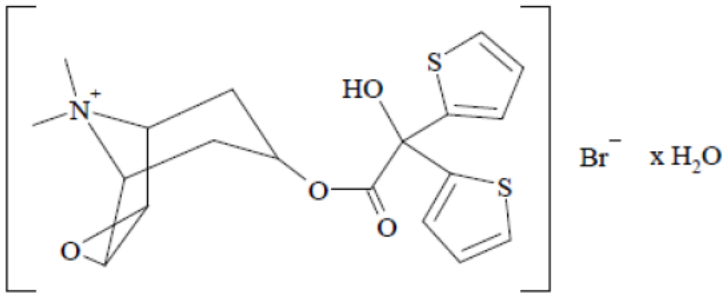
| CLINICAL PHARMACOLOGY REVIEW | |
|---|---|
| NDA Number: | 021936 SDN484 |
| Submissions Date: | 08/15/2016 |
| Submission Type: | Pediatric Supplement |
| Proposed Brand Name: | SPIRIVA RESPIMAT |
| Generic Name: | Tiotropium bromide |
| Sponsor: | Boehringer Ingelheim |
| Route of Administration: | Inhalation |
| Dosage Form: | Metered Inhalation spray: 1.25 µg tiotropium per actuation with the Spiriva Respimat |
| Dosage Strength: | 1.25 µg tiotropium in (b) (4) aqueous solution per actuation |
| Proposed Dosing Regimen: | 2 inhalations of SPIRIVA RESPIMAT 1.25 µg once-daily |
| Proposed Indication(s): | The long-term, once-daily, maintenance treatment of asthma |
| Proposed Population(s): | Patients (b) (4) and older |
| OND Divisions: | Division of Pulmonary, Allergy, and Rheumatology Products |
| OCP Division: | Clinical Pharmacology II |
| Reviewer: | Yunzhao Ren, M.D., Ph.D. |
| Team Leader: | Bhawana Saluja Ph.D. |
| Molecular Structure: |  |

## TABLE OF CONTENTS



# 1. EXECUTIVE SUMMARY

Boehringer Ingelheim (BI) has submitted sNDA 021936 pediatric supplement (SDN484) seeking the marketing approval for tiotropium bromide aqueous inhalation solution with the RESPIMAT device (SPIRIVA RESPIMAT®, or TR as the product), for the indication of "The long-term, once-daily, maintenance treatment of asthma in patients (b) (4) of age and older." The proposed dose regimen is two inhalations (1.25 µg tiotropium each inhalation) once daily. The dosage form is an inhalation spray and each actuation delivers 1.25 µg tiotropium (equivalent to 1.562 µg tiotropium bromide monohydrate) with the SPIRIVA RESPIMAT inhaler. Each RESPIMAT device is capable of delivery of 60 metered actuations.

SPIRIVA RESPIMAT® was first approved for "the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations" under NDA 021936 on 09/24/2014. The second indication "the long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older" was approved under NDA 207070 on 9/15/2015. The approved dose in asthma patients (2.5µg once daily) is half of the approved dose in COPD patients (5 µg once daily).

In this pediatric supplement, BI conducted four pediatric clinical studies (Studies 205.425, 205.445, 205.446, and Study 205.443). Blood and urine PK samples measuring tiotropium concentrations were collected in Study 205.425; and only urine PK samples were collected in Study 205.443.

In addition, BI submitted a meta-analysis report (metaanalysis-p5-tiotropium-in-asthma-pediatric--study-report.pdf) comparing the tiotropium exposure in children and adults.

Pharmacokinetics (PK) and bronchodilatory effect of tiotropium in children 6 to 11 years of age were investigated in a Phase 2 dose ranging Study 205.425. The FEV1 peak$_{0\text{-}3h}$ response was superior in all the active treatment arms compared to placebo arm; the response was numerically highest following 4-week 2.5µg (TR2.5) QD treatment. PK results showed that mean steady state $C_{0.083,ss}$ and the mean urine

excretion fraction of unchanged tiotropium within 24 hours post-dose ($fe_{0-24,ss}$) in children 6 to 11 years of age following 4-week TR2.5 treatment was 2.42 pg/mL and 10.3%, respectively. The values were comparable to that observed in adults with asthma ($C_{0.083,ss}$=2.38pg/mL, $fe_{0-24,ss}$=12.7%) following the same dosing regimen. Therefore, PK results from study 205.425 supports the safety profiles collected in children 6 to 11 years of age.

PK and efficacy of tiotropium in children 1 to 5 years of age were investigated in a Phase 2/3 Study 205.443. A valved facemask (Aerochamber Plus Flow-Vu® valved holding chamber with facemask) in combination with the Respimat® inhaler was used for children aged 1 to 4 years in this study. (b) (4) PK results showed that at steady state, on average 1.08% of the inhalation dose was excreted unchanged in the urine within 3 hours post-dose ($fe_{0-3,ss}$) in children of this age group following TR2.5 treatment. The value was only about 40% of that from adults with asthma (2.61%) following the same dosing regimen. Since $fe_{0-3,ss}$ only represents approximately one-fifth the value of $fe_{0-24,ss}$ value in adults, the clinical meaning of $fe_{0-3,ss}$ result in children 1-5 years of age is unclear.

### 1.1 Recommendation

The pediatric supplement (SDN484) to NDA 021936, submitted on 08/15/2016, is acceptable from a clinical pharmacology perspective.

### 1.2 Phase 4 Commitments

None

### 1.3. Summary of Clinical Pharmacology Findings

#### 1.3.1 Background

SPIRIVA RESPIMAT® was first approved for "the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations" under NDA 021936 on 09/24/2014. The second indication "the long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older" was approved under NDA 207070 on 9/15/2015. The approved dose in asthma patients (2.5µg once daily with two inhalations of 1.25 µg) is half of the approved dose in COPD patients (5 µg once daily with two inhalations of 2.5 µg).

The PPSP of Spiriva Respimat pediatric program was submitted on 4/9/2014. The pediatric written request was issued by FDA on 2/12/2016. FDA acknowledged in the written request that BI has already completed several pediatric clinical studies in accordance with EMA. These include:

- *A 4-week dose-ranging study in pediatric patients aged 6 to 11 years with moderate asthma.*
- *A 12-week PK, safety, and efficacy (lung function) study in pediatric patients aged 6 to 11 years of age with severe asthma.*
- *A nonclinical study in juvenile rats to support studies in pediatric patients < 2 years of age.*
- *A 12-week safety and efficacy study in pediatric patients aged 1 to 5 years of age with persistent asthma.*

[redacted] (b) (4)

It should be noted that the reports of completed pediatric study were submitted under IND 065127. In order to obtain the needed pediatric information on tiotropium bromide inhalation solution, FDA made a formal Written Request that BI submit information from the studies described below:

- *A Nonclinical study characterizing of the dose delivery from the Respimat inhaler with at least one U.S.-marketed spacer.*
- *A clinical efficacy and safety study with double-blind, randomized, parallel group, placebo-controlled study design in children ages 6 to 11 years with asthma who are symptomatic despite maintenance therapy with a stable medium-dose ICS either alone or in combination with another controller medication (e.g., LABA or leukotriene modifier). The duration must be at least 48 weeks, and the study must include at least two doses of tiotropium bromide inhalation solution.*

### 1.3.2 Cross Study Comparison for Systemic Exposure of Tiotropium in Children and Adults

Spiriva Respimat® was approved in asthmatic adolescents together with asthmatic adults on 9/15/2015 and was supported by two Phase 3 adolescent efficacy/safety studies (Studies 205.444 and 205.456). The approved dose and dose regimen (TR2.5 QD) were the same in adolescents and adults. The PK results from Phase 2 Study 205.424 showed that the steady state systemic geometric mean $C_{0.083,ss}$ and $fe_{0-24,ss}$ in adolescents following TR2.5 QD treatment was 2.19 (CV=88%) pg/mL and 14.3% (CV=70%), respectively (Table 1.1). The results were comparable to that of adults [2.38 (CV=54%) pg/mL and 12.7% (CV=84%), respectively].

Study 205.425 was a randomized, placebo-controlled, double-blind, 4-treatment (placebo, TR1.25, TR2.5, and TR5 following QD regimen), 3-period (4-week each), and incomplete crossover study in children 6 to 11 years old with moderate persistent asthma. PK results showed that mean steady state $C_{0.083,ss}$ (the concentration around $t_{max}$) in children 6-11 years old was 2.42 (CV=49%) pg/mL following 4-week TR2.5 treatment. The mean steady state $fe_{0-24,ss}$ of unchanged tiotropium in the urine from children in this age group was 10.3% (CV=63%) following 4-week TR2.5 treatment. Both values were comparable to that of adults (Table 1.1).

Study 205.443 was a randomized, placebo-controlled, double-blind, parallel group study in children 1 to 5 years old with moderate to severe persistent asthma. Only urine samples were collected in this study. PK results showed that at mean steady state urine excretion of unchanged tiotropium within 3-hour post-dose ($fe_{0-3,ss}$) was 1.08% (CV=66%) of the inhalation dose following TR2.5 treatment. The value was 41% of that from adults with asthma [2.61% (CV=84%)] following the same dosing regimen. In adults, the mean $fe_{0-3,ss}$ value only represents 21% the value of $fe_{0-24,ss}$. Due to the lack of tiotropium plasma concentration and urine samples over a longer duration of time, the systemic exposure of tiotropium in children 1 to 5 years of age following inhalation of Spiriva Respimat is unknown. The clinical meaning of $fe_{0-3,ss}$ results obtained in study is unclear.

