CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021936Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

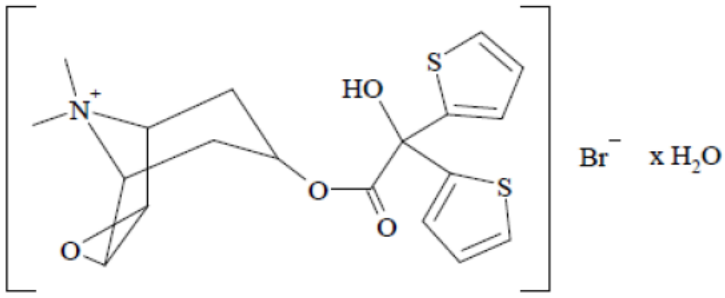
CLINICAL PHARMACOLOGY REVIEW	
NDA Number:	21936 (Related NDA 21935, related IND 65127)
Submissions Date:	03/24/2014
Submission Type:	505(b)(1) resubmission
Proposed Brand Name:	Spiriva RESPIMAT
Generic Name:	Tiotropium bromide
Sponsor:	Boehringer Ingelheim
Route of Administration:	Inhalation
Dosage Form:	Aqueous inhalation solution
Dosage Strength:	2.5 µg tiotropium in (b) (4) aqueous solution per actuation
Proposed Dosing Regimen:	5 µg tiotropium (2 actuations) daily
Proposed Indication(s):	Maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). Reduction of exacerbations in COPD patients.
Proposed Population(s):	COPD patients
OND Divisions:	Division of Pulmonary, Allergy, and Rheumatology Products
OCP Division:	Clinical Pharmacology II
Reviewer:	Yunzhao Ren, M.D., Ph.D.
Team Leader:	Satjit Brar, Pharm.D., Ph.D.
Molecular Structure:	

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Boehringer Ingelheim has submitted NDA 21936 (as a resubmission) 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 "maintenance treatment of patients with chronic obstructive pulmonary disease (COPD) and reduction of exacerbations in COPD patients." The proposed dosing regimen is two inhalations (2.5 µg tiotropium each) once daily.

Majority of the clinical pharmacology studies, including general clinical pharmacology and dose-ranging studies, have been previously reviewed in NDA 21936 (Dr. Yun Xu, DARRTS date 07/31/2008). The Sponsor supports this NDA resubmission with 4 clinical studies, two of which are clinical pharmacology studies.

In the current resubmission package, the Sponsor included the following new clinical pharmacology studies:

Study 205.458 was a randomized, placebo controlled, 5-way crossover trial to evaluate PK, efficacy and safety between 5 arms [once daily of tiotropium Handihaler ® (THH) 18 µg, tiotropium Respimat ® (TR) 1.25 µg, 2.5 µg, 5 µg, 10 µg, and placebo (TR and placebo were double-blind) for 4 weeks] in patients with COPD (conducted in Europe). A total of 210 patients entered study with 154 patients treated. A total of fourteen (14) blood samples and 3 urine samples per subject per period were collected at the end of each 4-week treatment. The intent of the study was to obtain a robust PK profile of tiotropium after administration by Handihaler and Respimat devices.

Study 205.291 was a randomized, double-blind, double-dummy, 2-way crossover trial to evaluate PK, efficacy and safety between TR5 and THH18 (once daily for 4 weeks) in Japanese patients with COPD. A total of 157 patients entered study and all the patients were treated. A total of four (4) blood samples per and two (2) urine samples per subject per period were collected at the end of each 4-week treatment.

The following points are the major findings of the current review:

1) With regard to tiotropium plasma exposure, $AUC_{0\text{-}6,ss}$ of TR5 was lower than THH18 [ratio as 0.75 (90% CI=0.69, 0.81)]; C_{max} of TR5 was lower than THH18 [ratio as 0.80 (90% CI=0.73, 0.88), N=109]. The shape of plasma concentration-time profile of TR5 and THH18 was similar, indicating a similar absorption and elimination pattern.

2) Tiotropium dose-exposure proportionality was observed within dose range from 1.25 µg to 10 µg for TR. Based on average exposures for both Cmax and AUC, THH 18 had the highest exposure while TR 5 > TR2.5 and TR 1.25.

3) The current conclusion is not discordant to the conclusion from Dr. Xu in the initial review where, in regard to the prior submission he states: "*Comparable systemic exposure and urine excretion was observed for tiotropium 5 µg inhalation via the RESPIMAT inhaler and tiotropium 18 µg via HandiHaler inhaler as steady state.*" The previous conclusion was based on initially submitted sparse sampling PK studies (studies 205.249 and 205.250) with their limitations. The new study 205.458 was a rich PK sampling study to be more reliable than the sparse sampling study as the rich PK sampling study describes the time-concentration PK profile more precisely and captured the early absorption phase (C_{max}) of tiotropium. In addition, study 205.458 has much greater sample size for study design, and less variability for the results, along with a more sensitive and accurate bioanalytical method for the quantification of tiotropium in plasma and urine.

4) Following 4-week once daily administration of TR5, mean C_{10min} of TR5 in Asians from study 205.291 was about 50-60% higher compared to that of Caucasians from study 205.249 and 205.250. The reviewer concludes the difficulty in interpreting these results as the difference could be contributed by ethnicity or inter-study variability, or both.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II has reviewed the NDA 21936 resubmitted on March 24, 2014 and has found the application approvable 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).

Tiotropium bromide was previously formulated as dry powder by Boehringer Ingelheim for oral inhalation with the HandiHaler® device. Tiotropium Spiriva® HandiHaler® (THH) was approved by FDA on January 30, 2004 under NDA 21395. The approved dosing regimen is two inhalations of the powder contents of a single Spiriva capsule (18 µg tiotropium) once daily.

Boehringer Ingelheim subsequently developed tiotropium bromide aqueous inhalation solution with the RESPIMAT device (Tiotropium Spiriva® RESPIMAT®, or TR as the product) and submitted an application under NDA 21936 on November 16, 2007, seeking approval for the same indication. The proposed dosing regimen is two inhalations (2.5 μg tiotropium each) once daily. Dr. Yun Xu, from the Office of Clinical Pharmacology /Division of Clinical Pharmacology 2 has reviewed the initial NDA 21936 on July 31, 2008 and found it acceptable.

The application received a Complete Response on September 16, 2008. The major deficiencies were as follows:

1) The submitted data do not provide substantial evidence of safety to support the use of TR in patients with COPD. Increased frequencies of death were observed in patients treated with TR compared to placebo in the two 48-week studies [RR = 2.1 (95% CI 0.7-5.9)]. Increased frequencies of stroke were observed in patients treated with tiotropium bromide compared to placebo in a pooled analysis of clinical study data with THH and TR.

2) The submitted data do not provide substantial evidence to support the proposed claim of reduction of COPD exacerbation. Results of the two individual 48-week studies are not sufficient for replication because only one of the two studies showed a statistically significant difference from placebo.

On April 26, 2013, Boehringer Ingelheim submitted a meeting request for the purpose of discussing the resubmission. The meeting was granted as written responses only. With respect to the questions for Clinical Pharmacology, the reviewer accepted the proposals from the Sponsor regarding the clinical pharmacology aspects of the submission.

In the current resubmission package, the Sponsor included the following new studies:

1) Study 205.452 provides safety data to support the use of TR in COPD patients.
2) Study 205.372 provides data to support the claim of reduction of COPD exacerbation.
3) Two (2) safety, efficacy and pharmacokinetics (PK) comparison studies between THH and TR in Japanese (study 205.291) and European (study 205.458) patients, and a meta-analysis report U13-2380 of tiotropium non-compartmental PK parameters across various trials in COPD patients.

To be noted, the RESPIMAT device used in the all the studies in the resubmission package was version A5. The RESPIMAT device used in the all the pivotal studies from the initial NDA 21936 submission package was version A4. The key development step from A4 to A5 was the inclusion of a locking mechanism to lock the A5 after the labeled number of doses. The dose delivery performance was comparable between A4 and A5.

For efficacy and safety assessments, refer to the Clinical and Statistics reviews. The efficacy and safety information from clinical studies 205.452 and 205.372 was reviewed by the medical officer (Dr. Robert Lim) from DPARP. The safety/mortality data in 205.452 was reviewed by the statistics reviewer, Dr. Bo Li, from OTS/OB/DBVII.

1.3.2 PK Characteristics

Absorption:
Following inhalation of Spiriva RESPIMAT by young healthy volunteers, urinary excretion data suggests that approximately one third of the inhaled dose reaches the systemic circulation. Tiotropium peak plasma concentration was reached approximately 7 minutes after inhalation. Approximately two- to three-fold

accumulation of plasma concentration was observed on day 14 in healthy volunteers. Tiotropium systemic exposure generally increases proportionally within studied dose range from 1.25 μg to 10 μg.

Distribution:
The drug has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung.

Metabolism:
The extent of metabolism appears to be small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium can be non-enzymatically cleaved to the alcohol *N*-methylscopine and dithienylglycolic acid, neither of which binds to muscarinic receptors. *In vitro* experiments show that a small fraction of tiotropium is oxidized by CYP 2D6 and 3A4 followed by glutathione conjugation.

Elimination:
The terminal elimination half-life of tiotropium was between 5-6 days following dry powder inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine.

1.3.3 Systemic Exposure Comparison between THH and TR

Test product: TR, 5 μg QD
Reference product: THH, 18 μg QD

For both TR and THH, tiotropium is formulated for inhalation that exerts local effects in the lungs; the systemic bioavailability of tiotropium is not an expected determinant of efficacy, but rather to address potential safety concerns. The steady state systemic exposure of tiotropium was compared between THH18 (THH 18 μg) and TR5 (TR 5 μg) in multiple studies (Table 1) from the current resubmission and the initial submission. The goal of this comparison is not to establish the bioequivalence between TR and THH, but rather to provide the information on the comparison of tiotropium systemic exposure between TR and THH.

Table 1 List of Studies with Steady State PK Comparison between TR 5 μg and TH 18 μg

Study ID	Phase	Design	Duration	Subjects Entered	Dose	Ethnicity composition**	Post-dose PK Samples
205.249*	3	Cross-over	4-week	131	TR 5, TR 10, THH18, P	128C, 3B	3/subject
205.250*	3	Cross-over	4-week	76	TR 5, TR 10, THH18, P	75C, 1O	3/subject
205.291	2	Cross-over	4-week	157	TR 5, THH18	157J	3/subject
205.458	2	Cross-over	4-week	154	TR 1.25, TR 2.5, TR 5, THH18, P	153C, 1B	13/subject

*** From the initial submission**
** **C: Caucasian; B: Black; O: Other; J: Japanese**
(Source: reviewer's summary based on section 2.7.6, synopses of individual studies)

In the initial submission package, the Sponsor included two replicate pivotal studies 205.249 and 205.250 comparing efficacy, safety and steady state PK profile between THH and TR in COPD patients. The investigations were randomized, double-blind, double-dummy, placebo-controlled, 4-period, crossover studies including four treatment arms (once daily of THH 18 µg, TR 5 µg, TR 10 µg, and placebo for 4 weeks). The four 4-week treatment periods were separated by 4-week washout period. There were total 207 patients entered studies (131 from 205.249 and 76 from 205.250) with 158 completed studies (86 from 205.249 and 72 from 205.250). Plasma and urine samples were collected at the end of each 4-week treatment. A total of four blood samples per subject per period were collected (before inhalation of the test drug, 10 min, 1 h and 6 h after test drug inhalation). A total of three urine samples per patient per period were collected (-2 to 0 h, 0 to 2 h, and 2 to 12 h).

To be noted, the majority of plasma concentrations taken at 6 hours in studies 205.249 and 205.250 were below the limit of quantification (BLQ) as the LLOQ of plasma tiotropium was 2.50 pg/mL (Table 2). Therefore the study design and method were modified during later studies: study 205.291 changed the last PK sampling to 4 hours post-dose in lieu of 6 hours; study 205.458 increased the performance of bioanalytical method which the LLOQ was 1.0 pg/mL.

Table 2 Bioanalytical Performance of Plasma Tiotropium Quantification by LC-MS/MS

Study ID	205.249	205.250	205.291	205.458
LLOQ (pg/mL)	2.50	2.50	2.50	1.00
Calibration range (pg/mL)	2.50 - 150	2.50 – 150	2.50 - 150	1.00 - 100
Linearity (r^2)	0.99494	0.99494	0.99911	0.99734
Precision (CV%) at LLOQ	8.38	8.38	7.63	11.42
Accuracy (bias%) at LLOQ	2.66	2.66	1.94	1.87

LLOQ – lower limit of quantification
(Source: reviewer's summary based on section 5.3.1.4. U10-1855-01, page 5, Table1:1; Dr Yun Xu's review, DARRT date 07/31/2008)

In the current resubmission package, the Sponsor included studies 205.458 and 205.291. Study 205.458 was a randomized, placebo controlled, 5-way crossover trial to evaluate PK, efficacy and safety between 5 arms [once daily of THH 18 µg (open label), TR 1.25 µg, TR 2.5 µg, TR 5 µg, TR 10 µg, and placebo (TR and placebo were double-blind) for 4 weeks] in patients with COPD (conducted in Europe). There was no washout period between each treatment. Total 210 patients entered study with 154 patients treated. Plasma and urine samples were collected at the end of each 4-week treatment. A total of fourteen (14) blood samples per subject per period were collected (before inhalation of the test drug, 2 min, 5 min, 7 min, 9 min, 12 min, 15 min, 20 min, 30 min, 40 min, 1 h, 2 h, 4 h, and 6 hours after test drug inhalation). Three urine samples per patient per period were collected (-1 to 0 h, 0 to 2 h, and 2 to 6 h).

Study 205.291 was a randomized, double-blind, double-dummy, 2-way crossover trial to evaluate PK, efficacy and safety between TR5 and THH18 (once daily for 4 weeks) in Japanese patients with COPD. The two 4-week treatment periods were separated by 4-week washout period. A total of 157 patients entered study and all the patients were treated. Plasma and urine samples were collected at the end of each 4-week treatment. A total of four (4) blood samples per subject per period were collected (before inhalation of the test drug, 10 min, 1.5 h and 4 hours after test drug inhalation). Two urine samples per patient per period were collected (0 to 2 h and 2 to 4 h).

Tiotropium systemic exposure at steady state ($AUC_{0\text{-}t,ss}$) was compared between TR5 and THH18 for the 4 studies (Table 3). Study 205.249 showed that $AUC_{0\text{-}6,ss}$ was slightly higher in TR5 than THH18 [ratio of

TR5/THH18 as 1.31 (90% CI=1.10, 1.55)], study 205.250 and 205.291 showed that $AUC_{0\text{-}t,ss}$ was similar between TR5 and THH18 (ratios as 1.07 and 1.02, respectively). Study 205.458 showed that $AUC_{0\text{-}6,ss}$ of TR5 was lower than THH18 [ratio as 0.75 (90% CI=0.69, 0.81)]; C_{max} of TR5 was lower than THH18 [ratio as 0.80 (90% CI=0.73, 0.88), N=109] (reviewer's analysis). However, the shape of plasma concentration-time profile of TR5 and THH18 was similar, indicating a similar absorption and elimination pattern (Fig.1). Tiotropium dose-exposure proportionality was observed within dose range from 1.25 µg to 10 µg by comparing $C_{0.167,\ ss}$ (including C_{9min} and C_{10min}) and $Ae_{0\text{-}2,ss}$ (amount of tiotropium eliminated in urine within 2 hours post-dose) values at different doses (Fig.7).

Table 3 Comparison of $AUC_{0\text{-}t,ss}$ between TR 5 µg and THH 18 µg Following 4-week Once Daily Administration

Study ID	THH18 $AUC_{0\text{-}6h,ss}$ * (pg·h/mL)	TR5 $AUC_{0\text{-}6h,ss}$ * (pg·h/mL)	Ratio (TR5/THH18) **
205.249	20.2 (73.9%, N=54)	26.1 (77.4%, N=52)	1.31 (1.10, 1.55, N=49)
205.250	24.2 (71.0%, N=35)	26.8 (78.4%, N=34)	1.07 (0.85, 1.35, N=34)
205.291	29.6 (66.5%, N=140)***	30.4 (60.4%, N=141)***	1.02 (0.93, 1.13, N=128)
205.458	28.4 (52.4%, N=113)	22.1 (47.8%, N=107)	0.75 (0.69, 0.81, N=103)

*** geometric mean (CV, subject number)**
**** unadjusted geometric mean (90% confidence interval, subject number)**
***** $AUC_{0\text{-}4h,ss}$**
(Source: reviewer's analysis)

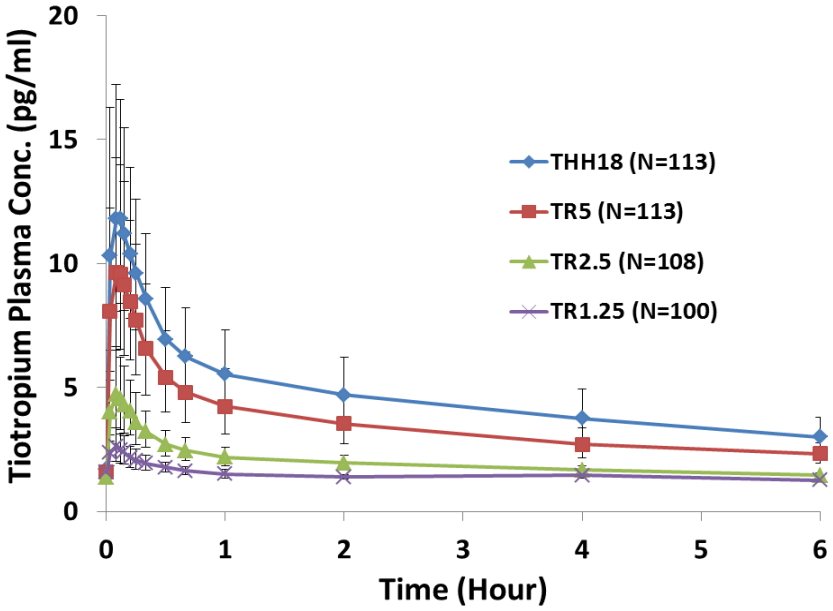


Fig.1 Tiotropium plasma concentration-time profile at steady state following 4-week once daily administration of TR 1.25 µg, 2.5 µg, 5 µg, or THH 18 µg from study 205.458, observations represent the geometric mean (+/- 95% CI) for each time point. (Source: reviewer's analysis)

