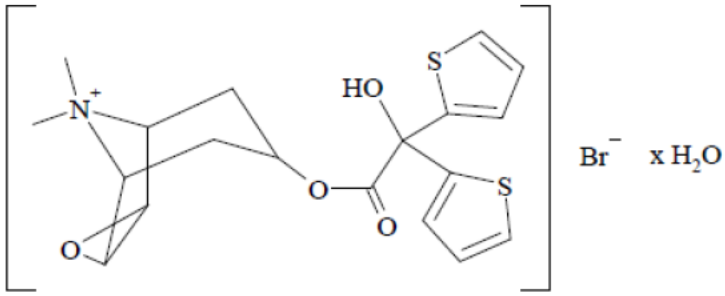
CLINICAL PHARMACOLOGY REVIEW	
NDA Number:	207070 (Related NDA 21936, related IND 065127)
Submissions Date:	08/15/2014
Submission Type:	505(b)(1)
Proposed Brand Name:	SPIRIVA RESPIMAT
Generic Name:	Tiotropium bromide
Sponsor:	Boehringer Ingelheim
Route of Administration:	Inhalation
Dosage Form:	Aqueous inhalation solution
Dosage Strength:	(b) (4)
Proposed Dosing Regimen:	(b) (4) µg tiotropium (2 actuations) daily
Proposed Indication(s):	Long-term, once-daily, add-on maintenance treatment of asthma patients who remain symptomatic on at least inhaled corticosteroids
Proposed Population(s):	Asthma patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Yunzhao Ren, M.D., Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
Molecular Structure:	 $Br^- \times H_2O$

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1. EXECUTIVE SUMMARY

Boehringer Ingelheim has submitted NDA 207070 under 505(b)(1) pathway 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 "Long-term, once-daily, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids." The proposed dosing regimen is two inhalations (b) (4) µg tiotropium each) once daily. The dosage form is an inhalation spray and each actuation delivers (b) (4) µg tiotropium (equivalent to (b) (4) mcg tiotropium bromide monohydrate with the SPIRIVA RESPIMAT inhaler.

The same product (b) (4) was approved for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbation under NDA 21936 on September 24, 2014. The relevant PK conclusions, including mass balance study and metabolism study results, acquired previously as part of NDA 21936 are applicable to this indication as well.

To be noted, during the development of the asthma program, the major Phase 3 studies (205.416, 205.417, 205.418, and 205.419) were started earlier than the major Phase 2 dose ranging study 205.380 (Table 2.1). In addition, Phase 3 studies 205.416 and 205.417 were started earlier than the Phase 2 dosing regimen exploration study 205.420. For review purpose, the Phase 2 results involved in dose selection or dose-response relationship were extensively covered in this review. But the interpretation of these results should be evaluated in the context of the time frame of the drug development and integrated with the overall conclusions from Phase 3 studies that contained many more subjects with much longer study durations (Table 2.1). For further discussion on safety and efficacy, refer to clinical review by Dr. Stacy Chin.

The PK of TR in asthma patients were evaluated in 6 clinical studies (Phase 2 studies 205.380 and 205.420, and Phase 3 studies 205.416, 205.417, 205.418 and 205.419). All these studies were conducted in asthma patients on maintenance treatment of inhaled corticosteroids (ICS). In each study, more than 9 blood samples per subject were collected during each studied dosing interval and the PK parameters were derived by non-compartment analysis.

The following are the major findings of the current review:

1) Tiotropium steady state was achieved following 7-day 2.5 µg once daily inhalation. At steady state, tiotropium $C_{max,ss}$, $AUC_{0-6,ss}$ and $Ae_{0-24,ss}$ values were 2.61 pg/mL (N=102, CV=59%), 10.4 pg·h/mL (N=39, CV=36%), and 0.319 µg (N=112, CV=83%), respectively. The peak plasma concentrations were attained approximately 5 minutes post-dose.

2) Following 4-week once daily treatment, tiotropium dose-response relationship from TR 1.25 to TR 10 was not clearly established in Phase 2 studies (205.P5 Phase 2 dose response meta-analysis). Although FEV1 $peak_{0-3h}$ and FEV1 AUC_{0-3h} responses were statistically greater in TR5 group than in TR2.5 group, the differences were numerically small (~ 40 to 60 mL). In addition, there was no statistical difference between TR10 group and TR5 group on FEV1 $peak_{0-3h}$ responses. The FEV1 $peak_{0-3h}$ responses were numerically higher in TR1.25 group than in TR2.5 group.

   Efficacy results from Phase 3 studies predominantly showed that FEV1 $peak_{0-3h}$ response, the (co)primary endpoint, was numerically higher in TR2.5 group than TR5 group (studies 205.418, 205.419, 205.442, and 205.456). In addition, co-primary endpoint FEV1 trough was numerically higher in TR2.5 group than TR5 group in two Phase 3 pivotal studies (205.418 and 205.419).

   Overall, the submitted data does not seem to provide additional benefit for the TR 5 QD dose over TR 2.5 QD dose.

3) [redacted] (b) (4) In addition, the Phase 2 dosing regimen exploring studies 205.420 and 205.441 were started later than the Phase 3 studies 205.416 and 205.417. The primary endpoint FEV1 AUC_{0-24h} response was shown to be comparable between TR5 QD and TR2.5 BID in studies 205.420 and 205.441. These results supported the QD dosing regimen.

4) Tiotropium bronchodilatory effect following the first dose in asthma patients on ICS maintenance treatment was evaluated in study 205.380. The FEV1 response following the first dose of TR5 appeared similar to the FEV1 response following 4-week TR5 once-daily treatment. The adjusted mean FEV1 response (change from baseline) gradually improved to ~ 0.20 L at ~ 1 hour post-dose and kept at that level at least 3 hours post-dose. The clinical relevance of the bronchodilatory effect size of tiotropium as an add-on therapy in asthma patients is deferred to Dr. Stacy Chin.

1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the NDA 207070 submitted on August 15, 2014 and is recommending approval from a clinical pharmacology perspective.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

1.3.1 Background

Tiotropium is a long-acting muscarinic antagonist (LAMA). Once inhaled, it binds to the M_3 muscarinic receptor on the smooth muscle surrounding the bronchioles and causes muscle relaxation (bronchodilation). However, it has been widely debated whether the bronchodilatory effect size of LAMA is clinically meaningful in asthma patients[1-3]. So far none of the LAMA products has been approved by the FDA for asthma indication, nor has their use been recommended in the current asthma guideline from American Lung association.

FDA approved two tiotropium bromide products from Boehringer Ingelheim indicated for maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbation. NDA 21395 SPIRIVA Handihaler (THH) is a dry powder inhaler approved on January 30, 2004. NDA 21936 TR, the same product proposed in this NDA submission, is an inhalation spray approved on September 24, 2014.

When THH was developed under IND 046687 (initiated on November 30, 1994), the original intended indication was as a "bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis, emphysema, and moderate to severe (b) (4) asthma." Subsequently, in an Annual Report dated April 29, 1999, the Sponsor notified the Division that clinical development in patients with asthma had been discontinued. The Sponsor stated in a report (dated October 8, 2001) that studies of the product in adults with asthma had failed to demonstrate effectiveness. An IR was issued by DPARP on 10/15/2014 requesting the Phase 2 study reports related to THH asthma program. The Sponsor submitted study reports on clinical trial 205.121, 205.201, 205.202 and 205.203. No PK studies were conducted in those trials. The bronchodilatory effect of THH in these studies is reviewed by Medical Officer Dr. Stacy Chin.

Early development of TR indicated for asthma was associated with IND 065127. The Sponsor first initiated asthma indication in an end-of-Phase 2 meeting on June 26, 2008.

The Sponsor held a Type C meeting with the FDA on August 25, 2009 for further discussions. The summary of PK samples and sampling schedules-related comments from the FDA is listed as following:

1) Both plasma and urine samples should be collected in Phase 3 studies.
2) PK samples from first dose in Phase 3 studies should be collected.
3) PK samples should be collected after the proposed 6 hour time point.
4) More PK samples should be taken at more time points in pediatric study to better describe the full time-concentration profile.

The summary of dose selection-related comments from the FDA from that Type C meeting is listed as following:

1) Your Phase 3 program is currently proceeding at risk, as the appropriate dose and dosing frequency in asthma has yet to be determined. If a dose or frequency other than the ones being tested is later determined to be the appropriate dose/regimen, further trials may be required.
2) Choosing the appropriate dose also requires identification of non-efficacious or suboptimal dose. While 2.5 µg once daily may be suboptimal, if it shows equal efficacy to the 5 µg dose, further trials will likely be required.

3) Your proposed dose-regimen trial (205.420) compares only a single dose once versus twice daily, which is insufficient to adequately explore the full dose and interval range. Include additional lower dosing arm(s) to the trial in order to ensure that the appropriate dose/regimen has been identified. Consider conducting this study prior to initiating further Phase 3 trials to ensure that the appropriate dose(s) have been chosen for your pivotal trials.

Based on the totality of the clinical data, it appears that:

1) The Sponsor proceeded with the Phase 3 program before completion of Phase2 dose-ranging studies.
2) TR2.5 QD was numerically better than TR5 QD in 4 out 5 Phase 3 studies in terms of the primary endpoint FEV1 $peak_{0\text{-}3h}$.
3) The make-up Phase 2 studies 205.420 and 205.441 supported once daily dosing regimen.

Nevertheless, the decision on dose selection and approval is based on the totality of the efficacy and safety data from both Phase 2 and Phase 3 studies. As such, refer to clinical review by Dr. Stacy Chin for final assessment of safety and efficacy.

Since the asthma program was developed following the COPD program during which the A5 device was finalized, the to-be-marketed formulation/device (A5 device) was the same as the formulation/device used in clinical development.

1.3.2 PK Characteristics

Absorption:
Following inhalation of TR in 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. At steady state, maximum tiotropium plasma concentrations were observed approximately 5 minutes after inhalation in asthma patients.

Distribution:
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. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier.

Metabolism:
The extent of metabolism is small. This is evident from urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, neither of which binds to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Elimination:
At steady state following 2.5 µg once daily inhalation, the effective half-life of tiotropium was approximately 1.5 days in asthma patients. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. In asthma patients, pharmacokinetic steady-state was reached by day 7 with no accumulation thereafter.
Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). At steady state, 24-hour urinary excretion is 18.6% (0.93 mcg) and 12.8% (0.32 mcg) of the dose in patients with COPD (5 µg once daily) and asthma (2.5 µg once daily), respectively. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine.

1.3.3 Summary of Phase 2 Dose-Ranging Studies

3 dose-ranging studies with once-daily regimen were conducted during Phase 2 stage (Table 2.1): study 205.341 (TR5 and TR10) and study 205.380 (TR1.25, TR2.5 and TR5) in adult patients, and study 205.424 (TR1.25, TR2.5 and TR5) in adolescent patients. Two studies, 205.420 and 205.441 tested TR 5 QD and TR 2.5 BID. Study 205.342 tested TR 5 QD. In addition, a dose-response meta-analysis was conducted by including efficacy data from 6 Phase 2 trials (205.341, 205.342, 205.380, 205.420, 205.441, and 205.424) covering an 8-fold dose range of TR. The purpose of this meta-analysis is to provide an overview for dose-response relationship of tiotropium during Phase 2 stage.

To be noted,

1) The major dose-ranging study 205.380 was started later than the major Phase 3 studies (205.416, 205.417, 205.418, and 205.419).
2) None of the Phase 2 studies pre-defined the dose-response relationship of tiotropium as a primary endpoint. All the analysis comparing the FEV1 responses (the efficacy endpoints) between different doses of tiotropium were conducted in an exploratory manner.

Comparisons of TR2.5 QD and TR5 QD in terms of primary FEV1 response endpoints from different studies and meta-analysis are listed in Table 1.1.

The primary endpoint FEV1 $peak_{0\text{-}3h}$ response following 4-week treatment was numerically higher in TR5 group than in TR2.5 group in both adults (study 205.380) and adolescents (study 205.424), though the difference was only significant in adults (60 mL).

However, the dose-response relationship between TR2.5 and TR1.25 was not established as FEV1 $peak_{0\text{-}3h}$ response was numerically higher in TR1.25 group than in TR2.5 group in both adults (study 205.380) and adolescents (study 205.424) (Table 1.1). In addition, there was no statistical significance between TR5 group and TR10 group on FEV1 $peak_{0\text{-}3h}$ response.

Table 1.1 Summary FEV1 Responses from Phase 2 Trials - FAS

Trial	Study population	Treatments	N in FAS	Primary endpoint	Primary endpoint[1] result	Diff. to placebo	Sign. vs. PBO	Trough FEV_1[1,2]	Diff. to placebo	Sign. vs. PBO
205.341	Adults; severe asthma[3]	Placebo	103	FEV_1 $peak_{0–3h}$	0.313 L			0.049 L		
		Tio R5	104		0.451 L	0.139 L	✓	0.136 L	0.086 L	✓
		Tio R10	103		0.483 L	0.170 L	✓	0.162 L	0.113 L	✓
205.380	Adults; moderate asthma[5]	Placebo	144	FEV_1 $peak_{0–3h}$	0.116 L			0.006 L		
		Tio R1.25	146		0.255 L	0.138 L	✓	0.131 L	0.125 L	✓
		Tio R2.5	147		0.244 L	0.128 L	✓	0.138 L	0.132 L	✓
		Tio R5	145		0.304 L	0.188 L	✓	0.149 L	0.143 L	✓
205.420	Adults; moderate asthma[5]	Placebo	91	FEV_1 $AUC_{0–24h}$	0.091 L			0.143 L		
		Tio R2.5 bid	89		0.241 L	0.149 L	✓	0.254 L	0.111 L	✓
		Tio R5	90		0.250 L	0.158 L	✓	0.275 L	0.133 L	✓
205.441	Adults; moderate asthma[5]	Tio R2.5 bid	98	FEV_1 $AUC_{0–24h}$	0.219 L	N.a.	N.a.	0.203 L	N.a.	N.a.
		Tio R5	97		0.217 L	N.a.	N.a.	0.207 L	N.a.	N.a.
205.424	Adolescents (12 to 17 y); moderate asthma[5]	Placebo	75	FEV_1 $peak_{0–3h}$	0.489 L			0.292 L		
		Tio R1.25	75		0.556 L	0.067 L	–	0.384 L	0.092 L	✓
		Tio R2.5	75		0.546 L	0.057 L	–	0.353 L	0.062 L	–
		Tio R5	79		0.602 L	0.113 L	✓	0.442 L	0.151 L	✓

1 Adjusted mean response from trial baseline. Trial 205.341: ANCOVA adjusted for pooled center, patient within pooled center, period, and treatment. Trials 205.380, 205.420, 205.441, and 205.424: MMRM adjusted for treatment, period, patient, and baseline.
2 Secondary endpoint in all trials
3 Trial medication given in addition to high-dose ICS + LABA
4 Patients had to be homozygous for arginine at the 16th position of the β2-adrenergic receptor
5 Trial medication given in addition to medium-dose ICS
(Source: 205-p5-dose-response-analysis.pdf, page 8, Table 2)

Efficacy results from Phase 3 studies were in favor of TR2.5 treatment (Table 1.2). FEV1 $peak_{0-3h}$ response was defined as the (co)primary efficacy endpoint in 5 Phase 3 studies that contained both TR2.5 and TR5 treatment groups (205.418, 205.419, 205.442, 205.456. and 205.444). 4/5 studies displayed that FEV1 $peak_{0-3h}$ values were numerically higher in TR2.5 group than TR5 group. In addition, co-primary endpoint FEV1 trough was numerically higher in TR2.5 group than TR5 group in two Phase 3 pivotal studies (205.418 and 205.419). The Sponsor attributed the Phase 2/3 differences to the lower variability observed in Phase 2 trials (see section 2.4.1).

Table 1.2 Comparisons of Efficacy Results of TR5 and TR2.5 from Phase 3 Trials – FAS

Trial	Study population	Maintenance asthma therapy	Endpoint of interest	P or S	Treatments	N in FAS	Endpoint of interest result[1]	Sign. vs. placebo
205.418	Adults; moderate asthma	Medium-dose ICS	FEV_1 $peak_{0-3h}$ response	P	Placebo	265	0.053 L	
					Tio R2.5	259	0.289 L	✓
					Tio R5	261	0.250 L	✓
					Sal 50 bid	271	0.266 L	✓
			Trough FEV_1 response	P	Placebo	265	−0.036 L	
					Tio R2.5	259	0.148 L	✓
					Tio R5	261	0.115 L	✓
					Sal 50 bid	271	0.086 L	✓
205.419	Adults; moderate asthma	Medium-dose ICS	FEV_1 $peak_{0-3h}$ response	P	Placebo	253	0.075 L	
					Tio R2.5	256	0.287 L	✓
					Tio R5	252	0.244 L	✓
					Sal 50 bid	264	0.252 L	✓
			Trough FEV_1 response	P	Placebo	253	−0.012 L	
					Tio R2.5	256	0.164 L	✓
					Tio R5	252	0.121 L	✓
					Sal 50 bid	264	0.094 L	✓
205.418/419	Adults; moderate asthma	Medium-dose ICS	Proportion of ACQ responders[2]	P	Placebo	518	57.7%	
					Tio R2.5	515	64.5%	✓
					Tio R5	513	64.3%	✓
					Sal 50 bid	535	66.5%	✓
205.442	Adults; mild asthma	Low-dose ICS	FEV_1 $peak_{0-3h}$ response	P	Placebo	155	0.134 L	
					Tio R2.5	154	0.293 L	✓
					Tio R5	155	0.262 L	✓
			Trough FEV_1 response	S	Placebo	155	0.015 L	
					Tio R2.5	154	0.125 L	✓
					Tio R5	155	0.137 L	✓
205.464	Adults (Japan); moderate to severe asthma	Medium-dose ICS± LABA	Trough FEV_1 response[3]	S	Placebo	56	0.075 L	
					Tio R2.5	114	0.087 L	–
					Tio R5	114	0.187 L	✓
205.456	Adolescents; severe asthma	Medium-dose ICS+ ≥2 controllers or high-dose ICS+ ≥1 controller	FEV_1 $peak_{0-3h}$ response	P	Placebo	135	0.438 L	
					Tio R2.5	127	0.550 L	✓
					Tio R5	130	0.528 L	–
			Trough FEV_1 response	S	Placebo	135	0.230 L	
					Tio R2.5	127	0.345 L	–
					Tio R5	130	0.284 L	–
205.444	Adolescents; moderate asthma	Medium-dose ICS	FEV_1 $peak_{0-3h}$ response	P	Placebo	138	0.373 L	
					Tio R2.5	125	0.507 L	✓
					Tio R5	134	0.547 L	✓
			Trough FEV_1 response	S	Placebo	138	0.283 L	
					Tio R2.5	125	0.367 L	–
					Tio R5	134	0.400 L	✓

(Source: section 2.5, clinical-overview-tio-in-asthma-us.pdf, page 42, Table 4.2.2.1:1)

Nevertheless, interpretation of the dose-response results from Phase 2 studies should be evaluated in the context of the time frame of the drug development and integrated with the overall clinical conclusion from Phase 3 studies that contained many more subjects with much longer study durations.

1.3.4 Bronchodilatory Effect of Tiotropium

- Bronchodilatory effect of tiotropium following the first-dose inhalation in asthma patients on maintenance treatment (ICS alone or combination with LABA/SABA)

The Sponsor defined tiotropium as a bronchodilator in the proposed label. Therefore, both the bronchodilatory effect and the clinical meaning of this bronchodilatory effect in asthma patients with add-on therapy need to be justified. The effect size of bronchodilation in naïve asthma patients (i.e., patients not on controller medications) is critical for the justification. However, the Sponsor does not have such studies conducted by Respimat device under NDA 207070. In a response to the Information Request issued on 10/15/2014, the Sponsor submitted study reports of clinical trials 205.121, 205.201, 205.202 and 205.203 (dated 10/21/2014) under HandiHaler development program. Study 205.121 was the only study in naïve asthma patients, but the primary endpoint was not FEV1 response. A dose-response relationship was observed in terms of methacholine responsiveness. The bronchodilatory effect of tiotropium under THH program is reviewed by Medical Officer Dr. Stacy Chin.

The asthma program of Respimat device under NDA 207070 only contained one study (205.380) assessing the bronchodilatory effect following inhalation of the first dose of TR in asthma patients on maintenance treatment with a medium, stable dose of ICS, either alone or in a fixed-dose combination with a LABA or SABA for at least 4 weeks before the screening visit. Almost all patients (143 of 149 randomized patients) used albuterol PRN for rescue before the screening visit. Although there was a 4-week period between the screening visit and the first-dose treatment visit, the recording of β2-agonist information in this period was inconsistent and not reliable. Therefore, it is impossible to identify a subgroup of even short-term β2-agonist-free patients before the first-dose treatment. Based on this, the bronchodilatory effect of tiotropium could only be evaluated as an add-on effect on background ICS and β2-agonist treatment.

The Office of Clinical Pharmacology issued two Information Requests (dated 01/07/2015 and 02/24/2015) to the Sponsor for additional analysis of tiotropium bronchodilatory effect following the first dose of tiotropium in study 205.380.

In response, the Sponsor provided the FEV1 $peak_{0\text{-}3h}$ analysis (Table 1.3) following the first dose inhalation of tiotropium (submission date 03/03/2015). The FEV1 $peak_{0–3h}$ responses (difference from placebo) of TR1.25, TR2.5 and TR5 were 0.073L, 0.140L and 0.136L, respectively. The FEV1 $peak_{0–3h}$ response was numerically higher in TR2.5 group than the TR5 group following the first dose inhalation of TR.

Table 1.3 Comparison of the Adjusted Mean FEV1 $Peak_{0\text{-}3h}$ Response between Active Treatment and Placebo Following the First Dose Treatment – FAS

		FEV_1 $peak_{0–3h}$ response [L][1]		Difference from placebo [L][1]			
Treatment	N	Mean	(SE)	Mean	(SE)	95% CI	p-value
Placebo	36	0.149	(0.042)				
Tio R1.25	38	0.222	(0.041)	0.073	(0.059)	(-0.043, 0.189)	0.2165
Tio R2.5	38	0.289	(0.041)	0.140	(0.059)	(0.024, 0.256)	0.0186
Tio R5	36	0.285	(0.042)	0.136	(0.060)	(0.017, 0.254)	0.0250

[1]Adjusted for treatment, pooled center and study baseline
Source: response-to-info-req.pdf dated 03/03/15, page 1, Table 1

The FEV1-time profile (Fig. 1.1) showed that the bronchodilatory effect (difference from placebo) of TR2.5 was numerically better following the first-dose treatment (0.140 L) than following 4-week treatment (0.128 L, Table 4.5) in asthma patients on maintenance treatment with a medium, stable dose of ICS, either alone or in a fixed-dose combination with a LABA or SABA. The

clinical meaning of these FEV1 response values following the first-dose or chronic treatment of TR5 is reviewed by Medical Officer Dr. Stacy Chin.

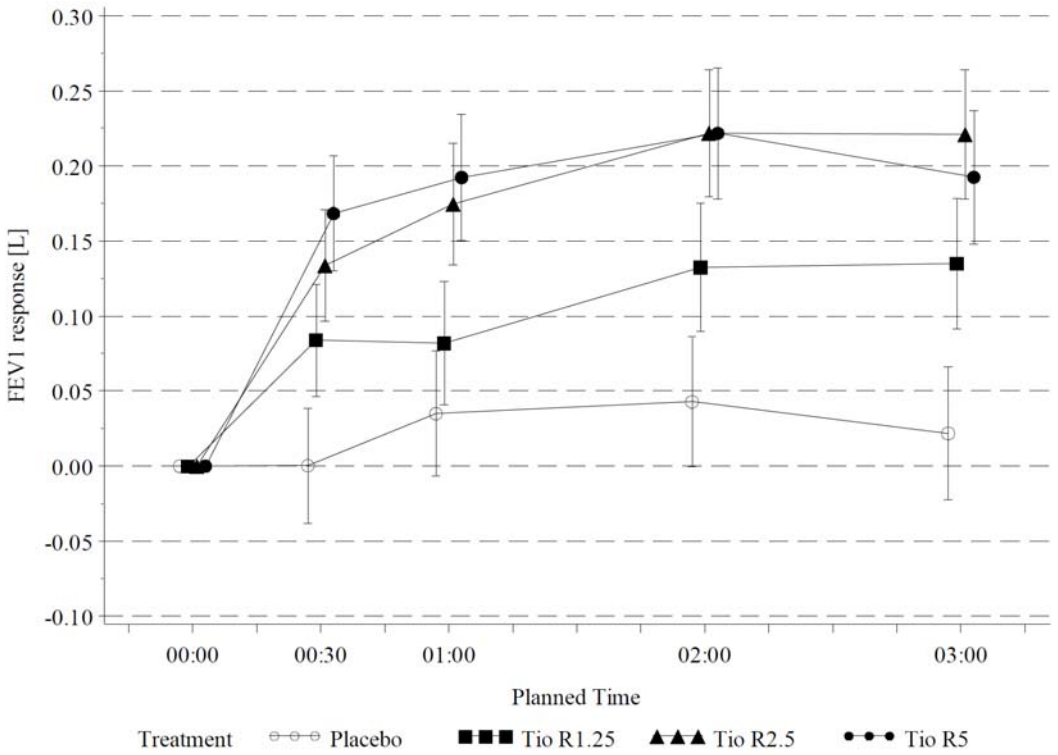

Fig.1.1 FEV1 response over time following the first dose inhalation of different treatment [Placebo (N=36), TR1.25 (N=38), TR2.5 (N=38), and TR5 (N=36)] in study 205.380. The means were adjusted for treatment, pooled center, and baseline (Source: response-to-info-request 0-20-2015, page 3, Figure 1).

- Bronchodilatory effect of tiotropium compared to other bronchodilators (SABA/LABA)

  Comparison the FEV1 response values following the first-dose inhalation between tiotropium and other bronchodilators such as SABA or LABA would further characterize the bronchodilatory effect of tiotropium. Although the FEV1 time-profile of the active control LABA, salmeterol, was similar to tiotropium in Phase 3 trials (study 205.418 and 205.419), the FEV1 responses were evaluated at Week 24, but not at Day 1.

  Since the FEV1-time profiles following the first-dose treatment are usually available in the labels for SABA/LABAs that were approved for asthma, the maximal mean FEV1 response from baseline (adjusted by placebo effect) was collected and compared with tiotropium (Table 1.5).

Table 1.4 Comparison of Maximal Mean FEV1 Changes between Tiotropium and Different SABA/LABAs from FEV1-Time Profile following the First-Dose Treatment in Asthma Patients

NDA # (Proprietary Name)	Active Ingredient (Dosage Form)	Studied Dose	Background Treatment	Time to mean FEV1 peak*	Maximal Mean FEV1 Adjusted by Placebo
207070 (Respimat)	Tiotropium (spray)	2.5 µg	ICS alone or with LABA/SABA maintenance	2 hours	0.18 L
205636 (RespiClick)	Albuterol (MDPI)	180 µg	ICS or recue use of SABA	1 hour	~ 0.3 L[1]
020236 (Serevent aerosol)	Salmeterol (CFC)	42 µg	Allow ICS	2 hours	~ 15%[2,#]
020692 (Serevent Diskus)	Salmeterol (DPI)	50 µg	Allow ICS	3 hours	~ 10%[3,#]
021279 (Foradil)	Formoterol (powder)	12 µg	unknown	3 hours	~ 0.6L[4]
NDA 204275 (Breo Ellipta)	Vilanterol (powder)	25 µg	ICS	3 hour	~ 0.28 L[5]

[#] PPFEV1 (%)
[1] Fig. 1.2
[2] Fig. 1.3. Presuming that the predicted FEV1 value being ~3 to 4 L, the numerical FEV1 improvement should be ~ 0.45 to 0.6 L.
[3] Fig. 1.4. Presuming that the predicted FEV1 value being ~3 to 4 L, the numerical FEV1 improvement should be ~ 0.3 to 0.4 L.
[4] Fig. 1.5
[5] Fig. 1.6

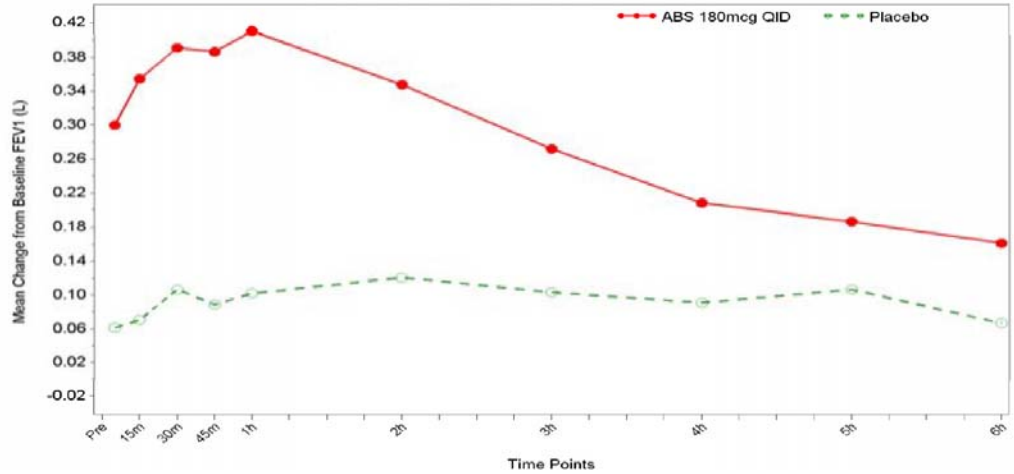

Fig.1.2 FEV1-time profile following first-dose treatment of 180 µg albuterol sulfate (SABA) dry powder (Proair RespliClick) inhalation. Source: NDA 205636 label

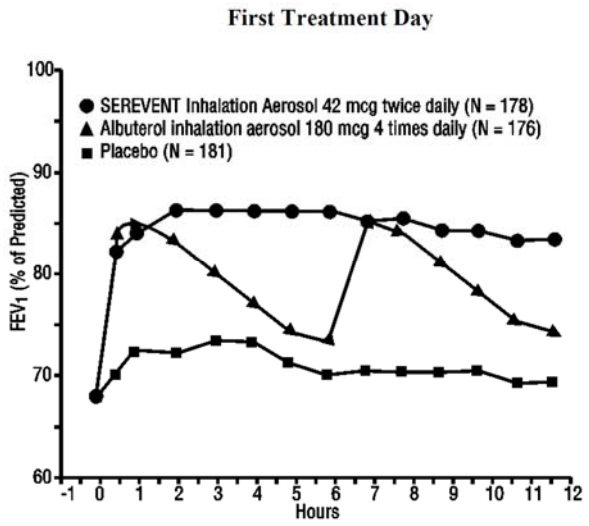

Fig.1.3 FEV1-time profile following first-day treatment of 42 µg BID salmeterol (LABA) CFC aerosol (Serevant) inhalation. Source: NDA 020236 label

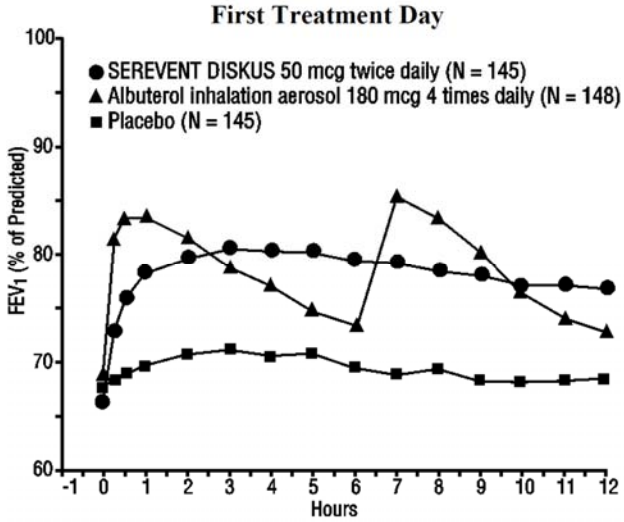

Fig.1.4 FEV1-time profile following first-day treatment of 50 µg BID salmeterol (LABA) dry powder (Serevant Diskus) inhalation. Source: NDA 020692 label

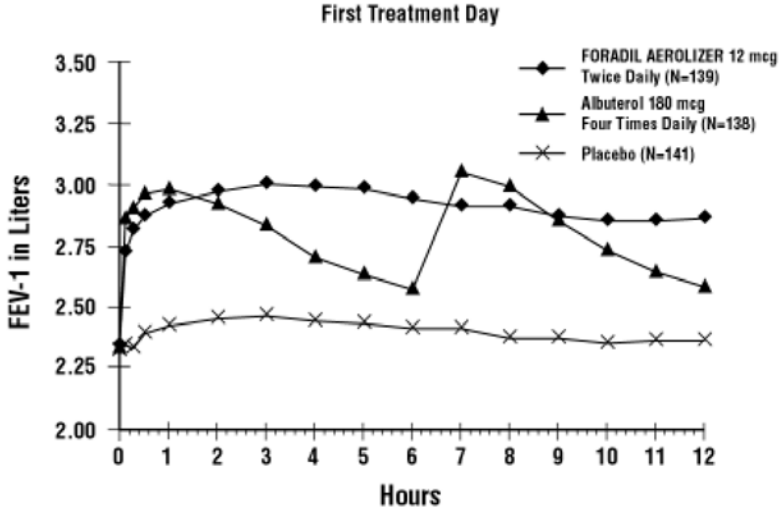

Fig.1.5 FEV1-time profile following first-day treatment of 10 µg BID formoterol (LABA) dry powder (Foradil Aerolizer) inhalation. Source: NDA 021279 label

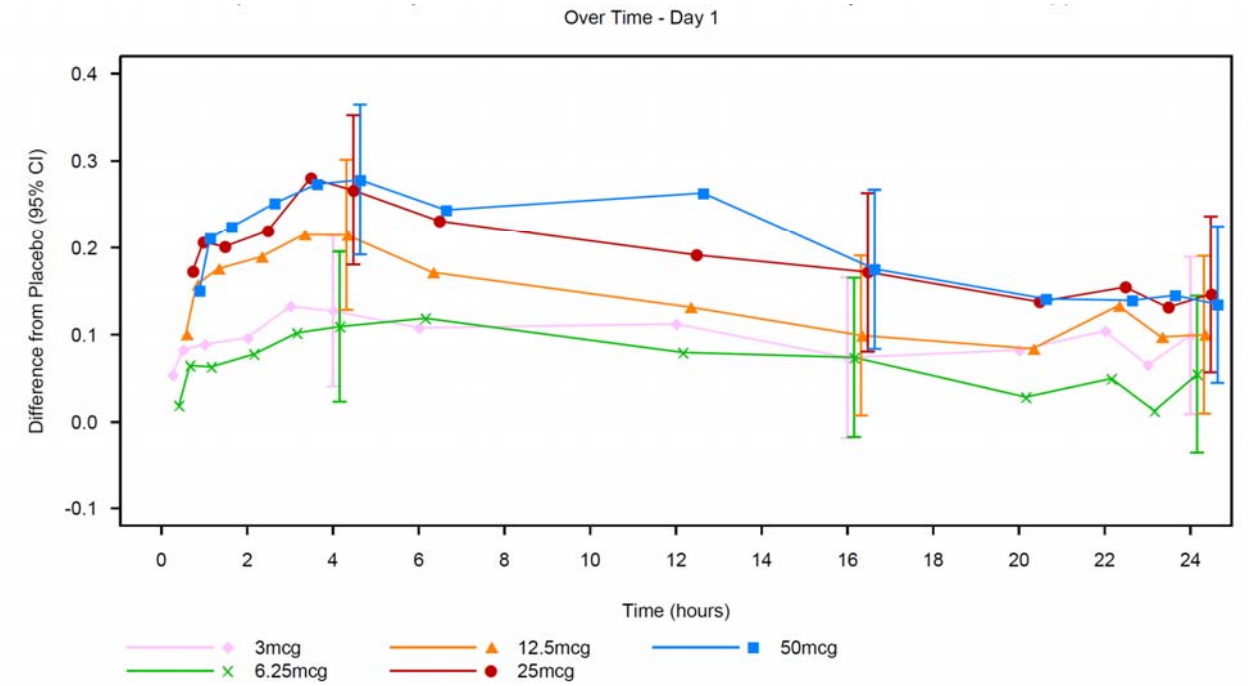

Fig.1.6 FEV1-time profile (adjusted by placebo) following first-day treatment of 3.0 - 50 µg vilanterol (LABA) dry powder inhalation. Source: NDA 204275 CSR B2C109575, currently under review

In summary, in asthma patients on background therapy, the bronchodilatory effect (maximal mean FEV1 change from baseline, adjusted by placebo) of TR2.5 is at least 40% less than those of approved SABA/LABA products, and 35% less than vilanterol, a LABA intended to combine with ICS, which is currently under review. Indacaterol was a LABA only approved in COPD patients. The bronchodilatory effect of indacaterol in asthma patients is unclear. Whether the reported tiotropium FEV1 response following the first-dose inhalation in asthma patients renders tiotropium as a "bronchodilator" *per se*, refer to clinical review by Dr. Stacy Chin.