**Table 1.1 Descriptive Summary of Steady State Tiotropium Plasma PK Parameters following Administration of TR2.5 by Age Groups**

| Age Group | $fe_{0-3,ss}$ (%) | $fe_{0-24,ss}$ (%) | $C_{0.083,ss}$ (pg/mL) |
|---|---|---|---|
| **1-5 y** | 1.08% (N=12, CV=66%) | N/A | N/A |
| **6-11 y** | 2.88 (N=11, CV=48%) | 10.3 (N=11, CV=63%) | 2.42 (N=6, CV=49%) |
| **12-18 y** | 2.42 (N=10, CV=80%) | 14.3 (N=12, CV=70%) | 2.19 (N=3, CV=88%) |
| **≥ 18 y** | 2.61 (N=49, CV=111%) | 12.7 (N=102, CV=84%) | 2.38 (N=89, CV=54%) |

$fe_{0-3,ss}$, urine excretion fraction of unchanged tiotropium within 3 hours post-dose at steady state
$fe_{0-24,ss}$, urine excretion fraction of unchanged tiotropium within 24 hours post-dose at steady state
$C_{0\ 083,ss}$, tiotropium plasma concentration at 5 minutes post-dose at steady state
Source: adapted from Table 4.1.5, 4.1.6, and 4.1.10

### 1.3.3 Vital signs Change from Baseline following Spiriva Respimat® Treatment

Study 205.425 and Study 205.433 showed that mean post-dose systolic blood pressure, diastolic blood pressure, and pulse rate at steady state had minimal change from baseline in all the active treatment groups and the results were comparable to that of placebo group in children 1-11 years old.

# 2. QUESTION BASED REVIEW

## 2.1 List the in vitro and in vivo Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the sNDA

In total four pediatric studies were submitted under this sNDA (Table 2.1): Study 205.425, Study 205.443, Study 205.445, and Study 205.446. Among them, Study 205.425 was a Phase 2 dose ranging study in which both plasma samples and urine samples were collected for measuring tiotropium concentration. In addition, only urine samples were collected in Phase2/3 Study 205.443.

**Table 2.1 List of Five Clinical Pharmacology Studies in sNDA205636 Pediatric Submission Package**

| Type of study | Study identifier (study no. [document no.]) | Location of study report | Objective(s) of the study | Study design and type of control | Test product(s); dosage regimen; route of administration | Number of patients treated | Healthy subjects or diagnosis of patients | Duration of treatment | Study status; type of report |
|---|---|---|---|---|---|---|---|---|---|
| **Phase II trial** | | | | | | | | | |
| Efficacy and safety | 205.425 [U13-1322] | Module 5.3.5.1 | Dose ranging, efficacy, safety, and PK | Incomplete crossover; placebo-controlled | Tiotropium bromide solution for inhalation; 5 µg (once daily), or 2.5 µg (once daily), or 1.25 µg (once daily); oral inhalation via the RESPIMAT | Placebo[1]: 76<br>Tio R1.25[1]: 75<br>Tio R2.5[1]: 74<br>Tio R5[1]: 76 | Children (6 to 11 years) with moderate[2], persistent asthma | 12 weeks (three 4-week treatment periods) | Complete; Full |
| **Phase II/III trial** | | | | | | | | | |
| Safety and efficacy | 205.443 [c03067178] | Module 5.3.5.1 | Safety, efficacy, and PK | Parallel-group; placebo-controlled | Tiotropium bromide solution for inhalation; 5 µg (once daily), or 2.5 µg (once daily); oral inhalation via the RESPIMAT with or without a spacer | Placebo[1]: 34<br>Tio R2.5[1]: 36<br>Tio R5[1]: 31 | Children (1 to 5 years) with persistent asthma[3] | 12 weeks | Complete; Full |
| **Phase III trials** | | | | | | | | | |
| Efficacy and safety | 205.445 [c03521500] | Module 5.3.5.1 | Confirmatory, efficacy, and safety | Parallel-group; placebo-controlled | Tiotropium bromide solution for inhalation; 5 µg (once daily), or 2.5 µg (once daily); oral inhalation via the RESPIMAT | Placebo[1]: 131<br>Tio R2.5[1]: 135<br>Tio R5[1]: 135 | Children (6 to 11 years) with moderate[2], persistent asthma | 48 weeks | Complete; Full |
| Efficacy and safety | 205.446 [c03243044] | Module 5.3.5.1 | Confirmatory, efficacy, and safety | Parallel-group; placebo-controlled | Tiotropium bromide solution for inhalation; 5 µg (once daily), or 2.5 µg (once daily); oral inhalation via the RESPIMAT | Placebo[1]: 134<br>Tio R2.5[1]: 136<br>Tio R5[1]: 130 | Children (6 to 11 years) with severe[4], persistent asthma | 12 weeks | Complete; Full |

Source: section 5.2, Tabular listing of all clinical studies

## 2.2 General Attributes of the Drug

### 2.2.1 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

The drug substance, tiotropium bromide monohydrate is (1α, 2ß, 4ß, 5α, 7ß)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9- dimethyl-3-oxa-9-azoniatricyclo[3.3.1.02,4] nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

All four pediatric studies in this supplement used the approved aqueous solution of 0.023% (w/v) tiotropium bromide monohydrate delivered by the Respimat (b) (4) device used in adults and adolescents with asthma. Table 2.2 outlines the quantities of each active ingredient and excipient (mass per each actuation). Each QD dose requires two actuations with each actuation delivering 1.25 tiotropium.

**Table 2.2 Composition of SPIRIVA RESPIMAT Inhalation Spray (2.5 µg per Two Actuations)**

| Ingredients | Mass per Dose (mg) |
|---|---|
| Tiotropium<br>(corresponds to tiotropium bromide monohydrate*) | 0.0025<br>(0.0031) |
| Benzalkonium chloride | (b) (4) |
| Edetate disodium | |
| (b) (4) Hydrochloric acid | |
| Water for injection | |
| (b) (4) | |
| Total mass | |

* The declared quantity of active ingredient refers to tiotropium (cation) as the active moiety of tiotropium bromide monohydrate. The conversion factor is 1.2494.
Source: adapted from section 3.2.P.2 Formulation.pdf, page 8, Table 2

### 2.2.2 What are the proposed mechanism of action and therapeutic indications?

Refer to the approved label of NDA 207070, "Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects was dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect."

The proposed therapeutic indication of in this pediatric supplement is to extend "The long-term, once-daily, maintenance treatment of asthma in patients" from "12 years of age and older" to "(b) (4) of age and older."

### 2.2.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage is once-daily inhalation of 2.5µg tiotropium (2 inhalations of 1.25µg each) via Spiriva Respimat®. The route of administration is oral inhalation.

## 2.3 General Clinical Pharmacology

### 2.3.1 What are the PK endpoints in clinical pharmacology studies?

PK parameters ($C_{0.083}$, $Ae_{t1\text{-}t2}$, and $fe_{t1\text{-}t2}$ following the first dose; and $AUC_{t1\text{-}t2}$, $C_{max,ss}$, $C_{0.083,ss}$, $t_{max,ss}$, $Ae_{t1\text{-}t2}$, and $fe_{t1\text{-}t2}$, $CL_{R\ t1\text{-}t2,ss}$, $R_{A,C0.083}$, and $R_{A,Ae.}$ following 4-week QD treatment) were determined in Study 205.425. $Ae_{t1\text{-}t2}$, $fe_{t1\text{-}t2}$, RA, and $Ae_{0\text{-}3}$ were determined in Study 205.433.

### 2.3.2 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The parent compound, tiotropium, is the active moiety. Tiotropium plasma and urine concentrations were measured by validated High Performance Liquid Chromatography-Tandem Mass Spectrometry (HPLC-MS/MS) method.

## 2.4 PK Characteristics of the Drug

### 2.4.1 What are the characteristics of drug absorption?

Refer to the approved label of NDA 207070, "*Following inhalation of the solution by young healthy volunteers, urinary excretion data suggests that approximately 33% of the inhaled dose reaches the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3%. Food is not expected to influence the absorption of tiotropium for the same reason. Following 4-week SPIRIVA RESPIMAT once daily dosing, maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation in COPD and asthma patients*".

### 2.4.3 What are the characteristics of drug distribution?

Refer to the approved label of NDA 207070, "*The drug has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg after an intravenous dose to young healthy volunteers*".

### 2.4.4 What are the characteristics of drug metabolism?

Refer to the approved label of NDA 207070, "*The extent of metabolism is small. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, neither of which binds to muscarinic receptors*".

### 2.4.5 What are the characteristics of drug elimination?

Refer to the approved label of NDA 207070, "*The terminal half-life of tiotropium in asthma patients following once daily inhalation is* (b) (4)*. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. 12.8% (0.32 mcg) of the dose was excreted unchanged in the urine over 24 hours at steady state after inhalation of 2.5 mcg in patients with asthma*".

## 2.5 Intrinsic Factors

### 2.5.1 How is the systemic exposure in children compared to that in adults?

Geometric mean steady state $C_{0.083,ss}$ and $fe_{0-24,ss}$ in adolescents and children 6-11 years of age were comparable with the values in adults following TR2.5 treatment (Table 1.1).

The systemic exposure of tiotropium in children 1-5 years of age following Spiriva Respimat® treatment could not be determined since tiotropium plasma concentrations were not available in this age group. In addition, the urine samples were collected only up to 3-hour post-dose in this age group and the clinical meaning of $fe_{0-3}$ or $fe_{0-3,ss}$ is unclear.

### 2.5.2 Renal Impairment

Refer to the approved label of NDA 207070, "*Following 4-week SPIRIVA RESPIMAT 5 mcg once daily dosing in patients with COPD, mild renal impairment (creatinine clearance 60 - <90 mL/min) resulted in 23% higher AUC0 6,ss and 17% higher Cmax,ss values; moderate renal impairment (creatinine clearance 30 - <60 mL/min) resulted in 57% higher AUC0 6,ss and 31% higher Cmax,ss values compared to COPD patients with normal renal function (creatinine clearance >90 mL/min)*".

### 2.5.3 Hepatic Impairment

Refer to the approved label of NDA 207070, "*The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied*".

## 2.6 Extrinsic Factors

### 2.6.1 Drug-drug interactions (DDI)

Refer to the approved label of NDA 207070, "*An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once-daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC0-4h, a 28% decrease in the renal clearance of tiotropium and no significant change in the $C_{max}$ and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium*".

### 2.6.2 Co-medications

Refer to the approved label of NDA 207070, "*Common concomitant medications (LABA, ICS) used by patients with COPD were not found to alter the exposure to tiotropium. Similarly, common concomitant medications (LABA, ICS+LABA combinations, oral corticosteroids and leukotriene modifiers) used by patients with asthma were not found to alter the exposure to tiotropium*".

## 2.7 Analytical Section

### 2.7.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

Only the plasma and urine concentrations of parent drug (tiotropium) were measured in the pediatric studies submitted in this supplement.