Table 4 Comparison of Ratios of non-compartmental PK Parameters of Tiotropium Following 4-week Once Daily Administration via RESPIMAT (Different Doses) or HandiHaler

Parameter [units]	Tio R 1.25/Tio HH 18		Tio R 2.5/Tio HH 18		Tio R 5/Tio HH 18		Tio R 10/Tio HH 18	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
$RC_{max,ss,T/R}$[1]	100	0.200 (60.6)	107	0.393 (63.4)	109	0.804 (64.7)	---	---
$R"C_{0.167,ss}",_{T/R}$[2]	94	0.192 (54.5)	104	0.379 (64.0)	185	0.921 (67.1)	16	3.17 (71.8)
$RAUC_{0-6,ss,T/R}$[3]	20	0.220 (27.0)	74	0.397 (39.1)	103	0.747 (49.1)	---	---
$RAe_{0-2,ss,T/R}$[4]	104	0.171 (52.8)	103	0.337 (63.2)	298	1.04 (104)	74	3.15 (128)
$RAe_{0-6,ss,T/R}$[4]	100	0.167 (47.5)	102	0.340 (52.1)	100	0.741 (50.8)	---	---
$RAe_{0-12,ss,T/R}$[4]	---	---	---	---	70	1.33 (96.4)	73	2.69 (95.6)

R= Reference arm and T = Test arm
[1]Ratio of $C_{max,ss}$ value between test (one of three doses of Tio RESPIMAT) and reference (Tio HH 18) treatments
[2]Ratio of "$C_{0.167,ss}$" value between test (one of three doses of Tio RESPIMAT) and reference (Tio HH 18) treatments
[3]Ratio of $AUC_{0-6,ss}$ value between test (one of three doses of Tio RESPIMAT) and reference (Tio HH 18) treatments
[4]Ratio of $Ae_{t1-t2,ss}$ value between test (one of three doses of Tio RESPIMAT) and reference (Tio HH 18) treatments
Source data: [Appendix 10, Table 3.1.1] – data from following trials included: 205.458, 205.249, 205.250 and 205.291

(Source: CSR 205-Metaanalysis-copd-pk, page 40, Table 7.2.2:2)

In the Sponsor's meta-analysis report 205-Metaanalysis-copd-pk (which all the BLQ data was ignored), pooled data from study 205.458, 205.249 and 205.250 (Table 4) showed that ratios (TR5/THH18) of $C_{max,ss}$, $C_{0.167,ss}$ (combination of C_{9min} and C_{10min}), and $AUC_{0-6h,ss}$ were all less than 1 (ratios were generated from PK parameters listed in Table 17 in 4.1.4). The ratio of $AUC_{0-6h,ss}$ was less than 0.80, which was lower than the bioequivalence lower boundary (0.80, 1.25).

Reviewer's comments:
Generally the result from the rich PK sampling study is more reliable than the sparse sampling study as the rich PK sampling study describes the time-concentration PK profile more precisely. Study 205.458 was the only study with rich PK sampling schedule that captured the early absorption phase (C_{max}) of tiotropium (Fig 1). In addition, study 205.458 has much greater sample size for study design, and less variability for the results (Table 3), lower LLOQ and more accuracy (Table 2) for bioanalytical method, than study 205.249 and 205.250. The meta-analysis results were consistent as patient number from study 205.458 dominated in the pooled data source.

1.3.4 Ethnicity Effect

There was no dedicated clinical pharmacology study conducted to evaluate the effect of ethnicity on tiotropium exposure in the NDA 21395 THH application. In addition, there was no similar study listed in the initial submission package of NDA 21936. There was a highly skewed race composition in the previous clinical pharmacology studies. In study 205.112, all the subjects were Caucasians. In study 205.249 and 205.250, 96 out of the 98 subjects with pharmacokinetic data were Caucasians. However, results from recently completed 4-year efficacy and safety UPLIFT trial (Understanding the Potential Long-term Impact of Tiotropium) of THH showed that the mortality rate was higher in Asian patients with COPD (tiotropium 16–19%; control 22–24%) relative to the whole COPD population (tiotropium 13–14%; control 14–16%)[1]. Dr. Bo Li from OTS/OB/DBVII will review study 205.452 and 205.372 to probe if the similar ethnicity trend on mortality happened to TR as well. The Asian compositions of these two studies were 14% and 30%, respectively.

Study 205.291 was the only dedicated PK trial conducted in the Asian population, or more specifically, the Japanese population. Unfortunately, there was no other ethnicity demographic enrolled in this study and the PK sampling schedule in this study was different from other studies conducted mostly in Caucasians (Table 1). Since only post-dose time point of 10 minutes was shared by three sparse sampling studies, C_{10min} of TR5 was compared. It seems that mean C_{10min} of TR5 in the Japanese was about 50-60% higher compared to Caucasians. A similar result was obtained in COPD patients administered THH18 (Table 5).

Table 5 Comparison of TR5 C_{10min} between Study 205.291 in Japanese and Studies 205.459/205.250 mostly in Caucasians

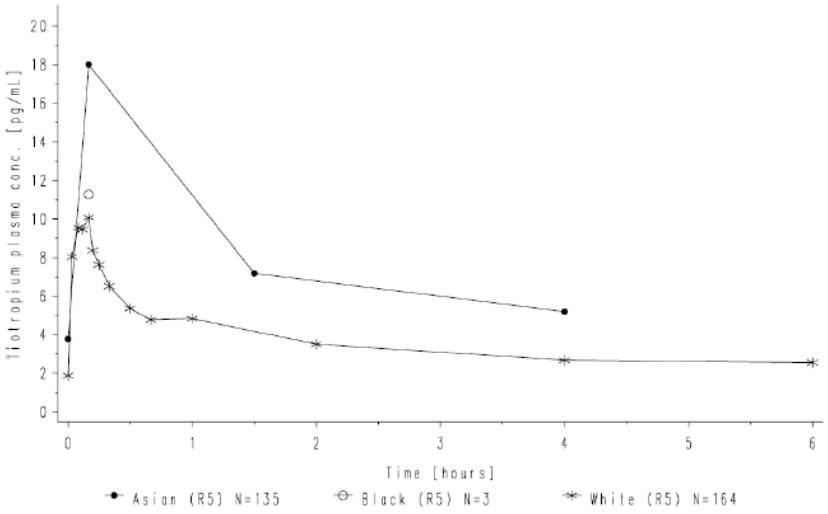
Study ID	Ethnicity Composition	Post-dose PK Sampling Schedule	C_{10min}*	Ratio (205.291/)
205.249	128C, 3B	10 min, 1h, 6h	11.7 (99.1%, N=53)	1.46 (1.06, 1.53)
205.250	75C, 1O	10 min, 1h, 6h	10.5 (114%, N=34)	1.63 (1.11, 1.78)
205.291	157J	10 min, 1.5h, 4h	17.1 (68.3%, N=141)	—

*** geometric mean (CV, subject number)**
**** ratio (90% CI)**
(Source: reviewer's analysis)

Since tiotropium is predominantly excreted in urine with 74% of the dose as unchanged drug, amount of tiotropium excreted unchanged in urine within 2 hours of dosing ($Ae_{0-2, ss}$) was also compared between Asians and Caucasians. Mean $Ae_{0-2,ss}$ in Asians from study 205.291 was 0.200 (CV=64.8%, N=137), which was comparable with mean $Ae_{0-2,ss}$ [0.182 (CV=74.4%, N=111)] in Caucasians from study 205.458. A similar result was obtained in COPD patients administered THH18. This indicates that Asians may have a relatively lower tiotropium renal clearance than Caucasians, since the systemic exposure is higher in Asians.

In the Sponsor's meta-analysis report 205-Metaanalysis-copd-pk (in which all the BLQ data was ignored), pooled data from study 205.458, 205.249, 205.250, and 205.191 showed similar results that, irrespective of the device, the mean plasma concentration time profile of tiotropium was higher in Asians compared to Caucasians (Fig.2). $C_{0.167, ss}$ (including C_{10min} and C_{9min}) was 78% and 59% higher in Asians than in Caucasians for TR5 and THH18, respectively (Table 21 in 4.1.4).

A



B

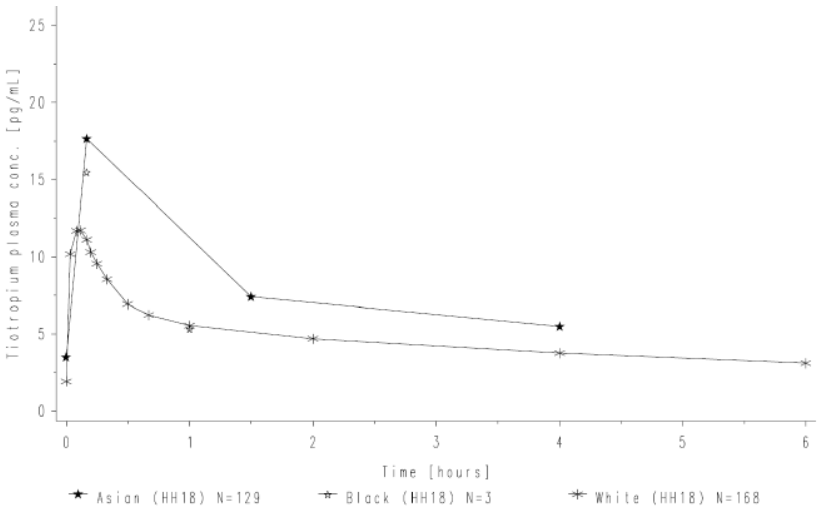


Fig.2 Tiotropium plasma concentration-time profile at steady state following 4-week once daily administration of TR5 (A) or THH18 (B) in different races. Observations represent the geometric mean for each time point. (Source: CSR 205-Metaanalysis-copd-pk, page 73, Figure 7.2.3.7:1)

Reviewer's comments:
It has been observed from other oral inhalation products that Asians have higher lung absorption[3]*. However for this submission, it is difficult to fully interpret what causes the higher* C_{10min} *of TR5 in Japanese as the difference could be contributed by ethnicity or inter-study variability, or both. Furthermore, the higher mortality rate of TR5 treatment in the Asian COPD patients could be contributed by the higher mortality baseline in the Asian COPD patients*[1]*.*

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 6 List of Three Clinical Pharmacology Studies in NDA 21936 Resubmission Package

Phase	Study ID	Objectives of the study	Dosing Regimen	Treatment Duration	Number of patients treated	Study Population
2	205.291	To compare efficacy, safety and PK of TR5 and THH18	TR: 5 µg QD THH: 18µg QD	4 weeks	157	Asian (Japanese)
2	205.458	To compare PK of TR5 and THH18; to evaluate dose-ranging efficacy and safety	TR: 1.25 µg QD TR: 2.5 µg QD TR: 5 µg QD THH: 18µg QD	4 weeks	154	Mostly Caucasian
Meta-analysis	U13-2380	To identify best estimates of PK parameters			347 from TR 359 from THH	Mostly Caucasian and Asian

(Source: reviewer's summary based on section 2.7.6, synopses of individual 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 0.023% (w/v) tiotropium bromide monohydrate (Table 7). Each actuation of the RESPIMAT inhaler delivers 2.5 µg of tiotropium (equivalent to 3.124 µg tiotropium bromide monohydrate) from the mouthpiece. One dose of 5 µg of tiotropium consists of two actuations.

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. Tiotropium is a LAMA with K_i of approximately 10 pM in heterologous competition experiments against [N-methyl-^{3}H] scopolamine methyl chloride[2]. Competitive displacement of acetylcholine from mAChR M_3 by tiotropium causes bronchial smooth muscle relaxation. The dissociation half-life of tiotropium from mAChR M_3 is approximately 27 hours.

The therapeutic indications of Spiriva RESPIMAT are for the long-term, once daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations.

Table 7 Qualitative and Quantitative Composition of Spiriva RESPIMAT Inhalation Spray

Name of ingredient	Per dose [1] (Label claim) [mg]	Per cartridge (b) (4) [4] [mg]	Percentage formula [g/100ml]	Function	Reference to standards
Tiotropium [2] (corresponds to tiotropium bromide monohydrate)	0.005	(b) (4)	0.02262	Drug substance	Company standard
Benzalkonium chloride [3]	(b) (4)			Preservative	NF
Edetate disodium				Stabilizer	USP
1 M Hydrochloric acid				pH-adjustment	Company Standard [5]
Water for Injection (WFI)				(b) (4)	USP
Total mass	22.1	(b) (4)	100.0		

(Source: section 3.2.P.1 A133787, page 2, Table 1)

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

The proposed dosing regimen of Spiriva RESPIMAT is two inhalations (2 inhalations of 2.5 µg each) of the spray once-daily.

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

Tiotropium is the first LAMA approved in the U.S. with Spiriva HandiHaler (NDA (b) (4)) as the first approved tiotropium dry powder inhaler. Aclidinium is the second LAMA approved in the U.S. with Tudorza Pressair (NDA 202450) as the first approved aclidinium dry powder inhaler.

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?

Spirometry endpoints such as FEV1 AUC_{0-t}, trough FEV1, FVC AUC_{0-t}, trough FVC were selected as efficacy endpoints for study 205.291 and study 205.458. The selection basis is that these endpoints all directly measure the pulmonary ventilation function. All these endpoints were measured by spirometer.

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 concentration in plasma or urine was 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-response (concentration) 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 was not predefined in study 205.458. Referring to 4.1.3, it seems that all the TR treatments (TR1.25, TR2.5, and TR5) were significantly different from placebo in terms of primary efficacy endpoint FEV_1 $AUC_{0\text{-}6h}$.

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

No formal exposure-response relationship of safety was evaluated. Serious adverse events (SAE) were not correlated with dose in study 205.458 (total 9 patients reported one or more SAEs during at least one treatment period: 3 patients each for placebo and TR5 treatment, 2 patients each for TR1.25 and THH18 treatment, no patient on TR2.5 treatment). For more information, refer to the Clinical Pharmacology review for the initial submission.

2.4.3 Does this drug prolong the QT or QTc interval?

No QT-related ECG parameters revealed any clinically relevant changes in study 205.291. The analyses of the QT/QTcN and PR intervals as well as the QRS complex did not reveal any relevant effects associated with tiotropium as compared with placebo in study 205.458. For QT information from other studies, refer to the Clinical Pharmacology review for the initial submission.

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

Refer to the Clinical Pharmacology review for the initial submission for dose selection discussions.

2.5 PK Characteristics of the Drug

2.5.1 What are the characteristics of drug absorption?

Referring to study 205.112 from the initial submission package, following daily treatment of TR (8 µg, 16 µg, and 32 µg via device A3) in healthy volunteers, about 29% on day 7 and 20.1% to 24.5% on day 14 of the inhaled dose was excreted unchanged in urine within 24 hours after dose. Referring to the approved label of THH, following an i.v. infusion in healthy young volunteers, 73.6% of tiotropium dose is excreted in urine as unchanged drug. Therefore, it suggests an average of 33% of the inhaled dose reaches the systemic circulation in healthy volunteers.

Results from study 205.458 showed that, following 4-week once daily administration of TR5 in COPD patients, median T_{max} was 7 min (ranging from 2 min to 20 min), geometric mean of steady state $C_{max, ss}$ and trough concentration $C_{pre,ss}$ were 10.5 (CV=66.4%) pg/mL and 1.60 (CV=35.8%) pg/mL, respectively.

2.5.2 What are the characteristics of drug distribution?

The apparent volume of distribution during the terminal phase at steady state (V_z/F) was not estimated in trial 205.458 as the terminal elimination phase was not investigated in the study. Referring to the approved label of THH, tiotropium volume of distribution is 32 L/Kg following an i.v. infusion, indicating that the drug binds extensively to tissues. The human plasma protein binding for tiotropium is 72%.

2.5.3 What are the characteristics of drug metabolism?

No dedicated *in vivo* and *in vitro* metabolism study was conducted under NDA12936. Referring to the approved label of THH, tiotropium is non-enzymatically 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 CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a nominal portion of the administered dose.

2.5.4 What are the characteristics of drug elimination?

No mass balance study was conducted under NDA 12936. Referring to the approved label of THH, following an i.v. infusion in healthy young volunteers, 73.6% of tiotropium dose is excreted in urine as unchanged drug, indicating renal pathway is the major route of elimination. In a meta-analysis report 205-Metaanalysis-copd-pk, following inhalation of TR5, patients in the age group of < 65 years of age had a renal clearance ($CL_{R,0-6,ss}$) of 347 mL/min (Table 20 in 4.1.4). This is higher than the normal creatinine clearance of 120 mL/min and is indicative of active renal secretion of tiotropium.

Referring to the approved label of THH, The terminal elimination half-life of tiotropium was between 5-6 days following dry powder inhalation. The terminal half-life was 4.84 days following i.v. administration.

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

Results from study 205.458 showed that $C_{max,ss}$ values increased proportionally with increasing dose of tiotropium (Table 14 in 4.1.3). However, the $AUC_{0-6,ss}$ values did not increase proportional to dose. This is because plasma concentration of numerous patients in the 1.25 μg dose group fell below LLOQ after 1 hour post-dosing, and $AUC_{0-6,ss}$ values from TR1.25 cannot be accurately estimated.

Results from meta-analysis report 205-Metaanalysis-copd-pk also showed that tiotropium systemic exposure increased proportionally within the dose range from 1.25 μg to 10 μg (Fig.7 in 4.1.4).

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

There was no single-dose PK study submitted in the resubmission package. Referring to study results from trial 205.112 in the initial submission, tiotropium showed approximately two- to three-fold accumulation in plasma on day 14 after repeated once daily inhalation in healthy volunteers, though it was unclear when the steady state was reached. For details, refer to the Clinical Pharmacology review for the initial submission. Referring to the approved label of THH, pharmacokinetic steady state was reached after 2–3 weeks.

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

There was no evidence for a circadian rhythm of the PK.