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 NDA

Table 2.1 List of Clinical Studies Containing PK/PD evaluation in Patients with Asthma

Study ID	Study Date	Study Design[1]	Objective	Treatment Groups[2]	Treatment Duration	Patients Number[6]	Primary Endpoints
205.341	08/07/2006 - 11/08/2007	Phase 2, crossover	Proof-of-concept, efficacy , safety, PG	Placebo, TR5 (QD)[4], TR10 (QD)[4]	8 wk	107 (0) Severe	FEV1 peak0-3
205.342[5]	07/17/2006 - 09/10/2008	Phase 2, parallel	Proof-of-concept, efficacy and safety	Placebo, TR5 (QD)[3], Salmeterol 50 µg (BID)	16 wk	388 (0) Moderate	PEF
205.380	11/19/2010 - 01/09/2012	Phase 2, crossover	Dose ranging, efficacy, safety and PK	Placebo, TR1.25 (QD)[3] TR2.5 (QD)[3], TR5 (QD)[3]	4 wk	149 (52) Moderate	FEV1 peak0-3
205.420	07/05/2010 - 08/19/2011	Phase 2, crossover	Dosing regimen testing, efficacy, safety and PK	Placebo, TR2.5 (BID), TR5 (QD)[3]	4 wk	94 (29) Moderate	FEV1 AUC0-24
205.441	10/08/2012 - 06/20/2013	Phase 2, crossover	Dosing regimen testing, efficacy, safety and PK	TR2.5 (BID), TR5 (QD)[3]	4 wk	98 (35) Moderate	FEV1 AUC0-24
205.416	10/30/2008 - 07/25/2011	Phase 3, parallel	Confirmatory efficacy, safety and PK	Placebo, TR5 (QD)[3]	48 wk	459 (71) Severe	FEV1 peak0-3, trough FEV1, time to first exacerbation
205.417	11/03/2008 - 07/22/2011	Phase 3, parallel	Confirmatory efficacy, safety and PK	Placebo, TR5 (QD)[3]	48 wk	453 (76) Severe	FEV1 peak0-3, trough FEV1, time to first exacerbation
205.418	09/07/2010 - 11/13/2012	Phase 3, parallel	Confirmatory efficacy, safety and PK	Placebo, TR2.5 (QD)[3], TR5 (QD)[3], Salmeterol 50 µg (BID)	24 wk	1071 (140) Moderate	FEV1 peak0-3, trough FEV1, responder rate
205.419	08/24/2010 - 11/07/2012	Phase 3, parallel	Confirmatory efficacy, safety and PK	Placebo, TR2.5 (QD)[3], TR5 (QD)[3], Salmeterol 50 µg (BID)	24 wk	1032 (100) Moderate	FEV1 peak0-3, trough FEV1, responder rate
205.424	06/17/2010 - 04/11/2011	Adolescent, Phase 2, crossover	Dose ranging, efficacy, safety and PK	Placebo, TR1.25 (QD)[3] TR2.5 (QD)[3], TR5 (QD)[3]	4 wk	105 (14) Moderate	FEV1 peak0-3
205.P		Meta-analysis					

[1]All trials were conducted in a randomized, double-blinded, and placebo-controlled manner except 205.441 which was not placebo-controlled.
[2]All treatments were given as add-on therapy to usual care.
[3]In the evening
[4]In the morning
[5]In ADRB2 B16-Arg/Arg patients
[6]Patients number in efficacy/safety study (patient number in PK subset)
(Source: reviewer's summary based on section 5.2, TABULAR LISTING OF 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.

The tiotropium inhalation solution for use with the RESPIMAT device is a sterile aqueous solution of (b) (4) % (w/v) tiotropium bromide monohydrate. Four strengths of 0.625, 1.25, 2.5, and 5 µg tiotropium per actuation were developed during asthma program (Table 2.2). The strength of (b) (4) µg tiotropium is the marketed product.

Table 2.2 Composition of SPIRIVA RESPIMAT Inhalation Spray Used in Clinical Studies (Mass per Dose)

Strength	0.625 µg per actuation	1.25 µg per actuation	2.5 µg per actuation	5 µg per actuation	Placebo
Name of ingredient	Mass per dose [mg][2]				
Tiotropium (corresponds to tiotropium bromide monohydrate [1])	0.00125 (0.00016)	0.0025 (0.0031)	0.0050 (0.0062)	0.010 (0.012)	0
Benzalkonium chloride	(b) (4)				
Edetate disodium					
(b) (4) Hydrochloric acid					
Water for injections					
(b) (4)					
Total mass					
Commercial Formulation					

[1]The declared quantity o monohydrate. The conversion factor is 1.2494.
[2] Dose consists of 2 actuations.
(Source: section 3.2.P.2 Formulation.pdf, page 8, Table 2)

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

Muscarinic acetylcholine receptor (mChR) type M_3 is a G_q-protein-coupled receptor expressed on the surface of bronchial smooth myocytes. Upon binding with ligand such as acetylcholine, the receptor triggers downstream pathway causing muscle contraction. As a muscarinic antagonist, tiotropium has similar affinity to the subtypes of muscarinic receptors from M_1 to M_5 with values approximately 10 pM. However, the dissociation half-live of tiotropium is longer for receptor M_3 than M_2 with values of 27 hours and 2.6 hours, respectively[1]. Competitive displacement of acetylcholine from mAChR M_3 by tiotropium causes bronchial smooth muscle relaxation.

The therapeutic indication of TR is Long-term, once-daily, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids.

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

The proposed dosing regimen of TR is two inhalations (2 inhalations of (b) (4) µg each) of the spray once-daily. The route of administration is oral inhalation.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the U.S.?

Although tiotropium is approved for COPD, currently LAMA is not approved for asthma in the U.S. In a report dated October 8, 2001, the Sponsor notified the Division that that studies of THH (IND 046687) in adults with asthma had failed to demonstrate effectiveness.

Currently there are at least 5 classes of drugs approved for long-term control of persistent asthma:

1) Corticosteroids which inhibit airway inflammation
2) Mast cell membrane stabilizer such as cromolyn
3) Immunomodulators such as anti-IgE antibody
4) Leukotriene modifiers such as montelukast and zafirlukast
5) Long-acting adrenergic antagonists (LABA)

2.3 General Clinical Pharmacology

2.3.1 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Lung function endpoints, FEV1 peak0-3h and trough FEV1 response (change from trial baseline), at Week 24 were chosen as the co-primary endpoints in each of the Phase 3 efficacy trials in adult patients with severe (205.416 and 205.417) or moderate (205.418 and 205.419) asthma. Time to first severe asthma exacerbation was also analyzed as a primary endpoint (co-primary, tested hierarchically) using pooled data from the 48-week trials 205.416/417. Lung function endpoints were measured by spirometry.

Asthma control questionnaire (ACQ) responder rate was analyzed as a primary endpoint (co-primary, tested hierarchically) using pooled data from the 24-week trials 205.418/419. The ACQ score was calculated as the mean of the responses to the 7 questions, and was analyzed as an absolute value at each time point. The ACQ responder rate was based on an improvement in the patient's ACQ score (i.e. a decrease in score) of $\geq$0.5 points.

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 local concentrations in the lung was not available. However, tiotropium plasma or urine concentrations were measured by High Performance Liquid Chromatography-Tandem Mass Spectrometry (HPLC-MS/MS). Tiotropium concentrations from plasma or urine samples were precisely and accurately measured.

2.4 Exposure response

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

No exposure (concentration) - response relationship for efficacy was evaluated. Tiotropium inhaler delivers tiotropium to the lung and the efficacy is considered to be a local effect. The systemic bioavailability of tiotropium is not a determinant of efficacy.

The dose-response relationship for efficacy of asthma exacerbation was not studied in Phase 2 and Phase 3 trials. The dose-response relationship for bronchodilation effect was evaluated in Phase 2 trials.

In response to an information request issued by Office of Clinical Pharmacology on 10/15/2014, the Sponsor conducted a dose-response meta-analysis by including FEV1 response results from 6 Phase 2 trials (205.341, 205.342, 205.380, 205.420, 205.441, and 205.424) and submitted on 11/03/2014. The dose range covered once-daily dose from 1.25 µg to 10 µg. In total, results from 836 adults and 105 adolescents with moderate to severe asthma were pooled together (Table 1.1). All patients were on maintenance background therapy: ICS in the moderate asthma population and ICS+ LABA in the severe asthma population. Three response variables were considered for the integrated analyses: FEV1 $peak_{0-3h}$, FEV1 trough, and FEV1 AUC_{0-3h} (Table 2.3). The pooled data were analyzed using a mixed effects model for repeated measures (MMRM) and non-linear regression to characterize the dose response relationship.

The results showed that none of the tiotropium treatment cohort had more than 0.2 L improvement of FEV1 $peak_{0-3h}$, FEV1 trough, and FEV1 AUC_{0-3h}. In comparing TR10 and TR5, a numeric difference was observed in favor of TR10 for FEV1 $peak_{0-3h}$ (0.025 L [-0.024, 0.074], p=0.3127), trough FEV1 (0.006 L [-0.044, 0.057], p=0.8043) and FEV1 AUC_{0-3h} (0.009 L [-0.037, 0.055], p=0.7021) (Table 2.3, Fig. 2.1).

In comparing TR5 and TR2.5, a statistically significant difference was observed in favor of TR5 for FEV1 $peak_{0-3h}$ (0.050 L [0.014, 0.085], p=0.0058) and FEV1 AUC_{0-3h} (0.047 L [0.014, 0.080], p=0.0052) (Table 2.3, Fig. 2.1).
!
No statistical significant difference was observed between TR2.5 and TR1.25 for all 3 efficacy variables. TR1.25 was numerically better than TR2.5 (Table 2.3, Fig. 2.1).

In summary, although a meta-analysis of Phase 2 studies showed that FEV1 $peak_{0-3h}$ and FEV1 AUC_{0-3h} responses were statistically greater in TR5 group than in TR2.5 group, the difference was relatively small (~ 50 mL). The FEV1 responses were numerically greater in TR10 group than TR5 group with very small difference (6 to 25 mL). And the most important, TR1.25 was numerically better than TR2.5 for all 3 FEV1 response variables. Therefore, tiotropium dose-response relationship from TR 1.25 to TR 10 was not clearly established in asthma patients from the totality of Phase 2 data.

Table 2.3 Summary of Efficacy Comparisons between Different Doses of Tiotropium from Phase 2
!

Endpoint name	Treatment Comparison	Difference Adjusted*mean (SE)	95% CI	p-value
FEV1 Peak (0-3h) response [L]	Tio R10 vs Tio R1.25	0.066 (0.029)	(0.009 , 0.124)	0.0233
	Tio R10 vs Tio R2.5	0.075 (0.029)	(0.017 , 0.132)	0.0105
	Tio R10 vs Tio R2.5 bid	0.030 (0.031)	(-0.030 , 0.090)	0.3242
	Tio R10 vs Tio R5	0.025 (0.025)	(-0.024 , 0.074)	0.3127
	Tio R5 vs Tio R1.25	0.041 (0.018)	(0.006 , 0.076)	0.0223
	Tio R5 vs Tio R2.5	0.050 (0.018)	(0.014 , 0.085)	0.0058
	Tio R5 vs Tio R2.5 bid	0.005 (0.019)	(-0.033 , 0.043)	0.7919
	Tio R2.5 bid vs Tio R1.25	0.036 (0.025)	(-0.014 , 0.086)	0.1554
	Tio R2.5 bid vs Tio R2.5	0.044 (0.025)	(-0.005 , 0.094)	0.0795
	Tio R2.5 vs Tio R1.25	-0.008 (0.019)	(-0.046 , 0.029)	0.6617
FEV1 Trough response [L]	Tio R10 vs Tio R1.25	0.028 (0.030)	(-0.031 , 0.087)	0.3529
	Tio R10 vs Tio R2.5	0.031 (0.030)	(-0.028 , 0.090)	0.3062
	Tio R10 vs Tio R2.5 bid	0.017 (0.032)	(-0.045 , 0.079)	0.5957
	Tio R10 vs Tio R5	0.006 (0.026)	(-0.044 , 0.057)	0.8043
	Tio R5 vs Tio R1.25	0.022 (0.019)	(-0.015 , 0.058)	0.2439
	Tio R5 vs Tio R2.5	0.024 (0.018)	(-0.012 , 0.061)	0.1870
	Tio R5 vs Tio R2.5 bid	0.010 (0.020)	(-0.029 , 0.049)	0.5999
	Tio R2.5 bid vs Tio R1.25	0.011 (0.026)	(-0.040 , 0.062)	0.6691
	Tio R2.5 bid vs Tio R2.5	0.014 (0.026)	(-0.037 , 0.065)	0.5922
	Tio R2.5 vs Tio R1.25	-0.003 (0.020)	(-0.042 , 0.036)	0.8869
FEV1 AUC (0-3h) response [L]	Tio R10 vs Tio R1.25	0.049 (0.027)	(-0.004 , 0.103)	0.0721
	Tio R10 vs Tio R2.5	0.056 (0.027)	(0.002 , 0.109)	0.0406
	Tio R10 vs Tio R2.5 bid	0.016 (0.029)	(-0.040 , 0.072)	0.5756
	Tio R10 vs Tio R5	0.009 (0.023)	(-0.037 , 0.055)	0.7021
	Tio R5 vs Tio R1.25	0.040 (0.017)	(0.007 , 0.073)	0.0169
	Tio R5 vs Tio R2.5	0.047 (0.017)	(0.014 , 0.080)	0.0052
	Tio R5 vs Tio R2.5 bid	0.007 (0.018)	(-0.028 , 0.042)	0.6914
	Tio R2.5 bid vs Tio R1.25	0.033 (0.024)	(-0.013 , 0.080)	0.1634
	Tio R2.5 bid vs Tio R2.5	0.040 (0.024)	(-0.007 , 0.086)	0.0928
	Tio R2.5 vs Tio R1.25	-0.007 (0.018)	(-0.042 , 0.028)	0.7058

*** Adjusted for study, treatment, period, patient and baseline**
Common baseline mean (sd) at visit 2 = 2.372 (0.773)
(Source: 205-p5-dose-response-analysis.pdf, page 32, Table P.1.3.1:2)

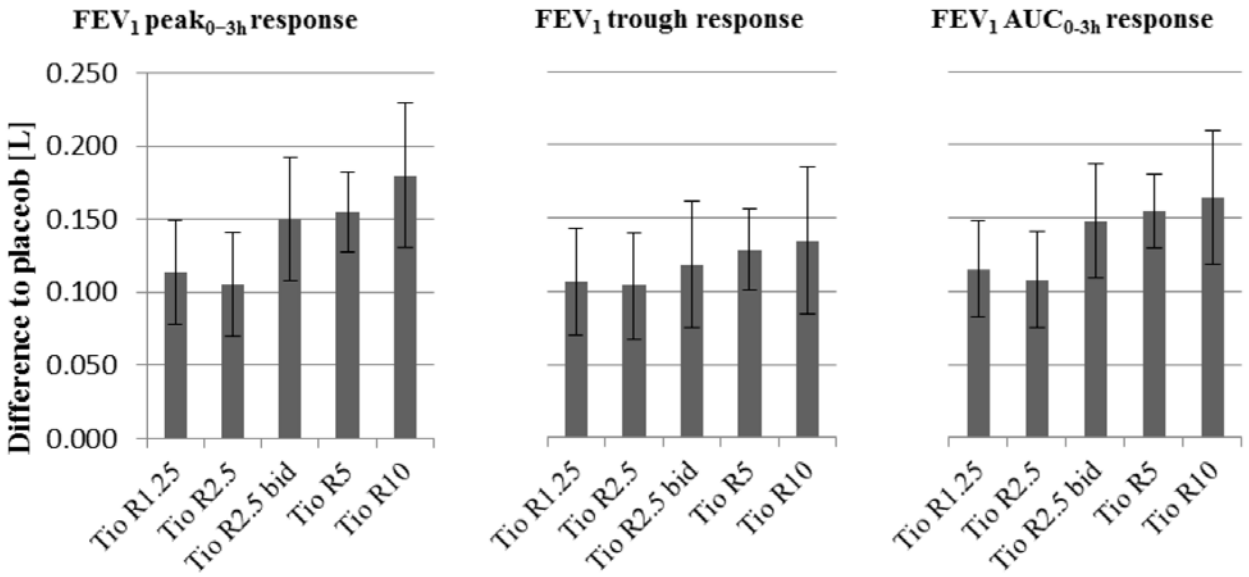

Fig.2.1 Tiotropium FEV1 peak$_{0\text{-}3h}$, FEV1 trough, and FEV1 AUC$_{0\text{-}3h}$ responses (difference to placebo) – adjusted mean and CI. (Source: 205-p5-dose-response-analysis.pdf, page 10, Figure 1)

The FEV1 response values between TR2.5 and TR5 groups were mixed in Phase 3 trials but generally in favor of TR2.5 (Table 1.2). TR2.5 FEV1 $peak_{0-3h}$ values were numerically higher than TR5 in study 205.418, 205.419, 205.442, 205.456 whereas TR2.5 $peak_{0-3h}$ value was only numerically lower than TR5 in study 205.444. TR2.5 FEV1 trough values were numerically higher than TR5 in study 205.418, 205.419, 205.456 whereas TR2.5 FEV1trough values were numerically lower than TR5 in study 205.442, 205.464, and 205.444.

The Office of Clinical Pharmacology issued an Information Request (dated on 10/15/2014) to the Sponsor for dose-response relationship clarification. In response, the Sponsor provided the following rationale (dated on 10/21/2014):

The reason a consistent dose response relationship was not observed in phase 3 trials, whereas it was in phase 2, is believed to be related to the overall lower variability observed for the phase 2 trials (see Table 2.4). The two phase 2 dose-ranging studies were designed specifically to characterize the dose response relationship (crossover, small number of participating countries), and thus, provide a more sensitive measure of the bronchodilator dose response of tiotropium Respimat in patients with asthma than the phase 3 trials…… Of note, the phase 3 trial conducted in Japan (study 205.464) was an exception in that it was conducted in a highly regimented single country, had variability comparable to the phase 2 studies, and demonstrated a clear dose response relationship.

Table 2.4 Observed Variability[1] for Trough FEV1

	Adults	Adolescents
Phase II 4-week crossover dose-ranging trials (205.380/205.424)	289 mL	299 mL
Phase III 12-week parallel-group trials (205.442/205.456)	333 mL	550 mL
Phase III 24-week parallel-group trials (205.418, 205.419/N.a.)	346 mL, 329 mL	N.A.
Phase III 48-week parallel-group trials (205.416, 205.417/205.444)	354 mL, 329 mL	470 mL
Phase III 52-week parallel-group trial conducted in Japan (205.464)	280 mL	N.A.

[1]Estimated standard deviation obtained from the primary MMRM model; within-patient variability for crossover trials and between-patient variability for parallel trials
(Source: Section 1.11.3, response-to-request10-15-14.pdf, page 4, Table 2)

Reviewer's comments:
It is not uncommon that the FEV1 dose-response relationship could not be consistently demonstrated within a 2-fold dose range (TR5 and TR2.5) for a bronchodilator. It might be true that the variability of FEV1 response in Phase 2 studies were relatively lower due to the cross-over study design, but Phase 3 studies enrolled many more patients and had much longer study duration. In addition, the major dose-ranging Phase 2 study 205.380 was started later than the major Phase 3 studies (205.416, 205.417, 205.418, and 205.419). Therefore, interpretation of the Phase 2 results should be evaluated in the context

of the time frame of the drug development and integrated with the overall risk/benefit clinical assessment from Phase 3 studies.

2.4.2 What are the characteristics of the exposure-response relationship for safety?

No formal exposure-response or dose-response relationships of safety were evaluated. The frequencies of patients with AEs were comparable between the TR5 group and the placebo group when safety data from 9 Phase 2/3 parallel-group trials were combined (Table 2.5).

Table 2.5 Overall Summary of Adverse Events in Adults and Adolescents, Pooled from All Parallel-Group Studies Investigating TR5 versus Placebo (205.342/416/417/418/419/442/444/456/464)

	Placebo N (%)	Tio R5 N (%)
Number of patients	1590 (100.0)	1634 (100.0)
Number of patients with AEs	953 (59.9)	960 (58.8)
Patients with severe AEs	80 (5.0)	99 (6.1)
Patients with drug-related AEs as defined by the investigator	60 (3.8)	86 (5.3)
Patients with other significant AEs (according to ICH E3)	26 (1.6)	21 (1.3)
Patients with AEs leading to discontinuation of trial drug	33 (2.1)	25 (1.5)
Patients with serious AEs[1]	67 (4.2)	60 (3.7)
Immediately life-threatening	1 (0.1)	5 (0.3)
Disability or incapacitation	0	2 (0.1)
Requiring hospitalization	62 (3.9)	54 (3.3)
Prolonging hospitalization	3 (0.2)	3 (0.2)
Other	3 (0.2)	7 (0.4)

(Source: section 2.7.4, summary-clin-safety.pdf, page 42, Table 1.2.1.1:1)

Table 2.6 Overall Summary of Adverse Events in Adults and Adolescents, Pooled from All Parallel-Group Studies Investigating TR2.5 versus Placebo (205.418/419/442/444/456/464)

	Placebo N (%)	Tio R2.5 N (%)
Number of patients	1008 (100.0)	1039 (100.0)
Number of patients with AEs	535 (53.1)	570 (54.9)
Patients with severe AEs	26 (2.6)	19 (1.8)
Patients with drug-related AEs as defined by the investigator	35 (3.5)	45 (4.3)
Patients with other significant AEs (according to ICH E3)	12 (1.2)	10 (1.0)
Patients with AEs leading to discontinuation of trial drug	17 (1.7)	9 (0.9)
Patients with serious AEs[1]	26 (2.6)	19 (1.8)
Immediately life-threatening	1 (0.1)	2 (0.2)
Disability or incapacitation	0	1 (0.1)
Requiring hospitalization	22 (2.2)	19 (1.8)
Prolonging hospitalization	2 (0.2)	1 (0.1)
Other	3 (0.3)	0

(Source: section 2.7.4, summary-clin-safety.pdf, page 43, Table 1.2.1.1:2)

Similarly, the frequencies of patients with AEs were comparable between the TR2.5 group and the placebo group when safety data from 6 Phase 3 parallel-group trials were combined (Table 2.6).

When comparing the frequencies of patients with AEs between the TR5 group and TR2.5 group, the frequencies were generally numerically higher in TR5 group. However, this observation may be confounded by inter-study differences as studies 205.416/417 were conducted in patients with severe asthma, and they only included TR5 treatment group, but not TR2.5 treatment group. Theoretically patients with severe asthma should have higher frequency of AEs than patients with moderate asthma. Indeed, the frequencies of AEs were also numerically higher in placebo group matching the TR5 group (Table 2.5) than the placebo group matching the TR2.5 group (Table 2.6).

2.4.3 Does this drug prolong the QT or QTc interval?

No dedicated thorough QT study was conducted in asthma patients. ECGs were performed on all patients at screening to assure eligibility for the trials. As stated in the exclusion criteria, a patient was not randomized to treatment if the ECG indicated the presence of a disease. No QT-related ECG parameters revealed any clinically relevant changes. One patient was reported with electrocardiogram ST segment depression, not assessed as drug-related by the investigator, and one patient was reported with electrocardiogram abnormal, assessed as drug-related by the investigator – both patients were in the Tio R5 treatment group.

According to the label from approved NDA 21395 tiotropium Spiriva HandiHaler, "In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30 to 60 msec was higher in the SPIRIVA HandiHaler group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical studies with SPIRIVA HandiHaler did not detect an effect of the drug on QTc intervals."

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

The systemic exposure of tiotropium is not an expected determinant of efficacy. In addition, tiotropium dose-response relationship from TR 1.25 to TR 10 was not clearly demonstrated in asthma patients from the totality of Phase 2/3 studies (see section 2.4.1).

Dosing regimens were compared between TR2.5 BID and TR5 QD on FEV1 responses in Phase 2 studies 205.420/441. In the assessment of dosing posology during the Type C meeting held on August 25, 2009, Sponsor's dose selection (2.5 µg BID and 5 µg QD) for trial 205.420 was considered to be a non-traditional approach as usually a lower BID dose (such as 1.25 µg BID) was used as a comparator. The Office of Clinical Pharmacology issued an Information Request (dated on 10/15/2014) to the Sponsor for further clarification for dosing regimen selection rationales. The Sponsor provided the following rationale in a response to the Information Request (dated on 10/21/2014):

As proposed at the 2009 Type C meeting, BI evaluated tiotropium RESPIMAT 1.25, 2.5 and 5 mcg once daily in the evening in patients with moderate asthma in two phase 2 trials to characterize the once daily dose response relationship and found that the lower doses of 1.25 and 2.5 mcg were suboptimal to the proposed dose of (b) (4) *mcg. As suggested by the Division at the 2009 Type C meeting, BI also explored the same daily dose of the final selected dose of* (b) (4) *mcg in* (b) (4) .

Trials 205.420 and 205.441 confirmed the comparable efficacy profile for tiotropium RESPIMAT 5 mcg administered as twice or once daily. In addition, the extensive 24-hour pulmonary function data generated in the phase 2 trials 205.341, 205.420, 205.441 and 205.424 and the phase 3 trials 205.416, 205.417, 205.418 and 205.419 provide substantial evidence supporting the 24-hour duration of action of range of once daily doses (1.25 to 10 mcg) of tiotropium RESPIMAT in patients 12 years and older with asthma.

In consideration of the vast amount of information supporting the once daily administration of tiotropium, further study of a total daily dose of (b) (4) *mcg as BID and QD would not provide meaningful information.*

Reviewer's comments:
In both Phase 2 studies (205.420 and 205.441) that compared the FEV1 responses between TR2.5 BID and TR5 QD, the efficacy results were all comparable between two dosing regimens. In study 205.420, the primary endpoint FEV1 AUC_{0-24h} responses from both TR2.5 BID and TR5 QD treatment groups were statistically significantly superior to the placebo group (Table 4.11) whereas no significant difference was detected between two active treatments (Table 4.12). In study 205.441, no significant difference was detected between TR2.5 BID and TR5 QD treatment groups for the primary endpoint FEV1 AUC_{0-24h} responses (adjusted mean FEV1 AUC_{0-24h} from baseline) (Table 4.16).

Therefore, based on the similar FEV1 response between two dosing regimens (TR2.5 BID and TR5 QD), the QD dosing regimen is acceptable.

2.5 PK Characteristics of the Drug

No new PK studies were conducted elucidating the basic ADME characteristics and special populations. Instead, information obtained previously from NDA 21936 is applied to this indication as well.

2.5.1 What are the characteristics of drug absorption?

The label of approved NDA 21936 tiotropium Spiriva Respimat states "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. "

Based on observed C_{trough} values from multiple studies, PK steady state was reached at the latest by day 7 in asthma patients and no accumulation was observed thereafter (Table 4.27, Table 4.29, and Table 4.31). The steady state $C_{trough,ss}$, $C_{max,ss}$ and $AUC_{0-6,ss}$ following TR2.5 QD inhalation were 1.54 pg/mL (N=35, CV=58%), 2.61 pg/mL (N=102, CV=59%), and 10.4 pg·h/mL (N=39, CV=36%), respectively (Table 4.40). At steady state, maximum tiotropium plasma concentrations were obtained approximately 5 minutes after inhalation in asthma patients.

2.5.2 What are the characteristics of drug distribution?

The label from approved NDA 21936 tiotropium Spiriva Respimat states, "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."

2.5.3 What are the characteristics of drug metabolism?

The label from approved NDA 21936 tiotropium Spiriva Respimat states, "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. *In vitro* experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4."

2.5.4 What are the characteristics of drug elimination?

The label from approved NDA 21936 tiotropium Spiriva Respimat states, "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%)."

At steady state following TR2.5 once daily inhalation, 12.8% (0.319 µg) of the dose was excreted unchanged in the urine over 24 hours post-dose in asthma patients (Table 4.40). The effective half-life (based on accumulation ratio of Ae_{0-24}) of tiotropium was approximately 1.5 days.

2.5.5 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

PK samples were collected from TR1.25, TR2.5 and TR5 treatment groups. Due to the fact that most PK samples obtained from TR1.25 were BLQ, there were insufficient AUC estimates available for the TR1.25 dose group. Based on $fe_{0-24,ss}$ data, the exposure increased in a dose-proportional manor from 1.25 µg to 5 µg (Figure 2.2, Table 4.41). Based on $C_{max,ss,\,norm}$ and $AUC_{0-6,ss,norm}$ data, the exposure increased in a dose-proportional manor from 2.5 µg to 5 µg (Table 4.41).

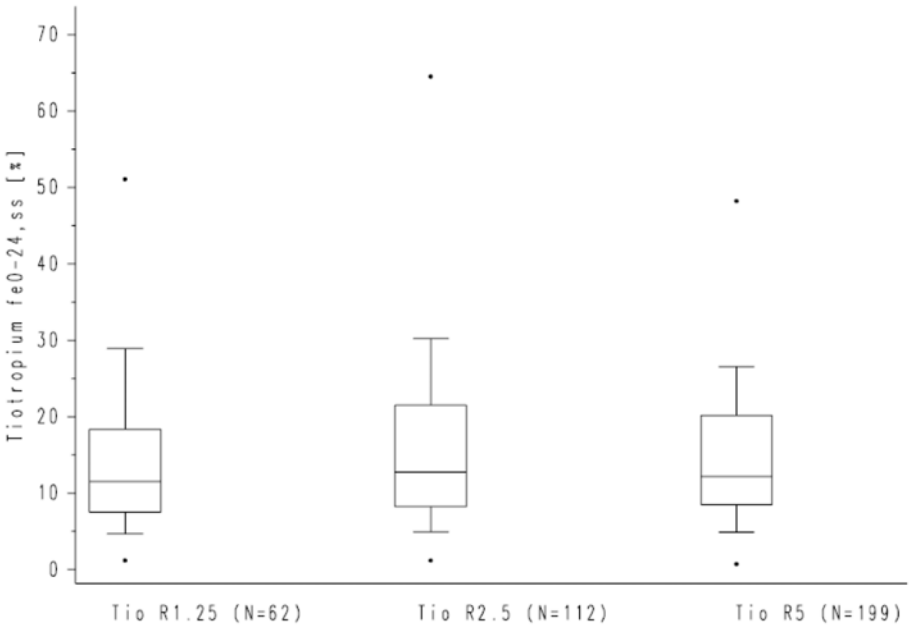

Fig.2.2 Box-plot of $fe_{0-24,ss}$ values of tiotropium at steady state in asthma patients by tiotropium once daily dose from pooled data including study 205.380/420/416/417/418/419/424/441. (Source: CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 38, Figure 7.2.21)

2.5.6 How do the PK parameters change with time following chronic dosing?

PK steady state was reached at the latest by day 7. At steady state following TR5 treatment in asthma patients, the accumulation ratio for C_{max} and Ae_{0-24} were 1.20 (N=52, CV=63%) and 2.74 (N=72, CV= 64%), respectively (Table 4.40).