For measuring the plasma concentration of tiotropium, the validated assay comprises solid phase and liquid/liquid extraction of human plasma with an internal standard ([D3]tiotropium bromide) and subsequent quantification by LC-MS/MS. The samples were analyzed on a Perkin Elmer Sciex API 3000 LC-MS/MS system.

For measuring the concentration of tiotropium in the acidified urine, the validated assay comprises solid phase and liquid/liquid extraction of human urine with an internal standard ([$^2$H3]tiotropium bromide) and subsequent quantification by LC-MS/MS. The samples were analyzed on a Perkin Elmer Sciex API 3000 LC-MS/MS system.

**2.7.2 For all moieties measured, is free, bound, or total measured?**

Due to the nature of the assay method, it's the total amount of tiotropium that was measured.

**2.7.3 What is the range of the standard curve? What is the limit of quantitation? What are the accuracy, precision, and selectivity at these limits? What is the sample stability under conditions used in the study?**

The summary of the validation results from analyzing tiotropium plasma concentrations is listed in Table 2.3. The range of calibration curves was 1.00 pg/mL to 100 pg/mL, with a lower limit of quantitation (LLOQ) of 1.00 pg/ml. The precision and accuracy of LLOQ, low, medium and high quality controls were all within ±15% of the nominal value. There was no significant interfering peak observed in the blank plasma samples. Tiotropium in plasma samples was stable during 3 freeze/thaw cycles, up to 24 h at room temperature, and up to 18 months in a freezer at -20°C or -70°C.

The summary of the validation results from analyzing tiotropium concentrations in acidified urine is listed in Table 2.4. The range of calibration curves is 10.0 pg/mL to 5000 pg/mL with a LLOQ of 10.0 pg/ml. The precision and accuracy of LLOQ, low, medium and high quality controls were all within ±15% of the nominal value. Tiotropium in acidified urine samples was stable during 3 freeze/thaw cycles and up to 392 days in a freezer at -20°C.

**Table 2.3 Summary of the Validation Results Analyzing Tiotropium Plasma Concentration**

| Compopund | Tiotropium |
|---|---|
| Calibration range [pg/mL] | 1.00 - 100 |
| Required sample volume [µL] | 400 |
| $r^2$ (mean) of the standard curves | 0.99734 |
| Precision (cv %) at the LLOQ; N=18 | 11.42 |
| Accuracy (% bias) at the LLOQ | -1.87 |
| Precision (cv %) at the low QC level; N=18 | 11.12 |
| Accuracy (% bias) at the low QC level | 6.07 |
| Precision (cv %) at the mid QC level; N=18 | 6.39 |
| Accuracy (% bias) at the mid QC level | 5.09 |
| Precision (cv %) at the high QC level; N=18 | 5.90 |
| Accuracy (% bias) at the high QC level | 6.94 |
| Selectivity | no significant interfering peaks were observed in the blank plasma samples. The method can be regarded as selective for human plasma |

Source: validation report U10-1855-01, page 5, Table 1.1

**Table 2.4 Summary of the Validation Results Analyzing Tiotropium Plasma Concentration**

| **Compound** | **Tiotropium** | | |
|---|---|---|---|
| Calibration range [pg/mL] | 10.0 - 5000 | | |
| Defined LLOQ [pg/mL] | 10.0 | | |
| Required sample volume [mL] | 2.00 | | |
| $r^2$ (mean) of the standard curves | 0.99924 | | |
| Precision (cv %) (at the LLOQ)[1] | 5.94 | | |
| Accuracy (% bias) (at the LLOQ)[1] | 5.84 | | |
| Accuracy and Precision of QC samples | Type 1 | Type 2 | Type 3 |
| Precision (cv %) at the LLOQ QC (10.0 pg/mL) | -[2] | 5.14 | 4.15 |
| Accuracy (% bias) at the LLOQ QC (10.0 pg/mL) | - | 9.62 | 9.49 |
| Precision (cv %) at QC 25.0 pg/mL | 4.02 | 1.61 | 2.03 |
| Accuracy (% bias) at QC 25.0 pg/mL | -4.43 | -0.96 | -1.83 |
| Precision (cv %) at QC 400 pg/mL | 4.69 | 1.19 | 2.59 |
| Accuracy (% bias) at QC 400 pg/mL | -5.37 | -2.61 | -2.91 |
| Precision (cv %) at QC 4000 pg/mL | 6.17 | 1.72 | 1.85 |
| Accuracy (% bias) at QC 4000 pg/mL | -4.56 | -3.38 | -2.32 |

Source: validation report U07-1752-01-AM1, page 20, Table 1

# 3 DETAILED LABELING RECOMMENDATIONS

## 12 CLINICAL PHARMACOLOGY

### 12.3 Pharmacokinetics

*Pediatric Patients*

The [redacted] exposure to tiotropium was not found to differ between [redacted] (aged [redacted] to 17 years) and adults with asthma. [redacted]

# 4. Appendix

## 4.1 Appendix – Individual Study Review

### 4.1.1 Study 205.425

**Study Type:** Phase 2 efficacy, safety, PK, crossover dose ranging study in asthma children (6 to 11 years)

**Title:** A phase II randomized, double-blind, placebo-controlled incomplete crossover trial with 4-week treatment periods to evaluate efficacy and safety of tiotropium inhalation solution (doses of 1.25 µg, 2.5 µg and 5 µg) delivered via Respimat® inhaler once daily in the evening in children 6 to 11 years old with moderate persistent asthma

**Objective:**
The objective of this trial was to investigate the efficacy and safety of 3 doses of tiotropium solution for inhalation in comparison to placebo delivered by the Respimat® inhaler on top of usual care in children (6 to 11 years old) with moderate persistent asthma. In addition, pharmacokinetic profiling in this age group was evaluated.

**Study Design and Method:**
This was a Phase 2, randomized, placebo-controlled, double-blind, incomplete crossover study with 4 treatments and 3 treatment periods (4-week for each period). The study planned to enroll 104 subjects and 101 children aged 6 to 11 years actually entered the study. Each child received 3 of the 4 QD treatments (placebo, TR1.25, TR2.5, and TR5) as shown in Figure 4.1.1. The once daily dose was given during evening. There was no washout between treatment periods.

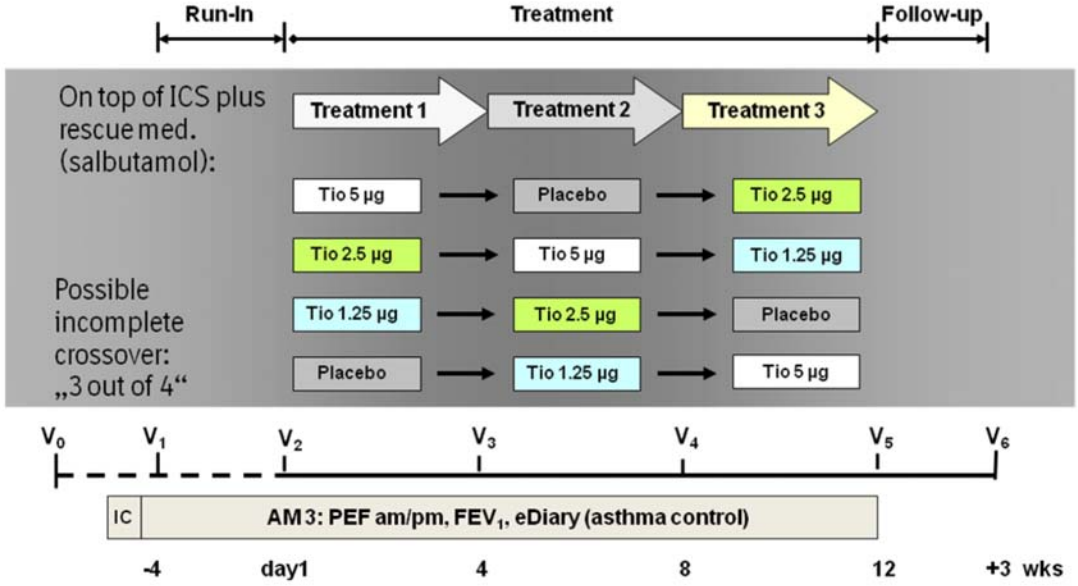



**Figure 4.1.1** Study design of Study 205.425 (Source: CSR Report 205.425, page 39, Figure 9.1:1)

Noteworthy inclusion criteria:

- Male or female patients between 6 years and 11 years of age (up to 1 day prior to their 12th birthday at Visit 1)
- All patients had to have at least a 6-month history of asthma at the time of enrolment into the trial. The diagnosis of asthma had to be confirmed at Visit 1 with a bronchodilator reversibility (15 to 30 min after 200 µg salbutamol) resulting in a FEV1 increase of ≥12%

- All patients had to have been on maintenance treatment with ICS at a stable medium dose, either as monotherapy or in combination with a LABA or leukotriene modifier for at least 4 weeks before Visit 1
- All patients had to be symptomatic (partly controlled) at Visit 1 (screening) and prior to randomization at Visit 2 as defined by an ACQ mean score of ≥1.5
- All patients had to have a pre-bronchodilator FEV1 ≥60% and ≤90% of predicted normal at Visit 1

Noteworthy exclusion criteria:

- Patients with a significant disease other than asthma
- Patients with clinically relevant abnormal screening hematology or blood chemistry results
- Patients with any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia that required intervention (e.g. pacemaker implantation, catheter ablation, etc) or a change in drug therapy within the past year
- Patients who were being treated with oral β-blocker medication
- Patients who had been treated with systemic (oral or intravenous) corticosteroids or systemic (oral or intravenous) β-agonists within 4 weeks prior to Visit 1
- Patients who had been treated with long-acting theophylline preparations within 4 weeks prior to Visit 1 or during the run-in period

In a subset of patients, blood samples for PK profiling were obtained. One blood sample was taken 5 min after administration of the first dose of trial drug (Visit 2), and 5 samples were taken at steady state [pre-dose, 5 min, 0.5 h, 1 h, and 3 h postdose at Visit 3 (end of Period 1)]. At each sampling time point, 6 mL of blood were drawn from a forearm vein using a collection tube containing potassium EDTA as anticoagulant (Vacutainer®).

In a subset of patients, urine samples for PK profiling were obtained. The pre-dose urine sample was obtained during 1 h prior to trial drug administration. Further collection intervals were from 0 to 3 h and 3 to 24 h postdose during Visit 2 (beginning of Period 1) and Visit 3 (beginning of Period 2).

