistent asthma, symptomatic despite ICS, is currently investigating two doses of tiotropium (once-daily 5 μg and 2.5 μg via the Respimat® SoftMist™ inhaler) compared with placebo Respimat® over a treatment period of 48 weeks.

Conflicts of interest

Christian Vogelberg has no conflicts of interest to declare.
Michael Engel is an employee of Boehringer Ingelheim.
Petra Moroni-Zentgraf is an employee of Boehringer Ingelheim.
Migle Leonaviciute-Klimantaviciene has no conflicts of interest to declare.
Ralf Sigmund is an employee of Boehringer Ingelheim.
John Downie is an employee of Boehringer Ingelheim.
Katja Nething is an employee of Boehringer Ingelheim.
Viktorija Vevere has no conflicts of interest to declare.
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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.2014.06.011.

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