2.5.7 Is there evidence for a circadian rhythm of the PK?

TR2.5 BID dosing regimen was investigated in study 205.420 and 205.441. The PK data was pooled and the PK parameters were compared between morning and evening dosing intervals. The ratios of $Ae_{0-12,ss}$, $C_{max,ss}$, $AUC_{0-12,ss}$ and $C_{trough,ss}$ (PM/AM) were between 1.04 and 1.1 (Table 4.39). There was no evidence for a circadian rhythm of tiotropium in asthma patients.

2.6 Intrinsic Factors

Renal function and race were the major intrinsic factors responsible for the inter-subject variability in exposure. Patients with more severe disease state as categorized by asthma severity and post bronchodilator percent predicted FEV1 may have higher exposure, but the subject numbers of patients with more severe disease are too few to draw a clear conclusion. Other intrinsic factors such as body weight and age were not shown to have significant effect on exposure.

2.6.1 Renal function

Results from PK meta-analysis report with pooled Phase 2/3 data showed that the systemic exposure of tiotropium is comparable between asthma patients with mild renal impairment (creatine clearance ≥ 60 and < 90 mL/min) and asthma patients with normal renal function (creatine clearance ≥ 90 mL/min). However, moderate renal impairment (creatine clearance ≥ 30 and < 60 mL/min) resulted in 116%, 37% and 36% higher dose-normalized $C_{max,ss,norm}$, $AUC_{\tau,ss,norm}$, and $AUC_{0-6,ss,norm}$ values (Figure 2.3 and Table 4.44). Accordingly, $fe_{0-24,ss}$ value was 26% lower in patients with moderate renal impairment compared to patients with normal renal function. Data from asthma patients with severe renal impairment was not available.

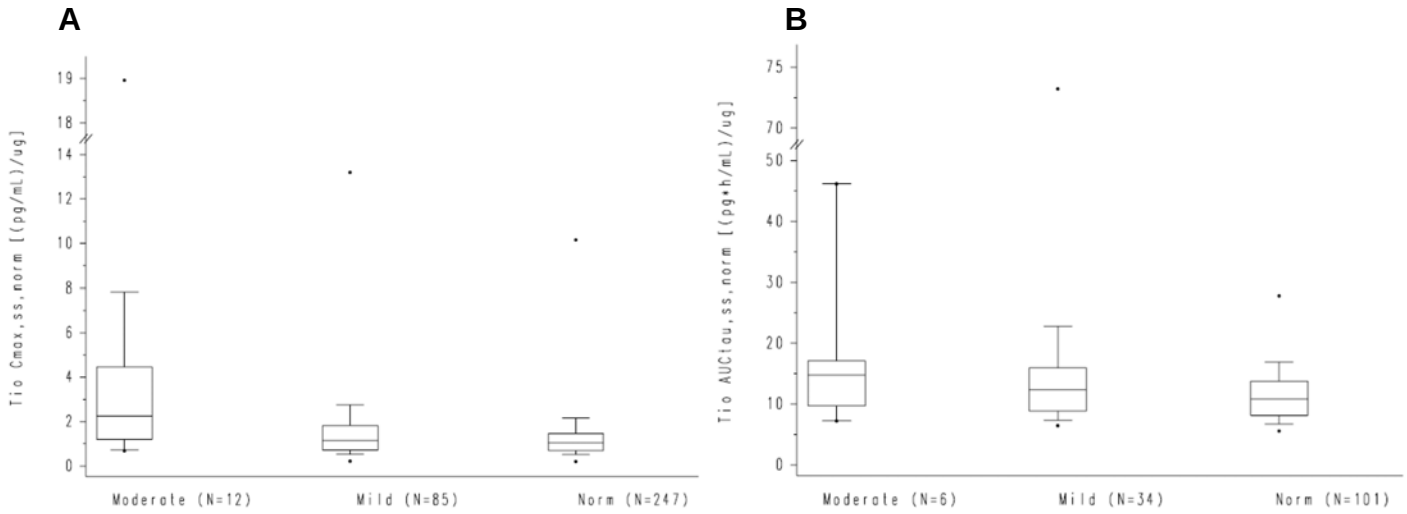

Fig.2.3 Box plot of A. $C_{max,ss,norm}$ and B. $AUC_{\tau,ss,norm}$ values of tiotropium at steady state via RESPIMAT inhaler in asthma patients by renal function.

The trend of renal impairment on tiotropium exposure was consistent with that observed in COPD patients. According to the label from approved NDA 21936: "Following 4-week SPIRIVA RESPIMAT once daily dosing in patients with COPD, mild renal impairment (creatinine clearance 60-90 mL/min) resulted in 23% higher $AUC_{0\text{-}6,ss}$ and 17% higher $C_{max,ss}$ values; moderate renal impairment (creatinine clearance 30-60 mL/min) resulted in 57% higher $AUC_{0\text{-}6,ss}$ and 31% higher $C_{max,ss}$ values compared to COPD patients with normal renal function (creatinine clearance >90 mL/min)."

2.6.2 Race

Results from PK meta-analysis report showed that at steady state in asthma patients, $C_{max,ss,norm}$, $AUC_{\tau,ss,norm}$, and $AUC_{0\text{-}6,ss,norm}$ values were 25%, 47%, and 35% higher in Asian patients than Caucasian patients (Figure 2.4 Table 4.46). Proportionally, $fe_{0\text{-}24,ss}$ value was 47% higher in Asian patients than Caucasian patients, which indicates the absorption of tiotropium might be higher in Asian population.

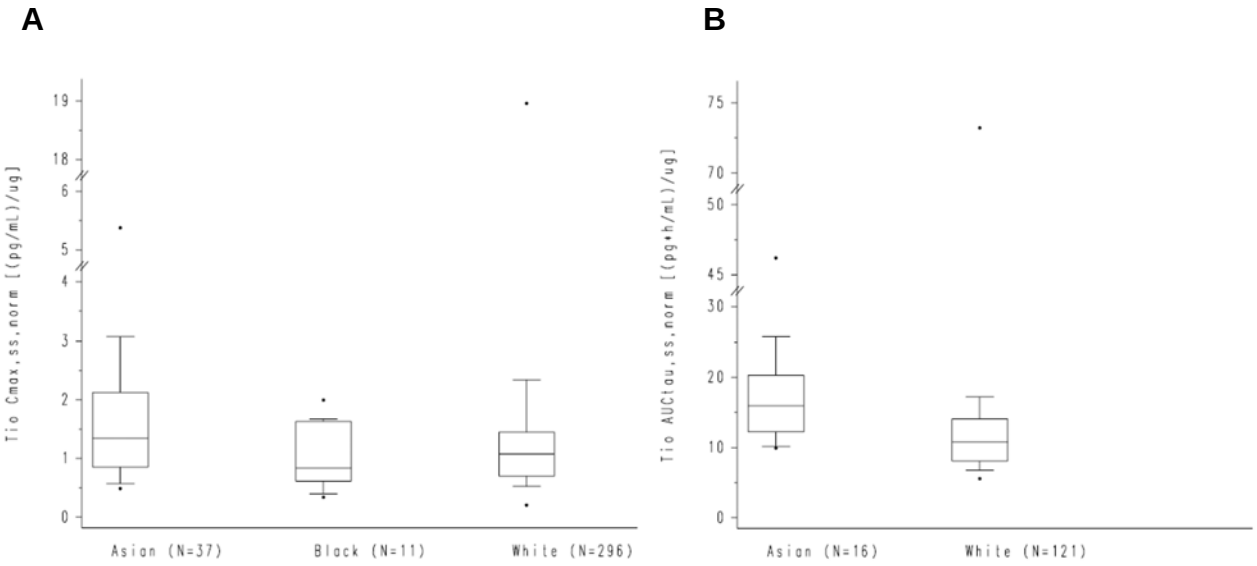

Fig.2.4 Box plot of A. $C_{max,ss,norm}$ and B. $AUC_{\tau,ss,norm}$ values of tiotropium at steady state via RESPIMAT inhaler in asthma patients by race.

The trend of race on tiotropium exposure was consistent with that observed in COPD patients. Refer to the Clinical Pharmacology review of NDA 21936 (Dr. Yunzhao Ren, review dated 8/29/2014), "At steady state in COPD patients, tiotropium $C_{0.167,ss}$ and trough concentration $C_{pre,ss}$ were 78% and 102% higher, respectively in Asians than Caucasians"

2.6.3 Severity of disease state

To be noted, Study 205. 416 and Study 206.417 were included for evaluation of the effect of disease severity on systemic exposure. The patient population in these two studies was COPD-like asthmatic patients as the inclusion criteria "FEV1 that was 70% or less than the forced vital capacity (FVC) at screening" is listed as one of the diagnosis criteria for COPD patients according to Global Initiative for Asthma.

Results from PK meta-analysis report showed that

- $AUC_{\tau,ss,norm}$, and $AUC_{0\text{-}6,ss,norm}$ values were 72% and 56% higher in patients with severe asthma than patients with moderate asthma (Table 4.42).

- $C_{max,ss,norm}$ and $AUC_{0-6,ss,norm}$ values were generally comparable between 60% ≤ PPFEV1 < 80% group and PPFEV1 ≥ 80% group. However, following TR5 QD inhalation, $C_{max,ss,norm}$ and $AUC_{0-6,ss,norm}$ values were 41% and 93% higher in patients with PPFEV1 < 60% than patients with PPFEV1 ≥ 80% (Table 4.43).

However, the tendency that tiotropium systemic exposure was higher in patients with more severe disease may not be over-interpreted:

- The subject numbers of patients with more severe asthma were too small. AUCs were only available in 9 - 13 patients with severe disease whereas AUCs were available in > 100 patients with mild disease (Table 4.42). When comparing PK parameters having more subject numbers, such as $C_{max,ss,norm}$ (N=33 and N=311 for patients with severe and moderate asthma, respectively), the values were similar (1.21 pg/mL/µg and 1.08 pg/mL/µg for severe and moderate asthma patients, respectively).
- Population overlapped between patients with severe asthma and patients with PPFEV1 < 60% (i.e., all the 5 patients with FEV1 < 60% summarized by their $AUC_{0-6,ss,norm}$ values in Table 4.43 were included in 13 patients with severe asthma summarized by their $AUC_{0-6,ss,norm}$ in Table 4.42).

2.6.4 Hepatic impairment

The effect of hepatic impairment on tiotropium exposure was not studied.

2.6.5 Pediatric and elderly patients

Pediatric PK data were obtained from study 205.424. Limited PK samples were collected from TR1.25 group (N=6) and TR2.5 group (N=4). In general, tiotropium systemic exposure was comparable between adolescent patients (12 to <18 years old) and adult patients 18 to < 65 years old with ratios of $C_{max,ss,norm}$ and $AUC_{0-6,ss,norm}$ (adolescent/adult) of 0.82 and 0.95, respectively (Table 4.45). $C_{max,ss}$ of adolescents increased dose-proportionally between TR 2.5 and TR5 QD groups (Table 2.7). $Ae_{0-24,ss}$ increased dose-proportionally from TR 1.25 to TR5 QD group.

Table 2.7 Overall Descriptive Summary of Steady State Tiotropium PK Parameters by Dosing (TR5, TR2.5, TR1.25) in Adolescent Asthmatic Patients

QD dose (µg)	$fe_{0-24,ss}$* (%)	$Ae_{0-24,ss}$* (ng)	$C_{max,ss}$* (pg/mL/µg)
1.25	12.8 (N=12, CV=79%)	160 (N=12, CV=79%)	1.97 (N=3, CV=54%)
2.5	13.5 (N=10, CV=73%)	337 (N=10, CV=73%)	2.22 (N=3, CV=91%)
5	13.7 (N=11, CV=88%)	685 (N=11, CV=88%)	3.95 (N=12, CV=47%)

*** geometric mean (N, geometric CV)**
(Source: reviewer's analysis from pk6p.xpt submitted under pk-meta-analysis in section 5.3.5.3)

(b) (4)

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Tiotropium systemic exposure was comparable between elderly patients (≥ 65 years old) and adult patients 18 to < 65 years old with ratios of $C_{max,ss,norm}$ and $AUC_{0-6,ss,norm}$ (adolescent/adult) of 0.91 and 1.14, respectively (Table 4.45).

2.6.6 What pregnancy and lactation use information is available?

The label of approved NDA 21936 states, "SPIRIVA RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

2.6.7 Does genetic variation impact exposure and/or response?

Study 205.342 recruited 388 moderate asthma patients who were homozygous on ADRB2 B16-Arg. However, no PK samples were collected in this study. Also the patients with wild type (ADRB2 B16-Gly) were included in this study. The primary endpoint (trough PEF) was not used as primary endpoint in other studies.

2.6.8 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Due to its local action, the systemic exposure of tiotropium is not an expected determinant of efficacy. Although the systemic exposure of tiotropium was higher in patients with moderate renal impairment and in Asian population, the increase was generally within or close to 2-fold change, which may not be clinically meaningful. Therefore, no dosage regimen adjustments were recommended based on intrinsic factors.

2.7 Extrinsic Factors

The effects of smoking status and co-medications on tiotropium exposure in asthma patients were investigated in PK meta-analysis report.

2.7.1 Smoking status

The patients in the pooled data for meta-analysis were either non-smokers or ex-smokers. The steady state PK parameters were comparable between non-smokers and ex-smokers following TR treatment with ratio (ex-smoker/never-smoker) of $C_{max,ss,\ norm}$ and $AUC_{0-6,ss,norm}$ as 1.09 and 1.01, respectively (Table 4.47).

2.7.2 Co-medications

- LABA: Among patients taking LABA, only 12 patients had PK data available. Tiotropium systemic exposures were comparable between patients with or without LABA treatment. The ratios (with LABA/without LABA) of $C_{max,ss,\ norm}$ and $AUC_{0-6,ss,norm}$ were 0.95 and 1.24, respectively (Table 4.49).

- ICS: Since all patients in the asthma program were on ICS, the patients were sub-classified into three categories based on budesonide equipotent dose: < 400 μg, ≥400 to ≤800 μg and >800 μg. The < 400 μg group had too few patients with PK parameters available (N=5) to draw any meaningful conclusions. Tiotropium systemic exposures was approximately 37% higher in >800 μg group than the ≥400 to ≤800 μg group (Table 4.48). However this observation was confounded

by disease severity as about half of the patients in >800 μg group had severe asthma whereas there were only about 7% of the patients in ≥400 to ≤800 μg group had severe asthma.

2.7.3 Is the drug a substrate of CYP enzymes?

Label from approved NDA 21936 tiotropium Spiriva Respimat states, "a fraction of the administered dose is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose."

2.7.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Label from approved NDA 21936 tiotropium Spiriva Respimat states "*In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4."

2.7.5 Is the drug a substrate and/or an inhibitor of P-glycoprotein (P-gp) transport processes?

Refer to the Clinical Pharmacology review for NDA 21395 tiotropium Spiriva HandiHaler (DARRTS date 9/18/2002): "an *in vitro* assay displayed that cyclosporine A, a P-gp substrate and inhibitor, did not change tiotropium uptake in CaCo2 cells."

2.7.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Since the renal clearance of tiotropium is higher than the normal creatinine clearance, tiotropium may be actively secreted by renal pathway. Refer to the label from approved NDA 21936 tiotropium Spiriva Respimat: "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 Cmax and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium. Common concomitant medications (long-acting beta2-adrenergic agonists (LABA), inhaled corticosteroids (ICS)) used by patients with COPD were not found to alter the exposure to tiotropium."

2.7.7 Is there a known mechanistic basis for pharmacodynamics drug-drug interactions?

Theoretically, the cholinergic antagonist tiotropium could interfere with some cholinergic agonist or have a synergistic effect with another cholinergic agonist. Refer to the label from approved NDA 21936 tiotropium Spiriva Respimat: "There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of SPIRIVA RESPIMAT with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects"

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Tiotropium bromide monohydrate is a hydrophilic substance, as reflected by its solubility data:

Table 2.8 Solubility of Tiotropium in Different Solutions

Solution	Solubility
Water	*c.* 2.5% w/v (independent of pH)
Methanol	*c.* 5% w/v
Methylene Chloride	< 0.1% w/v

(Source: adapted from section 2.3 Quality Overall Summary, page 10, Characterization)

Apparent partition coefficient (octanol / buffer pH 7.4) is 0.5%. No study was conducted to determine the permeability of tiotropium in both NDAs.

2.8.2 How is the proposed to-be-marketed formulation/device linked to the clinical development formulation/device?

Since the asthma program was developed following the COPD program during which the A5 device was finalized, the to-be-marketed formulation/device (A5 device) was the same as the formulation/device used in clinical development.

2.8.3 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

No BE studies were conducted under NDA 207070.

2.8.4 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Referring to the label from approved NDA 21936 tiotropium Spiriva Respimat: "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."

2.9 Analytical Section

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

Only parent drug (tiotropium) was measured. Specific and highly sensitive HPLC-MS/MS (high performance liquid chromatography coupled to tandem mass spectrometry) methods for tiotropium were developed and validated at (b) (4) , using human plasma and human urine samples. Plasma or urine was mixed with the internal standard [D3] tiotropium. The samples were subjected to solid phase extraction (SPE) and liquid-liquid extraction (LLE) and subsequently submitted to HPLC-MS/MS analysis.

2.9.2 For all moieties measured, is free, bound, or total measured?

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

2.9.3 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 plasma method reference for each PK study is listed Table 2.9. The urine method reference for all the PK studies was NDA 21936 U07-1752. Parameters of bioanalytical method validation of plasma tiotropium method reference are listed in Table 2.10. Parameters of bioanalytical method validation of urine tiotropium are listed in Table 2.11. The coefficient of variation of precision and the bias of accuracy were all within ±15% of the nominal value. After 392 days in the freezer, samples still showed acceptable values, with bias below ± 15%. Tiotropium in plasma or spiked non-acidified urine samples was stable during 3 freeze/thaw cycles, up to 24 h at room temperature, and up to 18 month in a freezer at -20°C or -70°C. Following acidification, tiotropium in urine samples was stable during 3 freeze/thaw cycles, up to 24 h at room temperature, up to 96 h at 5°C, and for 392 days in a freezer at -20°C

Table 2.9 Overview of Analytical Methods Used in Trials with PK Sampling

Study No.	Plasma Method Reference
205.380	NDA 21936 U10-1855
205.420	NDA 21936 U10-1855
205.441	NDA 21936 U10-1855
205.416	NDA 203108 U06-2246
205.417	NDA 203108 U06-2246
205.418	NDA 21936 U10-1855
205.419	NDA 21936 U10-1855
205.424	NDA 21936 U10-1855

(Source: adapted from section 2.7.1 summary-biopharm.pdf, page 10, Table1:3.3:1)

Table 2.10 Summary of Plasma Tiotropium Bioanalytical Validation Results at Different Range

Method Reference	Range (pg/mL)	LLOQ	Lower Range	Medium Range	Higher Range
NDA21936 U10-1885	1.00 - 100	1.00 pg/mL Accuracy: -1.87% Precision: 11.42% N=18	3.00 pg/mL Accuracy: 6.07% Precision: 11.12% N=18	20.00 pg/mL Accuracy: 5.09% Precision: 6.39% N=18	80.00 pg/mL Accuracy: 6.94% Precision: 5.90% N=18
NDA 203108 U06-2246	2.50 -150	2.50 pg/mL Accuracy: -9.91% Precision: 13.98% N=23	6.00 pg/mL Accuracy: -0.18% Precision: 8.44% N=24	30.00 pg/mL Accuracy: 1.53% Precision: 4.98% N=24	120.00 pg/mL Accuracy: -0.87% Precision: 4.05% N=24

(Source: adapted from section 2.7.1 summary-biopharm.pdf, page 7, Table1:3.1:1)

Table 2.11 Summary of Urine Tiotropium Bioanalytical Validation Results at Different Range

Method Reference	Range (pg/mL)	LLOQ	Lower Range	Medium Range	Higher Range
NDA21936 U07-1752	10.0 - 5000	10.0 pg/mL Accuracy: 9.49% Precision: 4.15% N=12	25.0 pg/mL Accuracy: -1.83% Precision: 2.03% N=12	400 pg/mL Accuracy: -2.91% Precision: 2.59% N=12	4000 pg/mL Accuracy: -2.32% Precision: 1.85% N=12

(Source: adapted from section 2.7.1 summary-biopharm.pdf, page 8, Table1:3.1:2)

2.10 Reference

1. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, Sigmund R, Seibold W, Moroni-Zentgraf P, Bateman ED. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012 Sep 27;367(13):1198-207

2. Lipworth B, Manoharan A, Short P. Tiotropium in asthma. N Engl J Med. 2012 Dec 27;367(26):2552

3. Turgeon R. Tiotropium in asthma. N Engl J Med. 2012 Dec 27;367(26):2552-3

3 DETAILED LABELING RECOMMENDATIONS

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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, M_1 to M_5. In the airways, it exhibits pharmacological effects through inhibition of M_3-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.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a multicenter, randomized, double-blind trial using tiotropium dry powder for inhalation that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30 to 60 msec was higher in the SPIRIVA group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical trials with SPIRIVA did not detect an effect of the drug on QTc intervals.

The effect of tiotropium dry powder for inhalation on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received tiotropium inhalation powder 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for tiotropium inhalation powder 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥60 msec.

12.3 Pharmacokinetics

Tiotropium is administered as an inhalation spray. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

A dedicated pharmacokinetic study in patients with COPD evaluating once-daily tiotropium delivered from the RESPIMAT inhaler (5 mcg) and as inhalation powder (18 mcg) from the HandiHaler resulted in a similar systemic exposure between the two products.

Absorption

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

Distribution

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. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier.

Elimination

Metabolism

The extent of metabolism is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, neither of which binds to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Excretion

The terminal half-life of tiotropium in COPD and asthma patients following once daily inhalation (b) (4) is (b) (4) 25 (b) (4) and 44 hours, respectively. 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%). Following 21-day once daily inhalation of 5 mcg of the solution by patients with COPD, 24-hour urinary excretion is 18.6% (0.93 mcg) of the dose. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. In comparison, 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. After chronic once-daily inhalation by COPD and asthma patients, pharmacokinetic steady-state was reached by day 7 with no accumulation thereafter.

Specific Populations

Geriatric Patients

As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (347 mL/min in COPD patients <65 years to 275 mL/min in COPD patients ≥65 years). This did not result in a corresponding increase in $AUC_{0-6,ss}$ and $C_{max,ss}$ values following inhalation of the solution. Exposure to tiotropium was not found to differ with age in patients with asthma.

Pediatric Patients

The exposure to tiotropium was not found to differ between adolescents (aged 12 to 17 years) and adults with asthma.

Renal Impairment

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 $AUC_{0-6,ss}$ and 17% higher $C_{max,ss}$ values; moderate renal impairment (creatinine clearance 30-60 mL/min) resulted in 57% higher $AUC_{0-6,ss}$ and 31% higher $C_{max,ss}$ values compared to COPD patients with normal renal function (creatinine clearance >90 mL/min). Following SPIRIVA RESPIMAT 2.5 mcg, once daily dosing in patients with asthma, mild renal impairment did not have any relevant impact on tiotropium exposure whereas moderate renal impairment resulted in 36% higher $AUC_{0-6,ss}$ and 116% higher $C_{max,ss}$ values compared to patients with normal renal function. There lacks sufficient data of tiotropium exposure in patients with severe renal impairment (creatinine clearance <30 mL/min) following inhalation of the SPIRIVA RESPIMAT (b) (4) However AUC_{0-4} and C_{max} were 94% and 52% higher, respectively, in patients with severe renal impairment following intravenous infusion of tiotropium bromide.

(b) (4)

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

Drug Interactions

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 AUC_{0-4h}, 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.

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.

4. Appendix

4.1 Appendix – Individual Study Review

4.1.1 Study 205.341

Study Type: Phase 2 efficacy and safety study in adults with severe persistent asthma

Title:
A Randomized, Double-Blind, Placebo-Controlled, Crossover Efficacy and Safety Evaluation of 8-Week Treatment Periods of Two Doses [5 μg (2 actuations of 2.5 μg) and 10 μg (2 actuations of 5 μg)] of Tiotropium Inhalation Solution Delivered by the Respimat® Inhaler as Add-on Therapy in Patients with severe persistent Asthma

Objective:
The primary objective of this study was to examine the efficacy and safety of tiotropium compared with placebo as add-on therapy in severe asthmatics according to Global Initiative for Asthma (GINA, 2005) step 4 classification.

Study Design and Method:
This investigation was a randomized, double-blind, placebo-controlled, 3-way cross-over study with 107 severe asthma patients randomized. The tiotropium or placebo was given once daily approximately the same time in the morning between 7:00 a.m. and 10:00 a.m. (± 30 minutes). The duration of treatment includes two-week run-in period followed by three 8-week treatment periods. There was no washout period between treatments.

Patient's post bronchodilator (i.e. 30 minutes after inhalation of 4 puffs of 100 μg salbutamol) FEV1 should be ≤80% of predicted normal and FEV1 should be ≤70% of FVC at Visit 1. Patients had to be symptomatic and had to have had at least 4 weeks on a high, stable dose of inhaled corticosteroids + a long-acting β-adrenergic (additional sustained release theophylline and/or leukotriene modifier and/or oral glucocorticosteroids were allowed in stable doses).

At starting of the first treatment period, pulmonary function tests (PFTs) were performed 10 minutes pre-first dose and at 0.5, 1, 2, and 3 hours post-first dose. PFTs were also performed at the end of each 8-weeek treatment period. In a subset of patients (N=67), PFTs were performed for a longer period 4, 6, 8, 10, 12, 14, 22, 23 and 24 hours post-dose.

Primary Endpoints:
The primary efficacy endpoint was the peak FEV1 response (within 3 hours post dosing) determined at the end of each 8-week treatment period. Peak FEV1 response was defined as the change from baseline in peak FEV1. Baseline was the pre-treatment FEV1 measured at starting of the first treatment period in the morning 10 minutes prior to administration of the first dose of study medication.

The following hypotheses ($\alpha = 0.025$ one-sided) was tested (all means are adjusted means):

- H_1: Superiority 10 μg

H_{10}: Peak FEV1 (TR10) ≤ Peak FEV1 (placebo)

If the null hypothesis H_{10} was rejected, then the following hypothesis was tested:

- H_2: Superiority 5 μg

H_{20}: Peak FEV1 (TR5) ≤ Peak FEV1 (placebo)

If the null hypothesis H_{20} was rejected, then the following hypothesis was tested:

- H_3: Non-inferiority

H_{30}: Peak FEV1 (TR5) ≤ Peak FEV1 (TR10) – 50 mL

Efficacy Results:

Results from 107 patients were included for full analysis set (FAS) and among them, 98 patients were included for the per-protocol set (PPS) analysis. The adjusted means of peak FEV1 at Week 8 are listed in Table 4.1.! The differences in peak FEV1 response between the active treatment groups and placebo are listed in Table 4.2. The peak FEV1 response following 8-week TR5 or TR10 treatment was significantly better than placebo with differences (placebo - TR) of -0.141 (95 CI = -0.184, -0.098) L and -0.174 (-0.217, 00.131) L, respectively, in PPS population. Although the difference between TR5 or TR10 was not significant (< pre-defined 50 mL), the peak FEV1 response of TR10 was numerically greater [0.033 (95% CI = -0.01, 0.076) L].

Table 4.1 Adjusted Means (SE) of Peak FEV1 [L] Response Values at Week 8

Population	Placebo	5 µg tiotropium	10 µg tiotropium
FAS	0.313 (0.016)	0.451 (0.016)	0.483 (0.016)
PP	0.314 (0.016)	0.455 (0.016)	0.488 (0.016)

(Source: CSR 0205-0341, page 62, Table 11.4.1.1:1)

The adjusted means of FEV1 response over 24-hour post-dose period following 8-week treatment are given in Fig 4.1.

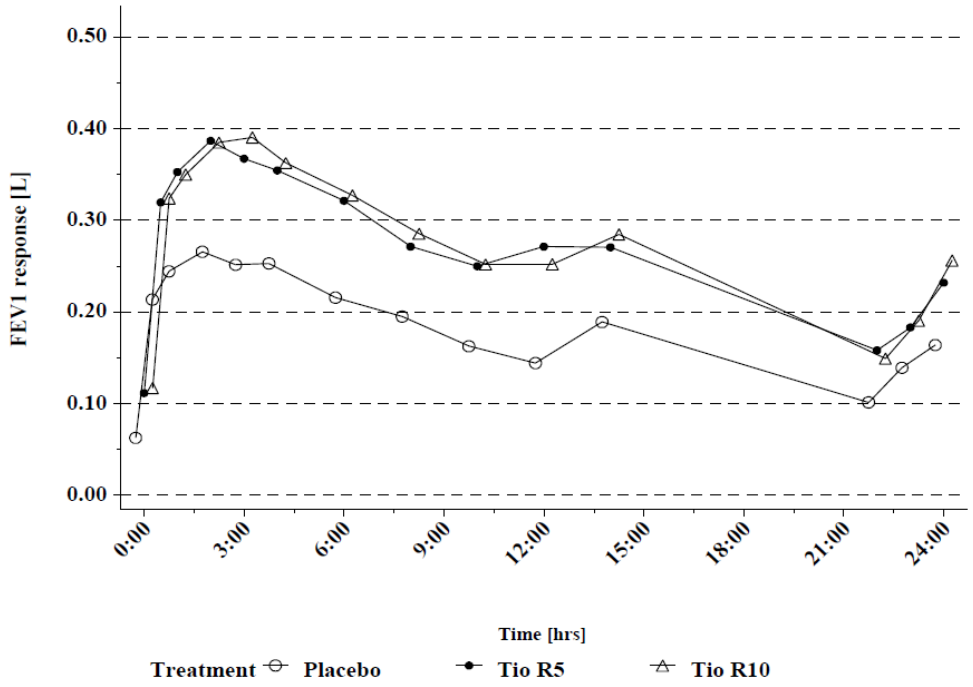


Fig.4.1 Adjusted means of FEV1 response values over time (24 hours) in 67 patients following 8-week once daily treatment. The dosing time was approximately between 7:00 a.m. and 10:00 a.m. (Source: CSR 0205-0341, page 74, Figure 11.4.1.2:6)

Table 4.2 Differences of Adjusted Means (SE) of Peak FEV1 [L] Response Values at Week 8

Comparison	Difference	95% CI	P-value
	FAS population		
Placebo - 5 µg tiotropium	-0.139 (0.022)	(-0.181, -0.096)	<0.0001
Placebo - 10 µg tiotropium	-0.170 (0.022)	(-0.213, -0.128)	<0.0001
5 µg tiotropium - 10 µg tiotropium	-0.032 (0.022)	(-0.075, 0.011)	0.4005*
	PP population		
Placebo - 5 µg tiotropium	-0.141 (0.022)	(-0.184, -0.098)	<0.0001
Placebo - 10 µg tiotropium	-0.174 (0.022)	(-0.217, -0.131)	<0.0001
5 µg tiotropium - 10 µg tiotropium	-0.033 (0.022)	(-0.076, 0.010)	0.4422*

***non-inferiority p-values (delta = 0.05 L)**
(Source: CSR 0205-0341, page 62, Table 11.4.1.1:2)

Pharmacogenetic Results:
There were literature reports that the polymorphism of beta 2 adrenergic receptor (ADRB2) at the 16th amino acid (B16) may play a role in different responses to SABA (albuterol)[2] and LABA (salmeterol)[3]. Changing nucleotide sequence from GGA (NM_000024.5) to CGA (rs1042713) renders amino acid changing from glycine (Gly) to arginine (Arg). In a 20-week albuterol treatment study in mild asthma patients, a significant decline in the peak expiratory flow (PEF) in the morning was observed in B16-Arg/Arg homozygous patients[2]. Compared to B16-Gly/Gly patients, PEF of B16-Arg/Arg patients reduced 23.8 ± 9.5 L/min ($N_{Arg/Arg}$=28, $N_{Gly/Gly}$=62, p=0.012)[2]. Meanwhile, the polymorphism on B27 did not reveal any significant changes in the response to albuterol. In another 28 –week (6-week triamcinolone + 16-week salmeterol + 6-week placebo), randomized, placebo-controlled, parallel-group study, the morning PEF mean value was 51.4 L/min lower in B16-Arg/Arg patients than B16-Gly/Gly patients ($N_{Arg/Arg}$=8, $N_{Gly/Gly}$=22, p=0.005)[3].

In this study, the Sponsor genotyped 87 patients on ADRB2 B16 and B27 polymorphisms, trying to compare their response to tiotropium. However, the number of B16-Arg/Arg patients was too low (N=6) to draw any meaningful conclusions.

Conclusions:
The primary endpoint of peak FEV1 response showed statistical significance for both doses of tiotropium compared with placebo, whereas the results of TR5 and TR10 treatments were comparable.

Reviewer's comments:
Although statistically significant (p<0.0001), the absolute values of the differences of peak FEV1 between placebo and two doses of tiotropium treatments were small (<0.18 L). The Sponsor justified that "An improvement by 100 mL in FEV1 was deemed clinically relevant for asthmatics who are already being treated with asthma-specific controller medications in accordance with the current guidelines."(Source: CSR 0205-0341, page 53) The acceptability of this justification is deferred to the clinical reviewer.

The study design was not powered enough to detect the difference (predefined as 50 mL) between TR5 and TR10. According to reviewer's analysis, when Peak FEV1 response is set around 0.45 L and SD is set around 0.25 L (Source: CSR 0205-0341, page 53), the power of 100 patients to detect a 0.05 L difference between treatments (α=0.05, two-sided) is approximately 50%. Therefore, this study is under-powered to detect dose-response relationship between TR5 and TR10.

4.1.2 Study 205.342

Study Type: Phase 2 efficacy and safety study in asthma adults with genotype of ADRB2 B16-Arg/Arg

Title:
A 16-week randomized, placebo-controlled, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of tiotropium inhalation solution delivered by the Respimat® inhaler (2 puffs of 2.5 μg once daily) with that of salmeterol from the hydrofluoroalkane metered dose inhaler (2 puffs of 25 μg twice daily) in moderate persistent asthma patients homozygous for B16-Arg/Arg

Objective:
The primary objective was to show non-inferiority of tiotropium versus salmeterol after 16 weeks of treatment. Superiority of tiotropium over placebo was also to be demonstrated.