Plasma and urine concentrations of tiotropium were determined by validated assays using high performance liquid chromatography (HPLC) coupled to tandem mass spectrometry (MS/MS). The calibration curves of undiluted samples were linear over the range of concentrations from 1.00 to 100 pg/mL tiotropium using a volume of 0.4 mL plasma and 10.0 to 5000 pg/mL tiotropium using a volume of 2 mL acidified urine.

**Endpoints:**

- The primary efficacy endpoint was FEV1 $peak_{0\text{-}3h}$ response, determined at the end of the 4-week treatment period. FEV1 $peak_{0\text{-}3h}$ was defined as the maximum FEV1 measured within the first 3 h post dosing. FEV1 $peak_{0\text{-}3h}$ response was defined as the difference of FEV1 $peak_{0\text{-}3h}$ and the FEV1 baseline measurement (at Visit 2).

- The secondary efficacy endpoints include trough FEV1, FVC $peak_{0\text{-}3h}$, FEV1 $AUC_{0\text{-}3h}$, $PEF_{am}/PEF_{pm}$, use of rescue medication, interviewer-administered asthma control questionnaire (ACQ), and night-time awakenings due to asthma symptoms.

- The following PK endpoints were determined if feasible:
  - Following the first dose: $C_{0.083}$, $Ae_{t1\text{-}t2}$, and $fe_{t1\text{-}t2}$
  - At the end of the Period 1: $AUC_{t1\text{-}t2}$, $C_{max,ss}$, $C_{0.083,ss}$, $t_{max,ss}$, $Ae_{t1\text{-}t2}$, and $fe_{t1\text{-}t2}$, $CL_{R\ t1\text{-}t2,ss}$, $R_{A,C0.083}$, and $R_{A,Ae.}$

- PD endpoints: treatment effects on serial vital signs (blood pressure, pulse rate) over 6 hours postdose. 12-lead electrocardiograph (ECG) and clinical laboratory tests were conducted at the end of treatment visit 2 or at the time of early discontinuation from the study.

- Measurement of safety and tolerability was based on the incidence and intensity of AEs, and changes in vital signs (including pulse rate, seated blood pressure in conjunction with spirometry until 3 h postdose at Visits 2 to 5, and in conjunction with a physical examination at Visit 6)

**Demographics:**
About two thirds of the patients were male (68.3%), all patients were White and non- Hispanic (Table 4.1.1). The mean age of all patients was 8.8 years (SD=1.7). Mean body weight was 34.2 kg (SD=10.5).

**Table 4.1.1 Demographic Information (Treatment Set)**

| | Total |
|---|---|
| Number of patients, N (%) | 101 (100.0) |
| Male | 69 (68.3) |
| Female | 32 (31.7) |
| Race, N (%) | |
| White | 101 (100.0) |
| Ethnicity, N (%) | |
| Not Hispanic/Latino | 101 (100.0) |
| Age [years] | |
| Mean (SD) | 8.8 (1.7) |
| Age classes, N (%) | |
| 6-8 years | 37 (36.6) |
| 9-11 years | 64 (63.4) |
| Weight [kg] | |
| Mean (SD) | 34.2 (10.5) |
| Height [cm] | |
| Mean (SD) | 138.9 (12.2) |
| BMI [kg/m$^2$] | |
| Mean (SD) | 17.4 (3.2) |
| Smoking exposure history, N (%) | |
| No exposure | 95 (94.1) |
| Exposure to household/ second-hand smoking | 6 (5.9) |
| Duration of asthma [years] | |
| Mean (SD) | 4.54 (2.27) |
| Duration of asthma by category, N (%) | |
| <1 year | 6 (5.9) |
| 1 year to <3 years | 18 (17.8) |
| ≥3 years | 77 (76.2) |

Source: CSR Report 205.425, page 91, Table 11.2.1:1

All 101 randomized patients had taken ICS within the last 3 months before Visit 1; all patients had taken the ICS required for participation in the study, while 27.7% had also taken intranasal glucocorticoids, and no patients had taken oral, intravenous, or intramuscular glucocorticoids. All 101 patients were taking $\beta_2$-adrenergic agonists; this included 36.6% of patients who took LABAs and 98.0% of patients who took

SABAs. Almost half of the patients were taking leukotriene modifiers (45.5%), 9.9% were taking systemic antihistamines, and 5.0% were taking anti-allergic agents (excluding corticosteroids) in the last 3 months before screening. Specific pulmonary concomitant therapies that were commonly taken by patients within the 3 months before screening included salbutamol (98.0%), fluticasone (74.3%), budesonide (31.7%), salmeterol (28.7%), formoterol (8.9%), mometasone (6.9%), and beclometasone (4.0%).

**Results of Primary efficacy endpoints:**
The mean baseline FEV1 value at Visit 2 for all patients in the full analysis set (FAS) was 1.638 L (SD=0.388). The adjusted mean FEV1 $peak_{0\text{-}3h}$ response after 4 weeks of treatment with tiotropium was superior to the response observed for patients on placebo. The difference between each active treatment and placebo was 0.075 L, 0.104 L, and 0.087 L for TR 1.25, TR2.5, and TR5, respectively (Table 4.1.2). The TR2.5 group numerically showed the highest increase of FEV1 $peak_{0\text{-}3h}$ response compared to the placebo group.

**Table 4.1.2 Comparison of The FEV1 $Peak_{0\text{-}3h}$ Response (L) between Three Active Treatment Groups and Placebo Group after 4 weeks of treatment (MMRM) - FAS**

| Treatment | N | Adjusted mean (SE)[1] | Adjusted mean difference (SE)[1] | 95% CI | p-value for superiority[2] |
|---|---|---|---|---|---|
| Placebo | 76 | 0.185 (0.025) | | | |
| Tio R1.25 | 75 | 0.261 (0.026) | 0.075 (0.023) | (0.030, 0.120) | 0.0011 |
| Tio R2.5 | 74 | 0.290 (0.026) | 0.104 (0.023) | (0.059, 0.149) | <0.0001 |
| Tio R5 | 75 | 0.272 (0.026) | 0.087 (0.023) | (0.042, 0.132) | 0.0002 |

[1] adjusted for treatment, period, patient, and baseline
[2] 2-sided p value for superiority
Source: CSR Report 205.425, page 97, Table 11.4.1.1.1:1

The FEV1 response over time up to 3-hour post-dosing is illustrated in Figure 4.1.2. For all the active treatment groups, the FEV1 response at all the time points up to 3-hour post-dosing was superior to the response observed in placebo group.

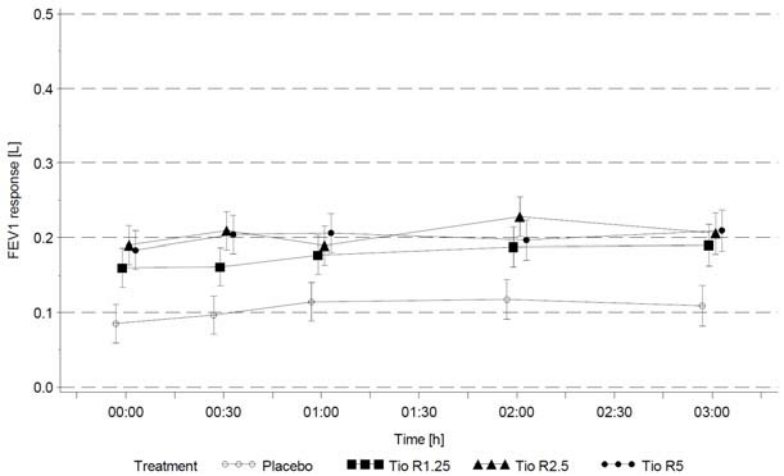



**Figure 4.1.2** Adjusted mean FEV1 response (L) up to 3-hour post-dosing after 4 weeks of treatment with TR1.25, TR2.5, TR5, or placebo (MMRM)-FAS (Source: CSR Report 205.425, page 107, Figure 11.4.1.3.1:1)

**PK Results:**
PK samples were collected from a total of 50 children, either plasma and urine samples or urine samples only, after the first dose and at the end of Period 1. The number of patients that provided PK samples for each study treatment is summarized in Table 4.1.3.

**Table 4.1.3 Number of Patients per Treatment Group That Provided PK Plasma and Urine samples or Urine Samples Only**

| Treatment | Plasma and urine samples N | Urine samples only N | Total number of patients N |
|---|---|---|---|
| Placebo | 9 | 6 | 15 |
| Tio R1.25 | 4 | 7 | 11 |
| Tio R2.5 | 6 | 6 | 12 |
| Tio R5 | 6 | 6 | 12 |
| Total number of patients | 25 | 25 | 50 |

Source: CSR Report 205.425, page 112, Table 11.5.2:1.

Tiotropium concentration was above the LLOQ of the bioanalytical method in 1 plasma sample of a patient assigned to placebo treatment due to an important protocol violation (patient no. 4251302 inhaled tiotropium instead of placebo at Visit 3). Tiotropium concentration was above the LLOQ in 6 out of 90 analyzed urine samples (6.7%) from patients assigned to placebo treatment. Out of 6 positive urine samples, 2 were due to the important protocol violation described above. The reason for the detection of tiotropium in remaining 4 urine samples was in most likelihood a result of contamination during sample handling. Similarly, tiotropium could be detected in the pre-dose urine fraction of first dose of 2 patients assigned to the TR5 group and 1 patient assigned to the TR1.25 group.

At least 0.5 mL/kg body weight/h urine was expected from patients over the 24 h urine collection period. Few patients had urine less than this predetermined amount (1 patient in the TR1.25 dose group at steady state, and 1 patient in the TR5 dose group after single dose administration and 2 patients at steady state). Given that besides asthma these were otherwise healthy children, the low urine volume collected was considered indicative of noncompliance to the 24 hours urine collection. Urinary PK parameter descriptive statistics were calculated with and without these individuals.

Although tiotropium concentrations following the first dose were above LLOQ in 2/4 patients from the TR1.25 and 2/6 patients from TR2.5 groups, there was insufficient data to report an average value for $C_{0.083}$ in these groups (Table 4.1.4). On the other hand, all $C_{0.083}$ from 6 subjects in the TR5 group were above LLOQ and the geometric mean was 5.93 pg/mL. The geometric mean urinary excretion amount of unchanged tiotropium during the 24 hours post-first-dose was 58.3, 79.2, and 216 ng for TR1.25, TR2.5, and TR5 group, respectively. The geometric mean urinary excretion fraction of unchanged tiotropium during the 24 hours post-first-dose was 4.66%, 3.17%, and 4.32% for TR1.25, TR2.5, and TR5 group, respectively.