2.6 Intrinsic Factors

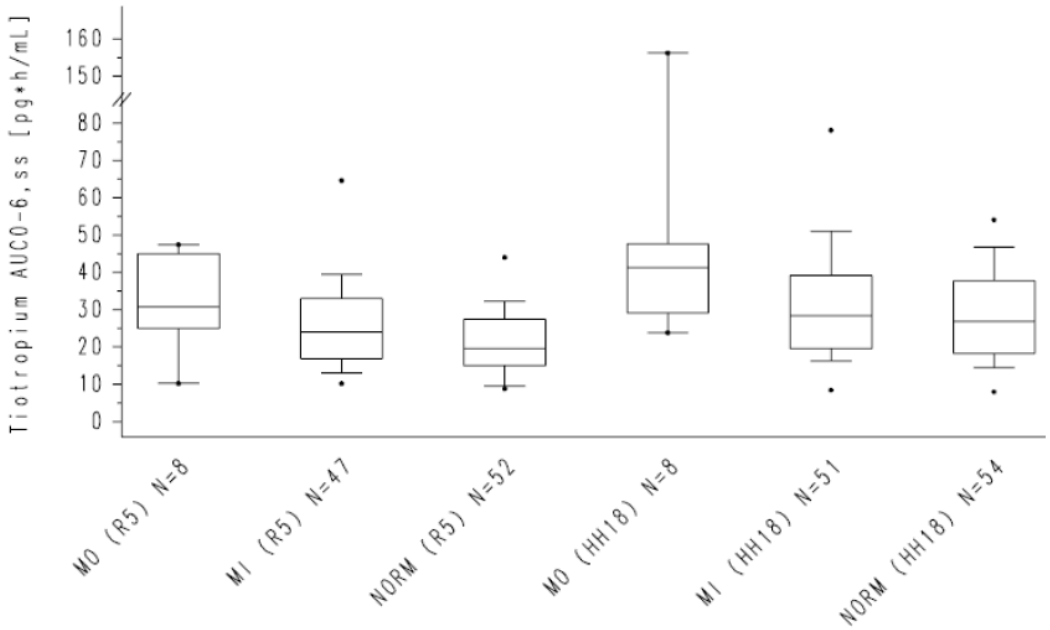
2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much is the variability?

Renal function and race are the major intrinsic factors responsible for the inter-subject variability in exposure. Tiotropium exposure was considered comparable in the range of variability when stratified by other intrinsic factors, such as FEV1, body weight, age, gender, and severity of disease state (GOLD categories). For more information, refer to discussions of 4.1.4.

2.6.1.1 Renal function

Results from meta-analysis report 205-Metaanalysis-copd-pk showed that, following 4-week once daily administration of TR5, $AUC_{0\text{-}6,ss}$ and $C_{max,ss}$ increased 23% and 17%, respectively, in COPD patients with mild renal impairment compared to patients with normal renal function (Fig.3). $AUC_{0\text{-}6,ss}$ and $C_{max,ss}$ increased 57% and 31%, respectively, in COPD patients with moderate renal impairment. There lacked sufficient data in COPD patients with severe renal impairment in this meta-analysis. Similar trend was observed for THH18 in the same meta-analysis ($AUC_{0\text{-}6,ss}$ and $C_{max,ss}$ both increased 6% in patients with mild renal impairment; $AUC_{0\text{-}6,ss}$ and $C_{max,ss}$ increased 54% and 15% in patients with moderate renal impairment). Referring to the approved label of THH, i.v. administration of tiotropium resulted in 82% increase of $AUC_{0\text{-}4}$ in COPD patients with moderate to severe renal impairment (creatinine clearance of <50 mL/min).

A



B

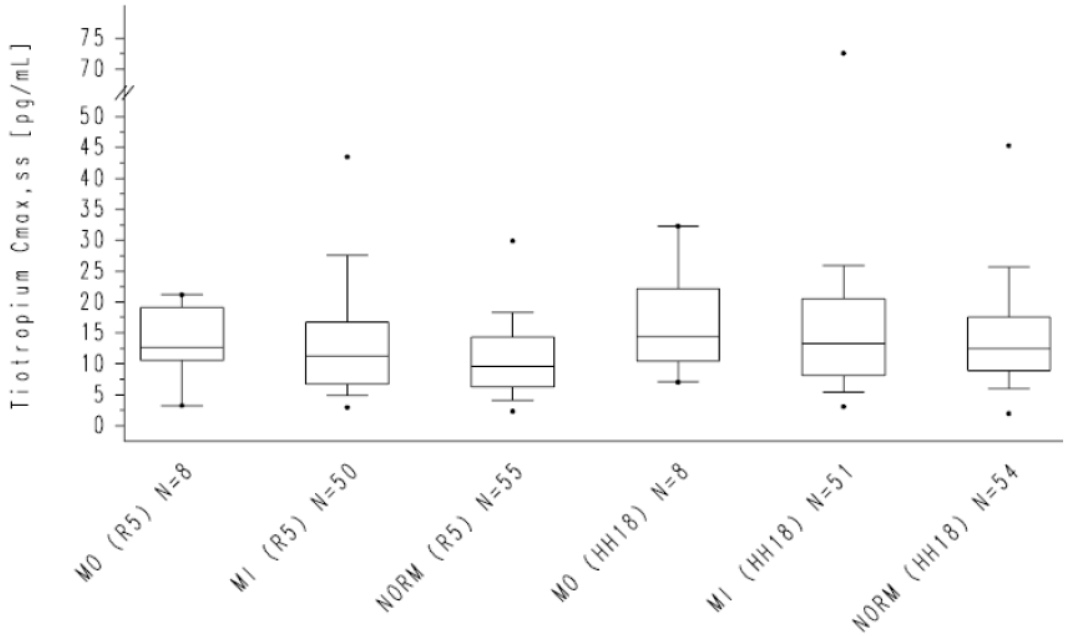


Fig.3 Box plot of geometric mean $AUC_{0\text{-}6,\,ss}$ (A) and $C_{max,\,ss}$ (B) of tiotropium after 4-week once daily administration of TR5 or THH18 in COPD patients by their renal function. MO, patients with moderate renal impairment (creatinine clearance ≥ 30 to <60 mL/min); MI: patients with mild renal impairment (creatinine clearance ≥ 60 to <90 mL/min); NORM: patients with normal renal function (creatinine clearance ≥ 90 mL/min). (Source: CSR 205-Metaanalysis-copd-pk, page 54, Figure 7.2.3.2:2)

2.6.1.2 Race

Study 205.291 was the only dedicated PK trial conducted in non-Caucasian (Asian) COPD patients. Following 4-week once daily administration of TR5, mean C_{10min} of TR5 in Asians from study 205.291 was about 50-60% higher than that of Caucasians from study 205.249 and 205.250 (Table 5 in 1.3.4). Meta-analysis report 205-Metaanalysis-copd-pk showed that $C_{0.167,ss}$ (including C_{9min} and C_{10min}) and trough concentration $C_{pre,ss}$ were 78% and 102% higher, respectively, in Asians compared to Caucasians (Table 21 in 4.1.4). Refer to 1.3.4 for more discussions.

2.6.1.3 Hepatic impairment

No dedicated study was performed to evaluate the effect of hepatic impairment on tiotropium exposure in NDA 21395 (THH) and NDA 21936. Referring to the approved label of THH, following an i.v. infusion in healthy young volunteers, 73.6% of tiotropium dose is excreted in urine as unchanged drug, indicating renal pathway is the major route of tiotropium elimination. The remaining fraction of the tiotropium dose undergoes non-enzymatic auto-cleavage.

2.6.1.4 Pediatric Patients

COPD does not normally occur in children. Drugs indicated for COPD are usually waived for pediatric studies. The PK, safety and effectiveness of tiotropium in pediatric patients have not been established.

2.6.1.5 What pregnancy and lactation use information is available?

There were no adequate and well-controlled studies in pregnant women in NDA 21395 THH and NDA 21936. Referring to the approved label of THH, "SPIRIVA HandiHaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

2.6.1.6 Does genetic variation impact exposure and/or response?

In NDA 21395 THH submission package, four subjects from study 205.222 were identified by their genotype. It was shown that AUC_{0-4h} was 33% higher in the 2D6 poor metabolizers compared to the 2D6 extensive metabolizers. The difference is within the range of variability. The sample size is too small to justify any statistical conclusion.

2.6.2 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. Referring to the initial submission, no clear dose-response relationship was established except for dry mouth.

Referring to the approved label of THH, no dosing regimen adjustment was needed for patients with renal impairment: "Patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects."

Referring to the approved label of THH, there was no dosing regimen adjustment for different races.

Reviewer's comments:
Renal impairment has been fully evaluated in NDA 21395 THH and NDA 21936 initial submission. Consistently, there was no dosing regimen adjustment for COPD patients with (moderate to severe) renal impairment. The PK assessment of the effects of renal function from meta-analysis report 205-Metaanalysis-copd-pk resulted in a similar conclusion. Therefore, no further dosing regimen adjustment in patients with renal impairment will be recommended from clinical pharmacology perspective.

The effect of ethnicity on tiotropium exposure (higher in Asians than Caucasians) was first described in this resubmission package. However, the effect of ethnicity was confounded by cross-study comparison. In addition, it's not clear if this observation can be generalized to the whole Asian population or it is just valid in Japanese population. Furthermore, the higher mortality rate of TR5 treatment in the Asian COPD patients could be contributed by the higher mortality baseline in the Asian COPD patients[1].The effect of ethnicity was presented during the NDA 21936 filing meeting and communicated with DPARP medical team. Dose adjustment may be required, but is pending on the totality of the clinical outcome data between different races.

2.7 Extrinsic Factors

2.7.1 What extrinsic factors (drugs herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

The effects of smoking status and co-medications on tiotropium exposure were investigated in meta-analysis report 205-Metaanalysis-copd-pk.

2.7.1.1 Smoking status

The patients in the pooled data for meta-analysis were either current smokers or ex-smokers. Following administration of TR5, the steady state mean $C_{max,ss}$ and $AUC_{0-6,ss}$ values were 30% and 11% lower, respectively, for patients who were ex-smokers than current smokers (Table 24 and Fig.10 in 4.1.4). Similar results were obtained following THH18 treatment ($C_{max,ss}$ and $AUC_{0-6,ss}$ values were 29% and 14% lower in ex-smokers). The differences were considered comparable between the ex-smokers and current smokers in the range of variability.

2.7.1.2 Co-medications

In the meta-analysis, the effects of the following commonly used pulmonary co-medications by patients with COPD were tested as extrinsic factors on exposure of tiotropium: long-acting beta 2 agonists (LABA), inhaled corticosteroids (ICS), ICS-LABA fixed combination. None of the tested co-medications appeared to have a relevant effect on the exposure to tiotropium.

2.7.2 Drug-drug interactions (DDI)

2.7.2.1 Is the drug a substrate of CYP enzymes?

Referring to the approved label of THH, up to 26.4% of i.v. dose is metabolized. Since tiotropium can undergo non-enzymatic cleavage, the exact fraction of tiotropium metabolized by enzymes is unknown. *In vitro* experiments with human liver microsomes and human hepatocytes suggest that this enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 may be involved in the enzymatic metabolic pathway.

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

Referring to the approved label of THH, *in vitro* studies using human liver microsomes showed that tiotropium, at supra-therapeutic concentrations (1 μM), did not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

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

Referring to the Clinical Pharmacology review for NDA 21395 THH, an *in vitro* assay displayed that cyclosporine A, a P-gp substrate and inhibitor, did not change tiotropium uptake in CaCo2 cells.

2.7.2.4 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. Referring to the approved label of THH, a DDI study was conducted to investigate the effect of cimetidine (400 mg TID) or ranitidine (300 mg QD), the renal tubular secretion inhibitors, on tiotropium exposure (14.4 μg i.v. over 15 minutes). Concomitant administration of cimetidine resulted in a 20% increase of tiotropium AUC_{0-4h}, but no significant change of tiotropium C_{max}. Co-administration ranitidine, however, did not affect the PK of tiotropium.

2.7.2.5 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. Referring to the approved label of THH,

1) Worsening of narrow-angle glaucoma (an ophthalmic disease may require cholinergic agonist treatment) may occur;
2) Avoid coadministration of SPIRIVA HandiHaler 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 8 Solubility of Tiotropium in Different Solutions

Solution	Solubility
Water	(b) (4)
Methanol	
Methylene Chloride	

(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?

Although the formulation remained unchanged between Phase 1, 2 and 3 clinical studies, there were 3 versions of the RESPIMAT device involved. The RESPIMAT device A5 was intended for marketing and used in the all the studies in the resubmission package. The RESPIMAT device A4 was used in the all the pivotal studies in the initial submission package. A5 differs from the A4 by following characteristics: 1) Addition of a locking mechanism that engages following the administration of the declared number of actuations, 2) a color change of turquoise cap, 3) an improved design of the dose indicator. The sponsor indicated that as agreed with the FDA no clinical bridging trials were conducted between A4 and A5. An *in vitro* study showed that the performance between two devices was comparable (Table 9).

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%?

Establishing bioequivalence between TR and THH was not the goal of NDA 21936 as it involves different dosing forms and devices. In addition, systemic exposure is not a determinant of efficacy. A full clinical development program was conducted for NDA 21936. It seems that the efficacy and safety results were comparable between TR5 and THH18 from the studies in the resubmission package. For details, clinical study 205.452 and 205.372 will be reviewed by medical officer (Dr. Robert Lim) from DPARP. The safety/mortality data in 205.452 will be reviewed by Dr. Bo Li from OTS/OB/DBVII.

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 approved label of THH, oral solutions of tiotropium have an absolute bioavailability of 2–3%. The food effect on tiotropium absorption has not been studied in both NDAs as the lung is the major absorption site.

Table 9 Comparison of *in vitro* Performance of RESPIMAT Device Version A4 and A5

	Clinical supply for Phase III studies prior to 2007 NDA submission	Clinical supply for Phase IIIb studies after 2007 NDA submission	Proposed market configuration	
			30 Dose size	14 Dose size
RESPIMAT type used	RESPIMAT A4	RESPIMAT A5	RESPIMAT A5	RESPIMAT A5
Batch no. solution / RESPIMAT inhaler	*e.g.*: 202948 / WE 01070187	*e.g.*: 002966 / 8L0025	*e.g.*: 706581 / 6L0047	*e.g.*: 002966-11L0107
Target delivered dose [µg]	5	5	5	5
Delivered dose [µg] *	(b) (4)			
Aerodynamic particle size distribution by ACI [% of target dose in Group 1a / 1b / 2 / 3]				
Aerodynamic particle size distribution by Laser [% of particles in Group 1a / 1b / 2 / 3]				

* Delivered dose values for Batch 202948 / WE 01070187 were determined according to the draft FDA Guidance *"Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products"*; for the other batches, they are given as start $_{(S)}$ and end $_{(E)}$ values of the spray content uniformity test.

(Source: adapted from section 2.3 Quality Overall Summary, page 21, Table 6)

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 in study 205.291 and 205.458. Plasma and urine concentrations of tiotropium were determined by validated assays using high performance liquid chromatography (HPLC) coupled to tandem mass spectrometry (MS/MS). [D_3] tiotropium was used as internal control.

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 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?

Parameters of bioanalytical method validation of plasma tiotropium from study 205.458 are listed in Table 10. Parameters of bioanalytical method validation of urine tiotropium are listed in Table 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%.

Table 10 Summary of Plasma Tiotropium Bioanalytical Validation Results

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

(Source: section 5.3.1.4. U10-1855-01, page 5, Table1:1)

Table 11 Summary of Urine Tiotropium Bioanalytical Validation Results

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

Type 1 matrix: not acidified
Type 2 matrix: 1 M citric acid +blank human urine 1:9 (v/v)

Type 3 matrix: 1 M citric acid +blank human urine 1:199 (v/v)
(Source: section 5.3.1.4. U07-1752, page 20, Table1)

2.10 Reference

1. Fukuchi Y, Fernandez L, Kuo HP, Mahayiddin A, Celli B, Decramer M, Kesten S, Liu D, Tashkin D. Efficacy of tiotropium in COPD patients from Asia: a subgroup analysis from the UPLIFT trial. Respirology. 2011 Jul;16(5):825-35.

2. Casarosa P, Bouyssou T, Germeyer S, Schnapp A, Gantner F, Pieper M. Preclinical evaluation of long-acting muscarinic antagonists: comparison of tiotropium and investigational drugs. J Pharmacol Exp Ther. 2009 Aug;330(2):660-8

3. Allen A1, Bal J, Cheesbrough A, Hamilton M, Kempsford R. Pharmacokinetics and pharmacodynamics of intravenous and inhaled fluticasone furoate in healthy Caucasian and East Asian subjects. Br J Clin Pharmacol. 2014 May;77(5):808-20

3 DETAILED LABELING RECOMMENDATIONS

10 OVERDOSAGE

High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium dry powder in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium dry powder.

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

Cardiovascular effects

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.

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%. Following 4-week SPIRIVA RESPIMAT 5 mcg once daily dosing, maximum tiotropium plasma concentrations were observed approximately 7 minutes after inhalation

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

The terminal half-life of tiotropium was between 5 and 6 days following dry powder inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers.

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

Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once-daily dry powder inhalation by COPD 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) following inhalation of the solution. This did not result in a corresponding increase in $AUC_{0-6,ss}$ and $C_{max,ss}$ values.

Renal Impairment

Following 4-week SPIRIVA RESPIMAT 5 mcg once daily dosing in COPD patients , 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 patients with normal renal function (creatinine clearance >90 mL/min). There lacks sufficient data of tiotropium exposure in patients with severe renal impairment (creatinine clearance <30 mL/min) following inhalation of the solution. However AUC_{0-4} and C_{max} were 94% and 52% higher in patients with severe renal impairment following intravenous infusion of tiotropium bromide.

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 (long-acting $beta_2$-adrenergic agonists (LABA), inhaled corticosteroids (ICS)) used by patients with COPD were not found to alter the exposure to tiotropium.

4. Appendix

4.1 Appendix – Individual Study Review

4.1.1 Study 205.249 and 205.250

These two studies have been reviewed by Dr. Yun Xu in the 2008 Clinical Pharmacology primary review. The design of two studies has been described in 1.3.2. Here cites the conclusion from Dr. Xu in the initial review:
"Dose proportionality in systemic exposure and urine excretion was observed for the 5 μg and 10 μg doses of tiotropium delivered via the RESPIMAT inhaler at steady state. Comparable systemic exposure and urine excretion was observed for tiotropium 5 μg inhalation via the RESPIMAT inhaler and tiotropium 18 μg via HandiHaler inhaler as steady state."