Study Design and Method:
This investigation was a randomized (1:1:1), double-blind, double-dummy, parallel design comparison of 3 groups [placebo, TR5 QD (evening dose), and salmeterol 50 μg BID] over a 16-week treatment period following a minimum 4-week open-label run-in period, and with a 4-week open-label follow-up period, both on stable dose of ICS and salmeterol 50 μg BID. 530 patients with moderate asthma were enrolled and 388 patients enter the study.

Patients had to be homozygous for arginine at the 16th amino acid position of the β2-adrenergic receptor (B16-Arg/Arg) as determined by a central laboratory. Patient had to be on maintenance treatment with inhaled corticosteroids (alone or in a fixed combination with a LABA or a SABA) with a total daily dose of 400 - 1000 μg budesonide or equivalent within the last three months and with a stable dose within the last three weeks prior to Visit 1. Patients who were on maintenance treatment with LABAs with a total daily dose of at least 100 μg salmeterol or at least 18 μg formoterol within the last three months and a stable dose within the last three weeks prior to Visit 1 were eligible if their pre-bronchodilator FEV1 was ≤90% of predicted normal at Visit 1. Patients who had not been treated with LABAs within the last year before Visit 1 were eligible if their pre-bronchodilator FEV1 is ≤80% of predicted normal at Visit 1.

B16-Arg/Arg genotype was determined by a central laboratory using buccal swabs samples for genetic test.

The patients received the Asthma Monitor® AM2+ (VIASYS Healthcare Clinical Services, Hoechberg, Germany) and used this device throughout the study including run-in and follow-up period. The AM2+ combined the features of an electronic peak flow meter (measurement of both PEF and FEV1) and an electronic diary in one handy device. Morning measurements of PEF and FEV1 were performed at approximately the same time of the day after waking and prior to inhalation of the trial medication and any rescue medication. The evening measurements of PEF and FEV1 were performed about 12 hours after the morning dose of study medication and prior to inhalation of the trial medication taken in the evening. Every morning and every evening the patient was asked to perform three acceptable expiratory maneuvers in the standing position with the AM2+. Only the highest PEF and the highest FEV1 out of three acceptable blows, but not necessarily from the same blow, were used for evaluation.

Primary Endpoints:
The primary efficacy endpoint was the change in mean weekly morning pre-dose PEF from the last week prior to the randomization visit to the last week of treatment.

The following hypotheses ($\alpha = 0.025$ one-sided) was tested (all means are adjusted means):

- Non-inferiority with regard to $PEF_{baseline-EOT}$
  H_0: $PEF_{baseline-EOT}$ (TR5) ≤ $PEF_{baseline-EOT}$ (salmeterol 50 µg) – 20 L/min

- Superiority with regard to $PEF_{baseline-EOT}$
  H_0: $PEF_{baseline-EOT}$ (TR5) ≤ $PEF_{baseline-EOT}$ (placebo)

Secondary endpoints included weekly means of daily morning and evening PEF, morning and evening FEV1 and peak flow variability.

Efficacy Results:
Pre-dose morning baseline values of PFTs were obtained before the 16-week treatment. The mean baseline values were numerically lower in the TR5 group compared to the salmeterol group; values for the placebo group were in-between those for the TR5 and the salmeterol group (Table 4.3).

Table 4.3 Weekly Mean Morning Baseline Values of PFTs before Treatment in FAS Patients

	Placebo (N=126)	TR5 QD (N=128)	Salmeterol 50 µg BID (N=134)
Morning FEV1 (L)	2.29 (0.750)	2.23 (0.763)	2.36 (0.742)
Morning PEF (L/min)	360.19 (113.72)	351.64 (121.70)	361.79 (112.26)

(Source: adapted from CSR 0205-0342, page 102, Table 11.2.4:1)

Adjusted means and adjusted response means (changes from baseline to the end of treatment) of mean weekly morning pre-dose PEF are presented in Table 4.4. The differences between treatments showed that both active treatments were statistically superior to placebo ($p<0.01$) and tiotropium was non-inferior to salmeterol ($p<0.01$).

Table 4.4 Adjusted Means (SE) and Adjusted Response (Change from Baseline) Means (SE) of Mean Weekly Morning Pre-dose PEF in FAS and PPS Patients

Population	Mean (SE) PEF (L/min)					
	Placebo		5 µg Tiotropium		50 µg Salmeterol b.i.d.	
Full analysis set						
N	125		128		134	
Baseline	357.92	(0.000)	357.92	(0.000)	357.92	(0.000)
EOT	333.29	(4.835)	353.99	(4.873)	354.77	(4.640)
Change from baseline to EOT	-24.63	(4.835)	-3.93	(4.873)	-3.15	(4.640)
Per protocol set						
N	94		90		94	
Baseline	357.50	(0.000)	357.50	(0.000)	357.50	(0.000)
EOT	331.05	(5.496)	360.32	(5.763)	355.70	(5.622)
Change from baseline to EOT	-26.45	(5.496)	2.82	(5.763)	-1.80	(5.622)

EOT: end of treatment
(Source: CSR 0205-0342, page 106, Table 11.4.1.1:1)

The mean change in morning pre-dose FEV1 from baseline to week 16 was -0.103 (SE=0.029) L, 0.010 (SE=0.030) L, and -0.012 (SE 0.028) L for the placebo group, for the tiotropium group, TR5 group and salmeterol group, respectively (Table 4.2). An exploratory statistical comparisons showed that both active

treatments of treatment groups were statistically superior to placebo ($p<0.05$) at every week of the study (except Week 9 for TR5).

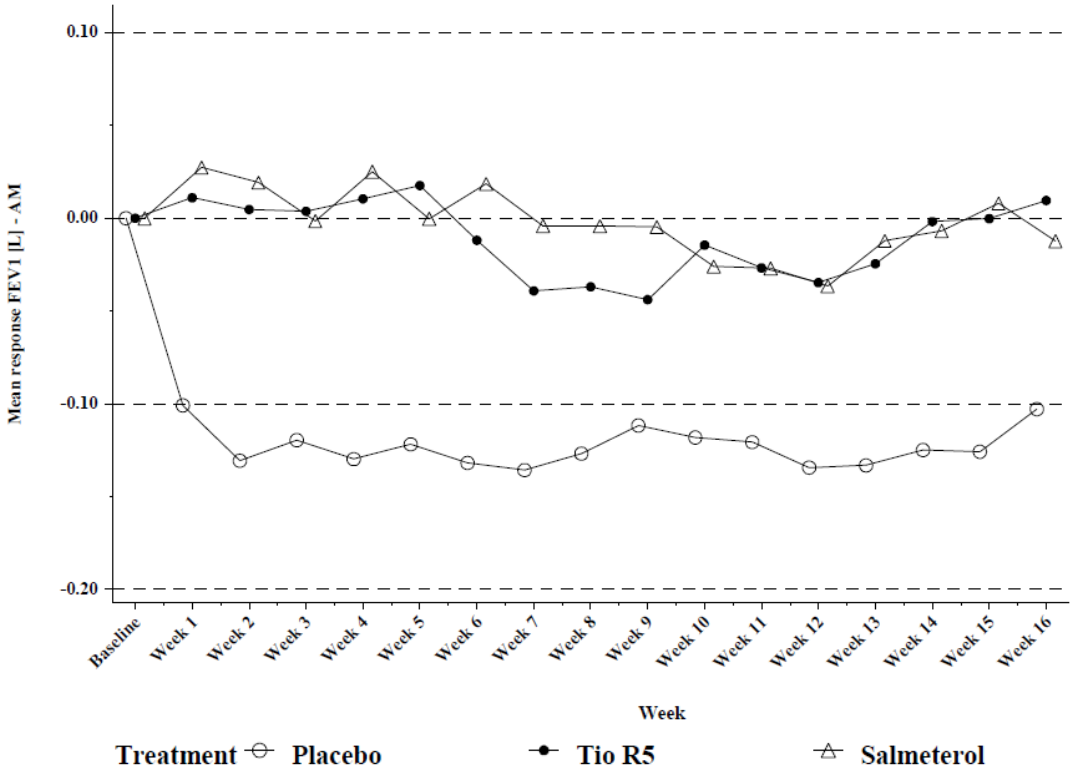


Fig.4.2 Adjusted means of mean weekly morning pre-dose FEV1 (L) response (change from baseline) during the double-blind treatment period –FAS. (Source: CSR 0205-0342, page 113, Figure 11.4.1.2.1:3)

Conclusions:
The primary endpoint of this study, the change in mean weekly morning predose PEF from baseline to the last week of treatment based on weekly means of electronic peak-flow meter recordings measured at home, demonstrated the statistical non-inferiority of TR5 once daily versus salmeterol 50 µg BID and the superiority of both active treatments versus placebo.

Reviewer's comments:
Study 205.142 was an exploratory study comparing the efficacy and safety of LAMA and LABA in B16-Arg/Arg patients. Although PEF was not widely accepted as a useful biomarker for lung function, a significant decline of PEF during beta-2 adrenergic agonist treatment was a consistent phenotype for B16-Arg/Arg patients in the literature reports[2,3]. The absolute values of mean PEF changes from baseline were -30.5 L/min and -29.9 L/min from albuterol study ($N_{Arg/Arg}=28$)[2] and salmeterol study ($N_{Arg/Arg}=8$)[3], respectively. However the significant decline of PEF was not observed in this dedicated study (-3.15 L/min, $N_{Arg/Arg}=134$) following 16-week treatment of salmeterol (Table 4.4). The differences in the results may partially contributed by study designs (disease severity, concomitant medications, duration and withdrawal period). Nevertheless, study 205.142 was the dedicated and neater study with the largest number of subjects. The study was designed to directly address the effect of long-time exposure (16-week) of LABA on PEF morning values in B16-Arg/Arg asthma patients. Although the B16-Gly/Gly patients were not enrolled in this study, the results alleviated the concern that B16-Arg/Arg patients might have a declined response towards LABA over time in terms of morning PEF values.

On the other hand, mean morning pre-dose FEV1 value is not a good biomarker to evaluate the bronchodilation effect of salmeterol. Therefore, the true efficacy comparison between TR5 and salmeterol was not well evaluated in this study.

4.1.3 Study 205.380

Study Type: Phase 2 dose-ranging, efficacy, safety and PK study in adults with moderate persistent asthma

Title:
A Phase II randomized, double-blind, placebo-controlled, crossover efficacy and safety comparison of three doses of tiotropium inhalation solution delivered via Respimat® inhaler (1.25, 2.5, and 5 µg once daily) versus placebo in patients with moderate persistent asthma

Objective:
The objective of this study was to evaluate the efficacy, safety and PK of 3 doses of tiotropium solution for inhalation in comparison to placebo delivered by the Respimat® inhaler in adult patients with moderate persistent asthma on top of maintenance therapy with inhaled corticosteroids (ICS).

Study Design and Method:
This investigation was a randomized, placebo-controlled, double-blind, crossover trial with four 4-week treatment periods (TR1.25, TR2.5, TR5 and placebo once daily in the evening) without washouts. In total 149 adults patients with moderate asthma entered the study and 52 among them participated in PK subset.

The diagnosis of asthma must have been confirmed at Visit 1 with bronchodilator reversibility (15 to 30 min after 400 µg salbutamol) resulting in a FEV1 increase of 12% or more and 200 mL or more from pre-bronchodilator baseline.! All patients had to have a pre-bronchodilator FEV1 of ≥60% and ≤90% of predicted normal FEV1 at Visit 1. All patients had to be on maintenance treatment with a medium, stable dose of ICS, either alone or in a fixed-dose combination with a LABA or SABA for at least 4 weeks prior to Visit 1.

PFTs, including FEV1, FVC, and PEF, were performed 10 min pre-dose and 2 h to 24 h post-dose at the first day of the treatment and the last day of each of the 4 periods. For patients participating in the optional 24-h PFT assessment (at the end of Period 2), an overnight stay at the site was required.

Blood samples for PK analysis were collected at the first day of the treatment (first dosing period) and the last day of each of the 4 periods. Samples were taken 15 min pre-dose and 2 min, 5 min, 7 min, 10 min, 15 min, 30 min, 1 h, 2 h, 3 h, and 23 h 45 min post-dose. At each time point, 6 mL or 4.9 mL of blood were drawn from a forearm vein using a Vacutainer or Monovette collection tube, respectively. Urine samples were collected between -1 h and 0 h prior to dosing as well as 0 h to 3 h, and 3 h to 24 h post-dose. In total, blood and urine samples were obtained from 53 patients during the first dosing period and 52 patients during multiple dosing periods.

Endpoints:

- The primary efficacy endpoint was the maximum FEV1 measured within the first 3 h after dosing (FEV1 $peak_{0–3h}$); it was determined at the end of each 4-week treatment period.

  The following hypotheses ($\alpha = 0.025$ one-sided) was tested (all means are adjusted means):

  Mean FEV1 peak0-3h response after each of the three 4-week active treatment ≤ Mean FEV1 peak0-3h response after 4 weeks treatment with placebo

- Secondary endpoints included FEV1 AUC_{0-3} and AUC_{0-24}. The latter was evaluated in subset of patients.

- PK endpoints included C_{max}, T_{max}, AUCs, λz, T1/2, CL/F, Vz/F for blood samples and Ae, fe for urine samples

Analytical Method:
Plasma and urine concentrations of tiotropium were determined by validated assays using HPLC coupled to tandem mass spectrometry. 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.

Efficacy Results:

- Primary endpoint FEV1 $peak_{0–3h}$

As a reference point, the mean FEV1 at study baseline (measured pre-dose on the first day before treatment) was 2.303 (SD=0.690) L for FAS population (148 patients). The FEV1 $peak_{0–3h}$ responses following 4-week treatment of placebo, TR1.25, TR2.5 and TR5 were 0.116 L, 0.255 L, 0.244 L and 0.304 L, respectively (Table 4.5). Differences from placebo were statistically significant ($p<0.0001$) at all doses; this showed the superiority of all active treatments over placebo. Similar conclusion was obtained from PPS analysis (source: CSR0205-308, page 92, Table 11.4.1.1:3).

Table 4.5 Comparison of the Adjusted Mean FEV1 $Peak_{0–3h}$ Response between Active Treatment and placebo – FAS

		FEV_1 $peak_{0–3h}$ response [L][1]		Difference from placebo [L][1]		
Treatment	N	Mean	(SE)	Mean	(SE)	95% CI
Placebo	144	0.116	(0.027)			
Tio R1.25	144	0.255	(0.027)	0.138	(0.024)	(0.090, 0.186)
Tio R2.5	144	0.244	(0.027)	0.128	(0.024)	(0.080, 0.176)
Tio R5	143	0.304	(0.028)	0.188	(0.024)	(0.140, 0.236)

[1] **Adjusted for treatment, period, patient, and study baseline**
(Source: CSR 0205-0380, page 91, Table 11.4.1.1:1)

The FEV_1 $peak_{0–3h}$ response was also compared between the 3 tiotropium treatments in an exploratory way for patients in the FAS. A significant difference was shown between TR5 and each of the 2 lower doses in terms of FEV_1 $peak_{0–3h}$ response; however, no significant difference was shown between TR2.5 and TR1.25 (Table 4.6).

!

Table 4.6 Comparison of the FEV1 $Peak_{0–3h}$ Response between the Active Treatments− FAS

	Adjusted[1] mean difference [L]		
		(SE)	95% CI
Tio R5 versus Tio R1.25	0.050	(0.024)	(0.002, 0.098)
Tio R5 versus Tio R2.5	0.060	(0.024)	(0.012, 0.108)
Tio R2.5 versus Tio R1.25	–0.010	(0.024)	(–0.058, 0.038)

[1] **Adjusted for treatment, period, patient, and study baseline**
(Source: CSR 0205-0380, page 92, Table 11.4.1.1:2)

!

The analysis in PPS population (115 patients) showed that the FEV_1 $peak_{0–3h}$ response was similar between the 3 tiotropium treatments (Table 4.7), though response of TR5 was numerically higher than 2 lower doses.

Table 4.7 Comparison of the FEV1 Peak$_{0-3h}$ Response between the Active Treatments− PPS

	Adjusted[1] mean difference [L]		
		(SE)	95% CI
Tio R5 versus Tio R1.25	0.020	(0.028)	(–0.036, 0.075)
Tio R5 versus Tio R2.5	0.040	(0.028)	(–0.015, 0.096)
Tio R2.5 versus Tio R1.25	–0.021	(0.028)	(–0.076, 0.035)

[1] **Adjusted for treatment, period, patient, and study baseline**
(Source: CSR 0205-0380, page 93, Table 11.4.1.1:4)

- Secondary endpoint FEV1 AUC$_{0-3}$

FEV1 AUC$_{0-3}$ responses following 4-week treatment of placebo, TR1.25, TR2.5 and TR5 were 0.025 L, 0.154 L, 0.152 L and 0.203 L, respectively. All 3 doses of tiotropium were superior to placebo ($p<0.0001$ in every case). A significant difference was shown between TR5 and each of the 2 lower doses; however, no significant difference was shown between TR2.5 and TR1.25 in terms of FEV1 AUC$_{0-3}$ (Fig.4.3).

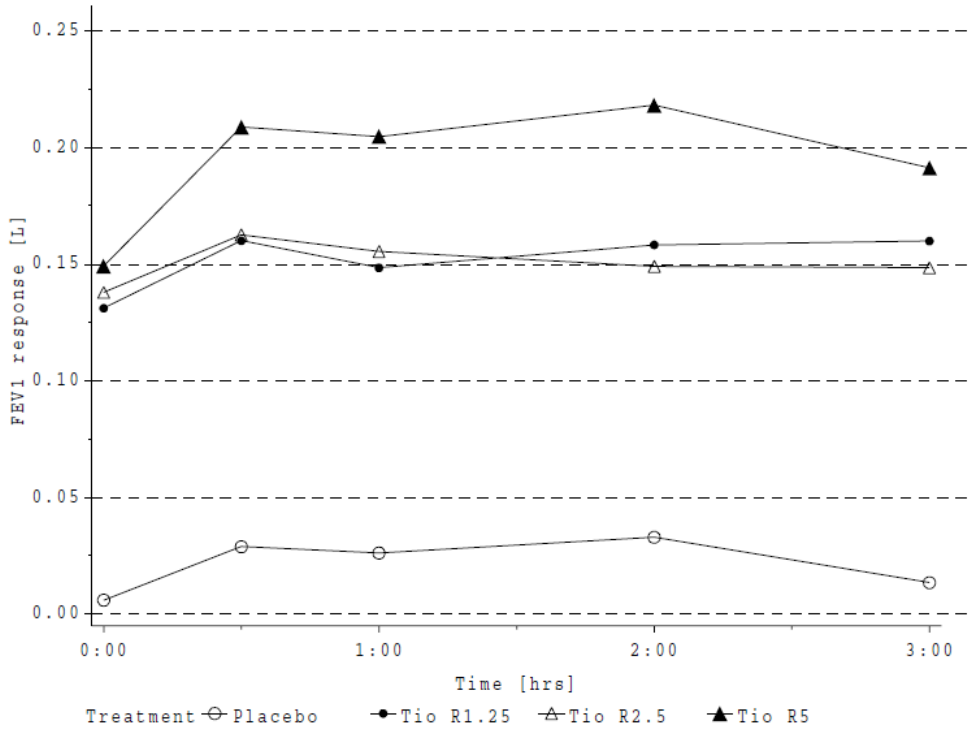


Fig.4.3 Evening FEV1 response over 3 hours post dose in FAS population from study 205.380. All the values represent adjusted means by treatment, period, patient and study baseline. (Source: CSR 0205-0380, page 96, Figure 11.4.1.2.1:1)

- Secondary endpoint FEV1 AUC$_{0-24}$

About 14% of patients participated in the optional 24-h PFT assessment during the end of period 2, the comparisons between different treatments were considered as a parallel design. FEV1 AUC$_{0-24h}$ responses following 4-week treatment of placebo, TR1.25, TR2.5 and TR5 were -0.001 L, 0.099 L, 0.141 L and 0.168 L respectively (Table 4.8). Only the difference between TR5 and placebo was statistically significant (p=0.033).

Table 4.8 Comparison of FEV1 AUC_{0-24h} Response between Active Treatments and Placebo

Parameter and treatment	N	Adjusted mean response [L][1] Mean	(SE)	Difference from placebo [L][1] Mean	(SE)	95% CI	p-value[2]
Placebo	21	–0.001	(0.057)				
Tio R1.25	24	0.099	(0.054)	0.100	(0.078)	(–0.056, 0.256)	0.2062
Tio R2.5	24	0.141	(0.054)	0.142	(0.078)	(–0.014, 0.297)	0.0731
Tio R5	24	0.168	(0.053)	0.169	(0.078)	(0.014, 0.324)	0.0333

[1] Adjusted for treatment, period, patient, and study baseline
(Source: CSR 0205-0380, page 106, Table 11.4.1.2.5:1)

PK Results:
Following the inhalation of the first dose of TR, tiotropium was rapidly absorbed with median T_{max} ranging from 5 minutes to 12 minutes. Tiotropium could be detected in plasma for a limited duration of time after the first dose (Fig. 4.4). For TR1.25, only 2 out of 13 patients had a plasma concentration above the LLOQ at 1 h post-dose. For TR2.5, only 2 out of 14 patients had a plasma concentration above LLOQ at 1 h post-dose. For TR5, 4 out of 14 patients had a plasma concentration above LLOQ at 3 h post-dose. Tiotropium could not be detected in the plasma of any of the patients that received placebo. The major PK parameters of tiotropium following the first dose treatment were listed in Table 4.9.

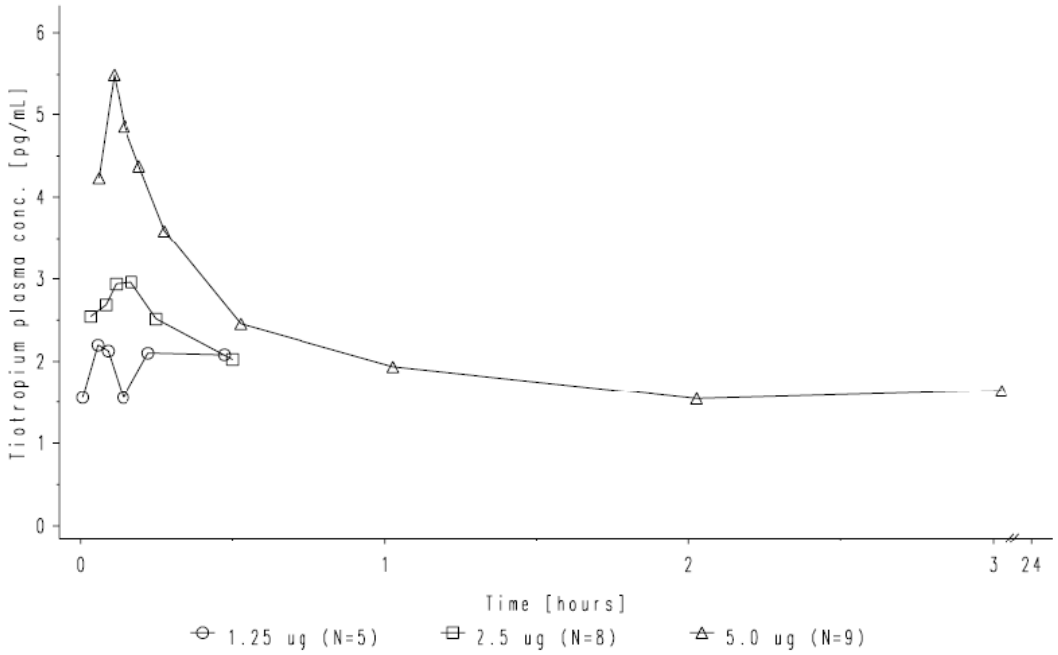


Fig.4.4 Geometric mean tiotropium plasma concentration-time profiles following the first dose TR inhalation in patients with moderate persistent asthma. All the BLQ data were excluded. (Source: CSR 0205-0380, page 110, Figure 11.5.2.1:1)

The descriptive summary of first dose PK parameters was listed in Table 4.9. All the BLQ data were excluded during analysis.

Table 4.9 Comparison of the First Dose PK Parameters of Tiotropium in Adult Patients

Parameter	TR1.25		TR2.5		TR5	
	N	gMean (CV)	N	gMean (CV)	N	gMean (CV)
$AUC_{0\text{-}0.167}$ (pg·h/mL)	5	0.306 (58.6%)	7	0.462 (80.5%)	9	0.736 (112%)
C_{max} (pg/mL)	6	2.89 (84.9%)	9	3.09 (92.7%)	10	4.93 (138%)
T_{max} (h)*	6	0.196 (0.01, 0.984)	9	0.072 (0.018, 1.67)	10	0.0745 (0.018, 0.151)
$Ae_{0\text{-}3}$ (ng)	13	15.1 (98.7%)	14	40.3 (213%)	14	63.4 (124%)
$fe_{0\text{-}3}$ (%)	13	1.21 (98.7%)	14	1.61 (213%)	14	1.27 (124%)
$Ae_{0\text{-}24}$ (ng)	11	66.8 (116%)	14	185 (91%)	14	240 (82.1%)
$fe_{0\text{-}24}$ (%)	11	5.35 (116%)	14	7.41 (91%)	14	4.79 (82.1%)

*** Median value (range)**
(Source: adapted from CSR 0205-0380, page 114, Table 11.5.2.3:1)

Following 4-week once daily inhalation, tiotropium was rapidly absorbed with median T_{max} ranging from 5 minutes to 7 minutes. Tiotropium could be detected in plasma up to 23 h 75 min post-dosing in 5 out of 52 patients administered 1.25 µg, 9 out of 50 patients administered 2.5 µg, and 24 out of 49 patients administered 5 µg tiotropium (Fig. 4.5). Tiotropium was measurable in 36 out of 690 analyzed plasma samples (5.2%) after following multiple dose placebo treatment. These concentrations could represent contaminations during sample handling.

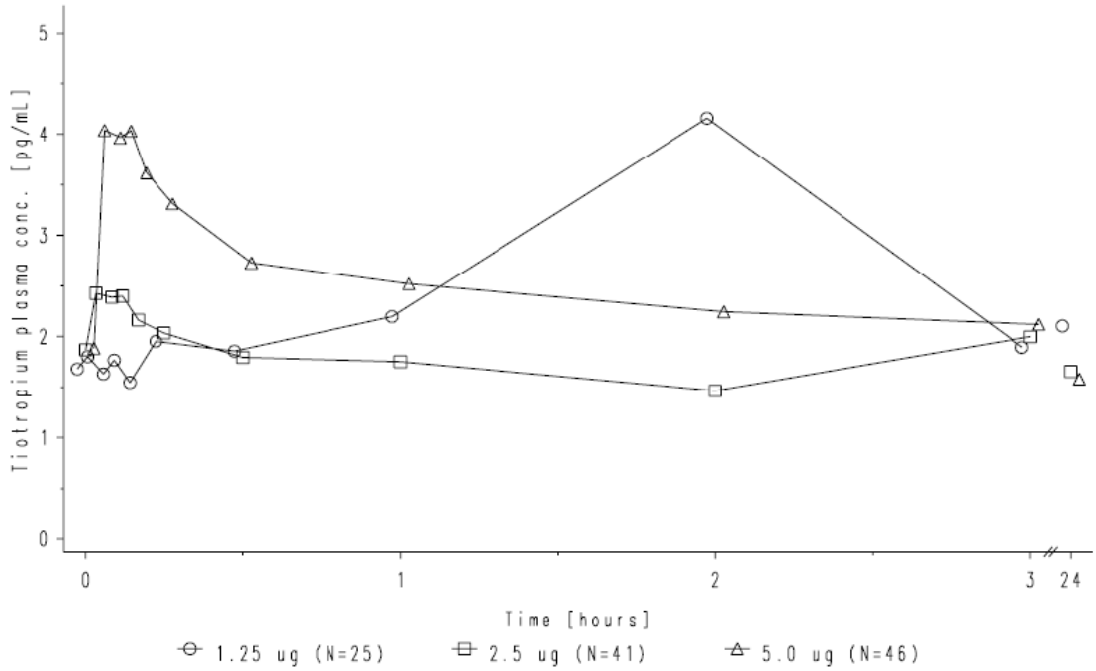


Fig.4.5 Geometric mean tiotropium plasma concentration-time profiles following 4-week once daily inhalation in patients with moderate persistent asthma. All the BLQ data were excluded. (Source: CSR 0205-0380, page 111, Figure 11.5.2.1:2)

Generally the PK parameters obtained from blood samples such as $C_{max,ss}$ and $AUC_{0\text{-}0.167,ss}$ increased less than dose proportionally from 1.25 to 5 µg. The PK parameters obtained from urine samples such as $Ae_{0\text{-}3,ss}$ and $Ae_{0\text{-}24,ss}$ appeared to be dose proportional from 1.25 µg to 5 µg. The renal clearance ($CL_{R,ss}$)of tiotropium was higher than the creatinine clearance, which is consistent with the approved label of NDA 21395 Spiriva Handihaler.

Table 4.10 Comparison of the PK Parameters following 4-week Once Daily Inhalation of Tiotropium in Adult Patients

Parameter	TR1.25		TR2.5		TR5	
	N	gMean (CV)	N	gMean (CV)	N	gMean (CV)
$AUC_{0\text{-}0.167,ss}$ (pg·h/mL)	18	0.296 (35.2%)	41	0.366 (63.2%)	46	0.609 (64.6%)
$C_{max,ss}$ (pg/mL)	33	2.38 (104%)	46	2.70 (69.7%)	49	4.52 (72.1%)
$T_{max,ss}$ (h)*	33	0.114 (0.014, 23.7)	46	0.101 (0.017, 23.7)	49	0.083 (0.02 to 23.7)
$AUC_{\tau,ss}$ (pg·h/mL)	N/A	N/A	6	46.2 (38.4%)	21	54.3 (39.8%)
CL/F_{ss} (mL/min)	N/A	N/A	6	902 (38.4%)	21	1540 (39.8%)
Vz/F_{ss} (L)	N/A	N/A	6	2920 (149%)	21	3870 (111%)
$T_{1/2,ss}$ (h)	N/A	N/A	6	37.4 (102%)	21	29.1 (72.7%)
$Ae_{0\text{-}3,ss}$ (ng)	50	32.0 (96.9%)	49	65.3 (111%)	48	119 (115%)
$fe_{0\text{-}3,ss}$ (%)	50	2.56 (96.9%)	49	2.61 (111%)	48	2.38 (115%)
$Ae_{0\text{-}24,ss}$ (ng)	50	141 (90.1%)	48	272 (94.8%)	48	531 (81.3%)
$fe_{0\text{-}24,ss}$ (%)	50	11.3 (90.1%)	48	10.9 (94.8%)	48	10.6 (81.3%)
$CL_{R,ss}$ (mL/min)	N/A	N/A	6	162 (62.6%)	20	254 (63.4%)

*** Median value (range)**
(Source: adapted from CSR 0205-0380, page 115, Table 11.5.2.3:2)

Conclusions:
The primary endpoint of (adjusted mean) FEV1 $peak_{0-3h}$ response (change from baseline after 4 weeks of treatment) was statistically better than placebo ($p<0.0001$) for all three tiotropium treatment groups. An exploratory comparison showed FEV1 $peak_{0-3h}$ from TR5 was statistically better than TR2.5 and TR1.25 in FAS population (148 patients) whereas the results were comparable between 3 doses in PPS population (115 patients).

Tiotropium was rapidly absorbed following single and multiple inhalations via the Respimat inhaler. The median $T_{max,ss}$ values ranged from 5 to 12 minutes. On an average, 4.79% to 7.41% of the tiotropium dose was excreted unchanged in the urine over 24 hours following the inhalation of a single dose of 1.25 μg to 5 μg tiotropium. At steady-state, an average of 10.6% to 11.3% of the dose was excreted unchanged in the urine over 24 hours. Administration of multiple doses of tiotropium did not result in accumulation in C_{max} and $AUC_{0\text{-}0.167}$ values. However, there was approximately 2-fold accumulation based on $Ae_{0\text{-}24}$ values. A dose proportional behavior was only observed from urine samples ($Ae_{0\text{-}3,ss}$ and $Ae_{0\text{-}24,ss}$) following 4-week treatment.

Reviewer's comments:
Although statistically significant ($p<0.0001$), the absolute values of the differences of FEV1 $Peak_{0-3h}$ between placebo and three doses of tiotropium treatments following 4-week administration were small (<0.19 L). The acceptability of this justification is deferred to the Clinical Reviewer.

The exploratory dose-response analysis was carried out and the results showed that the primary endpoint FEV1 $Peak_{0-3h}$ following TR5 treatment was statistically significantly better than TR2.5 and TR1.25 treatments in FAS population (N=148), but not in PPS population (N=115, Table 4.7). In addition, FEV1 $Peak_{0-3h}$ was numerically higher following TR1.25 treatment (0.255 L) than TR2.5 treatment (0.244L). Therefore, although some trends were observed, the dose-response relationship within TR1.25 and TR5 was not clearly displayed in this study.

Tiotropium plasma concentrations from most of the samples in TR1.25 group were BLQ following both single dose and multiple dose inhalations. This rendered the evaluation of TR1.25 PK profile unreliable from these samples.

Excluding the BLQ values from analysis would relatively increase the systemic exposure in lower dose groups. Therefore a less than dose proportional increase of systemic exposure was observed from blood samples. Since the BLQ problem was much less severe in urine samples, the dose proportional increase of systemic exposure was observed.

4.1.4 Study 205.420

Study Type: Phase 2 efficacy and safety study in adults with moderate persistent asthma

Title:
A Phase II, randomized, double-blind, placebo-controlled, crossover efficacy and safety comparison of tiotropium 5 µg administered once daily (in the evening) and tiotropium 2.5 µg administered twice daily delivered by the Respimat® inhaler for four weeks versus placebo in patients with moderate persistent asthma

Objective:
The objective of this study was to demonstrate the 24-h bronchodilator efficacy and safety of TR5 administered once daily (in the evening) for 4 weeks in comparison to placebo in patients with moderate persistent asthma. The study further aimed to evaluate the efficacy, safety and PK of TR2.5 administered twice daily in comparison to placebo and to TR5 QD.