**Table 4.1.4 Tiotropium PK Parameters following The First Dose Inhalation in Children 6-11 years Old with Moderate Persistent Asthma by Treatment**

| | | Tio R1.25 | | | Tio R2.5 | | | Tio R5 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter | Unit | N | gMean | gCV [%] | N | gMean | gCV [%] | N | gMean | gCV [%] |
| $C_{0.083}$ | [pg/mL] | - | - | - | - | - | - | 6 | 5.93 | 165 |
| $C_{0.083,\ norm}$ | [(pg/mL)µg] | - | - | - | - | - | - | 6 | 1.19 | 165 |
| $Ae_{0-3}$ | [ng] | 11 | 15.6 | 132 | 12 | 24.4 | 115 | 12 | 52.5 | 116 |
| $Ae_{0-24}$ | [ng] | 11 | 58.3 | 92.8 | 12 | 79.2 | 95.4 | 12 | 216 | 53.0 |
| $fe_{0-3}$ | [%] | 11 | 1.25 | 132 | 12 | 0.976 | 115 | 12 | 1.05 | 116 |
| $fe_{0-24}$ | [%] | 11 | 4.66 | 92.8 | 12 | 3.17 | 95.4 | 12 | 4.32 | 53.0 |

Source: CSR Report 205.425, page 116, Table 11.5.2:2.

Following multiple once-daily inhalation over 4 weeks, tiotropium was rapidly absorbed with a median $t_{max,ss}$ of 0.068 h to 0.078 h. Tiotropium could be detected in plasma up to 3 hours after inhalation in 1/4 patients in TR1.25 group, 3/6 patients in TR2.5 group, and 4/6 patients in TR5 group (Table 4.1.5). The geometric mean $C_{0.083,ss}$ was 2.42 and 3.65 pg/mL for TR2.5 and TR5 group, respectively. The geometric mean urinary excretion amount of unchanged tiotropium during the 24 hours at steady state was 170, 258, and 370 ng for TR1.25, TR2.5, and TR5 group, respectively. The geometric mean urinary excretion fraction of unchanged tiotropium during the 24 hours at steady state was 13.6%, 10.3%, and 7.39% for TR1.25, TR2.5, and TR5 group, respectively. The geometric renal clearance $CL_{R0-3,ss}$ of tiotropium (278 and 358 mL/min for the TR5 and TR2.5, respectively) was higher than the creatinine clearance.

**Table 4.1.5 Tiotropium PK Parameters following 4-week Once Daily Inhalation in Children 6-11 years Old with Moderate Persistent Asthma by Treatment**

| | | Tio R1.25 | | | Tio R2.5 | | | Tio R5 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter | Unit | N | gMean | gCV [%] | N | gMean | gCV [%] | N | gMean | gCV [%] |
| $AUC_{0-1,ss}$ | [pg·h/mL] | - | - | - | 3 | 2.08 | 31.7 | 5 | 3.04 | 38.3 |
| $AUC_{0-3,ss}$ | [pg·h/mL] | - | - | - | 3 | 5.21 | 32.1 | 4 | 7.76 | 29.2 |
| $AUC_{0-tz,ss}$ | [pg·h/mL] | - | - | - | 3 | 5.20 | 32.1 | 5 | 6.35 | 55.8 |
| $C_{max,ss}$ | [pg/mL] | 3 | 2.72 | 73.1 | 6 | 2.42 | 48.7 | 5 | 4.10 | 97.2 |
| $C_{max,ss,norm}$ | [(pg/mL)/µg] | 3 | 2.18 | 73.1 | 6 | 0.967 | 48.7 | 5 | 0.819 | 97.2 |
| $C_{0.083,ss}$ | [pg/mL] | 3 | 2.72 | 73.1 | 6 | 2.42 | 48.7 | 6 | 3.65 | 91.8 |
| $C_{0.083,ss,\ norm}$ | [(pg/mL)/µg] | 3 | 2.18 | 73.1 | 6 | 0.967 | 48.7 | 6 | 0.730 | 91.8 |
| $C_{pre,,ss}$ | [pg/mL] | - | - | - | - | - | - | 3 | 1.82 | 13.4 |
| $t_{max,ss}$[1] | [h] | 3 | 0.0780 | 0.0740-0.0800 | 6 | 0.0680 | 0.0540-0.0830 | 5 | 0.0780 | 0.0580-0.0970 |
| $t_{z,ss}$[1] | [h] | - | - | - | 3 | 3.00 | 2.99-3.00 | 5 | 3.01 | 1.00-3.07 |
| $R_{A,C0.083}$ | | - | | | - | - | - | 6 | 0.615 | 106 |
| $CL_{R0-3,ss}$ | [mL/min] | - | - | - | 3 | 358 | 7.06 | 4 | 278 | 17.9 |
| $Ae_{0-3,ss}$ | [ng] | 11 | 24.4 | 122 | 11 | 72.1 | 48.3 | 12 | 101 | 65.2 |
| $Ae_{0-24,ss}$ | [ng] | 9 | 170 | 44.1 | 11 | 258 | 62.7 | 12 | 370 | 86.3 |
| $R_{A,}$ $Ae_{0-24}$ | | 9 | 2.45 | 50.0 | 11 | 3.43 | 115 | 12 | 1.71 | 126 |
| $fe_{0-3,ss}$ | [%] | 11 | 1.96 | 122 | 11 | 2.88 | 48.3 | 12 | 2.02 | 65.2 |
| $fe_{0-24,ss}$ | [%] | 9 | 13.6 | 44.1 | 11 | 10.3 | 62.7 | 12 | 7.39 | 86.3 |

[1] median, minimum-maximum

Source: CSR Report 205.425, page 117, Table 11.5.2:3.

Steady state urinary PK parameter descriptive statistics excluding individuals with oliguria (24 hour urine volume < 0.5 mL/hour/kg) is listed in Table 4.1.6.

**Table 4.1.6 Tiotropium Urine PK Parameters following 4-week Once Daily Inhalation in Children 6-11 years Old Excluding Oliguria Samples**

| Age Group | 1.25 µg (N=9) | 2.5 µg (N=11) | 5 µg (N=10) |
|---|---|---|---|
| $Ae_{0-24,ss}$ (ng) | 170 (CV=44%) | 258 (CV=63%) | 410 (CV=72%) |
| $fe_{0-24,ss}$ (%) | 13.6% (CV=44%) | 10.3% (CV=63%) | 8.21% (CV=72%) |

Source: CSR Report 205.425, page 349-351, Table 15.6.2.1:7-9.

**Safety/vital signs results:**
Vital signs were measured at Visit 2 (end of Period 1) at pre-dose (10 minutes before dose), 30 minutes, 1 hour, 2 hours, and 3 hours post-dose following 4-week once daily treatment. The mean vital sign post-dose changes from pre-dose in all the dosing groups (including placebo) were numerically small and not considered to be clinically relevant (Table 4.1.7).

**Table 4.1.7 Blood Pressure and Pulse Rate Changes from Baseline-Treated Set**

| Vital Signs | | Placebo | TR1.25 | TR2.5 | TR5 |
|---|---|---|---|---|---|
| Patient N | | 76 | 75 | 74 | 76 |
| Mean Systolic BP (mmHg) | Baseline[1] | 102.7 | 103.3 | 102.8 | 103.6 |
| | 30 min post-dose[2] | 104.7 | 103.6 | 102.9 | 103.9 |
| | Change | 2 | 0.3 | 0.1 | 0.3 |
| Mean Diastolic BP (mmHg) | Baseline[1] | 63.8 | 63.2 | 63.4 | 64.4 |
| | 30 min post-dose[2] | 63.5 | 62.6 | 63.3 | 63.6 |
| | Change | 0.3 | -0.6 | -0.1 | -0.8 |
| Pulse Rate (bpm) | Baseline[1] | 81.3 | 81.1 | 81.3 | 81.1 |
| | 30 min post-dose[2] | 83.4 | 82.9 | 83.4 | 83.3 |
| | Change | 2.1 | 1.8 | 2.1 | 2.2 |

[1] Baseline was measured 10 minutes before inhalation at Visit 2
[2] post-dose vital sign values were similar at 30 minutes, 1 hour, 2 hours, and 3 hours in each treatment group
* Median (range)
Source: adapted from CSR Report 205.425, page 126, Table 11.5.1:1.

**PK and vital signs Conclusions:**

- Tiotropium was rapidly absorbed following oral inhalation with median $t_{max,ss}$ values ranging from 0.0680 h to 0.0780 h. At steady-state, an average of 7.39% to 13.6% of the dose was excreted unchanged in the urine over 24 h. There was approximately 1.7- to 3.4-fold accumulation based on $Ae_{0-24}$ values.

- Mean systolic blood pressure, diastolic blood pressure, and pulse rate were comparable between treatments both at baseline and up to 3 h post-dose after 4 weeks of treatment. Mean systolic blood pressure, diastolic blood pressure, and pulse rate remained relatively stable over the 3 h post-dose after 4 weeks of treatment.

### 4.1.2 Study 205.443

**Study Type:** Phase 2/3, safety, efficacy, PK, parallel group, dose ranging study in asthma children (1 to 5 years old)

**Title:** A phase II/III, randomized, double-blind, placebo-controlled, parallel group trial to evaluate safety and efficacy of tiotropium inhalation solution (2.5 µg and 5 µg) administered once daily in the afternoon via Respimat® Inhaler for 12 weeks in patients 1 to 5 years old with persistent asthma

**Objective:**
The primary objective of this trial was to evaluate the safety and efficacy of 2 doses of tiotropium inhalation solution delivered via the Respimat® inhaler once daily in the afternoon in patients (1 to 5 years old) with (moderate to severe) persistent asthma on top of adequate maintenance treatment (consisting of at least ICS treatment).

**Study Design and Method:**
This was a randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of 2 doses of tiotropium (TR2.5 and TR5 QD) as add-on therapy compared with placebo over 12 weeks (Figure 4.1.3). The study planned to enroll 102 subjects and 129 children aged 1 to 5 years actually entered the study. The once daily dose was given during afternoon.