4.1.2 Study 205.291

Study Type: Phase 2 efficacy, safety and steady state PK study in Japanese COPD patients

Title:
A randomized, double-blind, double-dummy, crossover efficacy and safety comparison of 4-week treatment periods of Ba 679 BR RESPIMAT® 5 μg and tiotropium inhalation capsule 18 μg in patients with COPD

Objective:
The objective of this trial was to compare the efficacy and the safety of Ba 679 BR RESPIMAT® 5 μg once daily with tiotropium HandiHaler® 18 μg (Spiriva® inhalation capsule) once daily in a crossover study of 4-week treatment periods in patients with COPD.

Study Design and Method:
This investigation was a randomized, double-blind, double-dummy, active-controlled, 2-period, cross-over study with 157 Japanese COPD patients entered. Each treatment (TR5 or THH18 once daily) was 4-week long and there was 4-week washout period between two treatments.

At the end of each treatment, blood samples were collected within 1 hour before the inhalation of study medication, 10 minutes (±3 minutes), 1.5 hours (±10 minutes), and 4 hours (±10 minutes) after the inhalation. Urine was collected 0-2 hours and 2-4 hours after the inhalation of study medication.

At starting of each treatment period and at end of each treatment, Pulmonary function tests (PFTs) were performed 10 minutes just before inhalation of study medication and, at 1, 2, and 3 hours after inhalation without a medication washout before the test.

Primary Endpoints:

- The primary endpoint of efficacy was trough FEV1 response determined at the end of each 4-week treatment period. The trough FEV1 was the morning FEV1 value measured at the end of each 4-week treatment period before the last administration of each treatment, approximately 24 hours after the last drug administration. Trough FEV1 response was defined as the change from baseline in trough FEV1.

- Hypothesis: Non-inferiority.
  H_0: Mean trough FEV1 response (TR5) ≤ Mean trough FEV1 response (THH18) – 0.05L

H_1: Mean trough FEV1 response (TR5) > Mean trough FEV1 response (THH18) – 0.05L

- Following PK parameters were calculated: $AUC_{0\text{-}t,\ ss}$, $AUC_{\tau,\ ss}$, CL/F_{ss}, $Ae_{0\text{-}t,\ ss}$ (amount of tiotropium eliminated in urine), $fe_{0\text{-}t,\ ss}$ (fraction of tiotropium eliminated in urine), $CL_{R,\ 0\text{-}t,\ ss}$ (renal clearance of tiotropium).

Analytical Method:
Samples were analyzed by HPLC-MS/MS with LLOQ at 2.50 pg/mL. The assay was validated from 2.50 pg/mL to 150 pg/mL in plasma and from10.0 pg/mL to 5000 pg/mL in urine. The assay precision and accuracy were 7.63% (CV) and 1.94% (bias) at the LLOQ-QC, respectively.

PK Results:
Tiotropium plasma concentration-time profiles following 4-week once daily administration of TR5 or THH18 were plotted in Fig.4. ½ LOQ was used for BLQ samples during calculation. Descriptive statistics of AUC and C_{10min} comparison between TR5 and THH18 was listed in Table 12. Ae was calculated from urine concentration and urine volume. $Ae_{0\text{-}2,\ ss}$ and $A_{e0\text{-}4\ ,ss}$ were compared between TR5 and THH18. Geometric mean ratios (TR5/THH18) of $AUC_{0\text{–}4,\ ss}$, $C_{10min,\ ss}$, $Ae_{0\text{-}2,\ ss}$ and $A_{e0\text{-}4,\ ss}$ were 1.02 (90% CI = 0.93, 1.13), 1.03 (90% CI = 0.91, 1.15), 1.07 (90% CI= 0.95, 1.20), 1.00 (90% CI=0.90, 1.11), respectively.

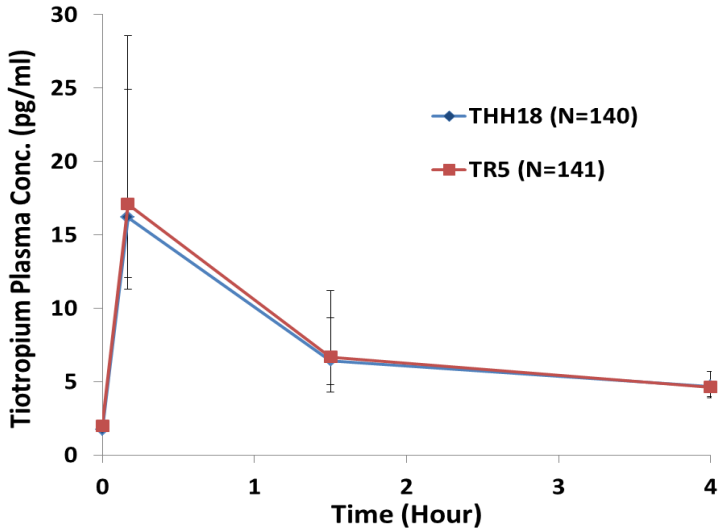


Fig.4 Tiotropium plasma concentration-time profile at steady state following 4-week once daily administration of TR5 or THH18 from study 205.291, observations represent the geometric mean for each time point. Error bars represent the 95% confidence interval. (Source: reviewer's analysis)

Table 12 Summary of PK Parameters of Tiotropium Following 4-week Once Daily Administration of TR 5 µg And THH 18 µg

PK Parameters	THH18*	TR5*	Ratio (TR5/THH18)**
$AUC_{0\text{-}4,\ ss}$ (pg*h/mL)	29.6 (66.5%, N=140)	30.4 (60.4%, N=141)	1.02 (0.93, 1.13, N=128)
$C_{10min,\ ss}$ (pg/mL)	16.2 (82.5%, N=140)	17.1 (68.3%, N=141)	1.03 (0.91, 1.15, N=128)
$Ae_{0\text{-}2,\ ss}$ (µg)	0.185 (80.5%, N=136)	0.200 (64.8%, N=137)	1.07 (0.95, 1.20. N=122)
$Ae_{0\text{-}4,\ ss}$ (µg)	0.336 (71.4%, N=135)	0.342 (58.8%, N=138)	1.00 (0.90, 1.11, N=122)

*** geometric mean (CV, subject number)**
**** unadjusted geometric mean (90% confidence interval, subject number)**
(Source: reviewer's analysis)

Efficacy Results:
Mean trough FEV1 response of TR5 was 0.008 L (95% CI = -0.009, 0.024) more than that of THH18 (Table 13), which excluded predefined 0.05L after full analysis set (FAS). Therefore H_0 hypothesis was rejected (TR5 trough FEV1 response was at least 0.05 L less than THH18, p<0.001).

Table 13 Trough FEV1 Response Following 4-week once daily Administration of TR 5 µg And TH 18 µg after FAS

Treatment	N	Mean (SE)	95% CI	p-value (non-inferiority)
Tio R 5	134	0.109 (0.006)	0.097 - 0.120	
Tio HH 18	134	0.101 (0.006)	0.089 - 0.113	
Tio R 5 - Tio HH 18	134	0.008 (0.009)	-0.009 - 0.024	<0.001

(Source: CSR 205-0291, page 83, Table 11.4.1.1:1)

Mean FEV1 $AUC_{0\text{-}3h}$ response at the end of TR5 treatment was 0.015 L (95% CI = -0.001, 0.030, p=0.0679) more than that of THH18 (Fig.5).

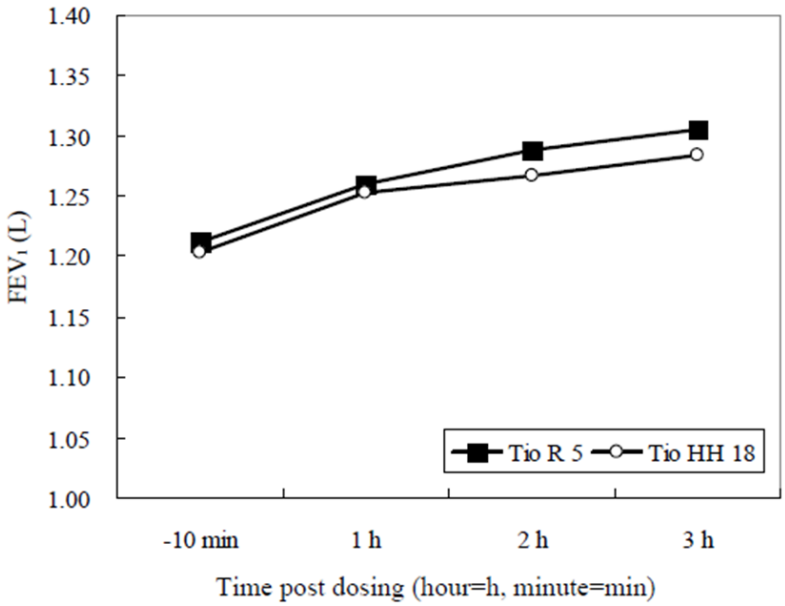


Fig.5 Mean FEV1-time response curve on test day 29 following 4-week once daily administration of TR5 or THH18 treatment in study 205.291 (Source: CSR 205-0291, page 85, Figure 11.4.1.2.1:1)

Conclusions:
Tiotropium PK profiles ($C_{10min,ss}$ and $AUC_{0\text{-}4,ss}$,$Ae_{0\text{-}2,ss}$, $Ae_{0\text{-}4,ss}$) were found similar between TR5 and THH18 following 4-week treatment. The 90% confidence intervals of all the ratios (TR5/THH18) of above PK parameters were within the range between 80% and 125%.

Mean trough FEV1 response of TR5 and THH18 after 4-week treatment was 0.109 L and 0.101 L, respectively. The difference was 0.008 L (95% CI = -0.009, 0.024). Non-inferiority was established for TR5. Mean FEV1 AUC0-3h responses between TR5 and THH18 were similar following 4-week treatment. The difference (0.015 L) was not statistically significant.

Reviewer's comments:
Although the 90% confidence intervals of $C_{10min,ss}$ and $AUC_{0-4,ss}$ ratios (TR5/THH18) were within the range between 80% and 125%, it is not reasonable to state the bioequivalence was established between TR5 and THH18 in Japanese. In accordance with FDA BA/BE studies guidance, both C_{max} and AUC information are required to evaluate bioequivalence between two products. Due to the nature of sparse PK sampling schedule of study 205.291, tiotropium $T_{max,ss}$ (around 5 minutes) was missed and therefore $C_{10min,ss}$ cannot be justified as $C_{max,ss}$.

4.1.3 Study 205.458

Study Type: Phase 2 efficacy, safety and steady state PK study in European COPD patients

Title:
A multi-center, randomized, placebo- and active-controlled, 5-way crossover trial to characterize the pharmacokinetics and evaluate the bronchodilator efficacy and safety of once-daily tiotropium delivered (double-blind) from the RESPIMAT® inhaler as solution for inhalation (1.25, 2.5, 5µg or placebo) and as inhalation powder (18µg) from the HandiHaler® (open-label) after 4-week treatment periods in patients with Chronic Obstructive Pulmonary Disease (COPD).

Objective:
- Compare the PK of TR5 with THH18;
- Evaluate dose-ranging efficacy (FEV1, FVC) and safety (Holter monitoring) of tiotropium solution for inhalation delivered from the RESPIMAT® Inhaler, at steady state in COPD patients.

Method:
This was a multi-center, randomized, placebo- and active-controlled, double-blind within the 4 RESPIMAT® treatments (once daily TR1.25, TR2.5, TR5, and placebo) but open-label for the HandiHaler® (once daily THH18) treatment, 5-way crossover study with 154 randomized COPD patients entered. Each treatment was 4-week long and there was no washout period between each treatment.

At the end of each 4-week treatment (between 26 and 28 days), blood samples were collected before the test drug inhalation, 2 min, 5 min, 7 min, 9 min, 12 min, 15 min, 20 min, 30 min, 40 min, 1 h, 2 h, 4 h, and 6 hours after test drug inhalation. Urine was collected -1-0 hours, 0-2 hours, and 2-6 hours post-dosing.

PFTs were conducted at the screening Visit and randomization Visit (Visit 2, just before inhalation of the first dose of study medication). At the end of each 4-week treatment, PFTs were conducted before (-10 minutes prior to inhalation) and for 6 hours after inhalation at the following times: 30, 60 minutes, 2, 3, 4, 5 and 6 hours.

Primary Endpoints:
- The primary PK endpoints of were $C_{max,ss}$ and $AUC_{0-6,ss}$.

- The primary endpoint of efficacy was FEV1 AUC_{0-6h} following 4 weeks of treatment administration in COPD patients. FEV1 AUC0-6h is defined as the FEV1 AUC normalized for time. Trough FEV1, FEV1 AUC_{0-3h}, FVC AUC_{0-6h}, Trough FVC and FVC AUC_{0-3h} were also evaluated.

- Hypothesis:
    - Bioequivalence of TR5 and THH18:

H_0 (inequivalence): $\mu_{TR5} - \mu_{THH18} \leq 0.80$ or $\mu_{TR5} - \mu_{THH18} \geq 1.25$ (i.e. the difference of the population average responses is either less than or equal to the lower bound or greater than or equal to the upper bound of the acceptance range).

H_a (equivalence): $0.80 \leq \mu_{TR5} - \mu_{THH18} \leq 1.25$ (i.e. the difference of the population average responses is both greater than the lower bound and less than the upper bound of the acceptance range).

- Efficacy:
  - To confirm the efficacy of TR5 compared to placebo
    H_0 (no effect): $\mu_{TR5} = \mu_P$
    H_a (efficacy): $\mu_{TR5} \leq \mu_P$ or $\mu_{TR5} \geq \mu_P$

  - To establish the efficacy of TR2.5 compared to placebo
    H_0 (no effect): $\mu_{TR2.5} = \mu_P$
    H_a (efficacy): $\mu_{TR2.5} \leq \mu_P$ or $\mu_{TR2.5} \geq \mu_P$

  - To show that TR1.25 is ineffective compared to placebo.
    H_0 (superiority): $\mu_T - \mu_{R \geq} \delta$
    H_a (lack of efficacy): $\mu_T - \mu_{R \geq} \delta$

    δ was taken to be 0.1 L·h. This was half the expected response of TR5 as measured by (TR5 – placebo) for FEV1 AUC0-6h.

Since THH18 treatment was open-label in this study, comparison of efficacy between TR (1.25, 2.5 and 5) and THH18 was not a main objective.

Analytical Method:
Plasma samples were analyzed by HPLC-MS/MS with LLOQ at 1.0 pg/mL. 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. The assay precision and accuracy were 11.42% (CV) and -1.87% (bias) at the LLOQ-QC, respectively.

To be noted, study 205.458 has the advantage of improved sensitivity of the bioanalytical methodology (LLOQ of 1 pg/mL in plasma) allowing for measurement of plasma concentrations over the entire collection interval of 6 hours post-dose for THH 18 and TR 5 in most patients. This combined with the extensive sampling around the $T_{max,ss}$ provided good estimates of $C_{max,ss}$ and $AUC_{0-6,ss}$ values of this trial, without the need of replacing BLQ values.

PK Results:
Tiotropium plasma concentration-time profiles following 4-week once daily administration of TR1.25, TR2.5, TR5, or THH18 were plotted in Fig.1. $C_{max,\ ss}$ increased proportionally with dose increase from 1.25 µg to 5 µg for TR. However, the $AUC_{0-6,ss}$ values did not increase proportional to dose. This is because plasma concentration of numerous patients in the 1.25 µg dose group fell below LLOQ after 1 hour post-dosing, and $AUC_{0-6,ss}$ values from TR1.25 cannot be accurately estimated. Descriptive statistics of $C_{max,ss}$, $AUC_{0-6,ss}$, T_{max}, and $Ae_{0-6,ss}$ comparisons between different treatments were listed in Table 14. Geometric mean ratios (TR5/THH18) of $C_{max,ss}$, $AUC_{0-6,ss}$, T_{max}, and $Ae_{0-6,ss}$ were 0.804 (90% CI = 0.732, 0.883), 0.747 (90% CI = 0.692, 0.806), 0.741 (90% CI= 0.684, 0.802), respectively. T_{max} were similar between different TR doses and THH18 (5 to 7 min).

Table 14 Summary of PK Parameters of Tiotropium Following 4-week Once Daily Administration of TR 1.25 µg, TR 2.5 µg, TR 5 µg, Or THH 18 µg in Study 205.458

Treatments	$C_{max, ss}$ (pg/mL)*	$AUC_{0-6, ss}$* (pg*h/mL)	T_{max}***	$Ae_{0-6, ss}$ (µg)*
R1.25	2.81 (53%, N=104)	10.0 (25.3%, N=22)	6min (2min - 2h)	0.0887 (68.0%, N=108)
R2.5	5.07 (61.8%, N=110)	12.8 (29.9%, N=76)	5min (2min - 6h)	0.177 (68.0%, N=110)
R5	10.5 (66.4%, N=113)	22.1 (47.8%, N=107)	7min (2min - 20min)	0.387 (65.9%, N=107)
THH18	12.9 (64.6%, N=113)	28.4 (52.4%, N=113)	7min (2min - 1h)	0.522 (53.8%, N=109)
Ratio (TR5/THH18)**	0.804 (0.732, 0.883, N=108)	0.747 (0.692, 0.806, N=103)	-	0.741 (0.684, 0.802, N=100)

*** geometric mean (CV, subject number) except the last row**
**** unadjusted geometric mean (90% confidence interval, subject number)**
***** median (range)**
(Source: reviewer's analysis)

Efficacy Results:
After four weeks of treatment, the adjusted mean treatment differences (and SE) compared to placebo (in liters) were 0.165 (0.012), 0.185 (0.012), 0.191 (0.012) and 0.196 (0.012) for TR1.25, TR2.5, TR5 and THH18, respectively, after full analysis set (FAS, Table 15 and Fig.6). FEV1 AUC_{0-6h} of both TR5 and TR2.5 were significantly different from placebo (both $p<0.0001$). Therefore H_0 hypothesis of TR5 and TR2.5 were rejected. FEV1 AUC_{0-6h} of TR1.25 was also significantly different from placebo ($p<0.05$). Therefore H_0 hypothesis of TR1.25 was accepted, i.e., TR1.25 was superior to placebo.