Study Design and Method:
This investigation was a randomized, placebo-controlled, double-blind, crossover trial with three 4-week treatment periods without washouts. In total 94 adults patients with moderate asthma entered the study and 29 among them participated in PK subset. Three treatments [TR2.5 BID, TR5 QD (TR5 + placebo), and placebo BID] will be administered.

All patients had at least a 3 month history of asthma at the time of enrolment into the trial. The diagnosis had to be confirmed at Visit 1 with bronchodilator reversibility (15 min after 400 µg salbutamol) resulting in a FEV1 increase of 12% or more and 200 mL or more from pre-bronchodilator baseline at Visit 1. All patients had to have a pre-bronchodilator FEV1 of 60% or greater but less than or equal to 90% of predicted normal at Visit 1.All patients had to be on maintenance treatment with a medium stable dose of ICS, either alone or in a fixed-dose combination with LABA or SABA for at least 4 weeks prior to Visit 1.

Measurement of the PFTs, including FEV1, FVC, and PEF, were performed in a 24-hour period at the end of each period.

Blood samples for PK analysis were collected at the first day of the treatment (first dosing period) and the last day of each of the 3 periods. Samples were taken 15 min pre-dose and 2 min, 5 min, 7 min, 10 min, 15 min, 30 min, 1 h, 3 h, 11 h 45 min following each BID dosing within 24 hours. At each time point approximately 5 to 6 mL of blood was drawn from a forearm vein using a Monovette or Vacutainer tube, respectively. Urine samples were collected between -1 h and 0 h prior to dosing as well as 0 h to 6 h, 6 h to 12 h, and 12 h to 24 h post-dose.

Endpoints:
- The primary efficacy endpoint was the FEV1 $AUC_{0\text{-}24h}$ (adjusted by baseline) at the end of each 4-week period.

  The following hypotheses ($\alpha = 0.025$ one-sided) was tested (all means are adjusted means):

  Mean FEV1 $AUC_{0–24h}$ after 4 weeks treatment with TR5 QD ≤ mean FEV1 $AUC_{0–24h}$ after 4 weeks treatment with placebo

  Mean FEV1 $AUC_{0–24h}$ after 4 weeks treatment with TR2.5 BID ≤ mean FEV1 $AUC_{0–24h}$ after 4 weeks treatment with placebo

- Secondary endpoints included FEV1 $AUC_{0\text{-}12h}$, $AUC_{12\text{-}24h}$, $peak_{0\text{-}24h}$ and trough FEV1.

- PK endpoints included C_{max}, T_{max}, AUCs, λz, T1/2, CL/F, Vz/F for blood samples and Ae, fe for urine samples

Analytical Method:
Plasma and urine concentrations of tiotropium were determined by validated assays using HPLC coupled to tandem mass spectrometry. 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.

Efficacy Results:

- Primary endpoint FEV1 $AUC_{0\text{-}24h}$

As a reference point, the mean FEV1 at study baseline (measured pre-dose on the first day before treatment) was 2.524 (SD=0.699) L in FAS population (92 patients). The FEV1 $AUC_{0\text{-}24h}$ responses following 4-week treatment of placebo, TR2.5 BID and TR5 QD were 0.091 L, 0.241 L, and 0.250 L, respectively (Table 4.11). Differences from placebo were statistically significant ($p<0.0001$) for both active treatments; which showed the superiority of active treatments over placebo. Similar conclusion was obtained from PPS population (80 patients, source: CSR0205-420, page 91, Table 11.4.1.1:3).

Table 4.11 Comparison of the Adjusted Mean FEV1 $AUC_{0–24h}$ Response between Active Treatment and placebo – FAS

		Adjusted mean FEV_1 $AUC_{0–24h}$ response [L][1]		Adjusted mean difference from placebo [L][1]		
Treatment	N	Mean	(SE)	Mean	(SE)	95% CI
Placebo	90	0.091	(0.043)			
Tio R2.5 bid	89	0.241	(0.044)	0.149	(0.024)	(0.102, 0.196)
Tio R5 qd	90	0.250	(0.044)	0.158	(0.024)	(0.111, 0.205)

[1] **Adjusted for treatment, period, patient, and study baseline**
(Source: CSR 0205-0420, page 90, Table 11.4.1.1:1)

The FEV_1 $AUC_{0\text{-}24h}$ response was also compared between the 2 active treatments in an exploratory way for patients in the FAS. No significant difference was shown between TR5 QD and TR2.5 BID in FAS population (Table 4.12). Similar conclusion was obtained from PPS population (source: CSR0205-420, page 91, Table 11.4.1.1:4). The FEV1 $AUC_{0\text{-}24h}$ response curves of two active treatments were also similar (Fig. 4.6).

Table 4.12 Comparison of the FEV1 $AUC_{0–24h}$ Response between the Active Treatments− FAS

	Adjusted mean difference [L][1]		
Treatment	Mean	(SE)	95% CI
Tio R2.5 bid			
Tio R5 qd	0.009	(0.024)	(−0.038, 0.056)

[1] **Adjusted for treatment, period, patient, and study baseline**
(Source: CSR 0205-0420, page 90, Table 11.4.1.1:2)

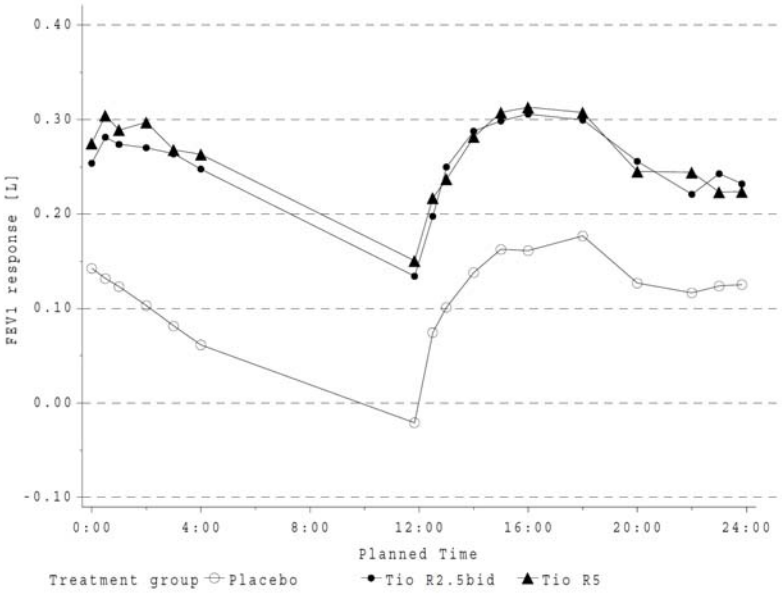


Fig.4.6 FEV1 response over 24 hours following 4-week treatment in FAS population from study 205.420. All the values represent adjusted means by treatment, period, patient and study baseline. (Source: CSR 0205-0420, page 94, Figure 11.4.1.2.1:1)

- Secondary endpoint

Summary of secondary endpoints (FEV1 $AUC_{0\text{-}12h}$, $AUC_{12\text{-}24h}$, $peak_{0\text{-}24h}$ and trough FEV1) were listed in Table 4.13. Differences from placebo were statistically significant for both active treatments for all the secondary endpoints.

PK Results:

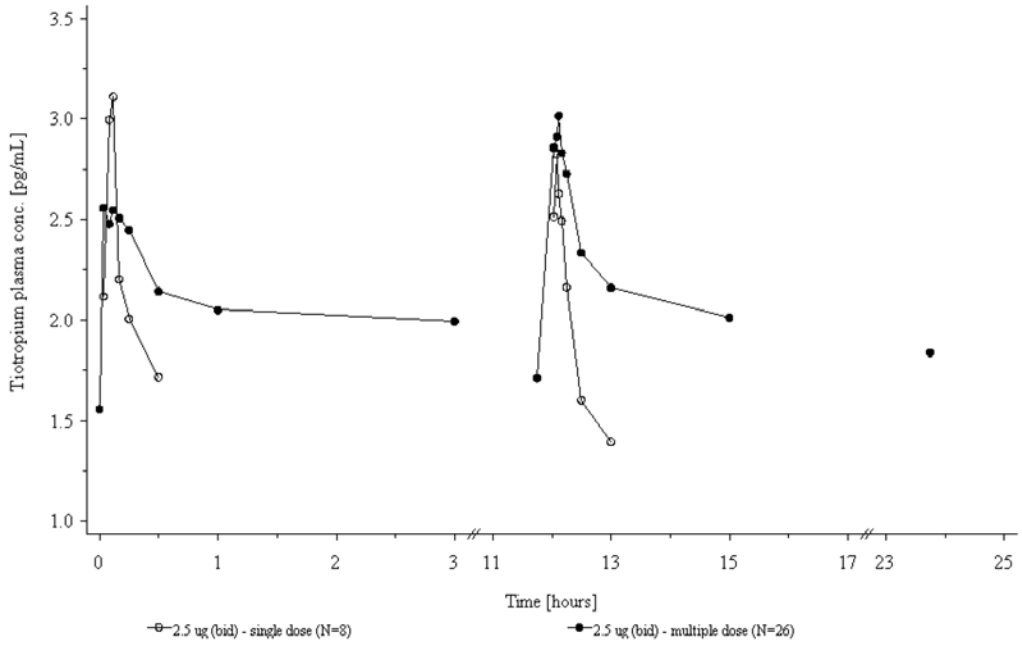
Tiotropium could be detected in plasma from 1/10 and 5/27 patients administered a single dose and multiple dose of placebo, respectively. Low amounts of tiotropium were detected in the urine samples from 15/28 patients following the administration of multiple doses of placebo. 2 and 5 patients administered single dose and multiple dose of TR5 QD exhibited a BID pattern, respectively. One patients administered multiple dose of TR2.5 (ID=4205106) exhibited a QD pattern.

Table 4.13 Summary of Secondary FEV1 endpoints – FAS

Parameter and treatment	N	Adjusted mean response[1] Mean	(SE)	Adjusted mean difference[1] Mean	(SE)	95% CI	p-value[2]
FEV_1 [L]							
FEV_1 AUC_{0-12h}							
Placebo	90	0.048	(0.044)				
Tio R2.5 bid	89	0.217	(0.044)	0.169	(0.025)	(0.120, 0.218)	<0.0001
Tio R5 qd	90	0.233	(0.044)	0.185	(0.025)	(0.136, 0.234)	<0.0001
FEV_1 AUC_{12-24h}							
Placebo	90	0.135	(0.044)				
Tio R2.5 bid	89	0.264	(0.045)	0.129	(0.026)	(0.077, 0.181)	<0.0001
Tio R5 qd	90	0.266	(0.044)	0.131	(0.026)	(0.079, 0.183)	<0.0001
FEV_1 $peak_{0-24h}$							
Placebo	90	0.337	(0.045)				
Tio R2.5 bid	89	0.469	(0.045)	0.132	(0.024)	(0.084, 0.179)	<0.0001
Tio R5 qd	90	0.468	(0.045)	0.131	(0.024)	(0.084, 0.179)	<0.0001
Trough FEV_1							
Placebo	90	0.143	(0.044)				
Tio R2.5 bid	89	0.254	(0.044)	0.111	(0.030)	(0.053, 0.170)	0.0002
Tio R5 qd	90	0.275	(0.044)	0.133	(0.029)	(0.074, 0.191)	<0.0001

[1] Adjusted for treatment, period, patient, and study baseline
(Source: CSR 0205-0420, page 93, Table 11.4.1.2.1:1)

A



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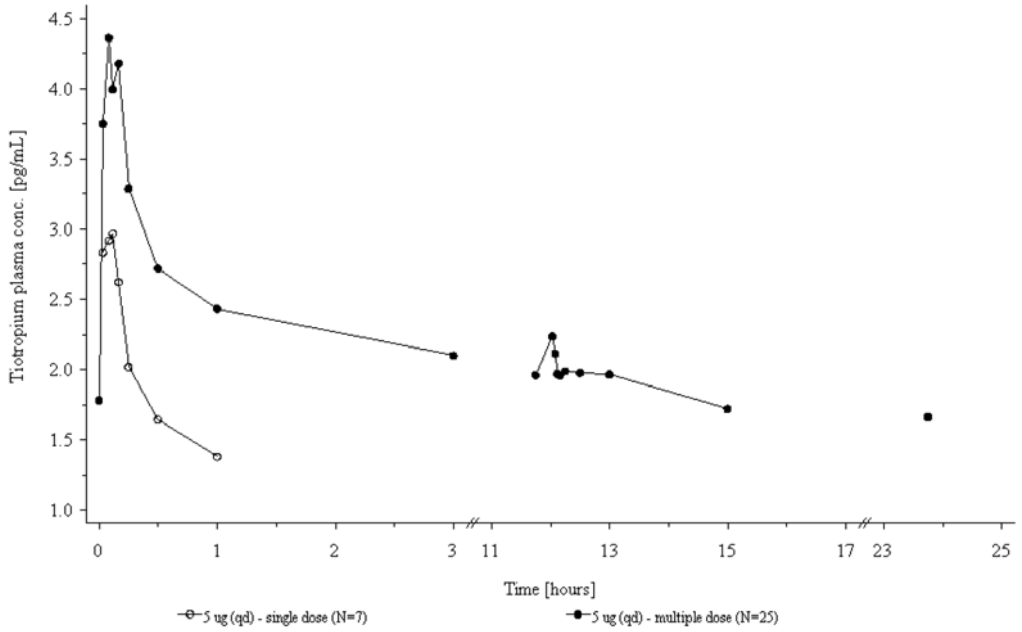


Fig.4.7 Geometric mean tiotropium plasma concentration-time profiles following single and multiple inhalations of TR2.5 BID (A) or TR5 QD (B) in patients with moderate persistent asthma. All the BLQ data were excluded. (Source: CSR 0205-0420, page 105, Figure 11.5.2.1:1 and 11.5.2.1:2)

Following the inhalation of the first dose of TR5 or TR2.5, tiotropium was rapidly absorbed with median T_{max} ranging from 2 minutes to 6 minutes (Fig. 4.7). Tiotropium could be detected in plasma for a limited duration of time only (median tz: 0.746 to 1.00 h) after the first dose. Following multiple oral inhalations

of TR2.5 BID or TR5 QD, tiotropium was rapidly absorbed with median T_{max} ranging between 5 min and 6 min post-dosing (Fig. 4.7).

Following the administration of the first dose, C_{max} of TR5 was 53% higher than TR2.5 whereas short-term AUCs of TR5 were 15% to 20% lower than that of TR2.5 (Table 4.14). Following 4-week administration, C_{max} of TR5 was 88% higher than TR2.5 whereas $AUC_{0-\tau,ss}$ was similar between two treatments (Table 4.15). The urine excretion amount (Ae_{0-24}) of TR5 QD and TR2.5 BID were similar.

Table 4.14 Comparison of Single Dose PK Parameters between TR5 and TR2.5

		2.5 µg bid			5 µg qd		
Parameter	Unit	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0-0.25}$	[pg·h/mL]	4	0.679	30.9	8	0.541	51.2
$AUC_{0-0.25,2}$	[pg·h/mL/µg]	7	0.599	37.0	0	---	---
$AUC_{0-0.5}$	[pg·h/mL]	3	1.23	37.8	7	1.05	40.1
$AUC_{0-0.5,2}$	[pg·h/mL/µg]	6	1.16	32.2	0	---	---
C_{max}	[pg/mL]	8	2.14	68.3	9	3.27	65.4
$C_{max,2}$	[pg/mL]	8	2.77	55.8	0	---	---
t_{max}*	[h]	8	0.0330	0.0140 to 0.161	9	0.0890	0.0200 to 12.1
$t_{max,2}$*	[h]	8	0.100	0.0330 to 0.250	0	---	---
Ae_{0-24}	[ng]	10	231	97.9	10	248	58.6
fe_{0-24}	[%]	10	4.61	97.9	10	4.95	58.6

*** Median, minimum-maximum**
Parameter, $_2$ is the results from second morning dose of TR2.5
(Source: CSR 0205-0420, page 107, Table 11.5.2.3:1)

Table 4.15 Comparison of PK Parameters between TR5 and TR2.5 following 4-week Treatment

		2.5 µg bid			5 µg qd		
Parameter	Unit	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0-24,ss}$	[pg·h/mL]	11	52.0	31.5	0	---	---
$AUC_{0-12,ss}$	[pg·h/mL]	0	---	---	22	27.4	39.7
$AUC_{0-\tau,ss}$	[pg·h/mL]	16	24.4	32.1	18	47.9	34.4
$AUC_{0-\tau,ss,2}$	[pg·h/mL]	13	26.1	32.5	0	---	---
$C_{max,ss}$	[pg/mL]	26	2.90	51.4	25	5.45	71.0
$C_{max,ss,2}$	[pg/mL]	25	3.33	56.4	0	---	---
$t_{max,ss}$*	[h]	26	0.0795	0.0190-0.250	25	0.0830	0.0210-13.0
$t_{max,ss,2}$*	[h]	25	0.104	0.0170-0.979	0	---	---
$t_{1/2}$	[h]	16	35.3	124	18	33.7	88.1
$t_{1/2,2}$	[h]	13	20.0	55.4	0	---	---
$Ae_{0-24,ss}$	[ng]	28	650	76.7	28	656	104
$fe_{0-24,ss}$	[%]	28	13.0	76.7	28	13.1	104
$RA_{,Cmax}$	---	7	1.45	59.7	7	1.79	71.3
$RA_{,Cmax,2}$	---	5	1.77	46.7	0	---	---
$RA_{,AUC0-0.5}$	---	2	1.51	39.9	6	1.97	64.3
$RA_{,AUC0-0.5,2}$	---	5	1.53	67.4	0	---	---
$RA_{,Ae0-24}$	---	9	3.96	71.9	10	1.84	189

*** Median, minimum-maximum**
Parameter, $_2$ is the results from second morning dose of TR2.5
(Source: CSR 0205-0420, page 107, Table 11.5.2.3:2)

Following 4-week dosing, the accumulation ratio of C_{max} was less than 2-fold for both TR5 QD (1.7-fold) and TR2.5 BID (1.2 to 1.4-fold) dosing regimens. The accumulation ratio of urine Ae_{0-24} was about 2.7-fold for both dosing regimens.

Conclusions:
The primary endpoint of (adjusted mean) FEV1 AUC_{0-24h} response (change from baseline following 4 weeks of treatment) was statistically better than placebo ($p<0.0001$) for both TR5 QD and TR2.5 BID treatment groups. An exploratory comparison showed FEV1 AUC_{0-24h} from TR5 QD group was comparable with TR2.5 BID group. Secondary endpoints such as FEV1 AUC_{0-12h}, AUC_{12-24h}, $peak_{0-24h}$ and trough FEV1 were also statistically significantly better than placebo for both active treatments. The FEV1 response curves were similar following 4-week administration of both treatments.

Following 4-week treatment, the total exposure was comparable between TR2.5 BID and TR5 QD based on $Ae_{0-24,ss}$ and $AUC_{0-24,ss}$ values. $C_{max,ss}$ values of TR2.5 BID as morning and evening dosing were 39 to 47% lower, respectively, than that of TR5 QD evening dosing. The accumulation ratios following 4-week treatment ranges from 1.2 to 2.7-fold, depending on which parameter was evaluated.

4.1.5 Study 205.441

Study Type: Phase 2 efficacy and safety study in adults with moderate persistent asthma

Title:
A randomized, double-blind, 2-way crossover study to determine 24-hour FEV1-time profile of inhaled tiotropium, delivered via the Respimat® inhaler, after 4 weeks of once daily (5 µg in the evening [2 actuations of 2.5 µg]) or twice daily (2.5 µg in the morning and evening [2 actuations of 1.25 µg]) administration in patients with moderate persistent asthma

Objective:
The primary objective of this trial was to determine the 24-h FEV1profile of tiotropium solution for inhalation after two 4-week treatment periods of 5 µg tiotropium administered once daily in the evening and 2.5 µg tiotropium administered twice daily with the Respimat® inhaler.

In addition, the PK of tiotropium was characterized in a subset of the study population. The objective of this sub-investigation was to compare the 24-hour PK profile of TR5 QD and TR2.5 BID.

Study Design and Method:
This investigation was a randomized, double-blind, 2-way crossover trial comparing two daily dose regimens of tiotropium for 4 weeks in addition to maintenance therapy with a medium dose of an ICS controller medication. In total 98 patients entered the study with 35 of them participated in PK subset.

The patient's diagnosis of asthma had to be confirmed at Visit 1 with bronchodilator reversibility (i.e. 10 minutes prior to and 15 to 30 minutes after inhalation of 400 µg salbutamol), defined as an FEV1 increase of ≥12% and ≥200 mL. All patients had a pre-bronchodilator FEV1 ≥60% predicted and ≤90% of predicted normal at Visit 1.All patients had to be on maintenance treatment with a medium stable dose of ICS, either alone or in a fixed-dose combination with a LABA or a SABA for at least 4 weeks prior to Visit 1.

The qualifying PFTs were conducted at the screening visit. On the first day of period 1, PFTs were performed pre-dose before inhalation of the first evening dose of study medication. At the end of each 4-week treatment period, PFTs were performed pre-dose and for a 24-hour period after inhalation of the last evening dose of trial medication.

Blood samples for PK analysis were collected at the first day of the treatment (first dosing period) and the last day of each of the 2 periods. Samples were taken 15 min pre-dose and 2 min, 5 min, 7 min, 10 min, 15 min, 30 min, 1 h and 3 h following each BID dosing within 24 hours. An additional PK sample for measuring trough concentration will be collected 15 minutes before the second day dose. At each time point approximately 4.9 to 6 mL of blood was drawn from a forearm vein using a Monovette® or Vacutainer® collection tube. A single urine collection predose (-1 hour to 0) and all urine voided during the sampling intervals 0 to 6, 6 to 12, and 12 to 24 hours post-dose were collected in separate containers.

Endpoints:
- The primary endpoint was the FEV1 $AUC_{0\text{-}24h}$ response determined at the end of each 4-week randomized treatment period.

  No hypothesis testing was planned. Treatment comparison was exploratory and the individual treatment group means and treatment difference were reported along with 95% confidence intervals (CIs)

- Secondary endpoints included FEV1 $AUC_{0\text{-}12h}$, $AUC_{12\text{-}24h}$, $peak_{0\text{-}24h}$ and trough FEV1.

- PK endpoints included C_{max}, T_{max}, AUCs, λz, T1/2, CL/F, Vz/F for blood samples and Ae, fe for urine samples

Analytical Method:
Plasma and urine concentrations of tiotropium were determined by validated assays using HPLC coupled to tandem mass spectrometry. 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.

Efficacy Results:

- Primary endpoint FEV1 $AUC_{0\text{-}24h}$

The mean (SD) study baseline FEV1at randomization was 2.634 L (SD=0.733). Both daily dose regimens of tiotropium provided notable bronchodilation compared to baseline in terms of the primary endpoint FEV1 $AUC_{0\text{-}24h}$ response (Table 4.16). A similar level of FEV1 $AUC_{0\text{-}24h}$ response was observed for the two treatments. The difference in adjusted means between the two treatments was -0.002 L (95% CI: -0.038, 0.034) in FAS population. Similar conclusion was obtained from PPS population (source: CSR0205-441, page 102, Table 11.4.1.1:2). The FEV1 $AUC_{0\text{-}24h}$ response curves of two treatments were also similar (Fig. 4.8).

Table 4.16 Comparison of the Adjusted Mean FEV1 $AUC_{0–24h}$ Response between Active Treatment – FAS

		Adjusted FEV_1 $AUC_{0–24h}$ response [L][1]		Adjusted difference between groups [L][1]		
Treatment	N	Mean	(SE)	Mean	(SE)	95% CI
Tio R2.5 b.i.d.	98	0.219	(0.031)	-0.002	(0.018)	(-0.038, 0.034)
Tio R5 q.d.	97	0.217	(0.031)			

[1] **Adjusted for treatment, period, patient, and study baseline**
(Source: CSR 0205-0441, page 102, Table 11.4.1.1:1)

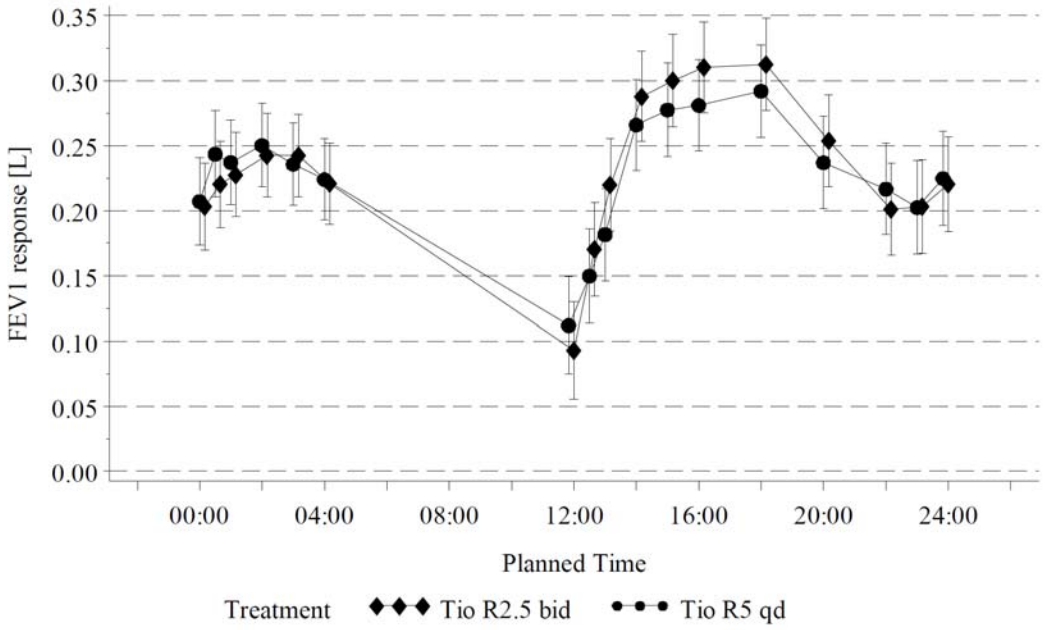


Fig.4.8 FEV1 response over 24 hours following 4-week treatment in FAS population from study 205.441. All the values represent adjusted means by treatment, period, patient and study baseline. (Source: CSR 0205-0441, page 104, Figure 11.4.1.2.1:1)

- Secondary endpoint

Summary of secondary endpoints (FEV1 $AUC_{0\text{-}12h}$, $AUC_{12\text{-}24h}$, $peak_{0\text{-}24h}$ and trough FEV1) were listed in Table 4.17. The difference in adjusted means for TR5 QD and TR2.5 BID were similar.

Table 4.17 Summary of Secondary FEV1 endpoints – FAS

Parameter and treatment	N	Adjusted response[1] Mean	(SE)	Adjusted difference between groups[1] Mean	(SE)	95% CI
FEV_1 [L]						
FEV_1 AUC_{0-12h}						
Tio R2.5 b.i.d.	98	0.182	(0.031)	0.010	(0.021)	(-0.032, 0.052)
Tio R5 q.d.	97	0.192	(0.031)			
FEV_1 AUC_{12-24h}						
Tio R2.5 b.i.d.	98	0.256	(0.033)	-0.014	(0.018)	(-0.050, 0.022)
Tio R5 q.d.	97	0.243	(0.033)			
FEV_1 $Peak_{0-24h}$						
Tio R2.5 b.i.d.	98	0.465	(0.031)	-0.014	(0.018)	(-0.051, 0.023)
Tio R5 q.d.	97	0.451	(0.031)			
Trough FEV_1						
Tio R2.5 b.i.d.	98	0.203	(0.033)	0.004	(0.032)	(-0.060, 0.068)
Tio R5 q.d.	97	0.207	(0.034)			

[1] Adjusted for treatment, period, patient, and study baseline
(Source: CSR 0205-0441, page 103, Table 11.4.1.2.1:1)

PK Results:

Following 4-week treatment of TR5 QD, 1 patient (ID=4411503) exhibited a plasma concentration time profile expected from a BID. Patient 4411501showed an increase of tiotropium concentration at a single time point (12.5 hours following TR5 QD), which indicated a potential contamination.

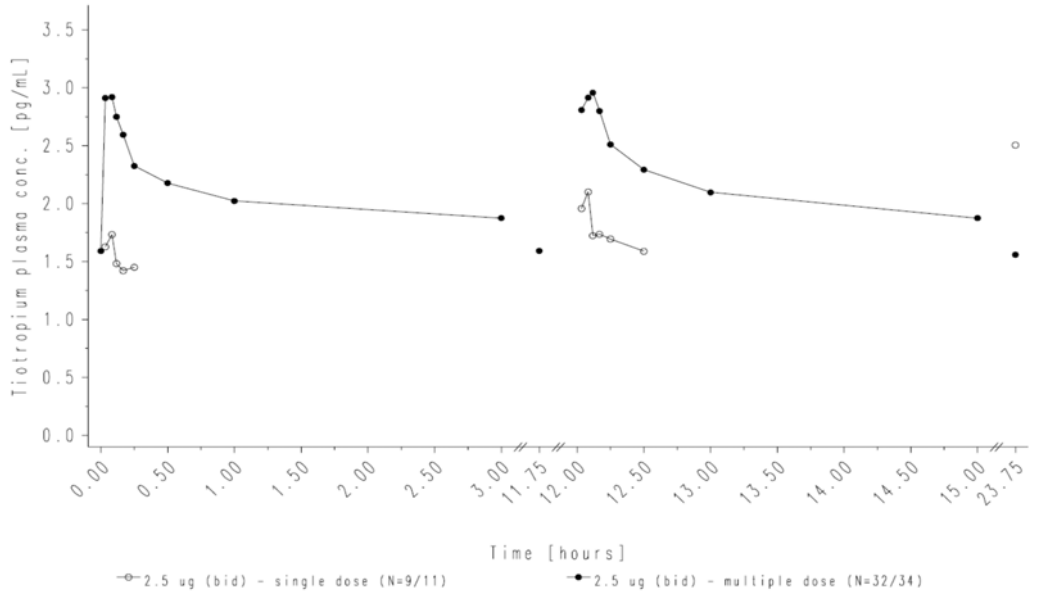
Following the inhalation of the first dose of TR5 or TR2.5, tiotropium was rapidly absorbed with median T_{max} ranging from 5 minutes to 6 minutes (Fig. 4.9). Tiotropium could be detected in plasma for a limited duration of time only (median tz: 0.167 to 1.00 h) after the first dose. Following 4-week administration, the steady state was reached for both dosing regimens as the C_{trough} was similar between two consecutive doses (Table 4.18).

Table 4.18 C_{trough} of Tiotropium following 4-week of TR2.5 BID or TR5 QD Treatment in Study 205.441

	-0.25 h (pre-dose)	11.75 h (post dose)	23.75 h (post dose)
TR2.5 BID C_{trough} (pg/mL)	1.59 (N=21, CV=27%)	1.59 (N=28, CV=33%)	1.56 (N=25, CV=22%)
TR5 QD C_{trough} (pg/mL)	1.43 (N=17, CV=26%)	-	1.56 (N=21, CV=38%)

Values are displayed as geometric mean (N, geometric covariant of efficient)
(Source: adapted from CSR 0205-0441, page 317, Table 15.6.1.1:5)

A



B

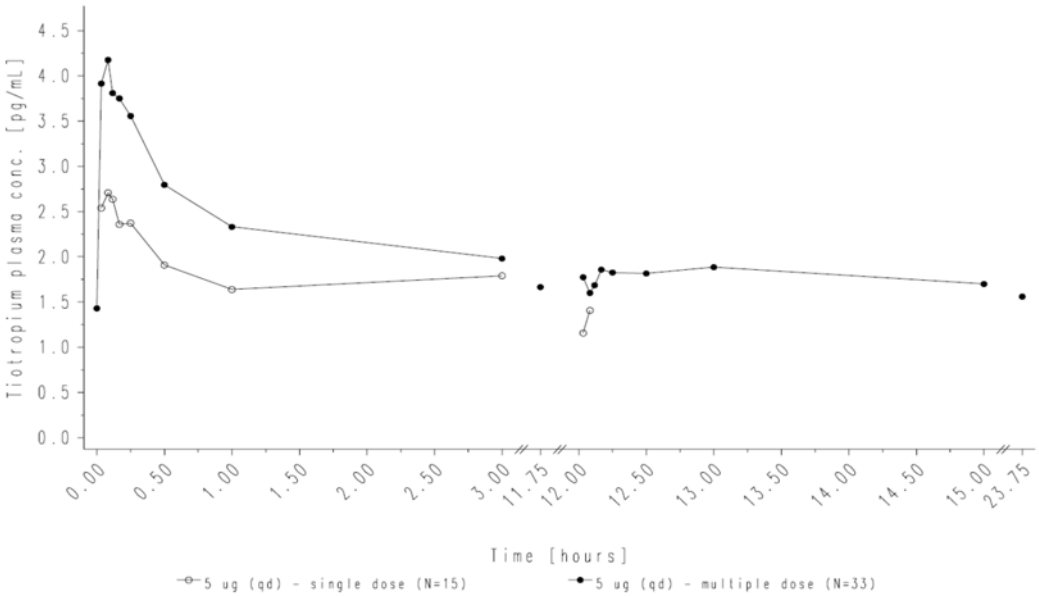


Fig.4.9 Geometric mean tiotropium plasma concentration-time profiles following single and multiple inhalations of TR2.5 BID (A) or TR5 QD (B) in patients with moderate persistent asthma. All the BLQ data were excluded. (Source: CSR 0205-0441, page 112-113, Figure 11.5.2.1:1 and 11.5.2.1:2)

Following the administration of the first dose, C_{max} and short-term AUCs were 32% to 42% lower than that of TR5 (Table 4.19). At steady state, C_{max} of TR2.5 was 35% to 37% lower than TR5 whereas $AUC_{0-\tau,ss}$ was similar between two treatments (Table 4.20). The urine excretion amount (Ae_{0-24}) of TR5 QD and TR2.5 BID were similar at steady state.

At steady state, the accumulation ratio of C_{max} was less than 2-fold for both TR5 QD (1.6-fold) and TR2.5 BID (1.6 to 1.8-fold) dosing regimens. The accumulation ratio of urine Ae_{0-24} was about 2.7-fold and 4.3-fold for TR5 QD and TR2.5 BID, respectively.