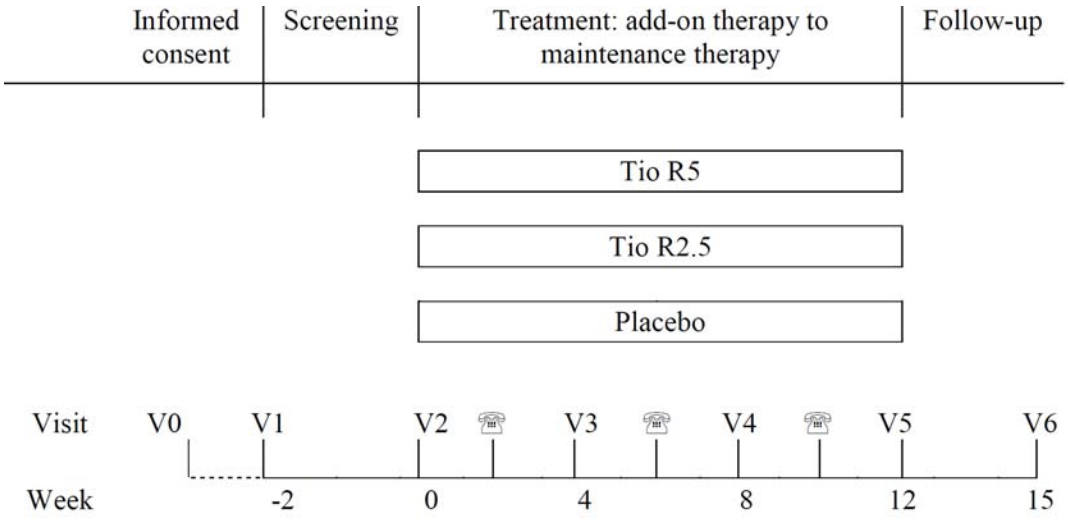



**Figure 4.1.3** Study design of Study 205.443 (Source: CSR Report 205.443, page 41, Figure 9.1:1)

Noteworthy inclusion criteria:

- Male or female outpatients between 1 and 5 years of age (up to 1 day prior to their 6th birthday at Visit 1)
- By a physician documented (at least 6 month) history of persistent asthma symptoms, including (but not limited to) wheezing, cough, and/or shortness of breath (persistent = need for ICS maintenance therapy to control asthma symptoms)
- All patients must have been on maintenance treatment with an inhaled corticosteroid at a stable dose, either as mono treatment or in combination with another controller medication, for at least 4 weeks before Visit 1
- All patients had to be symptomatic (partly controlled) as defined by the GINA guideline for children aged 5 years and younger (see Table 9.3.1: 1) in the week prior to Visit 1 (screening) and in the week prior to randomization (Visit 2)

Noteworthy exclusion criteria:

- Patients with a significant disease other than asthma
- Patients with clinically relevant abnormal screening hematology or blood chemistry results
- Patients with any unstable or life-threatening cardiac arrhythmia (in the opinion of the investigator), including cardiac arrhythmia requiring intervention (e.g. pacemaker implantation) or a change in drug therapy within the past year
- Patients with any acute asthma exacerbation or respiratory tract infection in the four weeks prior to Visit 1
- Patients requiring salbutamol/albuterol as asthma rescue medication (6 or more puffs by MDI or 3 or more nebulized treatments per day on more than 2 consecutive days) during the screening period in the 2 weeks prior to Visit 2
- Patients with known narrow-angle glaucoma, or any other disease where anticholinergic treatment would be medically contraindicated (in the opinion of the investigator)
- Patients with moderate to severe renal impairment, as defined by a creatinine clearance <50 mL/min/1.73 $m^2$

The three treatment arms were:

- TR2.5 QD for 12 weeks
- TR5 QD for 12 weeks
- Placebo solution for inhalation as delivered by Respimat® inhaler

For children aged 1 to 4 years of age, Aerochamber Plus Flow-Vu® valved holding chamber with facemask was used in combination with the Respimat® inhaler.

Urine samples were obtained predose, and from 0-2 h and 2-3 h post-dosing following the administration of the first dose and at Week 12 in a subset of 24 patients. Urine concentrations of tiotropium were determined by a validated HPLC-MS/MS assay. The analysis was performed at Nuvisan GmbH (Neu-Ulm, Germany). The calibration curves of undiluted samples were linear over the range of concentrations from 10.0 to 5000 pg/mL tiotropium using a volume of 2 mL acidified urine.

**Endpoint:**

- Primary Endpoints:
  - The combined daytime asthma symptom score as assessed by the Pediatric Asthma Caregiver Diary (PACD) in the last week of the 12-week treatment period
  - FEV1 peak0-3h (L) response after 12 weeks of treatment. This endpoint was only applicable to children aged 5 years at Visit 1 who were able to perform technically acceptable and reproducible pulmonary function testing.

- Secondary Endpoints:
  - Weekly mean PACD
  - All PFT endpoints were analyzed as response defined as the change from study baseline.

- The following urine PK parameters were determined using data from Visits 2 and 5 (Day 1 and 12 weeks of treatment):
  - $Ae_{t1\text{-}t2}$
  - $fe_{t1\text{-}t2}$
  - RA, $Ae_{0\text{-}3}$

**Demography:**
Demographic parameters were well balanced between the TR5, TR2.5, and placebo treatment groups (Table 4.1.8). Overall, the trial population contained more male patients (60.4%) than female patients (39.6%). The majority of the population was White (76.2%). Overall, the mean age was 3.1 years; 37 patients (36.6 %) were younger than 3 years, and 64 patients (63.4%) were aged between 3 and 5 years. The mean body weight was 16.2 kg.

**Table 4.1.8 Demographic Characteristics (Treated Set)**

| | Placebo | | Tio R2.5 | | Tio R5 | | Total | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) | N | (%) |
| Number of patients, N (%) | 34 | (100.0) | 36 | (100.0) | 31 | (100.0) | 101 | (100.0) |
| Male | 21 | (61.8) | 19 | (52.8) | 21 | (67.7) | 61 | (60.4) |
| Female | 13 | (38.2) | 17 | (47.2) | 10 | (32.3) | 40 | (39.6) |
| Race, N (%) | | | | | | | | |
| White | 24 | (70.6) | 28 | (77.8) | 25 | (80.6) | 77 | (76.2) |
| Asian | 7 | (20.6) | 5 | (13.9) | 5 | (16.1) | 17 | (16.8) |
| Black/African American | 3 | (8.8) | 3 | (8.3) | 1 | (3.2) | 7 | (6.9) |
| Ethnicity, N (%) | | | | | | | | |
| Not Hispanic/Latino | 34 | (100.0) | 36 | (100.0) | 31 | (100.0) | 101 | (100.0) |
| Hispanic/Latino | 0 | | 0 | | 0 | | 0 | |
| Age [years] | | | | | | | | |
| Mean (SD) | 3.2 | (1.4) | 3.1 | (1.5) | 3.1 | (1.3) | 3.1 | (1.4) |
| Weight [kg] | | | | | | | | |
| Mean (SD) | 16.3 | (3.8) | 16.4 | (5.2) | 16.0 | (3.5) | 16.2 | (4.2) |
| Height [cm] | | | | | | | | |
| Mean (SD) | 100.2 | (13.4) | 100.0 | (13.4) | 100.1 | (10.8) | 100.1 | (12.5) |
| BMI [kg/m$^2$] | | | | | | | | |
| Mean (SD) | 16.3 | (2.5) | 16.3 | (3.1) | 15.9 | (2.1) | 16.2 | (2.6) |
| Exposure to second hand smoke, N (%) | | | | | | | | |
| No | 33 | (97.1) | 31 | (86.1) | 28 | (90.3) | 92 | (91.1) |
| Yes | 1 | (2.9) | 5 | (13.9) | 3 | (9.7) | 9 | (8.9) |
| Household pets exposure history, N (%) | | | | | | | | |
| No | 25 | (73.5) | 28 | (77.8) | 21 | (67.7) | 74 | (73.3) |
| Yes | 9 | (26.5) | 8 | (22.2) | 10 | (32.3) | 27 | (26.7) |

Source: CSR Report 205.443, page 80, Figure 11.2.1:1

All 101 patients of the treated set had taken glucocorticoids within the last 3 months before Visit 1; all patients had taken ICS as required for participation in the trial. Furthermore, nearly all patients (96.0%) had taken $\beta_2$-adrenergic agonists; this included 95.0% of patients who took SABAs and 19.8% of patients who took LABAs. Leukotriene modifiers were being taken by 41.6% of patients, systemic antihistamines by 26.7% of patients, antibiotics by 19.8% of patients, and anti-allergic agents (excluding corticosteroids) by 11.9 % of patients. Specific pulmonary concomitant therapies that were commonly taken by patients within the 3 months before screening included salbutamol (95.0%), and fluticasone (80.2%).

**Results of Primary efficacy endpoints:**

[redacted] (b) (4)


**PK Results:**
Urine samples were obtained at predose, and from 0-2 h and 2-3 h post-dose following the first dose and at Week12 in a subset of 24 patients. Of the 24 patients in the PK subset, 9 received placebo; 12 received TR2.5, and 3 received TR5.

Tiotropium was not detected in the urine of any of the patients administered placebo in any urine collection interval. Tiotropium was detected in the pre-first dose urine sample of Patient # 4430751 who had been randomized to treatment with TR2.5. The reason for this was not clear but was probably because of contamination. Tiotropium concentrations were below the limit of quantification in the 2-3 h interval for Patient # 4430305 and 4431230 following the administration of the first dose. However, the reason for this was not clear.

Following the first-dose inhalation of TR2.5 or TR5, 0.238% to 0.414% of the dose was excreted unchanged in the urine over 3 h post-dose (Table 4.1.10). At steady state, approximately 1.08% to 1.53% of the dose was excreted unchanged in urine over 3 h post-dose following inhalation of TR2.5 and TR5, respectively. The accumulation ratio of $Ae_{0-3}$ was 2.61 and 6.42 at steady state for TR2.5 and TR5, respectively.