Although the study was not powered for comparisons between each TR dose and THH18, TR5 and TR2.5 provided comparable FEV_1 AUC_{0-6h} results ($p>0.05$). In comparison, TR 1.25 provided significantly lower FEV_1 AUC_{0-6h} values compared to THH18 (Table 15).

Table 15 Summary of FEV1 AUC_{0-6h} following 4-week Once Daily Administration of TR 1.25 µg, TR 2.5 µg, TR 5 µg, Or THH 18 µg in Study 205.458 (FAS, ANOVA Results)

	Placebo	Tio R 1.25	Tio R 2.5	Tio R 5	Tio HH 18**
Number of patients in analysis set	143	143	144	143	142
Number of analysed patients	143	143	144	143	142
Adjusted*mean (SE)	1.371 (0.046)	1.535 (0.046)	1.556 (0.046)	1.562 (0.046)	1.567 (0.046)
Comparison vs Placebo					
Adjusted* mean (SE)		0.165 (0.012)	0.185 (0.012)	0.191 (0.012)	0.196 (0.012)
95% Confidence interval*		(0.141 , 0.189)	(0.161 , 0.209)	(0.167 , 0.216)	(0.172 , 0.220)
p-value*			<.0001	<.0001	<.0001
Comparison vs Tio HH 18**					
Adjusted* mean (SE)		-0.031 (0.012)	-0.011 (0.012)	-0.005 (0.012)	
95% Confidence interval*		(-0.055 , -0.007)	(-0.035 , 0.013)	(-0.029 , 0.019)	

(Source: CSR 205-0458, page 98, Table 11.4.1.2:1)

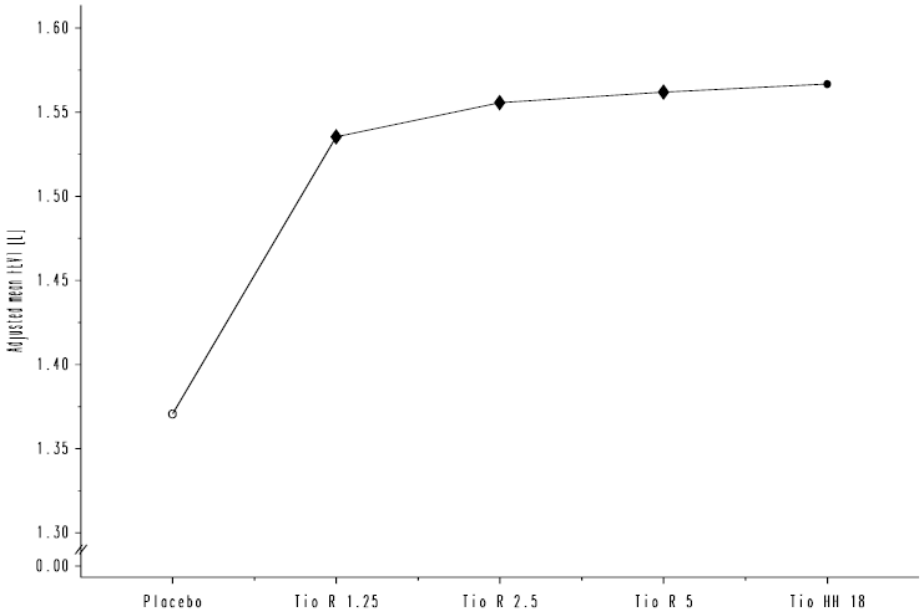


Fig.6 Mean FEV1 $AUC_{0\text{-}6h}$ following 4-week once daily administration of TR 1.25 µg, 2.5 µg, 5 µg, or THH 18 µg in study 205.458. (Source: CSR 205-0458, page 97, Figure 11.4.1.2:1)

Conclusions:
The systemic exposure ($C_{max,ss}$ and $AUC_{0\text{-}6,ss}$.) of tiotropium following 4-week treatment of TR5 was lower than that of THH18. The urine excretion profile ($Ae_{0\text{-}6,ss}$) of tiotropium also showed the same trend. Both T_{max} and concentration-time curves were similar between TR5 and THH18, indicating similar absorption and elimination process of tiotropium between TR5 and THH18.

Efficacy superior to placebo were established for TR1.25, TR2.5 and TR5. Numerically, FEV1 $AUC_{0\text{-}6h}$ (following 4-week treatment) of TR5 among different TR doses appeared the most comparable to THH18.

Reviewer's comments:
Study 205.458 was the first dedicated rich PK sampling BA/BE study to compare the systemic exposure between TR5 and THH18 during TR development. The PK comparison was prioritized as the primary objective of this study. Due to the improvement of analytical method (LLOQ decreased from 2.5 to 1.0 pg/mL), tiotropium concentration from most of the post-dose samples, including the last time point (6 hour), were able to be precisely measured, which greatly increased the reliability and the confidence of the results. The rich sampling schedule precisely compare the absorption phase and early elimination phase of tiotropium between TR5 and THH18. Although the systemic exposure of TR5 was lower than THH18, the shapes of the curves were similar.

4.1.4 PK Meta-analysis 205-Metaanalysis-COPD-PK

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

Objective:
The objectives of this study were:

- To identify best estimates of standard pharmacokinetic parameters for tiotropium in patients with COPD following inhalation via HandiHaler and following inhalation via RESPIMAT inhaler.

- To compare the exposure to tiotropium in patients with COPD following inhalation via HandiHaler or via RESPIMAT inhaler.
- To evaluation of dose proportionality of tiotropium following inhalation via the RESPIMAT inhaler.
- To describe the effect of intrinsic and extrinsic factors on drug exposure following inhalation via HandiHaler or via RESPIMAT inhaler.

Method:
The data from 4 clinical trials (205.249, 205.250, 205.458, and 205.291) were included in this meta-analysis. Included, total 347 patients were treated with THH18 and 359 patients were treated with TR (Table 16).

Table 16 Overall Summary of the Demographic Characteristics of COPD Patients Included in Meta-analysis by Device Given as Median (range) Or N

	HANDIHALER	RESPIMAT
N	347	359
Age [years]	67.0 (41.0-87.0)	66.0 (41.0-87.0)
Body weight [Kg]	66.80 (36.9-134.3)	67.10 (36.9-134.3)
Height [cm]	168 (145-196)	168 (145-196)
Gender (Female/Male)	48/299	50/309
Creatinine clearance [mL/min]	75.17 (27.3-233.2)	76.56 (24.8-233.2)
BMI [kg/m^2]	23.14 (14.8-46.5)	23.30 (14.8-46.5)
BSA [m^2]	1.75 (1.28-2.55)	1.76 (1.28-2.55)
FEV_1 at predose [L]	1.14 (0.3-3.1)	1.12 (0.3-3.1)
LABA* [%] No/Yes	74.4/25.6	77.2/22.8
ICS* [%] No/Yes	69.7/30.3	68.8/31.2
ICS-LABA [%] No/Yes	96.5/3.5	96.9/3.1

(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 initial bioanalytical report. Only concentrations within the validated concentration range were used for the calculation of PK parameters. For derivation of AUCs, the predose concentrations, which were below the lower limit of quantification (BLQ), were set to zero. Values below the lower quantification limit flagged with BLQ or no peak (NOP) in the lag-phase were also set to zero. All other BLQ/NOP values of the profile were ignored. Concentration data identified with NOS (no sample), NOR (no valid result), or NOA (not analyzed) were not considered in the evaluation of PK parameters for this meta-analysis.

The $C_{0.167,\,ss}$ and $C_{0.15,\,ss}$ values from study 205.249, 205.250 and 205.458 were pooled to come up with an estimate of "$C_{0.167,\,ss}$" value to enhance the precision of the comparison between TR5 and THH 18 including Test/Reference ratios.

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:

Dose proportionality in patients with COPD

An overall summary of pharmacokinetic parameters by dose across trials is provided in Table 17. Based on a comparison of $C_{0.167, ss}$ and $Ae_{0-2,ss}$ which the values could be obtained from all the TR doses (1.25 µg, 2.5 µg, 5 µg and 10 µg), tiotropium systemic exposure generally increases proportionally within dose range from 1.25 µg to 10 µg (Fig.7).

Table 17 Comparison of Non-compartmental PK Parameters of Tiotropium Following 4-week Once Daily Administration of TR 1.25 µg, TR 2.5 µg, TR 5 µg, Or THH 18 µg

Parameter [units]	Tio R 1.25		Tio R 2.5		Tio R 5		Tio R 10		Tio HH 18	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
$C_{max,ss}$[1] [pg/mL]	104	2.81 (53.0)	110	5.07 (61.8)	113	10.5 (66.4)	---	---	113	12.9 (64.6)
"$C_{0.167,ss}$"[2] [pg/mL]	97	2.40 (51.5)	108	4.30 (60.6)	145	10.1 (76.6)	37	30.3 (91.5)	148	11.2 (62.8)
$AUC_{0-6,ss}$[3] [pg*h/mL]	22	10.0 (25.3)	76	12.8 (29.9)	107	22.1 (47.8)	---	---	113	28.4 (52.4)
$t_{max,ss}$[4] [h] #	104	0.100 (0.0330-2.00)	110	0.0830 (0.0330-6.00)	113	0.117 (0.0330-0.333)	---	---	113	0.117 (0.0330-1.00)
$Ae_{0-2,ss}$[5] [ng]	112	38.9 (80.2)	110	79.8 (77.7)	195	177 (79.4)	82	352 (91.7)	191	174 (88.9)
$Ae_{0-6,ss}$[5] [ng]	108	88.7 (68.0)	110	177 (68.0)	107	387 (65.9)	---	---	109	522 (53.8)
$Ae_{0-12,ss}$[5] [ng]	---	---	---	---	82	530 (68.6)	82	1090 (84.2)	81	421 (69.9)

median and range
[1] $C_{max,ss}$ = maximum plasma concentration at steady-state
[2] "$C_{0.167,ss}$" = pooled plasma concentration 9 and 10 minutes at steady-state
[3] $AUC_{0-6,ss}$: area under the plasma concentration time curve at steady-state between time points 0 and 6 h. Limited $AUC_{0-6,ss}$ data available from lower doses due to concentrations being BLQ at later points in time. BLQ values were considered missing.
[4] $t_{max,ss}$ = time from dosing to maximum tiotropium plasma concentration (at steady-state) - median and range
[5] $Ae_{t1-t2,ss}$ = Amount of dose excreted unchanged into urine between times t1 and t2 h post-dose at steady-state
Source data: [Appendix 10, Table 3.1.1] – data from following trials included: 205.458, 205.249 and 205.250

(Source: CSR 205-Metaanalysis-copd-pk, page 39, Table 7.2.2:1)

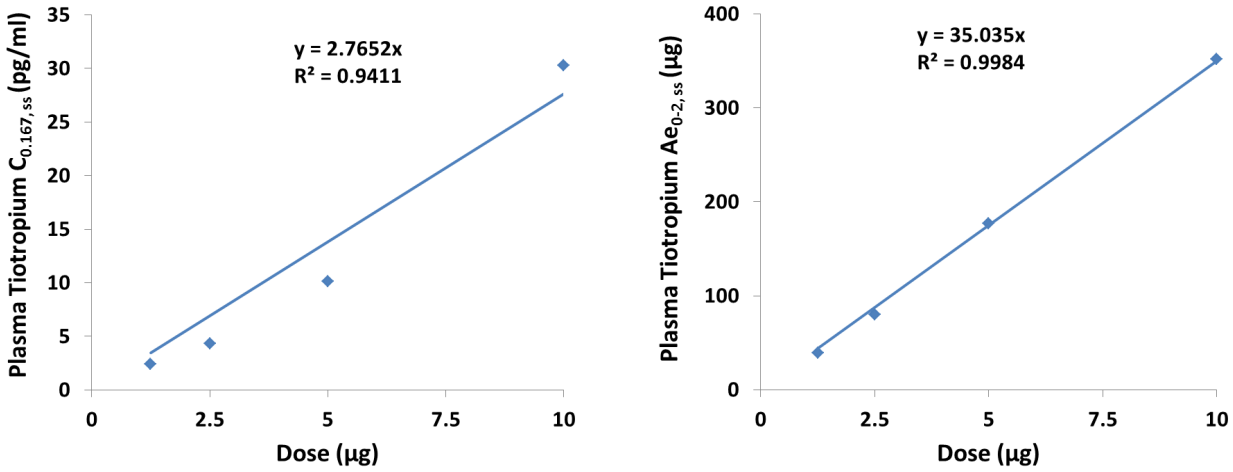


Fig.7 Tiotropium dose-exposure proportionality within dose range from 1.25 µg to 10 µg. The R squares of $C_{0.167,\,ss}$ (left) and $Ae_{0\text{-}2,ss}$ (right) are 0.941 and 0.998, respectively (data source: study 205.249, 205.250, and 205,258) (Source: reviewer's analysis)

Effective Half-life

Referring to the results from study 205.133 in NDA 21935 THH submission, the accumulation ratio based on 4 hour urine data in COPD patients ranges between 2.15 to 3.24 (Table 18). The Sponsor stated that the ratios provided an effective half-life estimate of 27-45 hours.

Table 18 Amount of Tiotropium Excreted Unchanged in Urine within 4 Hours Following Once Daily 18 µg Tiotropium Dry powder Inhalation in Study 205.133

	Younger patients*	Older Patients$
N	12	13
Day 1 $Ae_{0\text{-}4}$ (% of dose)	0.606	0.661
Day 7 $Ae_{0\text{-}4}$ (% of dose)	1.61 (2.66)#	1.42 (2.15)#
Day 14 $Ae_{0\text{-}4}$ (% of dose)	1.97 (3.24)#	1.42 (2.15)#

*** younger patients were ≤ 58 years of age.**
$ older patients were ≥70 years of age.
 # geometric mean (ratio of day7 or day 14 value over day 1 value)
(Source: Dr Yun Xu's review, DARRT date 07/31/2008)

Reviewer's comments:

To estimate the effective half-life, it's understandable that it's not feasible to estimate $AUC_{0\text{-}\tau}/AUC_{0\text{-}24}$ for tiotropium as tiotropium concentration possibly would all BLQ during later elimination phase. Unfortunately, the Sponsor never measured real C_{max} (through rich PK-sampling) from both single-dose and at steady state in one study. Therefore it's reasonable for the Sponsor to leave as is in NDA 21395 THH submission which no effective half-life was estimated.

However, it's not reasonable to calculate the effective half-life through accumulation ratios obtained from $Ae_{0\text{-}4}$, as urine secretion amount of tiotropium was not normalized by renal function, let alone the credibility to replace $AUC_{0\text{-}\tau}$ or C_{max} with $Ae_{0\text{-}4}$.This effective half-life estimation for tiotropium administered via dry powder is not acceptable.

Comparison of the bioavailability of TR5 and THH18

A comparison of pooled PK parameters of TR5 and THH18 at steady-state is listed in Table 17. Numerically, values of $C_{max,ss}$, $C_{0.167,ss}$ (combination of C_{9min} and C_{10min}), and $AUC_{0-6h,ss}$ of TR5 were all less than those of THH18. The ratio of $AUC_{0-6h,ss}$ was less than 0.80, which was lower than the bioequivalence lower boundary (0.80, 1.25) just by point estimation (Table 4).

It seems that the shape of the plasma concentration time profiles was similar between TR and THH (Fig.8). Tiotropium was rapidly absorbed following inhalation with median $T_{max,ss}$ of 5-7 minutes. The plasma concentration time profile appeared to be at least biphasic. Following the rapid changes in concentration during the initial approximate 30 minutes postdose, the plasma concentrations decreased slowly until the 6 hours post-dose time point.

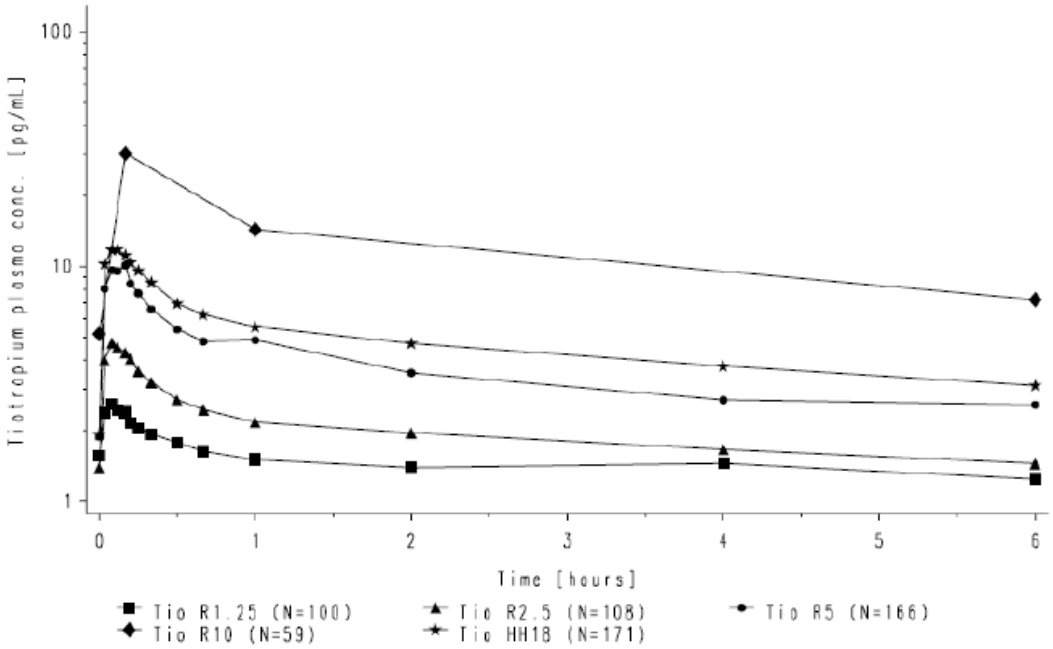


Fig.8 Semi-log scale of tiotropium plasma concentration-time profile at steady state following 4-week once daily administration of TR 1.25 µg, 2.5 µg, 5 µg, or THH 18 µg (data source: study 205.249, 205.250, and 205,258) (Source: CSR 205-Metaanalysis-copd-pk, page 38, Figure 7.2.2:1)

Effect of influence of intrinsic factors on tiotropium's PK:

- Renal function

Tiotropium is predominantly renally excreted (74% of the i.v. dose remains unchanged in the urine). The renal clearance of tiotropium exceeds the creatinine clearance, indicating there is an active renal secretion mechanism of tiotropium. Theoretically patients with renal impairment will have higher exposure and safety concern will be raised for patients with renal impairment.