Table 4.19 Comparison of Single Dose PK Parameters between TR5 and TR2.5

	Tio R2.5 b.i.d.			Tio R5 q.d.		
	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0\text{-}0.25}$ [pg*h/mL]	4	0.418	26.5	13	0.616	71.2
$AUC_{0\text{-}0.25,2}$ [pg*h/mL]	8	0.464	49.5	---	---	---
$AUC_{0\text{-}0.5}$ [pg*h/mL]	3	0.744	24.0	12	1.19	54.2
$AUC_{0\text{-}0.5,2}$ [pg*h/mL]	4	1.19	31.6	---	---	---
C_{max} [pg/mL]	10	1.77	39.3	17	3.05	71.6
$C_{max,2}$ [pg/mL]	13	2.08	80.2	---	---	---
t_{max}* [h]	10	0.0830	0.0330-2.92	17	0.100	0.0330-23.7
$t_{max,2}$* [h]	13	0.0830	0.0330-11.8	---	---	---
t_z* [h]	9	0.167	0.117-2.92	15	1.00	0.117-13.0
$t_{z,2}$* [h]	10	0.250	0.167-11.8	---	---	---
$Ae_{0\text{-}24}$ [ng]	17	168	49.9	18	250	66.1

*** Median, minimum-maximum**
Parameter, $_2$ is the results from second morning dose of TR2.5
(Source: CSR 0205-0441, page 114, Table 11.5.2.3:1)

Table 4.20 Comparison of PK Parameters between TR5 and TR2.5 following 4-week Treatment

	Tio R2.5 b.i.d.			Tio R5 q.d.		
	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0\text{-}24,ss}$ [pg*h/mL]	23	45.3	20.6	---	---	---
$AUC_{0\text{-}12,ss}$ [pg*h/mL]	---	---	---	31	23.4	33.5
$AUC_{0\text{-}tau,ss}$ [pg*h/mL]	26	21.5	25.3	24	43.8	28.9
$AUC_{0\text{-}tau,ss,2}$ [pg*h/mL]	25	23.0	24.4	---	---	---
$C_{max,ss}$ [pg/mL]	33	3.10	40.4	34	4.95	106
$C_{max,ss,2}$ [pg/mL]	34	3.23	50.8	---	---	---
$t_{max,ss}$* [h]	33	0.0830	0.0330-3.00	34	0.0830	0.0330-13.00
$t_{max,ss2}$* [h]	34	0.0830	0.0330-0.500	---	---	---
$t_{z,ss}$* [h]	32	11.8	0.500-12.2	34	23.7	0.117-23.9
$t_{z,ss,2}$* [h]	34	11.7	0.483-11.8	---	---	---
$Ae_{0\text{-}24,ss}$ [ng]	34	722	49.4	32	677	54.2
RA_{Cmax}	10	1.95	57.9	16	1.48	139
$RA_{Cmax,2}$	13	1.75	87.8	---	---	---
$RA_{AUC0\text{-}0.5}$	3	1.78	13.0	11	1.55	77.4
$RA_{AUC0\text{-}0.5,2}$	4	1.18	58.3	---	---	---
$RA_{Ae0\text{-}24}$	17	3.90	45.2	16	2.72	59.2
$RA_{Ae0\text{-}12}$	17	4.29	64.3	16	2.47	59.4
$RA_{Ae0\text{-}12,2}$	17	3.83	43.8	---	---	---

*** Median, minimum-maximum**
Parameter, $_2$ is the results from second morning dose of TR2.5

Conclusions:
For the primary endpoint of FEV1 $AUC_{0\text{-}24h}$ response, inhalation of tiotropium resulted in notable bronchodilation compared to baseline, with a similar effect size for FEV1 $AUC_{0\text{-}24h}$ response being observed for the two treatments (difference in adjusted mean of -0.002 L). Similarly, no notable differences were observed for all the secondary endpoints of PFTs (FEV1, FVC, and PEF).

At steady state, $C_{max,ss}$ values of TR2.5 BID as evening and morning dosing were 35 to 37% lower, respectively, than that of TR5 QD evening dosing. $AUC_{\tau,ss}$ values of TR2.5 BID as evening and morning dosing were about 50% of TR5 QD evening dosing. The plasma accumulation ratios at steady state range from 1.6 to 1.8-fold, depending on which parameter was evaluated.

Reviewer's comments:
Generally the efficacy results were similar between TR5 QD and TR2.5 BID treatments. The results were consistent with study 205-420.
Based on C_{trough} values, the steady state was reached following 4-week treatments by both dosing regimens. $AUC_{\tau,ss}$ of TR5 QD was comparable to the sum of morning and evening $AUC_{\tau,ss}$ of TR2.5 BID. $C_{max,ss}$ of TR5 QD was 60% and 53% higher than $C_{max,ss}$ of TR2.5 BID as evening and morning dosing.

4.1.6 Study 205.424

Study Type: Phase 2 efficacy and safety study in adolescents with moderate persistent asthma

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 adolescents (12 to 17 yrs old) with moderate persistent asthma

Objective:
The objective of the 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 in adolescents with moderate persistent asthma on iCS.

In addition, the PK of tiotropium was characterized in a subset of the study population. The objective of this sub-investigation was to compare the 24-hour PK profile of TR1.25, TR2.5, and TR5 QD.

Study Design and Method:
This investigation was a randomized, double-blind, placebo-controlled, incomplete crossover trial comparing three once daily evening dose of tiotropium (TR1.25, TR2.5, and TR5 QD) for 4 weeks in adolescent patients (12 to 17 years of age) with moderate persistent asthma. Eligible subjects were randomly allocated to the following treatment sequences: TR5/Placebo/TR1.25, TR1.25/TR5/TR2.5, Placebo/TR2.5/TR5, or TR2.5/TR1.25/Placebo. Each treatment in a treatment sequence was taken for 4 weeks before the next treatment was started. There was no washout period between treatments. In total 105 adolescent patients entered the study. Plasma samples were obtained from 6, 4, 12 and 9 patients administered doses of TR1.25, TR2.5, TR5 and placebo, respectively. Also, urine samples were obtained from 14, 13, 14 and 11 patients administered doses of TR1.25, TR2.5, TR5 and placebo, respectively.

All patients had to have at least a 3 month history of asthma at the time of enrolment into the trial. The diagnosis had to have been confirmed in the past and should have been documented by at least 1 of the following criteria:

- an increased hyper-responsiveness to histamine, methacholine, mannitol, or exercise challenge
- a positive trial of glucocorticosteroids or bronchodilator reversibility in response to a β2-adrenergic agonist drug that resulted in either
  a) forced expiratory volume in FEV1 increase of 12% or more and 200 mL from baseline.
  b) PEF increase of 20% or more

  either a diurnal PEF variability of 10% or more with 2 measurements per day or a diurnal PEF variability of 20% or more with more than measurements per day.

Patients had to have a pre-bronchodilator FEV1 of greater than 60% but 90% or less of the predicted normal. All patients had to be on maintenance treatment with iCS at a stable medium dose, either as monotherapy or in combination with a LABA or a LTRA for at least 4 weeks before Visit 1.

The qualifying PFTs were conducted at the screening visit. On the first day of period 1 and the last day of each period, PFTs were performed pre-dose and at 0.5 h, 1 h, 2 h and 3 h post-dose. 24 h PFTs were conducted in subset of patients.

Blood samples for PK analysis were collected during period 1. Samples were taken 15 min pre-dose and 2 min, 5 min, 7 min, 10 min, 15 min, 30 min, 1 h, 3 h and 23.45 h post dose on Day 1 and Day 28. An

additional PK sample for measuring trough concentration will be collected on Day 26. A single urine collection predose (-1 hour to 0) and all urine voided during the sampling intervals 0 to 3 and 3 to 24 hours post-dose were collected in separate containers.

Endpoints:
The primary endpoint for this study was the maximum FEV1 measured within the first 3 h post-dosing (FEV1 $peak_{0-3h}$), which was determined at the end of each 4-week treatment period. It was analyzed as a response.

The following hypotheses ($\alpha = 0.025$ one-sided) was tested (all means are adjusted means) for all the active treatments (TR1.25, TR2.5, and TR5):

H_0: Mean FEV_1 $peak_{0-3h}$ response after 4 weeks treatment with tiotropium (5 μg) ≤ mean FEV_1 $peak_{0-3h}$ response after 4 weeks treatment with placebo

After testing these 3 hypotheses, exploratory hypothesis comparing 3 active treatments will be tested.

- Secondary endpoints included pre-dose FEV1, FVC $peak_{0-24h}$, FEV1 AUC_{0-3} and FEF.
- PK endpoints included C_{max}, T_{max}, AUCs, λz, T1/2, CL/F, Vz/F for blood samples and Ae, fe for urine samples

Analytical Method:
Plasma and urine concentrations of tiotropium were determined by validated assays using HPLC coupled to tandem mass spectrometry. 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.

Efficacy Results:
- Primary endpoint FEV1 $peak_{0-3h}$

The mean (SD) study baseline FEV1at randomization was 2.746 L (SD=0.700) in FAS population. Among 3 active treatments, only TR5 showed to be superior to placebo following 4-week treatment (p=0.0043, Table 4.21). The superiorities of TR2.5 and TR1.25 over placebo were not established. By subgroup analysis, it appeared that the FEV1 $peak_{0-3h}$ response was greater for both placebo and active treatments in centers located in Latvia and Lithuania. The superiorities of TR5 and TR1.25 were established PPS population with p values of 0.0167 and 0.0497, respectively (source: CSR0205-424, page 254, Table 15.2.2.1:1).

Table 4.21 Comparison of the Adjusted Mean FEV1 $Peak_{0–3h}$ Response between Active Treatments and Placebo – FAS

		Adjusted[1] mean response [L]		Adjusted[1] mean difference (active treatment − placebo) [L]			
Treatment	N		(SE)		(SE)	95% CI	p-value[2]
Placebo	74	0.489	(0.047)				
Tio R1.25	73	0.556	(0.047)	0.067	(0.036)	(−0.005, 0.138)	0.0664
Tio R2.5	74	0.546	(0.047)	0.057	(0.039)	(−0.021, 0.135)	0.1484
Tio R5	77	0.602	(0.046)	0.113	(0.039)	(0.036, 0.190)	0.0043

[1] Adjusted for treatment, period, patient, and study baseline
(Source: CSR 0205-0424, page 92, Table 11.4.1.1.1:1)

The FEV_1 $peak_{0-3h}$ response was also compared between the 3 active treatments in an exploratory way for patients in the FAS. No statistical significant difference was observed between any pair of active treatments (Table 4.22).

Table 4.22 Comparison of the Adjusted Mean FEV1 $Peak_{0-3h}$ Response between Three Active Treatments – FAS

	Adjusted[1] mean difference [L]		
		(SE)	95% CI
Tio R5 versus Tio R1.25	0.046	(0.039)	(−0.031, 0.124)
Tio R5 versus Tio R2.5	0.056	(0.036)	(−0.014, 0.126)
Tio R2.5 versus Tio R1.25	−0.010	(0.040)	(−0.088, 0.069)

[1] **Adjusted for treatment, period, patient, and study baseline**
(Source: CSR 0205-0424, page 93, Table 11.4.1.1.1:2)

- Secondary endpoints

Summary of FEV1 secondary endpoints (FEV1 AUC_{0-3h} and trough FEV1) were listed in Table 4.23. The statistical significant differences for both endpoints were observed when comparing TR5 or TR1.25 with placebo (Fig. 4.10). However, none of the comparisons showed significant differences for FVC secondary endpoints (Source: CSR 0205-0424, page 96, Table 11.4.1.2.1:1).

Table 4.23 Comparisons of FEV1 secondary PFT endpoints-FAS

Parameter and treatment	N	Adjusted[1] mean response [L] (SE)		Adjusted[1] mean difference (active treatment − placebo) [L] (SE)	95% CI	p-value[2]
FEV_1						
Trough FEV_1						
Placebo	74	0.292	(0.045)			
Tio R1.25	73	0.384	(0.045)	0.092 (0.037)	(0.019, 0.165)	0.0134
Tio R2.5	74	0.353	(0.045)	0.062 (0.037)	(−0.011, 0.135)	0.0975
Tio R5	77	0.442	(0.045)	0.151 (0.036)	(0.079, 0.223)	<0.0001
FEV_1 AUC_{0-3h}						
Placebo	74	0.363	(0.045)			
Tio R1.25	73	0.455	(0.045)	0.092 (0.032)	(0.030, 0.155)	0.0042
Tio R2.5	74	0.434	(0.045)	0.071 (0.034)	(0.003, 0.138)	0.0398
Tio R5	77	0.497	(0.045)	0.133 (0.034)	(0.066, 0.200)	0.0001

[1] **Adjusted for treatment, period, patient, and study baseline**
(Source: CSR 0205-0424, page 96, Table 11.4.1.2.1:1)

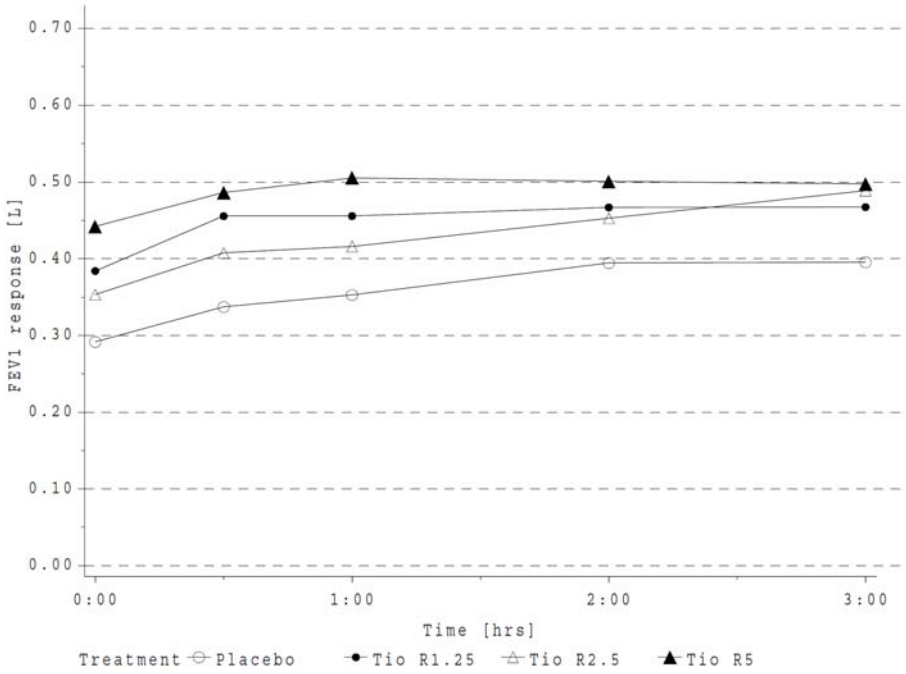


Fig.4.10 FEV1 response over 3 hours following 4-week treatment in FAS population from study 205.424. All the values represent adjusted means by treatment, period, patient and study baseline. (Source: CSR 0205-0424, page 98, Figure 11.4.1.2.1:1)

PK Results:

Urine data from patients 4240241 and 424245 in the single dose urine sampling intervals was excluded as data entry error was detected. Further, pre-dose plasma concentration (−0:15 min) of patient 4240208 following the administration of single dose was excluded as contamination was suspected. Tiotropium concentrations were detected in the plasma at a couple of time points for patients 4240014 and 4240055.! PK parameters were estimated if at least 3 individual values were available.

Table 4.24 Comparisons of the First Dose PK Parameters of Tiotropium in Adolescent Patients

		1.25 µg			2.5 µg			5 µg		
Parameter	Unit	N	gMean	gCV [%]	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0\text{-}0.167}$	[pg·h/mL]	---	---	---	---	---	---	7	0.413	71.6
$AUC_{0\text{-}0.5}$	[pg·h/mL]	---	---	---	---	---	---	6	1.21	47.8
$AUC_{0\text{-}1}$	[pg·h/mL]	---	---	---	---	---	---	4	2.08	33.9
$AUC_{0\text{-}tz}$	[pg·h/mL]	---	---	---	---	---	---	8	2.07	636
C_{max}	[pg/mL]	---	---	---	3	1.40	6.87	9	3.37	84.4
$C_{max,norm}$	[(pg/mL)/µg]	---	---	---	3	0.559	6.87	9	0.674	84.4
$C_{0.033}$	[pg/mL]	---	---	---	3	1.33	12.2	5	4.39	91.4
$C_{0.083}$	[pg/mL]	---	---	---	---	---	---	7	2.89	46.6
$C_{0.117}$	[pg/mL]	---	---	---	---	---	---	6	2.99	49.6
$C_{0.167}$	[pg/mL]	---	---	---	---	---	---	6	2.84	37.6
t_{max}*	[h]	---	---	---	3	0.0830	0.0330 to 0.250	9	0.100	0.0330 to 23.8
t_z*	[h]	---	---	---	---	---	---	8	0.750	0.167 to 23.8
$Ae_{0\text{-}3}$	[ng]	9	12.4	81.3	11	32.3	78.6	10	47.8	177
$Ae_{0\text{-}24}$	[ng]	12	41.0	68.3	11	106	73.6	10	202	103
$fe_{0\text{-}3}$	[%]	9	0.995	81.3	11	1.29	78.6	10	0.956	177
$fe_{0\text{-}24}$	[%]	12	3.28	68.3	11	4.24	73.6	10	4.04	103

*** Median, minimum-maximum**
(Source: CSR 0205-0424, page 117, Table 11.5.2:1)

Following the first dose of TR2.5 and TR5, C_{max} was reached with a median T_{max} of 5 to 6 minutes post-dosing (Table 4.24). C_{max} and $Ae_{0\text{-}24}$ value of TR5 was 2.4-fold and 1.9-fold as that of TR2.5, respectively. Tiotropium could be detected in plasma up to 45 min post-dose following TR5.

Following 4-week administration of TR2.5 and TR5, C_{max} was reached with a median T_{max} of 4 to 5 minutes post-dosing (Table 4.25). Both $C_{max,ss}$ and $Ae_{0\text{-}24,ss}$ values of TR5 was 1.8-fold as those of TR2.5.

Due to the limited sample size and large variation, C_{trough} measured at the end of the 4th week appeared fluctuating within a range of 1.5-fold (Table 4.26). Referring to adults' results from study 205-441, the steady state in adolescents may have been achieved on Day 26.At steady state, the accumulation ratio of C_{max} was 1.2-fold and 1.6-fold for TR5 and TR2.5, respectively. The accumulation of $Ae_{0\text{-}24}$ was 3.1-fold and 3.4-fold for TR5 and TR2.5, respectively (Fig. 4.11).

Table 4.25 Comparisons of PK Parameters of Tiotropium at Steady State in Adolescent Patients

		1.25 µg			2.5 µg			5 µg		
Parameter	Unit	N	gMean	gCV [%]	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0\text{-}0.167,ss}$	[pg·h/mL]	---	---	---	3	0.269	64.7	10	0.518	52.1
$AUC_{0\text{-}0.5,ss}$	[pg·h/mL]	---	---	---	---	---	---	9	1.51	47.7
$AUC_{0\text{-}1,ss}$	[pg·h/mL]	---	---	---	---	---	---	9	2.74	43.2
$AUC_{0\text{-}2,ss}$	[pg·h/mL]	---	---	---	---	---	---	9	4.93	38.9
$AUC_{0\text{-}3,ss}$	[pg·h/mL]	---	---	---	---	---	---	9	7.00	36.1
$AUC_{0\text{-}tz,ss}$	[pg·h/mL]	---	---	---	3	1.02	362	10	18.6	312
$AUC_{\tau,ss}$	[pg·h/mL]	---	---	---	---	---	---	9	36.9	45.2
$C_{max,ss}$	[pg/mL]	3	1.97	54.1	3	2.22	91.1	11	3.95	47.1
$C_{max,ss,norm}$	[(pg/mL)/µg]	3	1.58	54.1	3	0.890	91.1	11	0.790	47.1
$C_{0.033,ss}$	[pg/mL]	---	---	---	3	1.88	57.7	10	2.82	60.0
$C_{0.083,ss}$	[pg/mL]	---	---	---	3	2.19	87.7	11	3.22	61.2
$C_{0.117,ss}$	[pg/mL]	---	---	---	3	1.43	40.9	10	3.38	53.4
$C_{0.167,ss}$	[pg/mL]	---	---	---	3	1.82	120	9	3.46	57.8
$C_{pre,ss,29}$	[pg/mL]	---	---	---	---	---	---	7	1.41	29.7
$t_{max,ss}^{*}$	[h]	3	1.00	0.250 to 3.00	3	0.0830	0.0330 to 0.183	11	0.0670	0.0330 to 0.233
$t_{z,ss}^{*}$	[h]	---	---	---	3	0.500	0.250 to 3.02	10	23.7	0.267 to 23.8
$R_{A,Cmax}$	[---]	---	---	---	---	---	---	8	1.26	144
$t_{1/2,ss}$	[h]	---	---	---	---	---	---	9	24.3	87.8
$V_z/F_{,ss}$	[L]	---	---	---	---	---	---	9	4740	60.3
$CL_{R0\text{-}24,ss}$	[mL/min]	---	---	---	---	---	---	9	395	65.3
$Ae_{0\text{-}3,ss}$	[ng]	13	43.8	78.8	12	71.7	96.3	12	138	96.3
$Ae_{0\text{-}24,ss}$	[ng]	14	163	73.1	12	358	69.5	12	630	91.7
$fe_{0\text{-}3,ss}$	[%]	13	3.51	78.8	12	2.87	96.3	12	2.75	96.3
$fe_{0\text{-}24,ss}$	[%]	14	13.1	73.1	12	14.3	69.5	12	12.6	91.7

*** Median, minimum-maximum**
(Source: CSR 0205-0424, page 118, Table 11.5.2:2)

Table 4.26 C_{trough} of Tiotropium Following 4-week TR5 Once Daily Treatment during the End of Period 1 in Study 205.424

	$C_{pre,ss,Day\ 26}$	$C_{pre,ss,Day\ 28}$	$C_{pre,ss,Day\ 29}$
TR5 QD C_{trough} (pg/mL)	1.76 (N=8, CV=43%)	2.10 (N=6, CV=71%)	1.41 (N=7, CV=30%)

Values are displayed as geometric mean (N, geometric covariant of efficient)
(Source: adapted from CSR 0205-0424, page 451, Table 15.6.2.1:19)

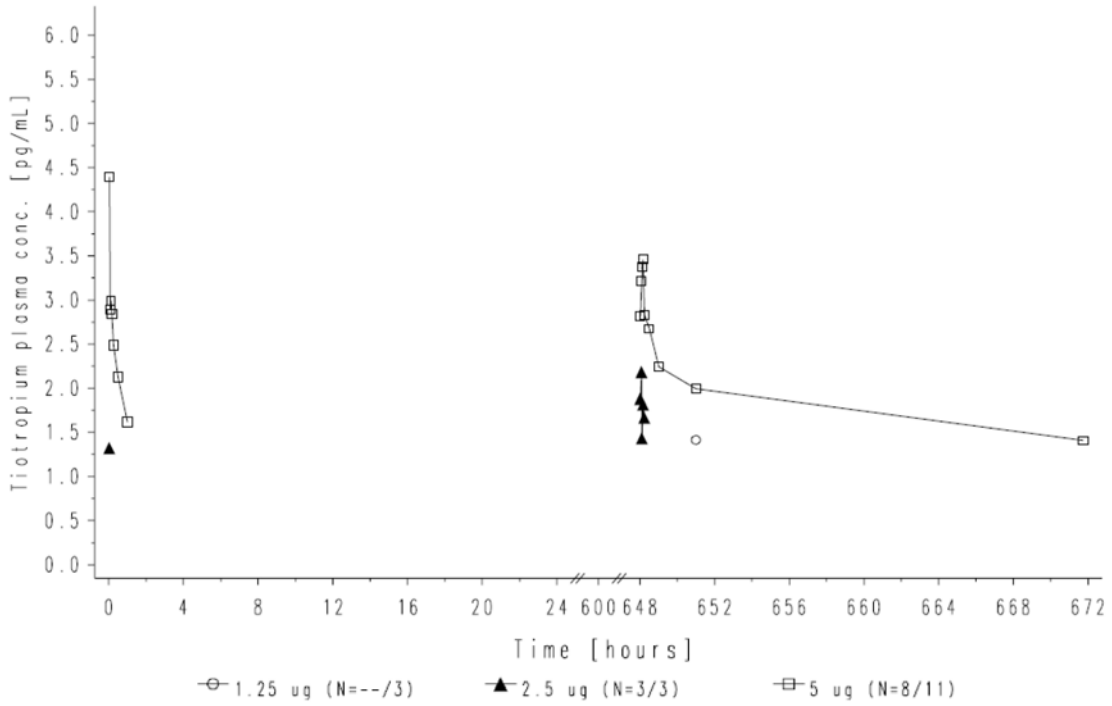


Fig.4.11 Geometric mean tiotropium plasma concentration-time profiles following single and multiple inhalations of TR1.25, TR2.5, and TR5 once daily over 4 weeks in adolescent. All the BLQ data were excluded. (Source: CSR 0205-0424, page 116, Figure 11.5.2:1)

Conclusions:
For the primary endpoint of FEV1 $peak_{0\text{-}3h}$ response, inhalation of TR5, QD for 4 weeks showed to be superior to placebo whereas there was no statistical significance observed when comparing TR5 or TR1.25 with placebo. The statistical significant differences for secondary endpoints (FEV1 $AUC_{0\text{-}3h}$ and trough FEV1) were observed when comparing TR5 or TR1.25 with placebo.

At steady state, both $C_{max,ss}$ and $Ae_{0\text{-}24,ss}$ values of TR5 was 1.8-fold as those of TR2.5. The accumulation ratio of C_{max} and $Ae_{0\text{-}24}$,ss was 1.2-fold and 3.1-fold for TR5, respectively.

Reviewer's comments:
Generally the efficacy size of primary endpoint (FEV1 $peak_{0\text{-}3h}$ difference from placebo) was numerically less in adolescents [0.113 L (N=77, SE=0.039)] compared to adults [0.188 (N=144, SE=0.024), from study 205.380]. Among 3 investigated doses, only TR5 showed superiority over placebo.

Following first dose of TR5, the C_{max} observed in adolescents was 3.37 pg/mL (N=9, CV=84%), which was comparable with adults' value from study 205.441 [3.05 pg/mL (N=17, CV=72%)]. At steady state, the $C_{max,ss}$ and $AUC_{\tau,ss}$ observed in adolescents were 3.95 pg/mL (N=11, CV=47%) and 36.9 pg·h/mL (N=9, CV=45%), respectively. The values were comparable with adults' results from study 205.441 [$C_{max,ss}$ = 4.95 pg/mL (N=34, CV=109%), $AUC_{\tau,ss}$ = 43.8 pg·h/mL (N=24, CV=29%)].

4.1.7 Study 205.416

To be noted, only the PK moiety of this Phase 3 study will be covered under this review.

Study Type: Phase 3 efficacy and safety study in patients with severe persistent asthma

Title:
A Phase III randomized, double-blind, placebo-controlled, parallel group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (5 µg/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma

Objective:
This trial was 1 of 2 confirmatory Phase 3 trials with identical protocols (205.416 and 205.417). The objective of this trial was to evaluate the long-term efficacy and safety of tiotropium solution for inhalation (5 µg) delivered by the Respimat® inhaler in comparison to placebo (both treatments on top of usual care) in adult patients with severe, uncontrolled, persistent asthma

In addition, the PK of tiotropium was characterized in a subset of the study population. The objective of this sub-investigation was to compare the steady state PK profile with the first dose PK profile.

PK Study Design and Method:
This investigation was a randomized, double-blind, placebo-controlled, parallel-group comparison of TR5 once daily in the morning versus placebo for 48 weeks in adult patients with severe, uncontrolled, persistent asthma. A total of 459 patients entered the study with 237 on TR5 treatment and 222 on placebo treatment. A subset of 71 patients participated in the PK portion of the study.

The patient must have had a post-bronchodilator (approximately 30 min after the inhalation of 4 puffs of 100 µg salbutamol) FEV1 that was 80% or less of predicted normal and 70% or less than the forced vital capacity (FVC) at screening. All patients must have had a diagnosis of severe persistent asthma and must have been symptomatic despite treatment with a high, stable dose of ICS and a LABA. All patients must have been on treatment with a high, stable dose of ICS and a LABA for at least 4 weeks before the screening visit. All patients must have had a history of 1 or more asthma exacerbations in the past year.

Blood samples were taken 15 min before administration of trial drug and 2 min, 5 min, 7 min, 10 min, 15 min, 30 min, 1 h, 2 h, 3 h, 6 h and 23.75 h following trial drug administration on Day 1 and Day 28. C_{trough} blood samples were taken 15 min before administration of trial during at on Day 7, Day14, and Day 21. All urine voided between -1 and 0 h pre-dose as well as 0 h to 2 h, 2 to 6 h, and 6 h to 24 h post-dose was collected in containers from some patients on Day 1 and Day 28.

However, following authority interaction, the sampling scheme was extended to over 24 h post-dosing at single and multiple dosing (referred to as the "new sampling scheme" in this document). 12 patients underwent blood and urine sampling according to the old sampling scheme and 25 patients according to the new sampling scheme. Unless otherwise stated, the results that follow are based on the new sampling scheme.

PK Endpoints:
PK endpoints included C_{max}, T_{max}, AUCs, λz, T1/2, CL/F, Vz/F for blood samples and Ae, fe for urine samples

Analytical Method:
Plasma and urine concentrations of tiotropium were determined by validated assays using HPLC coupled to tandem mass spectrometry. The calibration curves of undiluted samples were linear over the range of concentrations from 2.50 to 150 pg/mL tiotropium from plasma samples and 10.0 to 5000 pg/mL tiotropium from acidified urine samples.

PK Results:
Tiotropium was not detected in the plasma and urine of the patients who were administered placebo during the trial except for Patient 4160742, who had a tiotropium concentration of 37.6 pg/mL found in the 0 to 2 h urine collection interval following the administration of a single dose; this was attributed to contamination. There was an exceptional surge of tiotropium concentration at 3 h post-dosing following the first dose of TR5 (Fig.4.12). This surge was driven by data from 1 patient (Patient 4160737) and in most likelihood represents contamination.
!

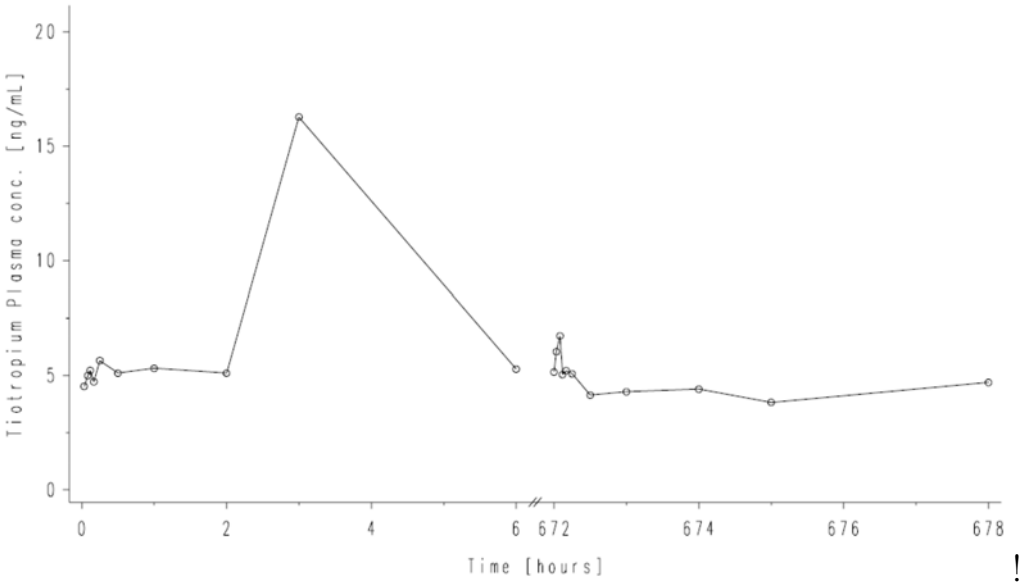


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Fig.4.12 Geometric mean tiotropium plasma concentration-time profiles following single and multiple inhalations of TR5 once daily over 28 days in severe asthma patients. All the BLQ data were excluded. (Source: CSR 0205-0416, page 155, Figure 11.5.2:1)

!

Due to the limited sample size, C_{trough} measured on Day 7, Day 21 and Day 28 appeared fluctuating within a range of 1.8-fold (Table 4.27). Referring to $C_{trough,ss}$ results from study 205.441, the steady state of tiotropium may have been achieved on Day 7. To be noted, $C_{trough,ss}$ values in study 205.416 were at least 2-fold as the $C_{trough,ss}$ values from study 205.441; this is because the LLOQ of study 205.416 was 2.50 pg/mL (LLOQ of study 205.441 was 1.00 pg/mL).

!

Table 4.27 C_{trough} of Tiotropium Following 28-day TR5 Once Daily Treatment in Study 205.416

	$C_{pre,Day\ 7}$	$C_{pre,Day\ 21}$	$C_{pre,Day\ 28}$
TR5 QD C_{trough} (pg/mL)	3.54 (N=3, CV=44%)	2.90 (N=3, CV=7%)	5.15 (N=6, CV=122%)

Values are displayed as geometric mean (N, geometric covariant of efficient)
(Source: adapted from CSR 0205-0416, page 1089, Table 15.6.2.1:8)

A summary of PK parameters following single and multiple inhalations of TR5 by patients with severe asthma is presented in Table 4.28. Dosing to steady-state resulted in 1.5-fold and 2.3-fold accumulation of C_{max} and Ae_{0-24}. Approximately 5.35% and 11.3% of the administered dose was excreted unchanged in urine within 24 hours following single and multiple inhalation of TR5, respectively.