**Table 4.1.10 Summary of Urine PK Parameters following The First Dose and at Steady State in TR2.5 and TR5 Treatment Group**

| | Tio R2.5 | | Tio R5 | |
|---|---|---|---|---|
| Parameter [unit] | N | gMean (gCV%) | N | gMean (gCV%) |
| $Ae_{0-3}$ [ng] | 9 | 10.4 (44.3) | 3 | 11.9 (154) |
| $Ae_{0-3,ss}$ [ng] | 12 | 26.9 (65.6) | 3 | 76.3 (14.7) |
| $fe_{0-3}$ [%] | 9 | 0.414 (44.3) | 3 | 0.238 (154) |
| $fe_{0-3,ss}$ [%] | 12 | 1.08 (65.6) | 3 | 1.53 (14.7) |
| RA,$Ae_{0-3}$ | 9 | 2.61 (89.7) | 3 | 6.42 (191) |

Source: CSR Report 205.443, page 97, Figure 11.5.2:1

**Safety/vital signs results:**
Mean systolic blood pressure values, mean diastolic blood pressure values, and also mean pulse rate at Week 4, 8, and 12 were comparable between the treatment groups at trial baseline (Table 4.1.11). No noteworthy changes in the mean values were observed during the treatment period for any parameter.

**Table 4.1.11 Descriptive Statistics of Vital Signs at Weeks 4, 8, and 12 – Treated Set**

| Parameter | Placebo | | | Tio R2.5 | | | Tio R5 | | |
|---|---|---|---|---|---|---|---|---|---|
| Time point | N | Mean | SD | N | Mean | SD | N | Mean | SD |
| Systolic blood pressure [mmHg] | | | | | | | | | |
| Baseline[1] | 34 | 95.1 | (9.2) | 36 | 95.4 | (11.6) | 31 | 97.5 | (10.1) |
| Change from baseline | | | | | | | | | |
| Week 4 | 34 | 1.0 | (6.7) | 36 | -0.8 | (8.0) | 31 | 0.3 | (10.3) |
| Week 8 | 34 | 1.7 | (6.5) | 35 | 0.9 | (8.2) | 31 | -1.8 | (10.2) |
| Week 12 (end of treatment) | 34 | 2.1 | (8.1) | 36 | 1.4 | (10.8) | 31 | -2.6 | (9.6) |
| Diastolic blood pressure [mmHg] | | | | | | | | | |
| Baseline[1] | 34 | 58.1 | (6.7) | 36 | 58.9 | (7.1) | 31 | 57.6 | (6.2) |
| Change from baseline | | | | | | | | | |
| Week 4 | 34 | 2.1 | (8.0) | 36 | 1.7 | (8.2) | 31 | 1.8 | (8.8) |
| Week 8 | 34 | 1.9 | (6.5) | 35 | 0.1 | (6.6) | 31 | -0.1 | (7.8) |
| Week 12 (end of treatment) | 34 | 2.3 | (7.9) | 36 | -0.2 | (6.7) | 31 | 1.4 | (6.3) |
| Pulse rate [beats per min] | | | | | | | | | |
| Baseline[1] | 34 | 94.5 | (15.9) | 36 | 97.4 | (19.6) | 31 | 96.2 | (13.8) |
| Change from baseline | | | | | | | | | |
| Week 4 | 34 | 2.1 | (11.4) | 36 | -1.9 | (11.9) | 31 | 2.8 | (10.3) |
| Week 8 | 34 | -1.1 | (11.8) | 36 | -2.0 | (10.4) | 31 | -2.3 | (9.1) |
| Week 12 (end of treatment) | 34 | 0.0 | (11.7) | 35 | -1.7 | (11.8) | 31 | 0.8 | (9.6) |

[1] Base line was defined as the pre-dose values measured prior to administration of the first dose of trial medication.
Source: CSR Report 205.443, page 109, Figure 12.5.1:1

**PK and vital sings conclusions:**

- Following the first inhalation of TR2.5 or TR5, 0.238% to 0.414% of the administered dose was excreted unchanged in the urine over 3 h post-dose. Following TR2.5 or TR5 inhalation at steady-state, 1.08% to 1.53% of the dose was excreted unchanged in urine over 3 h post dosing. The accumulation ratio of $Ae_{0-3}$ was 2.61 and 6.42 at steady state for TR2.5 and TR5, respectively. However, average TR5 PK parameters should be treated with caution as these were based on 3 patients only and were associated with high variability.

- Overall, the mean systolic blood pressure, diastolic blood pressure, and pulse rate were comparable between the treatment groups at baseline at each clinic visit during the 12-week treatment period.

### 4.1.3 PK Meta-analysis Report (c09166654-01)

**Title:** Meta-analysis of tiotropium non-compartmental pharmacokinetic parameters across various Tiotropium trials comparing pediatric data to adult data

**Objective:**

- To compare the pharmacokinetics of tiotropium in adult and pediatric patients with asthma
- To identify best estimates of standard PK parameters for tiotropium in pediatric patients with asthma

**Method:**

The data included in this meta-analysis originates from ten clinical trials (7 adults and 3 pediatric trials) that are briefly summarized in Table 4.1.12. Sampling for PK was done in a subset of patients in the various trials. The individual trials included PK data from 460 adult patients with asthma (385 with moderate asthma and 75 with severe asthma) and 91 pediatric patients with asthma (67 with moderate asthma and 24 with persistent asthma). The data from the TR2.5 BID arm in adults study was ignored.

**Table 4.1.12 Summary Table of Completed Trials including PK Evaluation in Patients with Asthma**

| Trial number [Reference] | Phase and design[1] | Asthma severity[2] | Objective | Treatment Duration | Treatment Groups[3] | Number of patients in PK subset per treatment group |
|---|---|---|---|---|---|---|
| **Phase II trials in adult patients** | | | | | | |
| 205.380 [U12-2075] | Phase II, cross-over | Moderate | Dose finding efficacy, safety and PK | 16 wk (4 x 4 wk) | Placebo<br>Tio R1.25 (qd)[4]<br>Tio R2.5 (qd)[4]<br>Tio R5 (qd)[4] | 51<br>52<br>51<br>49 |
| 205.420 [U12-2227] | Phase II, cross-over | Moderate | Dosing regimen testing, efficacy, safety and PK | 12 wk (3x 4 wk) | Placebo<br>Tio R2.5 (bid)<br>Tio R5 (qd)[4] | 29<br>29<br>28 |
| 205.441 [c02103425] | Phase II, cross-over | Moderate | Dosing regimen testing, efficacy, safety and PK | 8 wk (2x 4 wk) | Tio R2.5 (bid)<br>Tio R5 (qd)[4] | 29<br>28 |
| **Phase III trials in adult patients** | | | | | | |
| 205.416 [U12-1986] | Phase III, parallel-group | Severe | Confirmatory efficacy, safety and PK | 48 wk | Placebo[5]<br>Tio R5 (qd)[5] | 34<br>37 |
| 205.417 [U12-1987] | Phase III, parallel-group | Severe | Confirmatory efficacy, safety and PK | 48 wk | Placebo[5]<br>Tio R5 (qd)[5] | 38<br>38 |
| 205.418 [c02036039] | Phase III, parallel-group, active comparator | Moderate | Confirmatory efficacy, safety and PK | 24 wk | Placebo<br>Tio R2.5 (qd)[4]<br>Tio R5 (qd)[4]<br>Salmeterol[6] (50 µg) (bid) | 36<br>33<br>35<br>36 |
| 205.419 [c02036086] | Phase III, parallel-group, active comparator | Moderate | Confirmatory efficacy, safety and PK | 24 wk | Placebo<br>Tio R2.5 (qd)[4]<br>Tio R5 (qd)[4]<br>Salmeterol[6] (50 µg) (bid) | 23<br>28<br>23<br>26 |
| **Phase II/III trials in pediatric patients** | | | | | | |
| 205.424 [U11-2586] | Phase II, incomplete cross-over | Moderate | Dose finding efficacy, safety and PK | 12 wk (3x 4 wk) | Placebo<br>Tio R1.25 (qd)[4]<br>Tio R2.5 (qd)[4]<br>Tio R5 (qd)[4] | 11<br>14<br>13<br>14 |
| 205.425 [U13-1322] | Phase II, incomplete cross-over | Moderate | Dose finding efficacy, safety and PK | 12 wk (3x 4 wk) | Placebo<br>Tio R1.25 (qd)[4]<br>Tio R2.5 (qd)[4]<br>Tio R5 (qd)[4] | 15<br>11<br>12<br>12 |
| 205.443 [c03067178] | Phase II/III, parallel group | Persistent | Dose finding efficacy, safety and PK | 12 wk | Placebo<br>Tio R2.5 (qd)[4]<br>Tio R5 (qd)[4] | 9<br>12<br>3 |

Source: metaanalysis-p5-tiotropium-in-asthma-pediatric—study-report.pdf, page 13, Table 6.1:1

This meta-analysis included key PK parameters derived from plasma and urinary samples. All PK parameters included in this meta-analysis were derived by non-compartmental analysis based on the concentration data with all decimal places provided in the original bioanalytical report. Only concentrations within the validated concentration range were used for the calculation of PK parameters. For urine sample analysis, patients assumed to be noncompliant with urine collection (i.e., oliguria as defined by 24 hour urine volume less than 0.5 mL/hour/kg) were excluded.

For derivation of AUCs, the pre-dose concentrations, which were below the limit of quantification (BLQ), were set to zero. Values below the lower quantification limit flagged with BLQ or NOP in the lag-phase were also set to zero. The lag phase was defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ/NOP values of the profile were ignored. The same rules were applied to concentration time profiles obtained after multiple dosing.

Descriptive statistics report required at least 3 observations available within one category.

**Description of analysis datasets:**
An overview of the demographic characteristics by age groups is given in Table 4.1.13.