Geometric mean plasma concentration-time profile by renal function following administration of TR5 is shown in Fig.9. It appears that administration of TR5 to COPD patients with mild renal impairment (creatinine clearance ≥ 60 to < 90 mL/min) resulted in a 14% lower tiotropium renal clearance ($CL_{R,0-6,ss}$), 23% higher $AUC_{0-6,ss}$, and 17% higher $C_{max,ss}$. Administration of TR5 to COPD patients with moderate renal impairment (creatinine clearance ≥ 30 to < 60 mL/min) resulted in a 38% lower $CL_{R,0-6,ss}$, 57% higher $AUC_{0-6,ss}$, and 31% higher $C_{max,ss}$ (Table 19). The pooled data lacks of sufficient information in patients with severe renal impairment, therefore this population was not studied for

TR5. Similar trend (renal impairment increases systemic exposure) was observed in THH18-treated COPD patients as well. This is consistent with the current drug label of THH.

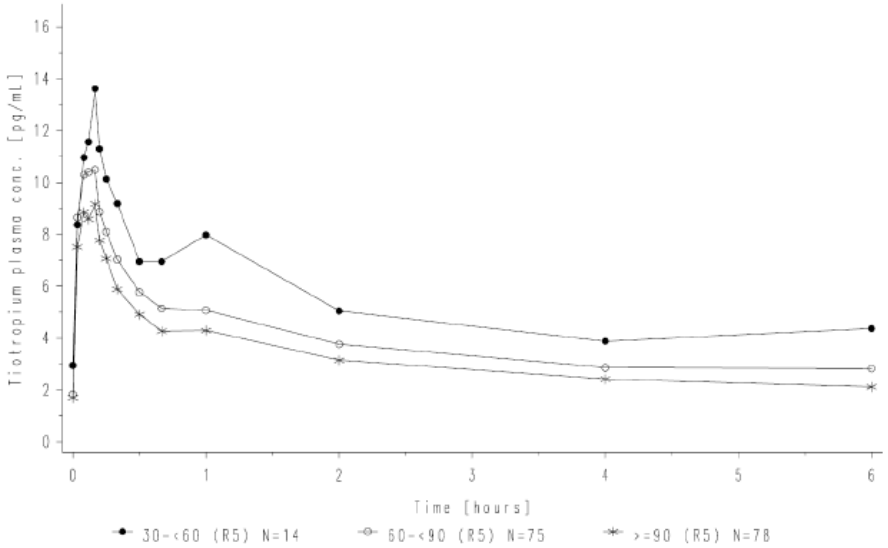


Fig.9 Tiotropium plasma concentration-time profile at steady state following 4-week once daily administration of TR5 in COPD patients with different renal function (creatinine clearance range ≥ 90 mL/min, 60 – 90 mL/min and 30 – 60 mL/min). (Source: CSR 205-Metaanalysis-copd-pk, page 51, Figure 7.2.3.2:1)

Table 19 Overall Summary Descriptive Statistics of Steady State Tiotropium PK Parameters in COPD Patients Treated with TR5 by Renal Function

Creatinine clearance categories (mL/min)	Average creatinine clearance[5] [mL/min]		$Ae_{0-2,ss}$[1] [ng]		$Ae_{0-6,ss}$[1] [ng]		$Ae_{0-12,ss}$[1] [ng]		$C_{max,ss}$[2] [pg/mL]		$AUC_{0-6,ss}$[3] [pg*h/mL]		$CL_{R,0-6,ss}$[4] [mL/min]	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
≥90	51	117.21 (17.7)	91	193 (76.5)	53	391 (55.6)	35	560 (74.4)	55	9.59 (62.7)	52	19.5 (44.9)	51	340 (29.1)
≥60 to < 90	43	74.79 (9.0)	88	167 (79.1)	46	384 (78.6)	38	528 (62.4)	50	11.2 (69.9)	47	24.0 (45.1)	43	291 (33.6)
≥30 to < 60	8	49.97 (19.3)	15	148 (98.6)	8	386 (66.6)	8	426 (82.1)	8	12.6 (66.7)	8	30.7 (56.0)	8	210 (45.3)

Source data - $Ae_{0-2,ss}$: data from trials 205.458; 205.249 and 205.250; $Ae_{0-12,ss}$: data from trials 205.249 and 205.250; $Ae_{0-6,ss}$, $CL_{R,0-6,ss}$, $C_{max,ss}$ and $AUC_{0-6,ss}$: data from trial 205.458
(Source: CSR 205-Metaanalysis-copd-pk, page 49, Table 7.2.3.2:1)

- Age

Subjects with advanced age are generally associated with decreased renal function. Pooled PK data from COPD patients was divided into two age categories, i.e., < 65 years and ≥ 65 years (Table 20). Following administration of TR5, COPD patients in the category of ≥ 65 years had 21% lower $CL_{R,0-6,ss}$, 8% lower $AUC_{0-6,ss}$, and 27% lower $C_{max,ss}$ compared to patients in the age range of 18 to < 65 yr. Similar trend (renal impairment increases systemic exposure) was observed in THH18-treated COPD patients as well, except that $AUC_{0-6,ss}$ was 5% higher in patients ≥ 65 years. However, the values can be considered comparable between the two age groups in the range of variability. The result from this meta-analysis is not necessarily consistent with the approved label of THH (AUC_{0-4} increased 43% in

elderly patients), as the age groups were categorized differently in NDA 21395 THH package (elderly subjects 69-80 years of age were compared with younger subjects 45-58 years of age).

Table 20 Overall Summary Descriptive Statistics of Steady State Tiotropium PK Parameters in COPD Patients by Age Groups

Device /dose	Age categories [yr]	$Ae_{0-2,ss}$ [1] [ng]		$Ae_{0-6,ss}$ [1] [ng]		$Ae_{0-12,ss}$ [1] [ng]		$C_{max,ss}$ [2] [pg/mL]		$AUC_{0-6,ss}$ [3] [pg*h/mL]		$CL_{R,0-6,ss}$ [4] [mL/min]	
		N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
Tio R 5	< 65	90	223 (71.6)	49	482 (52.9)	38	600 (68.0)	51	12.5 (61.5)	49	23.1 (48.4)	48	347 (39.1)
Tio R 5	≥ 65	105	146 (77.6)	58	322 (68.7)	44	477 (67.3)	62	9.07 (65.9)	58	21.2 (47.2)	54	275 (36.6)
Tio HH 18	< 65	90	190 (98.4)	50	597 (50.3)	40	412 (69.4)	51	13.8 (61.6)	51	27.6 (45.5)	50	365 (37.5)
Tio HH 18	≥ 65	101	160 (79.6)	59	465 (53.9)	41	429 (71.4)	62	12.3 (67.1)	62	29.0 (58.0)	59	271 (37.1)

Source data - $Ae_{0-2,ss}$: data from trials 205.458; 205.249 and 205.250; $Ae_{0-12,ss}$: data from trials 205.249 and 205.250; $Ae_{0-6,ss}$, $CL_{R,0-6,ss}$, $C_{max,ss}$ and $AUC_{0-6,ss}$: data from trial 205.458
(Source: CSR 205-Metaanalysis-copd-pk, page 45, Table 7.2.3.1:1)

- Race

Irrespective of the device, the mean plasma concentration time profile of tiotropium was higher in Asians compared to Caucasian COPD patients (Fig.2). At steady state of TR5 treatment, $C_{0.167,ss}$ and trough concentration $C_{pre,ss}$ were 78% and 102% higher, respectively in Asians than Caucasians (Table 21). However, the $Ae_{0-2,ss}$ values were comparable between Asians and Caucasians. Very limited (n =3) data are available from Black patients.

Table 21 Overall Summary Descriptive Statistics of Steady State Tiotropium PK Parameters in COPD Patients by Race

	Tio R 5								Tio HH 18							
Race	$Ae_{0-2,ss}$ [1] [ng]		"$C_{0.167,ss}$" [2] [mL/min]		$C_{pre,ss}$ [3] [pg/mL]		CL_{CR} [4] [mL/min]		$Ae_{0-2,ss}$ [1] [ng]		"$C_{0.167,ss}$" [2] [mL/min]		$C_{pre,ss}$ [3] [pg/mL]		CL_{CR} [4] [mL/min]	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
White	192	178 (79.2)	142	10.1 (76.8)	89	1.88 (54.5)	142	87.8 (31.6)	188	172 (88.5)	145	11.1 (62.1)	95	1.92 (55.9)	144	88.2 (30.0)
Black	3	154 (112)	3	11.3 (82.8)	---	---	3	91.7 (16.9)	3	293 (121)	3	15.5 (111)	---	---	3	91.7 (16.9)
Asian	137	200 (64.8)	91	18.0 (58.1)	60	3.79 (43.7)	91	63.7 (29.1)	136	185 (80.5)	95	17.7 (51.4)	44	3.50 (29.8)	95	64.4 (28.1)

[2] $C_{0.167,ss}$ – combination of C_{10min} and C_{9min}
[4] CL_{CR} – creatinine clearance
Source data - $Ae_{0-2,ss}$, $C_{pre,ss}$, and $C_{0.167,ss}$: data from trials 205.458; 205.249, 205.250, and 205.291.
(Source: CSR 205-Metaanalysis-copd-pk, page 72, Table 7.2.3.7:1)

- Gender

There were approximately 6 times males as many as females in the pooled data. Following administration of TR5, $AUC_{0-6,ss}$ and $C_{max,ss}$ were 17% and 34% higher, respectively, in females

compared to males (Table 22). However, the values can be considered comparable between the sexes in the range of variability. Similar result was obtained from THH18 treatment.

Table 22 Overall Summary Descriptive Statistics of Steady State Tiotropium PK Parameters in COPD Patients Treated by TR5 by Gender

Sex	$Ae_{0-2,ss}$[1] [ng]		$Ae_{0-6,ss}$[1] [ng]		$Ae_{0-12,ss}$[1] [ng]		$C_{max,ss}$[2] [pg/mL]		$AUC_{0-6,ss}$[3] [pg*h/mL]		$CL_{R,0-6,ss}$[4] [mL/min]	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
Females	44	198 (86.6)	20	411 (65.4)	21	551 (73.9)	22	14.7 (70.8)	22	25.6 (45.3)	20	249 (49.1)
Males	151	172 (77.1)	87	382 (66.3)	61	523 (67.4)	91	9.67 (62.0)	85	21.3 (47.7)	82	323 (35.4)

Source data - $Ae_{0-2,ss}$: data from trials 205.458; 205.249 and 205.250; $Ae_{0-12,ss}$: data from trials 205.249 and 205.250; $Ae_{0-6,ss}$, $CL_{R,0-6,ss}$, $C_{max,ss}$ and $AUC_{0-6,ss}$: data from trial 205.458
(Source: CSR 205-Metaanalysis-copd-pk, page 61, Table 7.2.3.3:1)

- GOLD categories (COPD severity grade)

Following administration of TR5, $AUC_{0-6,ss}$ and $C_{max,ss}$ were similar (Table 23) between two FEV1% prediction categories (30 - <50% and 50 - <80%). However, the patients number in category <30% was too few to draw a statistical conclusion. Similar result was obtained from THH18 treatment.

Table 23 Overall Summary Descriptive Statistics of Steady State Tiotropium PK Parameters in COPD Patients Treated by TR5 by GOLD Categories

FEV1% Pred. categories	$Ae_{0-2,ss}$[1] [ng]		$Ae_{0-6,ss}$[1] [ng]		$Ae_{0-12,ss}$[1] [ng]		$C_{max,ss}$[2] [pg/mL]		$AUC_{0-6,ss}$[3] [pg*h/mL]		"$C_{0.167,ss}$"[4] [mL/min]		$C_{pre,ss}$[5] [pg/mL]	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
<30%	13	232 (68.5)	---	---	11	581 (60.0)	---	---	---	---	8	21.3 (53.3)	4	2.03 (31.0)
30-<50%	75	171 (84.1)	34	356 (77.9)	39	550 (78.1)	36	11.0 (56.6)	34	23.2 (39.7)	50	10.3 (71.4)	36	2.03 (67.0)
50-<80%	107	176 (77.1)	71	399 (59.5)	32	492 (60.7)	75	10.1 (70.4)	71	21.3 (50.1)	87	9.35 (76.4)	51	1.78 (45.5)

Source data - $Ae_{0-2,ss}$ and $C_{pre,ss}$: data from trials 205.458; 205.249 and 205.250; $Ae_{0-12,ss}$: data from trials 205.249 and 205.250; $Ae_{0-6,ss}$, $CL_{R,0-6,ss}$, $C_{max,ss}$ and $AUC_{0-6,ss}$: data from trial 205.458
(Source: CSR 205-Metaanalysis-copd-pk, page 65, Table 7.2.3.4:1)

- Other intrinsic factors

Other intrinsic factors such as baseline (pre-treatment) FEV1, on-treatment trough FEV1, body weight, height, body mass index, and body surface area were not found to correlate with exposure to tiotropium in COPD patients treated by TR5 or THH18.

Effect of influence of extrinsic factors on tiotropium's PK:

- Smoking status

The patients were either current smokers or ex-smokers. Following administration of TR5, the steady state mean $C_{max,ss}$ and $AUC_{0-6,ss}$ values were 30% and 11% lower for patients who were ex-smokers

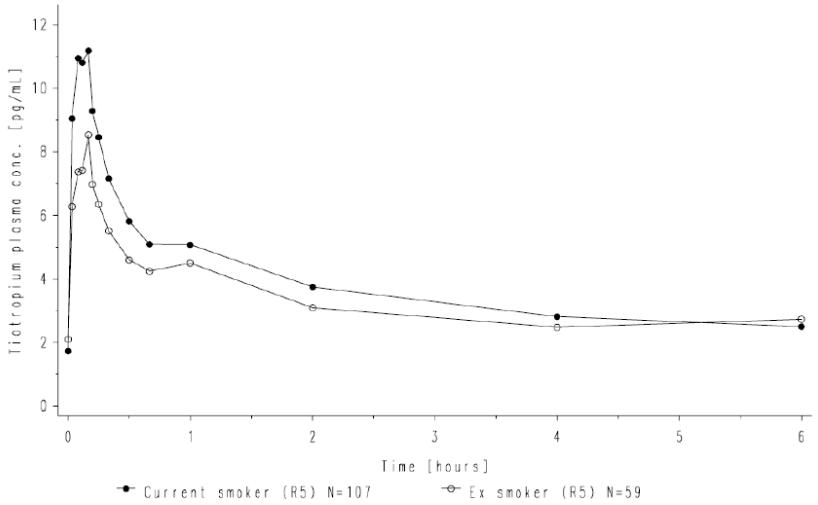
compared to current smokers (Table 24 and Fig.10). Mean $C_{pre,ss}$ value was 21% higher for ex-smokers compared to current smokers. However, the values can be considered comparable between the ex-smokers and current smokers in the range of variability. Similar result was obtained from THH18 treatment.

Table 24 Overall Summary Descriptive Statistics of Steady State Tiotropium PK Parameters in COPD Patients Treated by TR5 by Smoking Status

Smoking status	$Ae_{0-2,ss}$[1] [ng]		$Ae_{0-6,ss}$[1] [ng]		$Ae_{0-12,ss}$[1] [ng]		$C_{max,ss}$[2] [pg/mL]		$AUC_{0-6,ss}$[3] [pg*h/mL]		$CL_{R,0-6,ss}$[4] [mL/min]		$C_{pre,ss}$[5] [pg/mL]	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
Current smokers	115	204 (77.7)	73	431 (59.8)	40	578 (69.3)	76	11.8 (58.0)	74	22.9 (45.8)	72	317 (41.6)	51	1.73 (40.7)
Ex-smokers	80	144 (75.0)	34	308 (71.4)	42	489 (67.4)	37	8.24 (74.7)	33	20.4 (51.7)	30	283 (33.7)	40	2.10 (67.3)

Source data - $Ae_{0-2,ss}$ and $C_{pre,ss}$: data from trials 205.458; 205.249 and 205.250; $Ae_{0-12,ss}$: data from trials 205.249 and 205.250; $Ae_{0-6,ss}$, $CL_{R,0-6,ss}$, $C_{max,ss}$ and $AUC_{0-6,ss}$: data from trial 205.458
(Source: CSR 205-Metaanalysis-copd-pk, page 78, Table 7.2.4.1:1)

A



B

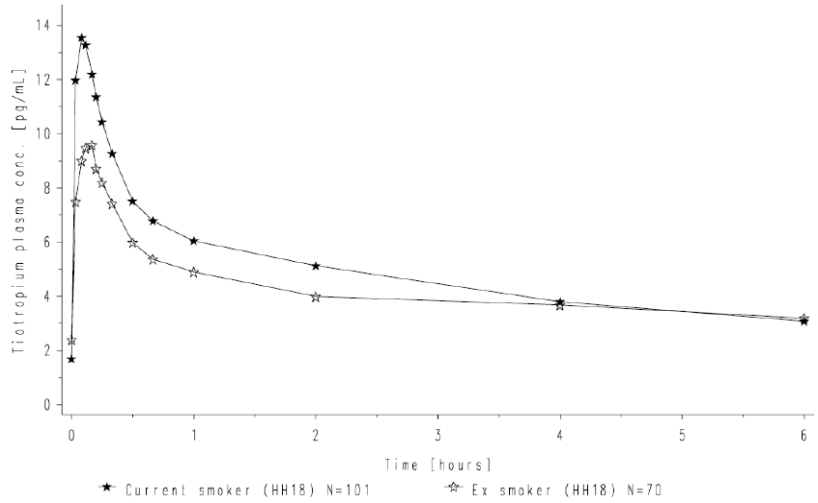


Fig.10 Tiotropium plasma concentration-time profile at steady state following 4-week once daily administration of TR5 (A) or THH18 (B) in COPD patients who were either current smoker or ex-smoker. (Source: CSR 205-Metaanalysis-copd-pk, page 79, Figure 7.2.4.1:1)

- Co-medications

The following commonly used pulmonary co-medications were tested as extrinsic factors: LABA, ICS, and ICS-LABA fixed combination (patients on ICS-LABA were included in ICS monotherapy and LABA monotherapy during analysis). None of the tested co-medications appeared to have a relevant effect on the exposure to tiotropium.