Table 4.28 PK parameters for All Patients following Single and Multiple Inhalations of TR5

	Unit	N	gMean	gCV [%]
Single dose PK parameters				
$AUC_{0-0.25}$ [1]	[pg*h/mL]	6	1.24	40.7
$AUC_{0-0.5}$ [1]	[pg*h/mL]	4	2.31	25.9
$C_{0.033}$ [1]	[pg/mL]	10	4.53	40.9
$C_{0.083}$	[pg/mL]	16	5.00	47.1
C_{max} [1]	[pg/mL]	13	5.37	77.5
t_{max} [1,2]	[h]	13	0.083	0.017 to 0.233
Ae_{0-24} [1]	[ng]	18	268	84.3
fe_{0-2}	[%]	29	1.04	133
fe_{0-6}	[%]	30	2.24	82.3
fe_{0-24} [1]	[%]	18	5.35	84.3
Steady-state PK parameters				
$AUC_{0-0.25,ss}$ [1]	[pg*h/mL]	15	1.23	43.3
$AUC_{0-0.5,ss}$ [1]	[pg*h/mL]	14	2.31	36.8
$C_{0.033,ss}$ [1]	[pg/mL]	14	6.04	53.0
$C_{0.083,ss}$	[pg/mL]	16	5.55	46.7
$C_{max,ss}$ [1]	[pg/mL]	19	5.70	50.7
$t_{max,ss}$ [1,2]	[h]	19	0.067	0.017 to 1.98
$C_{min,ss}$	[pg/mL]	26	2.93	19.4
$t_{1/2,ss}$	[h]	3	77.5	83.9
$V_z/F_{,ss}$	[L]	3	6200	94.2
$CL_{R,0-6,ss}$	[mL/min]	6	135	56.6
$Ae_{0-24,ss}$ [1]	[ng]	16	565	47.5
$fe_{0-2,ss}$	[%]	27	1.82	78.1
$fe_{0-6,ss}$	[%]	24	3.93	63.7
$fe_{0-24,ss}$ [1]	[%]	16	11.3	47.5
$R_{A,Ae0-6}$		21	1.97	49.0
$R_{A,Ae0-24}$ [1]		12	2.25	51.1
$R_{A,AUC0-0.25}$ [1]		4	1.50	45.2
$R_{A,AUC0-0.5}$ [1]		3	1.62	13.9
$R_{A,Cmax}$ [1]		12	1.45	34.1

*** New sampling scheme**
[#] Median (minimum – maximum)
(Source: CSR 0205-0416, page 157, Table 11.5.2:1)

Tiotropium PK data were available from 4 Japanese, 1 Asian outside Japan, 1 African American, and 31 White patients with severe, persistent asthma in this study. At steady state, Japanese patients had 23.50% higher $C_{0.083,ss}$ and 40.66% higher $Ae_{0-24,ss}$ values than the White patients.

PK Conclusions:
Steady state of tiotropium may be achieved on Day 7. At steady state, TR5 was rapidly absorbed following oral inhalation with a median $T_{max,ss}$ of 4 min post-dosing. Approximately 11.3% of the administered dose was excreted unchanged in the urine over 24 h post-dosing. At steady state, the accumulation ratios for C_{max} and Ae_{0-24} were 1.45-fold and 2.25-fold, respectively. Japanese patients had 23.50% higher $C_{0.083,ss}$ and 40.66% higher $Ae_{0-24,ss}$ values than the White patients.

4.1.8 Study 205.417

To be noted, only the PK moiety of this Phase 3 study will be covered under this review.

Study Type: Phase 3 efficacy and safety study in patients with severe persistent asthma

Title:
A Phase III randomized, double-blind, placebo-controlled, parallel group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (5 µg/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma

Objective:
This trial was 1 of 2 confirmatory Phase 3 trials with identical protocols (205.416 and 205.417). The objective of this trial was to evaluate the long-term efficacy and safety of tiotropium solution for inhalation (5 µg) delivered by the Respimat® inhaler in comparison to placebo (both treatments on top of usual care) in adult patients with severe, uncontrolled, persistent asthma

In addition, the PK of tiotropium was characterized in a subset of the study population. The objective of this sub-investigation was to compare the steady state PK profile with the first dose PK profile.

PK Study Design and Method:
This investigation was a randomized, double-blind, placebo-controlled, parallel-group comparison of TR5 once daily in the morning versus placebo for 48 weeks in adult patients with severe, uncontrolled, persistent asthma. A total of 453 patients entered the study with 219 on TR5 treatment and 234 on placebo treatment. A subset of 76 patients participated in the PK portion of the study.

The patient must have had a post-bronchodilator (approximately 30 min after the inhalation of 4 puffs of 100 µg salbutamol) FEV1 that was 80% or less of predicted normal and 70% or less than the forced vital capacity (FVC) at screening. All patients must have had a diagnosis of severe persistent asthma and must have been symptomatic despite treatment with a high, stable dose of ICS and a LABA. All patients must have been on treatment with a high, stable dose of ICS and a LABA for at least 4 weeks before the screening visit. All patients must have had a history of 1 or more asthma exacerbations in the past year.

Blood samples were taken 15 min before administration of trial drug and 2 min, 5 min, 7 min, 10 min, 15 min, 30 min, 1 h, 2 h, 3 h, 6 h and 23.75 h following trial drug administration on Day 1 and Day 28. C_{trough} blood samples were taken 15 min before administration of trial during at on Day 7, Day14, and Day 21. All urine voided between -1 and 0 h pre-dose as well as 0 h to 2 h, 2 to 6 h, and 6 h to 24 h post-dose was collected in containers from some patients on Day 1 and Day 28.

However, following authority interaction, the sampling scheme was extended to over 24 h post-dosing at single and multiple dosing (referred to as the "new sampling scheme" in this document). 12 patients underwent blood and urine sampling according to the old sampling scheme and 25 patients according to the new sampling scheme. Unless otherwise stated, the results that follow are based on the new sampling scheme.

PK Endpoints:
PK endpoints included C_{max}, T_{max}, AUCs, λz, T1/2, CL/F, Vz/F for blood samples and Ae, fe for urine samples

Analytical Method:
Plasma and urine concentrations of tiotropium were determined by validated assays using HPLC coupled to tandem mass spectrometry. The calibration curves of undiluted samples were linear over the range of concentrations from 2.50 to 150 pg/mL tiotropium from plasma samples and 10.0 to 5000 pg/mL tiotropium from acidified urine samples.

PK Results:
Sporadic tiotropium concentrations were detected in the plasma of 3 patients and urine of 2 patients who were administered placebo during the trial and are attributed to contamination.

Following the administration of the single dose, the average plasma concentration-time profile was only visible until 2 h post-dose. There was an exceptional surge of tiotropium concentration at 6 h post-dosing of TR5 on Day 28 (Fig.4.13).

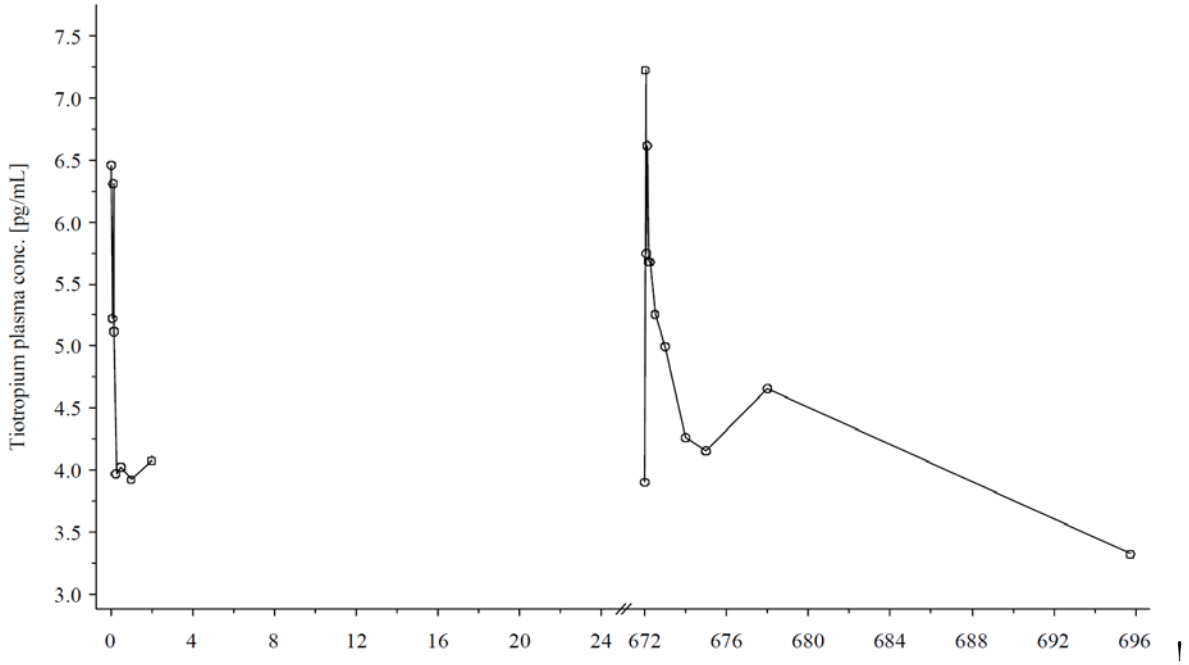

Fig.4.13 Geometric mean tiotropium plasma concentration-time profiles following single and multiple inhalations of TR5 once daily over 28 days in severe asthma patients. All the BLQ data were excluded. (Source: CSR 0205-0417, page 157, Figure 11.5.2:1)

Tiotropium steady state was achieved on Day 7 as C_{trough} measured on Day 7, Day 14, Day 21 and Day 28 fluctuated within a range of 24% (Table 4.29). The C_{trough} values were comparable to that from study 205.416. The C_{trough} results from this study were also more reliable than study 205.416 because much more subjects had their C_{trough} values available throughout the study.

Table 4.29 C_{trough} of Tiotropium Following 28-day TR5 Once Daily Treatment in Study 205.417

	$C_{pre,Day\ 7}$	$C_{pre,Day\ 14}$	$C_{pre,Day\ 21}$	$C_{pre,Day\ 28}$
TR5 QD C_{trough} (pg/mL)	3.62 (N=5, CV=34%)	3.29 (N=10, CV=19%)	3.14 (N=9, CV=17%)	3.90 (N=6, CV=28%)

Values are displayed as geometric mean (N, geometric covariant of efficient)
(Source: adapted from CSR 0205-0417, page 1221, Table 15.6.2.1:8)

A summary of PK parameters following single and multiple inhalations of TR5 by patients with severe asthma is presented in Table 4.30. Dosing to steady-state resulted in 1.2-fold and 1.5-fold accumulation of C_{max} and Ae_{0-24}. Approximately 6.67% and 6.93% of the administered dose was excreted unchanged in urine within 24 hours following single and multiple inhalation of TR5, respectively.

Table 4.30 PK parameters for All Patients following Single and Multiple Inhalations of TR5

	Unit	N	gMean	gCV [%]
Single dose PK parameters				
$AUC_{0-0.25}$ *	[pg·h/mL]	9	1.07	103
$AUC_{0-0.5}$ *	[pg·h/mL]	5	2.38	64.6
$C_{0.033}$ *	[pg/mL]	8	6.46	53.8
$C_{0.083}$	[pg/mL]	12	5.22	59.2
C_{max} *	[pg/mL]	10	6.19	60.7
t_{max} *#	[h]	10	0.0830	0.0330 to 1.97
Ae_{0-24} *	[ng]	15	333	85.1
fe_{0-2}	[%]	31	1.02	209
fe_{0-6}	[%]	30	2.99	195
fe_{0-24} *	[%]	15	6.67	85.1
Steady-state PK parameters				
$AUC_{0-0.25,ss}$ *	[pg·h/mL]	14	1.24	86.3
$AUC_{0-0.5,ss}$ *	[pg·h/mL]	14	2.52	72.1
$C_{0.033,ss}$ *	[pg/mL]	11	7.22	78.7
$C_{0.083,ss}$	[pg/mL]	20	5.75	63.8
$C_{max,ss}$ *	[pg/mL]	14	6.53	74.9
$t_{max,ss}$ *#	[h]	14	0.0750	0.0330 to 6.05
$C_{min,ss}$	[pg/mL]	25	3.06	15.7
$t_{1/2,ss}$	[h]	6	57.1	161
$V_z/F_{,ss}$	[L]	6	4300	321
$CL_{R,0-6,ss}$	[mL/min]	16	73.1	168
$Ae_{0-24,ss}$ *	[ng]	11	347	231
$fe_{0-2,ss}$	[%]	33	0.837	251
$fe_{0-6,ss}$	[%]	33	1.90	224
$fe_{0-24,ss}$ *	[%]	11	6.93	231
$R_{A,Ae0-6}$		31	0.874	442
$R_{A,Ae0-24}$		11	1.46	259
$R_{A,AUC0-0.25}$*		8	1.62	70.5
$R_{A,AUC0-0.5}$*		4	1.69	37.2
$R_{A,Cmax}$*		9	1.23	41.8

*** New sampling scheme**
 # Median (minimum – maximum)
(Source: CSR 0205-0417, page 159, Table 11.5.2:1)

Tiotropium PK data were available from 6 Japanese, 1 Asian outside Japan, 1 African American, and 29 White patients with severe, persistent asthma in this study. At steady state, $C_{0.083,ss}$ and $Ae_{0-24,ss}$ of Japanese patients were 2.05-fold and 4.9-fold as the values from White patients. The large difference on $Ae_{0-24,ss}$ between 2 races was probably due to the small urine $Ae_{0-24,ss}$ sample size (Japanese=3, White=6) available from both races.

PK Conclusions:
Steady state of tiotropium was achieved on Day 7. At steady state, TR5 was rapidly absorbed following oral inhalation with a median $T_{max,ss}$ of 4.5 min post-dosing. Approximately 6.94% of the administered dose was excreted unchanged in the urine over 24 h post-dosing. At steady state, the accumulation ratios for C_{max} and Ae_{0-24} were 1.07-fold and 1.04-fold, respectively. $C_{0.083,ss}$ and $Ae_{0-24,ss}$ of Japanese patients were 2.05-fold and 4.9-fold as the values from White patients at steady state.

4.1.9 Study 205.418

To be noted, only the PK moiety of this Phase 3 study will be covered under this review.

Study Type: Phase 3 efficacy and safety study in patients with severe persistent asthma

Title:
A Phase III randomized, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (2.5 and 5 µg once daily) compared with placebo and salmeterol HFA MDI (50 µg twice daily) over 24 weeks in patients with moderate persistent asthma

Objective:
This trial was 1 of 2 confirmatory Phase III trials with identical protocols (205.418 and 205.419). The objective of this trial was to evaluate the long-term efficacy and safety of 2 doses of tiotropium inhalation solution (2.5 µg and 5 µg) delivered by the Respimat® inhaler compared to placebo and to salmeterol (all treatments on top of medium-dose inhaled corticosteroid (ICS) maintenance therapy) in adults with moderate persistent asthma.

In addition, the PK of tiotropium was characterized in a subset of the study population. The objective of this sub-investigation was to compare the steady state PK profiles between two doses of tiotropium.

PK Study Design and Method:
This investigation was a randomized, double-blind, double-dummy, active- and placebo-controlled, parallel-group comparison of TR5 and TR2.5 once daily in the evening versus salmeterol 50 µg twice daily and placebo on top of medium-dose ICS maintenance therapy over 24 weeks. A total of 1071 patients were randomized with 269, 262, 265, and 275 patients assigned to placebo, TR2.5, TR5, and salmeterol treatment group. A subset of 140 patients participated in the PK portion of the study (placebo: 36 patients, TR2.5: 33 patients, TR5:35 patients, salmeterol: 36 patients).

All patients had to have a pre-bronchodilator FEV1 of ≥60% and ≤90% of predicted normal at Visit 1. The patient's diagnosis of asthma had to be confirmed at Visit 1; a bronchodilator reversibility (15 to 30 min after 400 µg salbutamol/albuterol) resulting in a FEV1 increase of ≥12% and ≥200 mL was required. All patients had to have been on maintenance treatment with a medium, stable dose of ICS (alone or in a fixed combination with a LABA or SABA) for at least for 4 weeks prior to Visit 1.

Blood samples were taken 15 min before administration of trial drug and 2 min, 5 min, 7 min, 10 min, 15 min, 30 min, 1 h, 2 h, 3 h, 6 h and 23.75 h following trial drug administration on Day 1 and Day 28. C_{trough} blood samples were taken 15 min before administration of trial during at on Day 7, Day14, and Day 21. All urine voided between -1 and 0 h pre-dose as well as 0 h to 2 h, 2 to 6 h, and 6 h to 24 h post-dose was collected in containers from some patients on Day 1 and Day 28.

PK Endpoints:
PK endpoints included C_{max}, T_{max}, AUCs, λz, T1/2, CL/F, Vz/F for blood samples and Ae, fe for urine samples

Analytical Method:
Plasma and urine concentrations of tiotropium were determined by validated assays using HPLC coupled to tandem mass spectrometry. The calibration curves of undiluted samples were linear over the range of concentrations from 1.00 to 100 pg/mL tiotropium from plasma samples and 10.0 to 5000 pg/mL tiotropium from acidified urine samples.

PK Results:
Isolated tiotropium concentrations were detected in the plasma and urine samples of few patients who were administered placebo or salmeterol and in most likelihood represent contaminations.

Following the administration of the first dose, tiotropium was rapidly absorbed with a median T_{max} of approximately 5 min post-dosing. Tiotropium concentrations were above the lower limit of quantification only until a median of 0.5 h and 3 h following the first dose of 2.5 and 5 µg, respectively. Following multiple dosing, concentrations remained above the lower limit of quantification until a median of 6 and 23.7 h post-dose for the 2.5 and 5 µg dose groups, respectively (Fig.4.14).

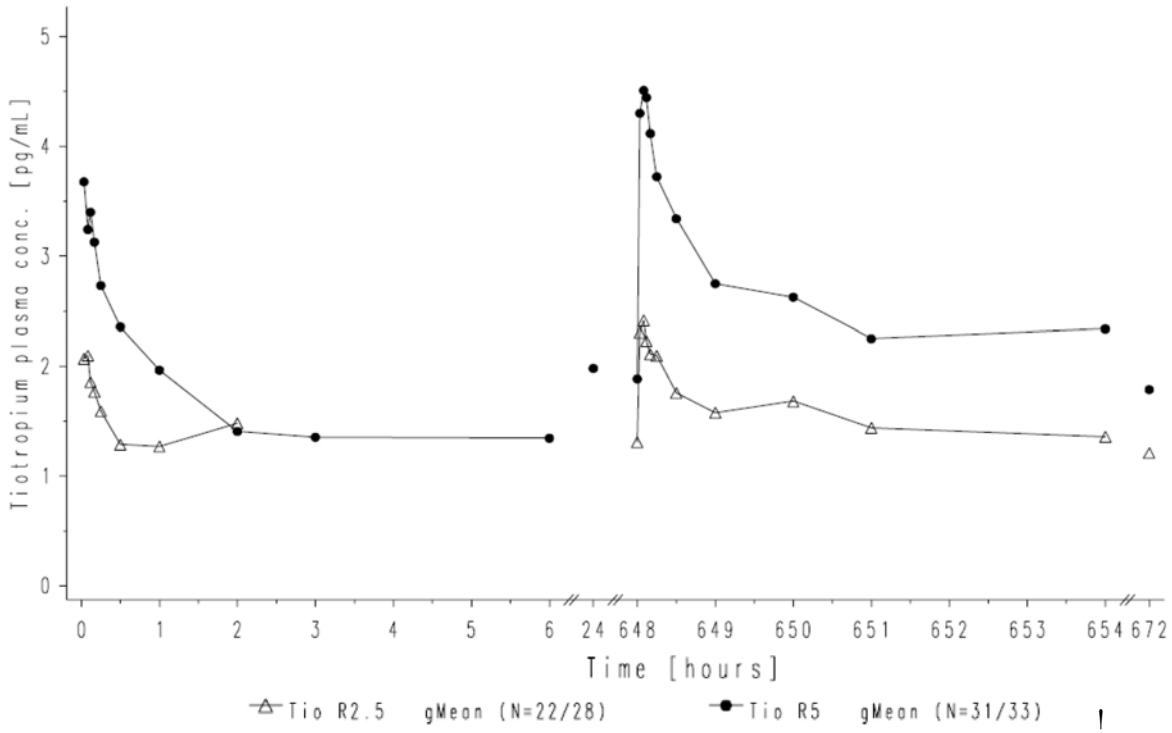

Fig.4.14 Geometric mean tiotropium plasma concentration-time profiles following single and multiple inhalations of TR5 or TR2.5 once daily over 28 days in moderate asthma patients. All the BLQ data were excluded. (Source: CSR 0205-0418, page 159, Figure 11.5.2:1)

Tiotropium steady state was achieved on Day 7 as C_{trough} measured on Day 7, Day 14, Day 21 and Day 28 fluctuated within a range of 12% and 11% for TR2.5 and TR5, respectively (Table 4.31). The C_{trough} results from this study were more precise than study 205.417 because the LLOQ is more sensitive in this study (1.00 pg/mL) than study 205.417 (2.50 pg/mL).

Table 4.31 C_{trough} of Tiotropium Following 28-day TR2.5 or TR5 Once Daily Treatment in Study 205.418

	$C_{pre,Day\ 7}$	$C_{pre,Day\ 14}$	$C_{pre,Day\ 21}$	$C_{pre,Day\ 28}$
TR2.5 QD C_{trough} (pg/mL)	1.39 (N=8, CV=26%)	1.31 (N=9, CV=20%)	1.24 (N=12, CV=16%)	1.31 (N=11, CV=26%)
TR5 QD C_{trough} (pg/mL)	1.71 (N=22, CV=39%)	1.91 (N=25, CV=40%)	1.89 (N=22, CV=40%)	1.89 (N=26, CV=40%)

Values are displayed as geometric mean (N, geometric covariant of efficient)
(Source: adapted from CSR 0205-0418, page 925, Table 15.6.1.1:4 and page 930, Table 15.6.1.1:5)

A summary of PK parameters following the first dose of inhalation of TR2.5 and TR5 in patients with moderate asthma is presented in Table 4.32. The exposure (based on C_{max} and Ae_{0-24} values) increased less than dose proportional manner between the 2.5 and 5 µg doses.

Table 4.32 PK parameters following the First Inhalation of TR2.5 and TR5 in Study 205.418

		Tio R2.5			Tio R5	
Parameter [unit]	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0-0.25}$ [pg*h/mL]	18	0.446	44.3	29	0.780	54.2
$AUC_{0-0.5}$ [pg*h/mL]	13	0.844	29.1	28	1.42	45.9
AUC_{0-1} [pg*h/mL]	9	1.64	15.5	24	2.53	39.8
AUC_{0-2} [pg*h/mL]	5	3.14	21.0	23	4.25	31.5
AUC_{0-3} [pg*h/mL]	---	---	---	21	5.84	26.7
AUC_{0-6} [pg*h/mL]	---	---	---	13	10.4	23.0
$C_{0.083}$ [pg/mL]	21	2.10	44.9	31	3.24	73.4
C_{max} [pg/mL]	25	2.19	52.3	31	4.22	56.4
Ae_{0-6} [ng]	31	54.2	80.7	32	101	97.9
Ae_{0-24} [ng]	31	133	67.3	32	228	83.3
fe_{0-6} [%]	31	2.17	80.7	32	2.02	97.9
fe_{0-24} [%]	31	5.32	67.3	32	4.57	83.3
t_{max} [h][1]	25	0.0760	0.0170-0.987	31	0.0780	0.00700-23.8
t_z [h][1]	22	0.499	0.104-5.98	31	3.00	0.156-23.8

[1] **Median (minimum – maximum)**
(Source: CSR 0205-0418, page 163, Table 11.5.2:1)

A summary of PK parameters following 28 days, once daily dosing of TR2.5 and TR5 in patients with moderate asthma is presented in Table 4.33. The exposure (based on $C_{max,ss,}$ AUC_{ss} and $Ae_{0-24,ss}$ values) increased in a dose proportional manner between the 2.5 and 5 µg doses.

Table 4.33 PK parameters following Multiple Inhalations of TR2.5 and TR5 in Study 205.418

		Tio R2.5			Tio R5	
Parameter [unit]	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0-0.25,ss}$ [pg*h/mL]	26	0.550	40.6	33	1.02	53.4
$AUC_{0-0.5,ss}$ [pg*h/mL]	24	1.06	34.7	33	1.92	51.4
$AUC_{0-1,ss}$ [pg*h/mL]	22	1.92	30.1	32	3.48	46.9
$AUC_{0-2,ss}$ [pg*h/mL]	20	3.61	29.6	32	6.15	43.4
$AUC_{0-3,ss}$ [pg*h/mL]	20	5.13	28.8	32	8.55	41.7
$AUC_{0-6,ss}$ [pg*h/mL]	18	9.25	24.9	31	15.6	37.7
$AUC_{0-\tau,ss}$ [pg*h/mL]	8	34.3	19.3	24	53.8	27.3
$C_{0.083,ss}$ [pg/mL]	28	2.41	43.8	33	4.51	57.4
$C_{max,ss}$ [pg/mL]	29	2.64	48.7	33	5.31	55.2
$Ae_{0-6,ss}$ [ng]	30	162	69.5	33	292	65.0
$Ae_{0-24,ss}$ [ng]	30	393	68.8	33	801	54.2
$fe_{0-6,ss}$ [%]	30	6.48	69.5	33	5.83	65.0
$fe_{0-24,ss}$ [%]	30	15.7	68.8	33	16.0	54.2
$RA_{,AUC0-0.5}$	11	1.24	43.5	27	1.45	51.4
$RA_{,Ae0-24}$	29	2.89	53.2	31	3.51	90.3
$RA_{,Cmax}$	23	1.21	48.0	30	1.26	49.1
t_{maxss}[1] [h]	29	0.0810	0.0190-2.05	33	0.0810	0.0180-23.7
$t_{z,ss}$[1] [h]	28	6.00	0.153-24.0	33	23.7	0.417-24.0
$t_{1/2,ss}$ [h]	6	47.3	38.3	21	34.5	54.0
$CL_{R,0-24,ss}$ [mL/min]	8	302	24.3	24	271	38.3

[1] **Median (minimum – maximum)**
(Source: CSR 0205-0418, page 164, Table 11.5.2:2)

At steady state, accumulation ratios of C_{max} were 1.2 and 1.3 for TR2.5 and TR5, respectively. Accumulation ratios of Ae0-24 were 3 and 3.5 for TR2.5 and TR5, respectively.

PK Conclusions:
Steady state of tiotropium was achieved on Day 7. At steady state, TR2.5 and TR5 was rapidly absorbed following oral inhalation with a median $T_{max,ss}$ of 5 min post-dosing. Approximately 16% of the administered dose was excreted unchanged in the urine over 24 h post-dosing for both doses. At steady state, accumulation ratios of C_{max} were 1.2 and 1.3 for TR2.5 and TR5, respectively. Accumulation ratios of Ae_{0-24} were 3 and 3.5 for TR2.5 and TR5, respectively.

4.1.10 Study 205.419

To be noted, only the PK moiety of this Phase 3 study will be covered under this review.

Study Type: Phase 3 efficacy and safety study in patients with severe persistent asthma

Title:
A Phase III randomized, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (2.5 and 5 µg once daily) compared with placebo and salmeterol HFA MDI (50 µg twice daily) over 24 weeks in patients with moderate persistent asthma

Objective:
This trial was 1 of 2 confirmatory Phase III trials with identical protocols (205.418 and 205.419). The objective of this trial was to evaluate the long-term efficacy and safety of 2 doses of tiotropium inhalation solution (2.5 µg and 5 µg) delivered by the Respimat® inhaler compared to placebo and to salmeterol (all treatments on top of medium-dose inhaled corticosteroid (ICS) maintenance therapy) in adults with moderate persistent asthma.

In addition, the PK of tiotropium was characterized in a subset of the study population. The objective of this sub-investigation was to compare the steady state PK profiles between two doses of tiotropium.

PK Study Design and Method:
This investigation was a randomized, double-blind, double-dummy, active- and placebo-controlled, parallel-group comparison of TR5 and TR2.5 once daily in the evening versus salmeterol 50 µg twice daily and placebo on top of medium-dose ICS maintenance therapy over 24 weeks. A total of 1032 patients were randomized with 254, 258, 254, and 266 patients assigned to placebo, TR2.5, TR5, and salmeterol treatment group. A subset of 100 patients participated in the PK portion of the study (placebo: 23 patients, TR2.5:28 patients, TR5:23 patients, salmeterol: 26 patients).

All patients had to have a pre-bronchodilator FEV1 of ≥60% and ≤90% of predicted normal at Visit 1. The patient's diagnosis of asthma had to be confirmed at Visit 1; a bronchodilator reversibility (15 to 30 min after 400 µg salbutamol/albuterol) resulting in a FEV1 increase of ≥12% and ≥200 mL was required. All patients had to have been on maintenance treatment with a medium, stable dose of ICS (alone or in a fixed combination with a LABA or SABA) for at least for 4 weeks prior to Visit 1.

Blood samples were taken 15 min before administration of trial drug and 2 min, 5 min, 7 min, 10 min, 15 min, 30 min, 1 h, 2 h, 3 h, 6 h and 23.75 h following trial drug administration on Day 1 and Day 28. C_{trough} blood samples were taken 15 min before administration of trial during at on Day 7, Day14, and Day 21. All urine voided between -1 and 0 h pre-dose as well as 0 h to 2 h, 2 to 6 h, and 6 h to 24 h post-dose was collected in containers from some patients on Day 1 and Day 28.

PK Endpoints:
PK endpoints included C_{max}, T_{max}, AUCs, λz, T1/2, CL/F, Vz/F for blood samples and Ae, fe for urine samples

Analytical Method:
Plasma and urine concentrations of tiotropium were determined by validated assays using HPLC coupled to tandem mass spectrometry. The calibration curves of undiluted samples were linear over the range of concentrations from 1.00 to 100 pg/mL tiotropium from plasma samples and 10.0 to 5000 pg/mL tiotropium from acidified urine samples.

PK Results:
Isolated tiotropium concentrations were detected in the plasma and urine samples of few patients who were administered placebo or salmeterol and in most likelihood represent contaminations.

Following the administration of the first dose, tiotropium was rapidly absorbed with a median T_{max} of approximately 4 - 5 min post-dosing. Tiotropium concentrations were above the lower limit of quantification only until a median of 0.93 h and 1.08 h following the first dose of 2.5 and 5 µg, respectively. Following multiple dosing, concentrations remained above the lower limit of quantification until a median of 6 and 23.7 h post-dose for the 2.5 and 5 µg dose groups, respectively (Fig.4.15).

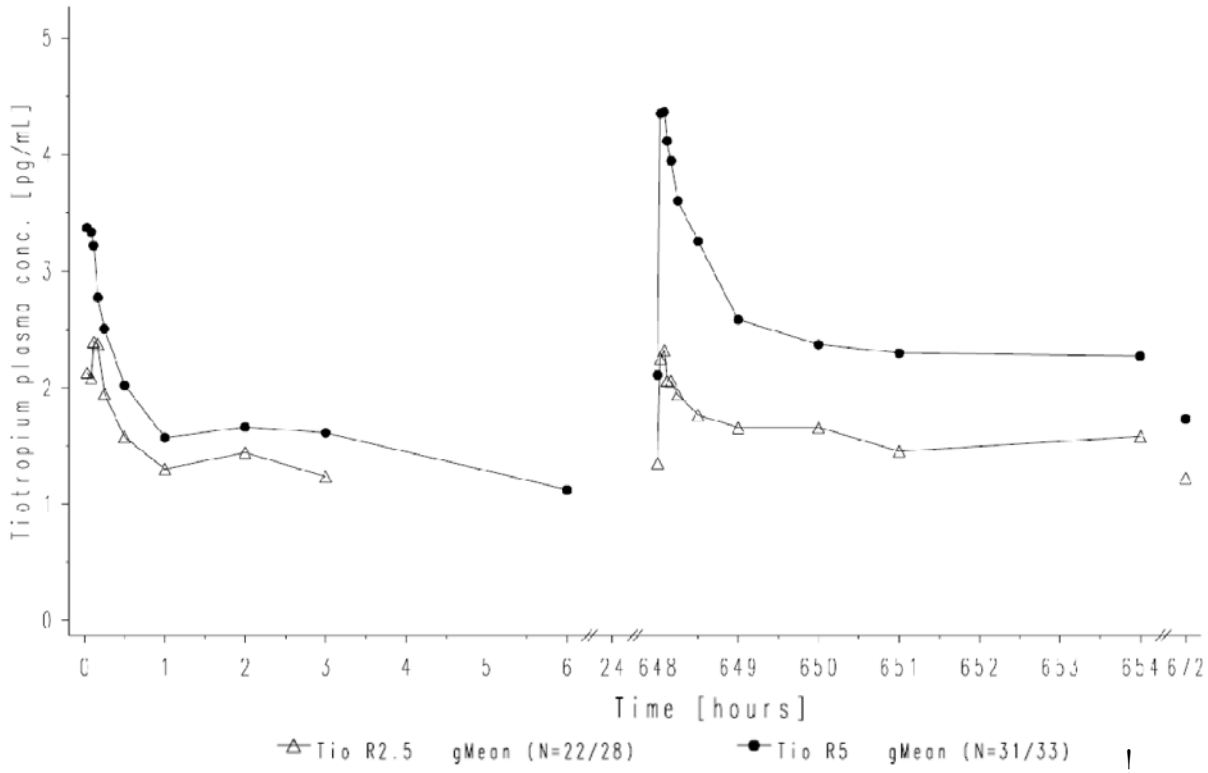

Fig.4.15 Geometric mean tiotropium plasma concentration-time profiles following single and multiple inhalations of TR5 or TR2.5 once daily over 28 days in moderate asthma patients. All the BLQ data were excluded. (Source: CSR 0205-0419, page 159, Figure 11.5.2:1)

Tiotropium steady state was achieved on Day 7 as C_{trough} measured on Day 7, Day 14, Day 21 and Day 28 fluctuated within a range of 34% and 32% for TR2.5 and TR5, respectively (Table 4.34). The C_{trough} results from this study were similar to C_{trough} values observed in study 205.418.