**Table 4.1.13 Summary of Demographic Characteristics of Asthma Patients by Age Given as Median (Range) or N**

| | 1 ≤ to ≤ 5 yr | 6 ≤ to ≤ 11 yr | 12 ≤ to < 18 yr | ≥ 18 yr | Overall |
|---|---|---|---|---|---|
| N | 15 | 35 | 41 | 311 | 402 |
| Age [years] | 4 (1-5) | 9 (6-11) | 14 (12-17) | 48 (18-75) | 43 (1-75) |
| Body weight [kg] | 18 (12-40) | 34.3 (23-63) | 60 (35-137) | 80 (42-146.5) | 75 (12-146.5) |
| Height [cm] | 111 (77-126) | 143 (116-162) | 167 (146-197) | 169 (144-196) | 166 (77-197) |
| Body Surface Area [$m^2$] | 0.76 (0.51-1.11) | 1.19 (0.91-1.63) | 1.68 (1.23-2.44) | 1.91(1.32-2.66) | 1.84 (0.51-2.66) |
| Gender Male/Female [N(%)] | 7/8 (46.7/53.3) | 11/24 (31.4/68.6) | 10/31 (24.4/75.6) | 183/128 (58.8/41.2) | 211/191 (52.5/47.5) |

Source: metaanalysis-p5-tiotropium-in-asthma-pediatric—study-report.pdf, page 21, Table 7.1:1

The proportion of BLQ/NOP $C_{0.083,ss}$ plasma samples excluded from descriptive statistics is summarized in Table 4.1.14.

**Table 4.1.14 Proportion of BLQ/NOP $C_{0.083,ss}$ Plasma Samples Excluded by Age and Dose**

| Age Group | TR1.25 | TR2.5 | TR5 |
|---|---|---|---|
| **6-11years** | 25% (1/4) | 0% (0/6) | 0% (0/6) |
| **12-17 years** | 60% (3/5) | 25% (1/4) | 0% (0/11) |
| **≥ 18 years** | 52% (27/52) | 19% (21/110) | 16% (38/236) |

Source: reviewer's analysis on dataset pk6p.xpt

The proportion of BLQ/NOP urine samples excluded for $fe_{0-24,ss}$ estimation is summarized in Table 4.1.15.

**Table 4.1.15 Proportion of BLQ/NOP Urine Samples Excluded in $fe_{0\text{-}24,ss}$ Estimation by Age and Dose**

| Age Group | TR1.25 | TR2.5 | TR5 |
|---|---|---|---|
| **6-11years** | 18% (2/11) | 0% (0/11) | 17% (2/12) |
| **12-17 years** | 0% (0/12) | 9.1% (1/11) | 8.3% (1/12) |
| **≥ 18 years** | 3.8% (2/52) | 5.6% (6/108) | 9.6% (20/208) |

Source: reviewer's analysis on dataset pk6p.xpt

**Analysis Results:**
The steady state plasma concentration time profile of tiotropium following the administration of TR2.5 (Figure 4.1.4) or TR5 (Figure 4.1.5) shows that the plasma profiles were similar by age groups. It should be noted that blood sampling for PK analysis was not done in the age group of 1 to 5 years (Study 205.433). Only sparse blood sampling was conducted in a subset of patients in the age group of 6 to 11 years old (Trial 205.425).

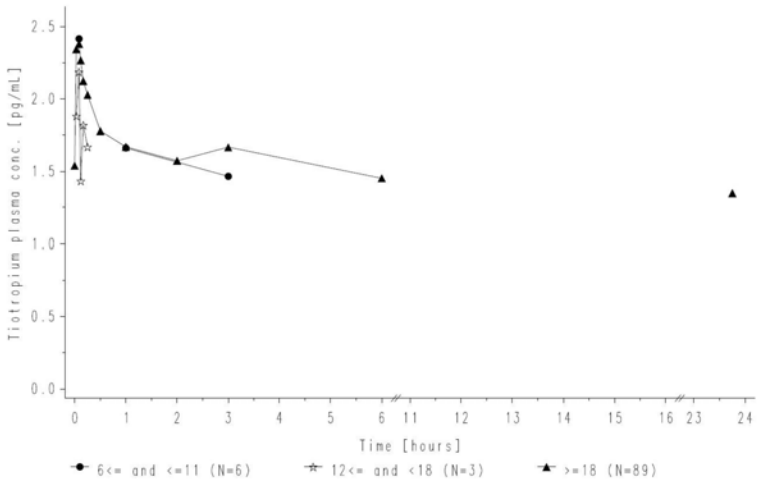



**Figure 4.1.4** Geometric mean steady state tiotropium plasma concentration-time following TR2.5 QD inhalation in patients with asthma by age. (Source: metaanalysis-p5-tiotropium-in-asthma-pediatric—study-report.pdf, page 23, Table 7.2.1:1)

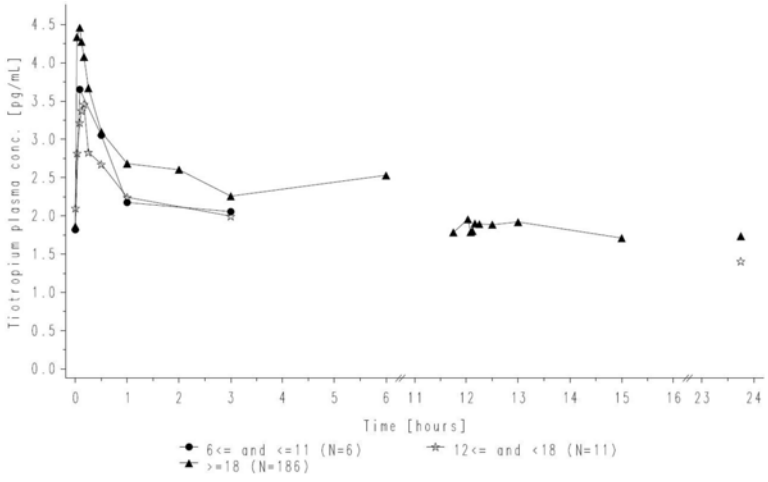


**Figure 4.1.5** Geometric mean steady state tiotropium plasma concentration-time following TR5 QD inhalation in patients with asthma by age. (Source: metaanalysis-p5-tiotropium-in-asthma-pediatric—study-report.pdf, page 24, Table 7.2.1:2)

The $fe_{0\text{-}24,ss}$ and dose-normalized $C_{0.083,ss}$ values in children 6-11 years were generally comparable to those of adults and adolescents (Table 4.1.16).

**Table 4.1.16 Overall Descriptive Summary of Dose-Normalized Steady State Tiotropium PK Parameters following Once daily Administration of TR1.25, TR2.5, and TR5 by Age Groups**

| Age category | $fe_{0\text{-}3,ss}$[1] [%] | | $fe_{0\text{-}24,ss}$[1] [%] | | $C_{0.083,ss,norm}$[2] [pg/mL/µg] | | $AUC_{0\text{-}3,ss,norm}$[3] [pg*h/mL/µg] | | $AUC_{\tau,ss,norm}$[3] [pg*h/mL/µg] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N[4] | gMean (gCV %) | N[4] | gMean (gCV %) | N[4] | gMean (gCV %) | N[4] | gMean (gCV %) | N[4] | gMean (gCV %) |
| 1 to 5 yr | 15 | 1.16 (59.7) | - | --- | - | --- | - | --- | - | --- |
| 6 to 11 yr | 31 | 2.43 (69.4) | 30 | 10.4 (63.0) | 15 | 1.02 (83.4) | - | --- | - | --- |
| 12 to <18 yr | 32 | 2.92 (85.8) | 33 | 13.3 (77.1) | 16 | 0.751 (68.6) | 12 | 1.81 (62.5) | 7 | 8.86 (27.5) |
| ≥ 18 yr olds | 147 | 2.52 (107) | 340 | 12.2 (84.6) | 312 | 0.953 (64.1) | 225 | 1.92 (55.1) | 134 | 11.5 (43.8) |

Source: metaanalysis-p5-tiotropium-in-asthma-pediatric—study-report.pdf, page 24, Table 7.2.1:1

Although the $fe_{0\text{-}3,ss}$ in the 1-5 year old patients was numerically lower than that of other age groups, after adjusting by BSA (body size parameter that are known to correlate with the lung volume); geometric mean $fe_{0\text{-}3,ss}$ value was 1.59%, 2.08%, 1.81%, and 1.32% for 1-5 years, 6-11 years, 12-17 years, and ≥ 18 years age group, respectively.

**Conclusions:**

- Geometric mean of dose-normalized steady state $C_{0.083,ss,norm}$ and 24-hour urinary excretion fraction $fe_{0\text{-}24,ss}$ in children 6-11 years was comparable to those of adolescents and adults.

- Geometric mean of steady state 3-hour urinary excretion fraction $fe_{0\text{-}3,ss}$ in children 1-5 years was numerically lower than that of older children and adults. However, since $fe_{0\text{-}3,ss}$ only represents fraction of $fe_{0\text{-}24,ss}$, the clinical meaning of $fe_{0\text{-}3}$ results in children 1-5 years of age is unclear.

***Reviewer's analysis:***
*Steady state systematic exposure comparison between children and adults by dose is summarized in Table 4.1.17. The steady state $fe_{0\text{-}24,ss}$ and $C_{0.083,ss}$ values in children 6-11 years of age following TR2.5 QD treatment were comparable to those of adults following the same dose treatment.*

**Table 4.1.17 Descriptive Summary of Steady State Tiotropium Plasma PK Parameters following Once Daily Administration of TR1.25, TR2.5, and TR5 by Age Groups**

| | **$fe_{0\text{-}24,ss}$ (%)** | | | **$C_{0.083,ss}$ (pg/mL)** | | |
|---|---|---|---|---|---|---|
| | **1.25 µg** | **2.5 µg** | **5 µg** | **1.25 µg** | **2.5 µg** | **5 µg** |
| **6-11 y[1]** | 13.6 (N=9, CV=44%) | 10.3 (N=11, CV=63%) | 8.21 (N=10, CV=72%) | 2.72 (N=3, CV=73%) | 2.42 (N=6, CV=49%) | 3.65 (N=6, CV=92%) |
| **12-18 y[2]** | 13.1 (N=14, CV=73%) | 14.3 (N=12, CV=70%) | 12.6 (N=12, CV=92%) | N/A | 2.19 (N=3, CV=88%) | 3.22 (N=11, CV=61%) |
| **≥ 18 y[3]** | 11.3 (N=50, CV=90%) | 12.7 (N=102, CV=84%) | 12.1 (N=188, CV=84%) | 1.63 (N=25, CV=37%) | 2.38 (N=89, CV=54%) | 4.58 (N=198, CV=70%) |

[1] from Table 4.1.6
[2] from CSR 205.424 page 118, Table 11.5.2:2
[3] reviewer's analysis on dataset pk6p.xpt

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

YUNZHAO REN
01/19/2017

BHAWANA SALUJA
01/19/2017