Conclusions:
Pooled PK data show that tiotropium exposure in COPD patients is lower following TR5 administration than THH18 administration. Of the various intrinsic and extrinsic factors tested, COPD patients with renal impairment have higher exposure than those with normal renal function; Asian patients with COPD had higher exposure than Caucasian patients with COPD.

Reviewer's comments:
Since all the post-dose BLQ concentrations were neglected in this meta-analysis, the total subject numbers included in the meta-analysis were less than the sum of subject numbers from all the individual studies. This preference favors study 205.458 that contains a much less proportion of BLQ samples due to increased performance of analytical methodology. Therefore the major conclusions of the meta-analysis are consistent with the results from study 205.458. The data from study 205.291 seems to be only used for evaluation of the effects of ethnicity on exposure.

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

/s/

YUNZHAO REN
08/29/2014

SATJIT S BRAR
08/29/2014

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-936	Submission Date(s): November 16, 2007
Brand Name	Spiriva Respimat
Generic Name	Tiotropium Bromide
Reviewer	Yun Xu, M.D. Ph.D.
Team Leader (Acting)	Wei Qiu, Ph. D.
OCP Division	DCPII
OND division	DPAP
Sponsor	Boehringer Ingelheim
Relevant IND(s)	IND 65-127
Submission Type	Original Submission
Formulation; Strength(s)	Respimat (Inhalation Spray); 2.5 mcg tiotropium per inhalation
Indication	Long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
Dosage and Administration	For oral inhalation only with Respimat For maintenance treatment of COPD: 5 mcg (2x2.5 mcg) once daily

Table of Contents

1 Executive Summary

This is a 505(b) (1) new drug application (NDA) for Spiriva Respimat (tiotropium bromide inhalation spray). Tiotropium bromide was previously approved for use as inhalation powder with the Handihaler inhalation device (Spiriva Handihaler, dry powder inhaler; 18 µg tiotropium under NDA 21-395) on January 30, 2004 for treatment of chronic obstructive pulmonary disease (COPD). For the same indication, Spiriva Respimat consists of tiotropium bromide inhalation spray delivered via the Respimat inhalation device. The proposed dosage of Spiriva Respimat is inhalation of 5 mcg tiotropium (two inhalations, 2.5 mcg tiotropium per inhalation), once daily, with the Respimat inhalation device.

Spiriva Respimat has been developed as a new inhalation drug product through a standalone clinical program. Since the majority of the basic properties of tiotropium are dependent on the drug substance, the sponsor has cross-referenced to the clinical pharmacology studies submitted with NDA 21-395 for Spiriva Handihaler. The labeling languages based on these studies remain the same for these two products. The pharmacokinetic profile of Spiriva Respimat was elucidated in four new clinical trials (Study 205.112, Study 205.127, Study 205.249, and Study 205.250). The clinical pharmacology program also contains one meta-analysis (Study 205.9991) analyzing tiotropium plasma concentrations and urinary excretion data with regard to renal function and age and one literature (P98.3499) to support a statement for lung disposition of Spiriva Respimat in the proposed labeling.

1.1 Recommendation

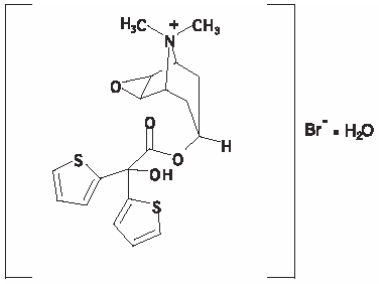
The Office of Clinical Pharmacology /Division of Clinical Pharmacology 2 has reviewed the original NDA 21-936 submitted on November 16, 2007 and found it acceptable, provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the labeling text.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Tiotropium bromide monohydrate is an anticholinergic drug with specificity for muscarinic receptors, proposed to be used for the long-term, once-daily, maintenance treatment of bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.



C19H22NO4S2Br • H2O MW 490.4

Chemical Structure of Tiotropium bromide monohydrate

Since Spiriva Respimat is a formulation for inhalation that exerts local effects in the lungs, the systemic bioavailability of tiotropium or bioequivalence (in terms of plasma concentrations) of Spiriva Respimat and Spiriva Handihaler is not a determinant of efficacy. However, tiotropium plasma concentrations and excretion of tiotropium in urine are measures of systemic exposure, which are relevant for the safety. The pharmacokinetic profile of Spiriva Respimat was elucidated in four trials (one Phase I, one Phase II and two Phase III trials) and compared to that of Spiriva Handihaler, and a meta-analysis was conducted to analyze tiotropium plasma concentrations and urinary excretion data with regard to renal function and age. The sponsor also referred to a published literature to support a statement (b) (4) of Spiriva Respimat in the proposed labeling. The results of these studies are summarized below. And details of the individual studies could be found in appendix 4.2. However, due to limited PK sampling time points in these trials, some PK parameters (e.g. $t_{1/2}$) could not be calculated for Spiriva Respimat. In addition, the doses and sampling schemes in different trials were inconsistent, which made it difficult to make comparison on pharmacokinetics across different trials.

Three versions of the Respimat device (A3, A4 and A5) were used in the development program of Spiriva Respimat. The A3 device was used in the Phase I and II trials; the A4 device was used in the Phase III trials; and the A5 device is the inhalation device intended for marketing. The sponsor indicated that as agreed with the FDA, no clinical bridging trials were conducted between the A4 inhaler and the A5 inhaler.

After a single inhalation, maximum tiotropium plasma concentration was observed at the first sampling time (5 min after inhalation) most of the time in healthy volunteers (study 205.112). The C_{max} values were 4.23 pg/mL, 12.5 pg/mL, and 22.1 pg/mL at 8, 16, and 32 μg, respectively, which generally increased dose-proportionally. After repeated once daily solution inhalation dosing, tiotropium showed a two- to three-fold accumulation in plasma on day 14. The unchanged tiotropium amount excreted in urine was generally dose-proportional in all dose groups on day 1, 7 and 14. It appears that the unchanged tiotropium amount excreted in urine was similar between day 7 and day 14. Between 20.1% and 24.5% of the inhaled dose was excreted unchanged in urine on day 14.

By testing five different doses of Spiriva Respimat (1.25, 2.5, 5, 10, and 20 μg) in COPD patients (study 205.127), no clear dose-response relationship was demonstrated. The study revealed that 5 μg, 10 μg and 20 μg doses were effective in terms of trough FEV1 improvement after 21 days, the rank order of the response was 5 μg, 20 μg, then 10 μg. Tiotropium amount excreted in urine (Ae_{-2-0hr} and Ae_{0-2hr}) increased with increased dose in a dose-proportional way. A dose between 5 μg and 10 μg Spiriva Respimat may achieve a comparable systemic exposure as 18 μg Spiriva Handihaler based on urine excretion data.

The sponsor claimed only minor changes in tiotropium plasma concentrations and urinary excretion was observed after day 7 based on results from study 205.102 and 205.127, indicating that pharmacokinetic steady state was essentially achieved by day 7. However, the data from these two studies suggested that the steady state was achieved later than day 7. Because of the limited PK sampling duration in these trials, it was inconclusive when the actual steady state was reached.

Studies 205.112 and 205.127 were conducted with device version A3. But no bioequivalence study has been conducted to compare the performance of this version and the final marketing version (A5). Therefore, the statements based on these two studies with device A3 should not be included in the label.

Two phase III studies (205.249 and 205.250) were conducted to compare tiotropium 5 and 10 μg delivered by the Respimat inhaler, tiotropium 18 μg delivered by Handihaler and placebo in COPD patients. Efficacy results showed the differences between each of the three active treatments and placebo were statistically significant ($p<0.0001$) for each of the two trials and for the pooled data. Pooling of the data demonstrated that both Respimat 5 μg and Respimat 10 μg doses resulted in statistically significant (at least at $p=0.03$) higher responses compared to Handihaler 18 μg for trough FEV1. Dose proportionality in systemic exposure and urine excretion was observed for the 5 μg and 10 μg doses of tiotropium delivered via the Respimat inhaler at steady state. Based on limited blood sampling points, comparable systemic exposure and urine excretion was observed for tiotropium 5 μg via the Respimat inhaler and tiotropium 18 μg via Handihaler inhaler at steady state.

Data from trials 205.249 and 205.250 were pooled to analyze tiotropium plasma concentrations and urinary excretion data with regard to renal function and age. In patients with impaired renal function, there was a trend towards an increase in tiotropium plasma concentrations and a decrease in excretion of unchanged drug in urine. For the two tiotropium doses delivered by the Respimat inhaler, there was a trend observed towards a lower systemic exposure to tiotropium assessed by $AUC_{0-4,ss}$ and C_{max} values in patients older than 70 years. For 18 µg tiotropium delivered by Handihaler the $AUC_{0-4,ss}$ and C_{max} values were found to be similar across the different age groups. Tiotropium urinary excretion was decreased in patients older than 70 years compared to patients younger than 58 years for tiotropium delivered by both devices.

Since the effects of renal function on pharmacokinetic properties are dependent on the drug substance rather than the inhalation device, and as the systemic exposure is comparable for Respimat 5 µg and Handihaler 18 µg based on available PK data, similar changes in terms of tiotropium plasma concentrations and drug clearance can be expected between the two devices in renal impairment patients. The sponsor cross-referenced to a definitive study in the Spiriva Handihaler submission (NDA (b) (4) U00-1289) assessing the effects of renal function on tiotropium pharmacokinetics. The results suggested that impaired renal function may affect the pharmacokinetics of tiotropium. Therefore, the statements concerning the pharmacokinetics of tiotropium in renal impairment patients included in the label of Spiriva Handihaler will also be used for the label of Spiriva Respimat.

The sponsor also referenced to a publish literature (study P98.3499) which measured the lung disposition of fenoterol and flunisolide administrated by the Respimat device using the pharmacoscintigraphic method. The sponsor claimed the device version in this study was A3. About 39% of the fenoterol dose and 45% of the flunisolide dose delivered by the Respimat device was deposited in the lungs. The sponsor claimed the study results could be extrapolated to tiotropium. In the proposed label by the sponsor, it was stated that (b) (4) However, the available data was inadequate to support such a claim in the label because of the different drugs and device version (A3) used in this study (b) (4) (b) (4) (b) (4) Therefore, this statement should be deleted.

2 Question Based Review

2.1 General Attributes of the Drug

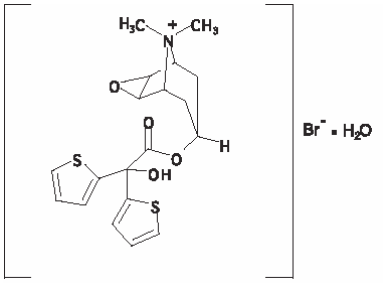
1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Tiotropium bromide monohydrate has been approved for use as inhalation powder with the Handihaler inhalation device (dry powder inhaler; 18 µg tiotropium; NDA 21-395; approved January 30, 2004). Spiriva Respimat consists of tiotropium bromide inhalation spray delivered via the Respimat inhalation device.

Spiriva Respimat has been developed as a new inhalation drug product through a standalone clinical program. However, the majority of the basic properties of tiotropium are dependent on the drug substance. So the sponsor has cross-referenced to the clinical pharmacology studies of Spiriva Handihaler (NDA 21-395). The languages in the labeling text based on these studies are the same between Spiriva Handihaler and Spiriva Respimat. The pharmacokinetic profile of Spiriva Respimat was elucidated in four trials (one Phase I, one Phase II and two Phase III trials) and compared to that of Spiriva Handihaler.

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1α, 2ß, 4ß, 5α, 7ß)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$] nonane bromide monohydrate (Figure 1). 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.



Structural formula for Tiotropium Bromide
Molecular Weight: 490.4
Molecular formula: $C_{19}H_{22}NO_4S_2Br \bullet H_2O$.

The tiotropium inhalation solution for use with the Respimat device is a sterile aqueous solution of tiotropium bromide monohydrate and two excipients, benzalkonium chloride (BAC), and edetate disodium (EDTA). One dose (2 actuations) of Spiriva Respimat provides a delivered dose (22.1 µL of solution) from the mouthpiece of 5 µg of tiotropium (which is equivalent to 6.25 µg of tiotropium bromide monohydrate). Spiriva Respimat Inhalation Spray has the following composition:

Table 1. Composition of Spiriva Respimat

Name of Ingredient	Function	Reference to Standards	Per dose 1 (Label Claim) (mg)	Percentage Formula (g/100ml)	Per cartridge [4] (mg)
Tiotropium [2]			0.005	(b) (4)	
corresponds to Tiotropium bromide monohydrate	Drug substance	In house standard	(b) (4)		
Benzalkonium chloride [3]	Preservative	NF			
Edetate Disodium	Stabilizer	USP			
(b) (4) Hydrochloric acid	(b) (4)	NF			
Water for injection	(b) (4)	USP			
(b) (4)					
Total weight			22.1	100.0	(b) (4)

(b) (4)

3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Tiotropium bromide is developed as a long-acting anticholinergic bronchodilator, around 24 hrs of duration of action (*in vitro* study showed that tiotropium binds to all five muscarinic receptor subtypes and the dissociation from the m_3 receptor seems to be slower than from m_1 and m_2 receptors). Spiriva Respimat is intended for the long-term maintenance treatment of bronchospasm and dyspnea associated with COPD including chronic bronchitis and emphysema.

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

The proposed dosage of Spiriva Respimat is inhalation of 5 µg tiotropium (two inhalations, 2.5 µg tiotropium per inhalation), once daily, with the Respimat inhalation device.

2.2 General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The basic clinical pharmacology properties of tiotropium are dependent on the drug substance. No new studies were conducted regarding the pharmacology for Spiriva Respimat, and the sponsor has cross-referenced to the approved labeling of Spiriva Handihaler for this NDA. The Pharmacokinetic data for Spiriva Respimat are extensively discussed in Section 2.7.1. Summaries of the clinical trials are presented below.

Ten clinical trials were conducted with SPRIVA Respimat (Table 2). A Phase I clinical program evaluated the safety, tolerability and pharmacokinetics of different doses of tiotropium administered via the Respimat inhaler in 36 healthy volunteers (study 205.112). The Phase II clinical program consisted of one multiple-dose, dose-ranging trial of Spiriva Respimat (205.127) taking into consideration previous experience with the Spiriva Handihaler program. The Phase III program consisted of six trials based on three replicate protocols. All trials were randomized and placebo-controlled. Two parallel group trials (205.254 and

205.255) were of 48-weeks duration on treatment; two parallel group trials (205.251 and 205.252) were of 12-weeks duration on treatment vs. active control (pMDI ATROVENT) and two crossover trials (205.249 and 205.250) were of 4-weeks duration on treatment per period vs. active control (Spiriva Handihaler). Further product characterization was performed with a Phase I trial (205.138) addressing safety following accidental ocular exposure of tiotropium in healthy volunteers and a Phase II tolerability trial (205.248) of the Respimat formulation in asthmatic patients. Supporting studies include a Phase IIIb/IV handling trial (215.1357) conducted with Berodual Respimat in patients with COPD, asthma and mixed COPD/asthma conditions and a Phase IIIb/IV 24-week, placebo-controlled study (205.266) conducted with Spiriva Handihaler in COPD patients that evaluated reductions in exacerbations.

Table 2. Summary of clinical studies with Spiriva Respimat

Phase	Trial No	Study Objective and Design	Dosing	No. and Type of Subjects	Duration
I	205.112 (U97-2426)	Safety and tolerability + PK Multiple increasing doses, pl-c, rand	10µg, 20µg, 40µg tiotropium bromide monohydrate o.d. vs. pl via Respimat	36 Healthy subjects	14 days
I	205.138 (U99-1355)	Safety and tolerability after ocular administration pl-c	0.02µg, 0.04µg, 0.08µg, 0.16µg, 0.28µg, 0.40µg tiotropium vs. pl	48 Healthy subjects	Single doses
II	205.127 (U00-0077)	Dose-ranging + PK md, rand, d-b, pg, pl-c and act-c	1.25µg, 2.5µg, 5.0µg, 10.0µg, 20.0µg, tiotropium via Respimat vs. pl vs. Tio HH18 o.d.	202 COPD	3 weeks
II	205.248 (U02-1222)	Safety and tolerability sd, rand, d-b, pl-c, 4-way c-o	Respimat pl (pH=2.7) Respimat pl (pH=3.4) Respimat pl (pH=3.7) vs. CFC-MDI pl	34 Asthmatic	Single doses
III	205.249 (U05-1949) 205.250 (U04-2041) Pooled data (U05-2161) Pooled PK data (U05-2108)	Non-inferiority of tiotropium in Respimat vs. Handihaler +PK md, rand, d-b, d-d, pl-c, act-c, c-o, 4 4-week periods	5µg, 10µg, tiotropium via Respimat vs. pl vs. Tio HH18 o.d.	131 (205.249) 76 (205.250) COPD	4 weeks
III	205.251 (U04-3400) 205.252 (U04-3343) Pooled data (U05-2162)	Comparison of efficacy/safety of tiotropium in Respimat to IB md, rand, d-b, d-d, pg, pl-c, act-c	5µg, 10µg tiotropium via Respimat o.d. vs. pl vs. 36µg IB via pMDI q.i.d.	361 (205.251) 358 (205.252) COPD	12 weeks
III	205.254 (U05-2112) 205.255 (U05-2113) Pooled data (U05-2249)	Efficacy, safety of tiotropium in Respimat vs. pl md, rand, d-b, pg, pl-c	5µg, 10µg tiotropium vs. pl via Respimat o.d.	983 (205.254) 1007 (205.255) COPD	48 weeks
IIIb	205.392 (U07-3356)	Retrospective vital status data collection for prematurely withdrawn patients from 205.254 & 205.255	5µg, 10µg tiotropium vs. pl via Respimat o.d.	456 COPD	48 weeks + 30 days

act-c: active-controlled, d-b: double-blind, c-o: cross-over, d-d: double-dummy, IB: ipratropium bromide, md: multiple dose, o d: once daily, pg: parallel group, PK: pharmacokinetics, pl: placebo, pl-c: placebo controlled, q i d : four times daily, rand: randomized, sd: single dose, Tio HH 18: tiotropium powder 18µg via Handihaler

Clinical Pharmacology Studies

The pharmacokinetics of Spiriva Respimat was evaluated in four clinical trials which used two different versions of the Respimat® inhaler (see Table 3). The sponsor also referred to a published literature to support a statement for (b) (4) Spiriva Respimat in the proposed labeling (P98.3499). Individual results of these studies are summarized in Appendix 4.2.