Table 4.34 C_{trough} of Tiotropium Following 28-day TR2.5 or TR5 Once Daily Treatment in Study 205.419

	$C_{pre,Day\ 7}$	$C_{pre,Day\ 14}$	$C_{pre,Day\ 21}$	$C_{pre,Day\ 28}$
TR2.5 QD C_{trough} (pg/mL)	1.39 (N=6, CV=25%)	1.81 (N=7, CV=56%)	1.65 (N=9, CV=63%)	1.35 (N=9, CV=26%)
TR5 QD C_{trough} (pg/mL)	1.60 (N=11, CV=28%)	1.85 (N=11, CV=35%)	1.69 (N=16, CV=39%)	2.11 (N=17, CV=63%)

Values are displayed as geometric mean (N, geometric covariant of efficient)
(Source: adapted from CSR 0205-0418, page 925, Table 15.6.1.1:4 and page 930, Table 15.6.1.1:5)

A summary of PK parameters following the first dose of inhalation of TR2.5 and TR5 in patients with moderate asthma is presented in Table 4.35. The exposure (based on C_{max} and Ae_{0-24} values) increased less than dose proportional manner between the 2.5 and 5 µg doses.

Table 4.35 PK parameters following the First Inhalation of TR2.5 and TR5 in Study 205.419

	Tio R2.5			Tio R5		
Parameter [unit]	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0-0.25}$ [pg*h/mL]	12	0.592	50.3	17	0.714	71.1
$AUC_{0-0.5}$ [pg*h/mL]	12	1.10	39.3	15	1.39	64.1
AUC_{0-1} [pg*h/mL]	10	1.88	34.8	11	2.74	61.9
AUC_{0-2} [pg*h/mL]	5	3.31	20.6	8	5.27	61.7
AUC_{0-3} [pg*h/mL]	3	5.02	1.99	6	8.44	46.0
AUC_{0-6} [pg*h/mL]	---	---	---	4	12.9	47.3
$C_{0.083}$ [pg/mL]	18	2.08	60.7	17	3.34	72.6
C_{max} [pg/mL]	21	2.20	59.8	18	3.97	79.7
Ae_{0-6} [ng]	26	48.8	95.8	20	92.1	114
Ae_{0-24} [ng]	26	121	63.3	20	183	107
fe_{0-6} [%]	26	1.95	95.8	20	1.84	114
fe_{0-24} [%]	26	4.85	63.3	20	3.66	107
t_{max} [h][1]	21	0.0720	0.0160-0.250	18	0.0810	0.0180-0.496
t_z [h][1]	15	0.983	0.155-23.7	17	1.08	0.246-23.7

[i] **Median (minimum – maximum)**
(Source: CSR 0205-0419, page 163, Table 11.5.2:1)

A summary of PK parameters following 28 days, once daily dosing of TR2.5 and TR5 in patients with moderate asthma is presented in Table 4.36. The exposure (based on $C_{max,ss,}$ and AUC_{ss} values) increased in a dose proportional manner between the 2.5 and 5 µg doses.

At steady state, accumulation ratios of C_{max} were 1.12 and 1.25 for TR2.5 and TR5, respectively. Accumulation ratios of Ae_{0-24} were 2.75 and 3.15 for TR2.5 and TR5, respectively.

PK Conclusions:
Steady state of tiotropium was achieved on Day 7. At steady state, TR2.5 and TR5 was rapidly absorbed following oral inhalation with a median $T_{max,ss}$ of 5 min post-dosing. Approximately 13.3% and 11.5% of the administered dose was excreted unchanged in the urine over 24 h post-dosing for TR2.5 and TR5, respectively. At steady state, accumulation ratios of C_{max} were 1.12 and 1.25 for TR2.5 and TR5, respectively. Accumulation ratios of Ae_{0-24} were 2.75 and 3.15 for TR2.5 and TR5, respectively.

Table 4.36 PK parameters following Multiple Inhalations of TR2.5 and TR5 in Study 205.418

	Tio R2.5			Tio R5		
Parameter [unit]	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0\text{-}0.25,ss}$ [pg*h/mL]	22	0.509	51.9	22	0.988	59.2
$AUC_{0\text{-}0.5,ss}$ [pg*h/mL]	19	1.04	47.7	22	1.80	54.9
$AUC_{0\text{-}1,ss}$ [pg*h/mL]	17	2.05	42.4	22	3.20	51.1
$AUC_{0\text{-}2,ss}$ [pg*h/mL]	16	3.83	38.9	21	5.96	45.3
$AUC_{0\text{-}3,ss}$ [pg*h/mL]	15	5.60	35.0	21	8.38	45.5
$AUC_{0\text{-}6,ss}$ [pg*h/mL]	12	10.7	32.0	21	15.5	48.2
$AUC_{0\text{-}\tau,ss}$ [pg*h/mL]	9	37.7	20.5	14	54.0	40.0
$C_{0.083,ss}$ [pg/mL]	20	2.32	52.2	22	4.37	63.3
$C_{max,ss}$ [pg/mL]	24	2.47	51.3	21	4.97	61.0
$Ae_{0\text{-}6,ss}$ [ng]	25	120	75.1	20	229	85.0
$Ae_{0\text{-}24,ss}$ [ng]	24	333	73.9	20	576	84.2
$fe_{0\text{-}6,ss}$ [%]	25	4.78	75.1	20	4.57	85.0
$fe_{0\text{-}24,ss}$ [%]	24	13.3	73.9	20	11.5	84.2
$RA_{,AUC0\text{-}0.5}$	8	1.24	55.9	15	1.47	65.5
$RA_{,Ae0\text{-}24}$	22	2.73	51.7	19	2.97	74.0
$RA_{,Cmax}$	18	1.27	67.2	16	1.25	87.4
t_{maxss}[1] [h]	24	0.0695	0.0160-1.99	21	0.0740	0.0100-6.02
$t_{z,ss}$[1] [h]	22	5.99	0.236-24.2	22	23.7	5.98-24.0
$t_{1/2,ss}$ [h]	7	48.0	43.3	12	39.6	73.4
$CL_{R,0\text{-}24,ss}$ [mL/min]	8	269	31.9	12	181	52.2

[1] **Median (minimum – maximum)**

(Source: CSR 0205-0419, page 164, Table 11.5.2:2)

4.1.11 PK Meta-analysis Report (205-p5-Metaanalysis-PK)

Title:
Meta-analysis of tiotropium non-compartmental pharmacokinetic parameters across various Tiotropium trials

Objective:

- To identify best estimates of standard pharmacokinetic parameters for tiotropium in patients with asthma.
- To describe the effect of intrinsic and extrinsic factors on drug exposure.
- To compare the pharmacokinetics of tiotropium between COPD patients, and patients with asthma.
- To compare the systemic exposure to tiotropium in patients with asthma by different posologies (2.5 µg BID vs 5 µg QD).

Method:
The data from 8 asthma Phase 2/3 clinical trials (205.380, 205.420, 205.441, 205.416, 205.417, 205.418, 205.419 and 205.424) were included in this meta-analysis. The individual trials included 352 patients with asthma (277 with moderate asthma and 75 with severe asthma). For PK comparison with COPD patients, 3 historical multiple dose COPD trials containing 213 patients were included. The demographic summary of these studies was listed in Table 4.37.

Table 4.37 Overall Summary of the Demographic Characteristics of asthma and COPD Patients Included in Meta-analysis by Device Given as Median (range) Or N

	Asthma	COPD	Overall
N	352	213	565
Age [years]	45.5 (12-75)	65.0 (41-87)	54.0 (12-87)
Body weight [kg]	78.0 (35.0-146.5)	75.0 (45.0-134.3)	77.0 (35.0-146.5)
Height [cm]	169 (144-197)	173 (145-196)	170 (144-197)
Gender	F: 193; M: 159	F: 46 ; M:167	F: 239; M: 326
Creatinine clearance [mL/min]	N=350 109 (43.8-268)	N=212 87.1 (24.8-233)	N=562 101 (24.8-267.5)
BSA [m^2]	1.89 (1.23-2.66)	1.88 (1.42-2.55)	1.88 (1.23-2.66)
BMI [kg/m^2]	27.2 (13.6-48.9)	25.6 (16.1-46.5)	26.5 (13.6-48.9)
Predose FEV_1 [L]	N=351 2.24 (0.500-4.64)	N=213 1.21 (0.300-3.10)	N=564 1.84 (0.300-4.64)

(Source: CSR 205-Metaanalysis-copd-pk, page 33, Table 7.1:1)

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 the derivation of AUCs, the pre-dose concentrations, which were below the lower 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. To be noted, The LLOQ values from study 205.416 and 205.417 were set at 2.50 pg/mL whereas LLOQ values from other studies were set at 1.00 pg/mL.

This meta-analysis aimed to analyze available PK data descriptively. Descriptive statistics were calculated when at least 3 observations were available within one category. For displays per trial, N, mean, coefficient of variation, standard deviation, geometric mean, geometric coefficient of variation, median, minimum and maximum were provided. For the combined datasets across trials, the 10th, 25th (Q1), 75th (Q3) and 90th percentiles were given in addition.

Results:

Comparison of tiotropium systemic exposure in patients with asthma and patients with COPD
Following multiple dose administration of TR5, tiotropium $C_{max,ss,norm}$, and $AUC_{0-6,ss,norm}$ values were 108% and 42% higher, respectively in COPD patients than asthma patients (Table 4.38). The trough concentration of tiotropium was similar between two populations. $fe_{0-24,ss}$ value was 99% higher in COPD patients than asthma patients, indicating the higher exposure in COPD patients might be due to higher absorption. The median time to peak concentration was 5 minutes following both single- and multiple-dose administration of TR5 in asthma patients (Table 4.39). The results were consistent to Tmax values obtained from COPD program (5 – 7 minutes, NDA 21936 label).

Table 4.38 Overall Descriptive Summary of Dose-Normalized Steady State Tiotropium PK Parameters following Administration of TR5 Compared by Indication

Indication	$C_{max,ss,norm}$ [2] [pg/mL/µg]		$AUC_{0-2,ss,norm}$ [3] [pg*h/mL/µg]		$AUC_{0-6,ss,norm}$ [3] [pg*h/mL/µg]		$fe_{0-6,ss}$ [1] [%]		$C_{pre,ss,norm}$ [4] [pg/mL/µg]	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
COPD	113	2.10 (66.4)	111	2.02 (55.8)	107	4.42 (47.8)	107	7.75 (65.9)	91	0.377 (54.1)
Moderate asthma	173	0.978 (72.7)	155	1.14 (44.3)	136	2.97 (41.1)	114	4.78 (80.6)	109	0.366 (54.0)
Severe asthma	33	1.21 (60.8)	22	1.74 (49.9)	13	5.17 (50.0)	57	2.58 (163)	14	0.879 (71.4)
All asthma severities	206	1.01 (71.3)	177	1.20 (47.4)	149	3.12 (45.1)	171	3.89 (115)	123	0.404 (64.6)

Source data: asthma program included study 205.380, 205.420, 205.416, 205.417, 205.418, 205.419, 205.424 and 205.441. COPD program included study 205.458, 205.249 and 205.250 (Cmax,ss,norm and AUCss,norm values are only available from 205.458)
(Source: CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 79, Table 7.2.6:2)

Comparison of tiotropium systemic exposure by posology
The exposure to tiotropium following administration of TR5 QD in the evening and TR2.5 BID (morning and evening) was compared in two trials, 205.420 and 205.441. Tiotropium $Ae_{0-24,ss}$, $AUC_{0-12,ss}$, and $AUC_{0-24,ss}$ were comparable between two dosing regimens (Table 4.39). Tiotropium trough concentration $C_{pre,ss}$ values were also similar between two dosing regimens. $C_{max,ss}$ value of TR5 QD was 1.6- to 1.7 fold as high as those of TR2.5 BID.

Table 4.39 Overall Descriptive Summary of Steady State Tiotropium PK Parameters following Administration of TR5 QD and TR2.5 BID

Posology	$Ae_{0-12,ss}$[1] [ng]		$Ae_{0-24,ss}$[1] [ng]		$C_{max,ss}$[2] [pg/mL]		$AUC_{0-12,ss}$[3] [pg*h/mL]		$AUC_{0-24,ss}$[3] [pg*h/mL]		$C_{pre,ss}$ [pg/mL]	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
2.5 µg PM	62	333 (68.2)	62	689 (62.0)*	59	3.01 (45.2)	42	22.5 (28.4)	34	47.3 (25.0)*	37	1.58 (29.0)
2.5 µg AM	63	351 (66.6)			59	3.27 (52.7)	38	24.0 (27.7)			46	1.64 (34.7)
5 µg PM	60	390 (79.0)	60	667 (77.8)	59	5.15 (90.7)	53	25.0 (36.7)	42	45.5 (31.3)	34	1.59 (42.5)

(Source: CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 72, Table 7.2.5:1)

Effective half-life

Since tiotropium concentrations from most of PK samples were below LLQ after 3 hours following single dose of TR2.5, it was not possible to estimate the $AUC_{0-\tau}$ over the entire dosing interval. Therefore the effective half-life of tiotropium was estimated based on a ratio of urinary excretion over 24 hours over steady-state and single dose (Table 4.40). The accumulation ratio based on 24 hour urine data was 2.74 (N=72, CV=64%) for TR2.5.

Table 4.40 Overall Descriptive Summaries of TR2.5 Single-Dose and Steady State PK Parameters

	AUC_{0-6}* (pg·h/mL)	C_{max}* (pg/mL)	Ae_{0-24}* (ng)	T_{max}# (hour)
Single-Dose	-	2.18 (N=76, CV=60%)	135 (N=81, CV=70%)	0.0745 (0.014-2.92)
Steady State	10.4 (N=39, CV=36%)	2.61 (N=102, CV=59%)	319 (N=112, CV=83%)	0.0825 (0.016-23.7)
Accumulation Ratio	-	1.20 (N=52, CV=63%)	2.74 (N=72, CV=64%)	-

*** geometric mean (N, geometric CV)**

 # median (minimum – maximum)

(Source: adapted from CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 223-225, Table 1.2.3.4)

This provides an effective half-life estimate of 36.6 hours, which is close to the steady state terminal half-life 44.1 hours (N=19, CV=60%, CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 224, Table 1.2.3.4).

Dose proportionality in patients with asthma

An overall summary of steady state PK parameters by dose across trials is provided in Table 4.41. Due to the fact that most PK samples obtained from TR1.25 were BLQ, the estimation of AUC for TR1.25 might not be reliable. Comparison of steady state PK parameters ($C_{max,ss,norm}$, $fe_{0-24,ss}$, and $AUC_{0-6,ss,norm}$) between TR2.5 and TR5 showed that tiotropium exposure followed a dose proportional manor.

Table 4.41 Overall Descriptive Summary of Dose-Normalized Steady State Tiotropium PK Parameters by Dosing (TR5, TR2.5, TR1.25)

Dose [µg]	$fe_{0\text{-}24,ss}$[1] [%]		$C_{max,ss,norm}$[2] [pg/mL/µg]		$AUC_{\tau,ss,norm}$[3] [pg*h/mL/µg]		$AUC_{0\text{-}6,ss,norm}$[3] [pg*h/mL/µg]	
	N	gMean (gCV %)	N	gMean (gCV %)	N	gMean (gCV %)	N	gMean (gCV %)
1.25	62	11.5 (87.3)	36	1.87 (99.7)	---	---	5	10.3 (81.0)
2.5	112	12.8 (82.7)	102	1.05 (59.0)	23	15.4 (27.3)	39	4.15 (35.6)
5	199	12.2 (83.7)	206	1.01 (71.3)	117	10.5 (38.8)	149	3.12 (45.1)

(Source: CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 37, Table 7.2.2:1)

Effect of intrinsic factors on tiotropium's PK:

- Asthma severity

The severity of asthma was classified according to patients' background medication:

- Severe asthma: Tiotropium + high-dose ICS+LABA versus placebo + high-dose ICS+LABA
- Moderate asthma: Tiotropium + medium-dose ICS versus placebo + medium-dose ICS
- Mild asthma: Tiotropium + low-dose ICS versus placebo + low-dose ICS

This severity classification was based on treatments that are recommended by American Lung association 2011 guideline for patients with different severities of asthma. According to this classification, PK data was only available in patients with moderate and severe asthma during the tiotropium development program. To be noted, the subject number of patients with severe asthma was much less than that of patients with moderate asthma (Table 4.42). $C_{max,ss,norm}$ value was comparable between patients with severe asthma and moderate asthma. $AUC_{\tau,ss,norm}$, and $AUC_{0\text{-}6,ss,norm}$ values were 72% and 56% higher in patients with severe asthma. Interestingly, $fe_{0\text{-}24,ss}$ and $fe_{0\text{-}6,ss}$ values were 26% and 49% lower in patients with severe asthma, indicating that the higher exposure in severe asthma patients may be partially contributed by reduced renal excretion. By checking the renal function in severe asthma patients, only 1 in 9 patients whose $AUC_{\tau,ss,norm}$ is available and 1 in 13 patients whose $AUC_{0\text{-}6,ss,norm}$ available had renal function severely impaired. By considering that AUCs values were available only in 9 -13 patients with severe asthma, the results may not be over-interpreted.

Table 4.42 Overall Descriptive Summary of Dose-Normalized Steady State Tiotropium PK Parameters by Disease Severity (moderate and severe)

Asthma Severity	$fe_{0\text{-}24,ss}$[1] [%]		$fe_{0\text{-}6,ss}$[1] [%]		$C_{max,ss,norm}$[2] [pg/mL/µg]		$AUC_{\tau,ss,norm}$[3] [pg*h/mL/µg]		$AUC_{0\text{-}6,ss,norm}$[3] [pg*h/mL/µg]	
	N	gMean (gCV %)	N	gMean (gCV %)	N	gMean (gCV %)	N	gMean (gCV %)	N	gMean (gCV %)
Moderate[4]	346	12.5 (80.6)	169	5.05 (78.7)	311	1.08 (75.5)	132	10.9 (41.1)	180	3.31 (48.4)
Severe[5]	27	9.26 (120)	57	2.58 (163)	33	1.21 (60.8)	9	18.8 (42.0)	13	5.17 (50.0)

Patient population on both TR2.5 and TR5 treatment were included in this analysis.
(Source: CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 43, Table 7.2.3.1:1)

- Post bronchodilator percent predicted FEV1 assessed at screening visit

The influence of the post bronchodilator percentage predicted FEV1from the screening visit on PK parameters was evaluated and the results are summarized in Table 4.43. There were no patients with post bronchodilator percentage predicted FEV1 < 60% in TR2.5 treatment group. The PK data was only available in 5 – 16 patients with post bronchodilator percentage predicted FEV1 < 60% in TR5 treatment group. Although tiotropium systemic exposure was generally comparable between patients with 60% ≤ PPFEV1 < 80% and patients with PPFEV1 ≥ 80%, a consistent trend was observed for $C_{max,ss,norm}$, $AUC_{0-3,ss,norm}$, and $AUC_{0-6,ss,norm}$ which patients with worse PPFEV1 values had higher exposure. In TR5 group, $C_{max,ss,norm}$ and $AUC_{0-6,ss,norm}$ values were 41% and 93% higher in patients with PPFEV1 < 60% than patients with PPFEV1 ≥ 80%. Interestingly, $fe_{0-24,ss}$ value was 37% lower in patients with FEV1 < 60% than patients with FEV1 ≥ 80%, indicating that the higher exposure in patients with worse lung function may be partially contributed by reduced renal excretion. The observed trend is consistent with the results obtained from asthma severity classifications, as the population with FEV1 < 60% overlapped with the population with severe asthma (i.e., all the 5 patients with FEV1 < 60% summarized by their $AUC_{0-6,ss,norm}$ values in Table 4.43 were included in 13 patients with severe asthma summarized by their $AUC_{0-6,ss,norm}$ in Table 4.42).

Table 4.43 Overall Descriptive Summaries of Dose-Normalized Steady State Tiotropium PK Parameters by FEV1% Predicted Post Bronchodilator Values from Screening

Dose [ug]	FEV1% predicted post-bronchodilator	$C_{max,ss,norm}$[1] [pg/mL/µg]		$AUC_{0-3,ss,norm}$[2] [pg*h/mL/µg]		$AUC_{0-6,ss,norm}$[2] [pg*h/mL/µg]		$fe_{0-6,ss}$[3] [%]		$fe_{0-24,ss}$[3] [%]	
		N	gMean (gCV %)	N	gMean (gCV %)	N	gMean (gCV %)	N	gMean (gCV %)	N	gMean (gCV %)
2.5	<60%[4]	---	---	---	---	---	---	---	---	---	---
	≥60% and < 80%	20	1.07 (45.0)	15	2.31 (43.8)	10	4.61 (49.7)	10	5.91 (72.7)	24	13.0 (76.0)
	≥80%	82	1.04 (62.4)	43	2.14 (31.4)	29	4.00 (29.9)	45	5.59 (74.9)	88	12.7 (85.0)
5	<60%	14	1.32 (61.9)	7	2.94 (30.3)	5	5.51 (25.4)	16	3.67 (118)	10	9.20 (116)
	≥60% and < 80%	58	1.14 (81.3)	46	1.94 (47.6)	40	3.63 (50.0)	66	2.99 (148)	54	12.1 (85.6)
	≥80%	134	0.935 (66.3)	116	1.56 (41.8)	104	2.86 (39.8)	89	4.78 (83.7)	135	12.6 (80.9)

(Source: CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 47, Table 7.2.3.2:1)

- Renal function

Tiotropium is predominantly renally excreted (74% of the i.v. dose secreted unchanged in the urine in healthy subjects). The renal clearance of tiotropium exceeds the creatinine clearance, indicating there is an active renal secretion mechanism of tiotropium. In COPD patients, mild renal impairment resulted in 23% higher $AUC_{0-6,ss}$ and 17% higher $C_{max,ss}$ values; moderate renal impairment resulted in 57% higher $AUC_{0-6,ss}$ and 31% higher $C_{max,ss}$ values (NDA 21936 label).

The PK data was only available in 6 – 15 asthma patients with moderate renal impairment. The PK data was only available in patients with severe renal impairment. The systemic exposure of tiotropium is comparable between patients with mild renal impairment (creatine clearance ≥ 60 and < 90 mL/min)

and patients with normal renal function (creatine clearance ≥ 90 mL/min). However, moderate renal impairment (creatine clearance ≥ 30 and < 60 mL/min) resulted in 116%, 37% and 36% higher in $C_{max,ss,norm}$, $AUC_{\tau,ss,norm}$, and $AUC_{0-6,ss,norm}$ values (Table 4.44). Accordingly, $fe_{0-24,ss}$ value was 26% lower in patients with moderate renal impairment comparing to patients with normal renal function.

Table 4.44 Overall Descriptive Summary of Dose-Normalized Steady State Tiotropium PK Parameters by Renal Impairment Categories

Renal function	$fe_{0-24,ss}$[1] [%]		$C_{max,ss,norm}$[2] [pg/mL/µg]		$AUC_{\tau,ss,norm}$[3] [pg*h/mL/µg]		$AUC_{0-6,ss,norm}$[3] [pg*h/mL/µg]	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
Normal renal function[4]	272	13.2 (78.4)	247	1.04 (66.9)	101	10.8 (36.5)	141	3.27 (43.1)
Mild renal impairment[5]	86	10.2 (93.8)	85	1.14 (79.5)	34	12.3 (55.1)	44	3.73 (64.0)
Moderate renal impairment[6]	15	9.79 (97.7)	12	2.25 (132)	6	14.8 (70.8)	8	4.44 (73.5)

(Source: CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 52, Table 7.2.3.3:1)

- Age

Subjects with advanced age are generally associated with decreased renal function. Theoretically the age may have an effect on tiotropium systemic exposure. Pooled PK data from asthma patients was divided into three age categories, i.e., 12 to < 18 years old, 18 to < 65 years old and ≥ 65 years old (Table 4.45). Tiotropium systemic exposure was comparable between 1) elderly patients and adult patients 18 to < 65 years old, 2) adolescent patients and adult patients 18 to < 65 years old.

Table 4.45 Overall Descriptive Summary of Dose-Normalized Steady State Tiotropium PK Parameters by Age Categories

Age categories	$fe_{0-24,ss}$[1] [%]		$C_{max,ss,norm}$[2] [pg/mL/µg]		$AUC_{0-3,ss,norm}$[3] [pg*h/mL/µg]		$AUC_{0-6,ss,norm}$[3] [pg*h/mL/µg]		$AUC_{\tau,ss,norm}$[3] [pg*h/mL/µg]	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
12 to < 18 years old	33	13.3 (77.1)	17	0.911 (59.5)	12	1.81 (62.5)	8	3.20 (53.2)	7	8.86 (27.5)
18 to < 65 years old	317	12.2 (86.5)	302	1.11 (75.5)	206	1.90 (54.0)	168	3.38 (48.9)	118	11.2 (43.0)
≥ 65 years old	23	11.2 (56.9)	25	1.03 (67.7)	19	2.09 (67.7)	17	3.87 (59.8)	16	13.2 (47.8)

(Source: CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 57, Table 7.2.3.4:2)

- Race

At steady state in COPD patients, tiotropium $C_{0.167,ss}$ and trough concentration $C_{pre,ss}$ were 78% and 102% higher, respectively in Asians than Caucasians (Dr. Yunzhao Ren, Clinical Pharmacology primary review of NDA 21936, DARRT date 8/29/2014). The Asian population in tiotropium COPD program was solely from study 205.291 conducted in Japanese patients. A potential inter-study variability could not be ruled out at that time.

At steady state in asthma patients, $C_{max,ss,norm}$, $AUC_{\tau,ss,norm}$, and $AUC_{0-6,ss,norm}$ values were 25%, 47%, and 35% higher in Asian patients than Caucasian patients (Table 4.46). The trend is consistent with the observation from COPD patients. $fe_{0-24,ss}$ value was 47% higher in Asian patients than Caucasian patients, indicating the absorption of tiotropium might be higher in Asian population. Although PK data was only available in 4 – 11 black patients, tiotropium systemic exposure was comparable between black patients and Caucasian patients.

Table 4.46 Overall Descriptive Summaries of Dose-Normalized Steady State Tiotropium PK Parameters by Race Categories

Race	$fe_{0-24,ss}$[1] [%]		$C_{max,ss,norm}$[2] [pg/mL/µg]		$AUC_{0-6,ss,norm}$[3] [pg*h/mL/µg]		$AUC_{\tau,ss,norm}$[3] [pg*h/mL/µg]	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
Asian	35	17.5 (60.6)	37	1.34 (65.8)	24	4.43 (53.5)	16	15.9 (42.3)
Black	10	9.70 (100)	11	0.832 (62.1)	6	3.07 (43.1)	4	10.6 (27.7)
White	328	11.9 (84.4)	296	1.07 (75.0)	163	3.29 (48.5)	121	10.8 (41.9)

(Source: CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 64, Table 7.2.3.5:1)

Effect of extrinsic factors on tiotropium's PK:

- Smoking status

The patients were either non-smokers or ex-smokers. The steady state PK parameters were comparable between non-smokers and ex-smokers following TR treatment (Table 4.47).

Table 4.47 Overall Summary Descriptive Statistics of Steady State Tiotropium PK Parameters following TR5 Treatment by Smoking Status

	$AUC_{0-3,ss,norm}$* (pg·h/mL/µg)	**$AUC_{0-6,ss,norm}$* (pg·h/mL/µg)**	**$C_{max,ss,norm}$* (pg/mL/µg)**	**$fe_{0-24,ss}$* (%)**	**$T_{max,ss}$# (hour)**
Ex-Smoker	1.94 (N=70, CV=40%)	3.43 (N=57, CV=40%)	1.16 (N=89, CV=58%)	13.7 (N=91, CV=62%)	0.0830 (0.01-23.7)
Non-Smoker	1.90 (N=167, CV=61%)	3.40 (N=136, CV=54%)	1.06 (N=255, CV=80%)	11.8 (N=282, CV=90%)	0.0830 (0.016-23.7)

*** geometric mean (N, geometric CV)**
 # median (minimum – maximum)
(Source: adapted from CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 487-489, Table 1.2.15.4)

- ICS dose

Since all patients in the asthma program were on ICS, the patients were sub-classified into three categories based on budesonide equipotent dose: < 400 µg, ≥400 to ≤800 µg and >800 µg. However, PK data was only available in 5 patients from < 400 µg group and 24 patients from >800 µg group (Table 4.48). The < 400 µg group had too less patients to draw any meaningful conclusions. As expected, the patients with severe asthma were over-represented in >800 µg group, as 4/10 patients with $AUC_{0-6,ss,norm}$ values available, and 12/24 patients with $C_{max,ss,norm}$ values available were severe asthma patients. Meanwhile, there were only about 7% of the patients in ≥400 to ≤800 µg group had severe asthma. Therefore the trend that ~ 37% higher systemic exposure ($AUC_{0-6,ss,norm}$ and $C_{max,ss,norm}$) in >800 µg group was confounded by the disease status.

Table 4.48 Overall Summary Descriptive Statistics of Steady State Tiotropium PK Parameters following TR Treatment by Budesonide Equivalent Dose

	$AUC_{0\text{-}3,ss,\ norm}$* (pg·h/mL/µg)	$AUC_{0\text{-}6,ss,\ norm}$* (pg·h/mL/µg)	$C_{max,ss,\ norm}$* (pg/mL/µg)	$fe_{0\text{-}24,ss}$* (%)	$T_{max,ss}$# (hour)
<400 µg	1.27 (N=3, CV=22%)	N=0	0.508 (N=4, CV=52%)	14.1 (N=5, CV=14%)	0.135 (0.082-0.525)
≤400 and ≤800 µg	1.88 (N=217, CV=53%)	3.37 (N=179, CV=50%)	1.08 (N=314, CV=73%)	12.5 (N=344, CV=81%)	0.083 (0.007-23.8)
>800 µg	2.86 (N=14, CV=74%)	4.62 (N=10, CV=35%)	1.49 (N=24, CV=71%)	9.10 (N=21, CV=125%)	0.106 (0.014, 3)

*** geometric mean (N, geometric CV)**
 # median (minimum – maximum)
(Source: adapted from CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 507-512, Table 1.2.16.4)

- LABA

PK data was only available in 12 patients who were on LABA add-on therapy (Table 4.49). Tiotropium systemic exposures were generally comparable between patients on LABA treatment and patients not on LABA treatment.

Table 4.49 Overall Summary Descriptive Statistics of Steady State Tiotropium PK Parameters following TR5 Treatment by Budesonide Equivalent Dose

	$AUC_{0\text{-}3,ss,\ norm}$* (pg·h/mL/µg)	$AUC_{0\text{-}6,ss,\ norm}$* (pg·h/mL/µg)	$C_{max,ss,\ norm}$* (pg/mL/µg)	$fe_{0\text{-}24,ss}$* (%)	$T_{max,ss}$# (hour)
Not Taking LABA	1.91 (N=232, CV=56%)	3.39 (N=189, CV=50%)	1.09 (N=333, CV=75%)	12.4 (N=361, CV=84%)	0.083 (0.01-23.7)
Taking LABA	2.15 (N=5, CV=15%)	4.19 (N=4, CV=22%)	1.04 (N=11, CV=50%)	8.41 (N=12, CV=53%)	0.083 (0.033-12.2)

*** geometric mean (N, geometric CV)**
 # median (minimum – maximum)
(Source: adapted from CSR 205-p5-study-report-body-metaanalysis-pk.pdf, page 407-409, Table 1.2.10.4)

Conclusions:
Major steady state PK comparison results following TR5 treatment in this meta-analysis were listed as below:

- Tiotropium exposure was higher in COPD patients than in asthma patients. $C_{max,ss,norm}$, and $AUC_{0\text{-}6,ss,norm}$ values in COPD patients were 108% and 42% higher, respectively, than in asthma patients.
- Tiotropium $Ae_{0\text{-}24,ss}$, $AUC_{0\text{-}12,ss}$, and $AUC_{0\text{-}24,ss}$ were comparable between TR5 QD and TR2.5 BID. $C_{max,ss}$ value of TR5 QD was 57% to 71% higher than that of TR2.5 BID.
- The effective half-life of tiotropium in asthma patients was estimated to be 34 hours, which was consistent with the terminal half-life (~36 hours).
- Patients with severe asthma or lower post bronchodilator percent predicted FEV1 tend to have higher exposure.
- Asthmatic patients with moderate renal impairment (creatine clearance ≥ 30 and < 60 mL/min) had 116%, 37% and 36% higher of $C_{max,ss,norm}$, $AUC_{\tau,ss,norm}$, and $AUC_{0\text{-}6,ss,norm}$ values compared to patients with normal renal function.
- Tiotropium exposure was higher in Asian patients. $C_{max,ss,norm}$, $AUC_{\tau,ss,norm}$, and $AUC_{0\text{-}6,ss,norm}$ values were 25%, 47%, and 35% higher in Asian patients than in Caucasian patients.

- Patients taking higher dose of ICS may have higher tiotropium exposure, but this might be confounded by disease severity which patients with severe asthma tend to have higher dose of ICS.

4.2 Appendix – New Drug Application Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**207070**	**Brand Name**	**Spiriva Respimat**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Tiotropium bromide**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Long-acting anti-muscarinic agent**
OCP Reviewer	**Yunzhao Ren MD, Ph. D**	**Indication(s)**	**long-term, once-daily, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids.**
OCP Team Leader	**Satjit Brar Pharm. D., Ph.D.**	**Dosage Form**	**Inhalation spray**
Other discipline reviewers	**-**	**Dosing Regimen**	**Two inhalations ((b) (4) mcg each) of the spray, once-daily**
Date of Submission	**8/15/2014**	**Route of Administration**	**Inhalation**
Estimated Due Date of OCP Review	**5/11/2015**	**Sponsor**	**Boehringer Ingelheim**
PDUFA Due Date	**6/15/2015**	**Priority Classification**	**Standard 505(b)(1)**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			HPLC with tandem mass spectrometry
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**9**	**9**	Study 205.341, 205.380, 205.420, 205.441, 205.416, 205.417, 205.418, 205.419, 205.424
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:				
gender:				
pediatrics:	**X**	**1**	**1**	Study 205.424
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Meta-analysis:	**X**	**1**	**1**	Meta-analysis 205.P5
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**	**1**	**1**	Study 205.341
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**X**	**10**	**10**	

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/s/

YUNZHAO REN
06/08/2015

SURESH DODDAPANENI
06/08/2015