Table 3. Clinical Studies in the Spiriva Respimat Program that included Pharmacokinetic Assessments

Trial [report no.]	Respimat® Inhaler Version	Study Description
205.112 [U97-2426]	A3	Multiple increasing dose tolerance study in healthy volunteers
205.127 [U00-0077]	A3	Dose ranging study in COPD patients
205.249 [U05-1949]	A4	Efficacy and safety comparison of tiotropium delivered by Respimat® and Handihaler® in COPD patients
205.250 [U04-2041]	A4	Efficacy and safety comparison of tiotropium delivered by Respimat® and Handihaler® in COPD patients

2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Tiotropium is an anticholinergic bronchodilator. In all Phase III clinical trials of Spiriva Respimat, the bronchodilator efficacy was primarily determined by trough FEV_1 (Forced Expiratory Volume in 1 sec) response; i.e. FEV_1 measured approximately 24 hours after the previous treatment dose (approximately 10 min before the final dose in the clinic). In addition, in the 1-year trials three further primary endpoints were investigated and sequentially analyzed to more fully characterize the clinical benefits of Spiriva Respimat, including:
(1) Health-related quality of life (HRQoL), which is measured by St. George's Respiratory Questionnaire (SGRQ). The SGRQ is a disease-specific, 76-item questionnaire comprising three domains: symptoms, activity and impacts, which together form the total score assessing the overall heath status on a weighted scale from zero (no distress) to 100 (worst possible distress).
(2) Dyspnea. Dyspnea is measured by the Mahler baseline and transition dyspnea indices (BDI)/TDI, which includes the components of functional impairment, magnitude of task and magnitude of effort. The BDI is used to characterize a patient's baseline status whereas the TDI is sensitive to changes from this baseline. The scores for each of these three domains are summed to create a TDI focal score.
(3) Reduction in COPD exacerbations. Currently there is no standardized definition of COPD exacerbation. Based on the available information, a COPD exacerbation was defined a priori in the protocol of trials by the sponsor. This definition takes into account the worsening and/or new onset of symptoms, the duration of symptoms and the need for intensifying bronchodilator therapy and/or additional treatment requiring antibiotics and/or oral corticosteroids.

Secondary endpoints and the long term effectiveness included forced vital capacity (FVC), airway resistance (Raw), peak expiratory flow rate (PEFR), pulmonary function, COPD symptom scores, physician's global evaluation (PGE), and patient's global rating (PGR).

3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The parent compound, tiotropium, is the active moiety. Tiotropium concentration in plasma or urine was measured by High Performance Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

methods. The LC-MS/MS assay for tiotropium after solid phase extraction and further purification by liquid/liquid ion pair extraction is able to measure concentrations down to 2.5 pg/mL and 10 pg/mL in human plasma and urine respectively, permitting serial monitoring following the small daily inhaled dose of 5 µg tiotropium from the Respimat inhaler.

4. Exposure-response

1) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Since Spiriva Respimat is a formulation for inhalation that exerts local effects in the lungs, the systemic exposure of tiotropium is not a determinant of efficacy. The dose selection for Phase III trials was based on a Phase I tolerability, chronic dose-ranging and pharmacokinetic trial in 36 healthy subjects (205.112) and a Phase II 3-week, multiple-dose, parallel groups pharmacodynamic and pharmacokinetic dose-ranging trial in 202 COPD patients (205.127).
In the Phase I trial three doses of Spiriva Respimat were studied (8, 16 and 32 µg) for 14 days and compared to placebo. Following inhalation of randomized treatment, airway resistance (Raw), a sensitive measure of large airway patency, was measured using body plethysmography. A small (~20%) but sustained decrease in Raw was observed following tiotropium administration, which was not dose-dependent.
In the Phase II trial, five doses of Spiriva Respimat were studied (1.25, 2.5, 5, 10 and 20 mcg) and compared to Spiriva Handihaler (18 mcg) as positive control, and two placebo groups (Respimat and Handihaler), and the result was summarized I Table 4. The primary endpoint was FEV1 at the end of the dosing interval (trough) on day 21. Doses of Spiriva Respimat 1.25 and 2.5 mcg were not found to be significantly different from the placebo. From Spiriva Respimat 5 µg dose on up, the mean change from baseline trough FEV1 seems to have reached a plateau: 5 mcg (152 mL, $p<0.05$), 10 mcg (131 mL; $p=0.06$) and 20 mcg (146 mL, $p<0.05$). The Spiriva HNDIHALER 18 mcg dose resulted in the greatest change from baseline (230 mL, $p<0.05$); this response was unusually high compared to those seen in previous trials. Spiriva Respimat 5, 10 and 20 mcg doses were effective and showed similar efficacy. Therefore, Spiriva Respimat 5, 10 mcg doses were chosen for the Phase III trials.

Table 4. Adjusted mean change of FEV1 from baseline in liters on Day 21 after once daily inhalation at various doses by Respimat or 18 µg by Handihaler

Device	Respimat®						HandiHaler®	
Dose (µg)	1.25	2.5	5	10	20	Pbo - R	18	Pbo - H
Total Randomized (N)	25	28	25	26	26	24	25	23
Trough FEV_1(L)	0.10	0.05	0.15*	0.13	0.15*	0.02	0.23**	-0.09
Average! FEV_1(L)	0.21*	0.18	0.30**	0.22*	0.30**	0.05	0.32**	-0.05
Trough FVC (L)	0.20	0.10	0.27	0.20	0.25	0.11	0.32**	-0.09
Average! FVC (L)	0.35	0.27	0.42*	0.36	0.51*	0.16	0.47**	-0.05

* Significantly different from placebo (* $p<0.05$, ** $p \leq 0.001$)
! Average over four hours post dose

In the Phase III trial, Spiriva Respimat (5 and 10 mcg) was compared to Spiriva Handihaler (18 mcg) and placebo. The primary endpoint was trough FEV1 response assessed before the final administration of randomized treatment. Both Spiriva Respimat doses of 5 mcg and 10 mcg were shown to be statistically significantly superior to placebo. The higher dose (10 mcg) had a numerical (~15 mL) but not statistically significant advantage over the lower dose (5 mcg). All three patient outcome measures (health status, dyspnea and reduction in COPD exacerbations) were statistically significantly improved by both doses compared to placebo with no apparent incremental benefit of the10 mcg dose over the 5 mcg dose.

2) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

No clear dose-response relationship was established except for dry mouth, the most common adverse effect for anti-cholinergic drugs. In both healthy volunteers and COPD patients, it was demonstrated that the incidence of dry mouth increased with increased dose.

3) Does this drug prolong the QT or QTc interval?

The sponsor cross-referenced to the approved labeling of Spiriva Handihaler® on QT/QT prolongation. In a multi-center, 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 30–60 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 studies with Spiriva did not detect an effect of the drug on QTc intervals.

ECGs and Holter monitoring were also undertaken in the clinical program of Spiriva Respimat. However, no signal was seen suggesting a safety concern with tiotropium on electrocardiology.

4) Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The marketing dose selection for Spiriva Respimat (5 mcg) is based on the data from the Phase III trials. In all Phase III trials the primary endpoint was trough FEV1 response assessed before the final administration of randomized treatment. Both Spiriva Respimat doses of 5 mcg and 10 mcg were shown to be statistically significantly superior to placebo. The higher dose (10 mcg) had a numerical (~15 mL) but not statistically significant advantage over the lower dose (5 mcg). All three patient outcome measures (health status, dyspnea and reduction in COPD exacerbations) were statistically significantly improved by both doses compared to placebo with no apparent incremental benefit of the 10 mcg dose over the 5 mcg dose. The pharmacokinetic data showed comparable systemic exposure for Spiriva Respimat 5 mcg dose and Spiriva Handihaler 18 mcg dose, whereas higher systemic exposure was obtained following inhalation of Spiriva Respimat 10 mcg dose. And the most sensitive anticholinergic side effect, 'dry mouth', was doubled following treatment with Spiriva Respimat 10 mcg dose. Therefore, the Spiriva Respimat 5 mcg dose was selected for marketing.

5. What are the PK characteristics of the drug?

1) What are the single dose and multiple dose PK parameters?

Due to limited PK sampling time points in these trials, some PK parameters (e.g. $t_{1/2}$) could not be calculated for Spiriva Respimat. Therefore, it is difficult to make a comparison on PK parameters between single and multiple doses. Based on available data, maximum plasma concentration was observed at 5 to 10 min after inhalation, the first plasma sampling time point, after a single or multiple inhalations. The unchanged tiotropium amount excreted in urine was generally dose-proportional in all dose groups after a single or multiple inhalations.

2) How does the PK of the drug in healthy volunteers compare to that in patients?

In both young healthy volunteers and COPD patients, maximum tiotropium plasma concentrations were observed five to ten minutes (the first time point after dose) most of the time after inhalation, then the plasma drug concentration declined quickly. C_{max}, plasma AUC and unchanged amount excreted in urine increased with dose in a proportional way in both young healthy volunteers and COPD patients. However, due to limited sampling time points, inconsistent doses and sampling schemes in trials between healthy

volunteer and COPD patients, it is difficult to make any further comparison on pharmacokinetics from the Spiriva Respimat trials.

From the review for Spiriva Handihaler, it was mentioned that plasma concentrations (e.g., C_{5min}, AUC) and urinary excretion of tiotropium in urine were lower in patients with COPD or asthma compared those in healthy subjects. In general, absorption of tiotropium could be affected by the disease state (COPD/asthma). However, this effect is hard to separate from the confounding effects of age.

3) What are the characteristics of drug absorption?

Following inhalation of Spiriva Respimat by young healthy volunteers and COPD patients, maximum tiotropium plasma concentrations were observed five to ten minutes most of the time after inhalation, then the plasma drug concentration declined quickly. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastrointestinal tract; Oral solutions of tiotropium have an absolute bioavailability of 2–3% (NDA (b) (4)).

Tiotropium has very poor oral bioavailability (about 2-3%, NDA (b) (4) so drug amount absorbed in the GI tract could be ignored. It was known from a former study in NDA (b) (4) that after intravenous administration of 14.4 µg tiotropium, 73.6% of the dose is excreted unchanged in urine (205.105, NDA (b) (4) (b) (4). The sponsor claimed since study 205.112 revealed that after inhalation between 20.1% and 29.4% of the inhaled dose was excreted unchanged in urine on day 7 and 14, it could be extrapolated that about 33% of the inhaled tiotropium dose reached the systemic circulation. This statement was not accurate since the extrapolation was based on the assumption that the pharmacokinetic steady state was reached by day 7, which could not be demonstrated by the study results. In addition, the device used in this study was version A3, and no bioequivalence study has been conducted to compare the performance of this version and the final marketing version (A5). Therefore, the data was not sufficient to support the sponsor's claim.

From a published literature (Study P98.3499), it was found about 39% of the fenoterol dose and 45% of the flunisolide dose delivered by the Respimat device was deposited in the lungs. The sponsor claimed the lung deposition in this study was assessed by γ-scintigraphy, which primarily depends on the inhaler and formulation characteristics (aqueous for both fenoterol and tiotropium) and not on drug substance characteristics. Therefore, the study results could be extrapolated to tiotropium. In the proposed label by the sponsor, it was stated that (b) (4) (b) (4). However, the data submitted could not support such a statement. The physical-chemical characteristics of drug may also affect of the lung deposition for the same device. Actually, the percentage of dose deposited in the lungs was different between the two test drugs in this study (39% for fenoterol and 45% for flunisolide). In addition, the sponsor claimed the device version in this study was A3. But no bioequivalence study has been conducted to compare the performance of this version and the final marketing version (A5). Moreover, determination of lung disposition by using the pharmacoscintigraphic method is generally not acceptable since radio-labeling of the drug substance may affect disposition of the drug. Therefore, this statement should be deleted.

4) What are the characteristics of drug distribution?

The sponsor cross-referenced to the approved labeling of Spiriva Handihaler (NDA (b) (4) Tiotropium shows a volume of distribution of 32 L/kg indicating that the drug binds extensively to tissues. The drug is bound by 72% to plasma proteins.

After Spiriva Respimat inhalation, peak tiotropium plasma levels at steady state in COPD patients were 10.5-11.7 pg/mL when measured 10 minutes after administration of a 5 mcg dose via the inhalation spray and decreased rapidly. Steady state trough plasma concentrations were 1.49-1.68 pg/mL. (study 205.249, 205.250). 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 readily penetrate the blood-brain barrier.

The sponsor claimed in the label that [redacted] Since only very limited plasma time points were taken in COPD patients (pre-dose, 10 min, 60 min, and 6 hr), the data was insufficient [redacted].

5) Does the mass balance study suggest renal or hepatic as the major route of elimination?

The sponsor cross-referenced to the approved labeling of Spiriva Handihaler (NDA [redacted] No mass balance study of tiotropium was conducted in human. The sponsor stated it was not possible due to the combination of analytical problems and the PK characteristics of tiotropium (i.e., large Vss, long t1/2, metabolism play a minor role in the excretion of tiotropium, inhalation route of administration, etc.). However, following an i.v. infusion in healthy young volunteers, 73.6% of the dose is excreted in urine as unchanged drug. The remaining approximately 26% of the dose undergo non-enzymatic hydrolysis and CYP 450 metabolism. This result suggests renal is the major route of elimination for tiotropium.

6) What are the characteristics of drug metabolism?

The sponsor cross-referenced to the approved labeling of Spiriva Handihaler (NDA [redacted] Results from an i.v. infusion study suggest renal is the major route of elimination for tiotropium, 73.6% of the dose is excreted in urine as unchanged drug. Since mass balance study was not conducted in human, tiotropium metabolism was investigated using *in vitro* studies. 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 (73.6% of an intravenous dose is excreted unchanged in the urine, leaving about 26% 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.

7) What are the characteristics of drug excretion?

The sponsor cross-referenced to the approved labeling of Spiriva Handihaler (NDA [redacted] Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers with an inter-individual variability of 22%. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). The remainder of the dose was mainly non-absorbed drug in the gut which is eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating active secretion into the urine. The terminal elimination half-life of tiotropium is between 5 and 6 days following dry powder (Handihaler) inhalation.

The terminal elimination half-life of tiotropium delivered by Spiriva Respimat could not be calculated due to limited pharmacokinetic sampling points. After inhalation of tiotropium by Respimat in health volunteers, urinary excretion is 20.1- 24.5% of the dose at day 14.

8) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

After a single inhalation of Spiriva Respimat in health volunteer, C_{max} were 4.23 pg/mL (37.8% CV), 12.5 pg/mL (28.9% CV), and 22.1 pg/mL (60.2% CV) at 8, 16, and 32 µg dose, which generally increased dose-proportionally. On day 7 and day 14, C_{max}, C_{min}, and $AUC_{0\text{-}20min}$ also generally increased dose-proportionally. (See study 205.112 summary for details.)

In study 205.249, after multiple once daily inhalations in COPD patients, C_{max} were 11.7 pg/mL (99.1% CV), 29.2 pg/mL (104% CV) at 5 and 10 µg dose on day 28, while C_{min} were 1.49 pg/mL (38.4% CV), 3.03 pg/mL (102% CV); and $AUC_{\zeta,ss}$ were 63.5 pg·h/mL (52.8% CV) and 148 pg·h/mL (83.2% CV), respectively. In study 205.250, after multiple once daily inhalations in COPD patients, C_{max} were 10.5 pg/mL (114% CV), 22.7 pg/mL (81.8% CV) at 5 and 10 µg dose on day 28, while C_{min} were 1.68 pg/mL (71.3% CV), 3.32 pg/mL (91.6% CV); and $AUC_{\zeta,ss}$ were 67.4 pg·h/mL (69.9% CV) and 143 pg·h/mL (61.8% CV), respectively. The result showed that the drug concentration increased in a dose-proportional way at steady state in COPD patients.

9) How do the PK parameters change with time following chronic dosing?
Tiotropium showed a two- to three-fold accumulation in plasma on day 14 after repeated once daily inhalation dosing via Spiriva Respimat in healthy volunteer (205.112). The sponsor claimed in healthy volunteer, only minor changes in tiotropium plasma concentrations and urinary excretion were observed after day 7, indicating that pharmacokinetic steady state was essentially achieved by day 7. According to the urine excretion data, the tiotropium amount excreted in urine was similar between day 7 and day 14. However, the plasma concentrations continued to increase between day 7 and day 14 according to Figure 1. More importantly, the trough drug concentration (C_{pre}) doubled between day 7 and day 14 at 16 and 32 µg dose groups (Figure 2), indicating the plasma steady state was not reached on day 7.

Figure 1. Geometric mean of tiotropium plasma concentration following once daily inhalation via the Respimat inhaler (version A3) at different doses (8 µg, 16 µg, 32 µg tiotropium), normalized to the recommended dose of Spiriva Handihaler (18 µg)

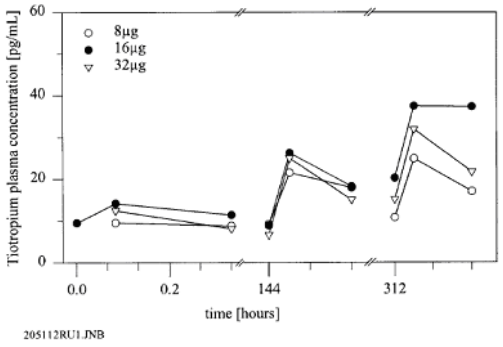
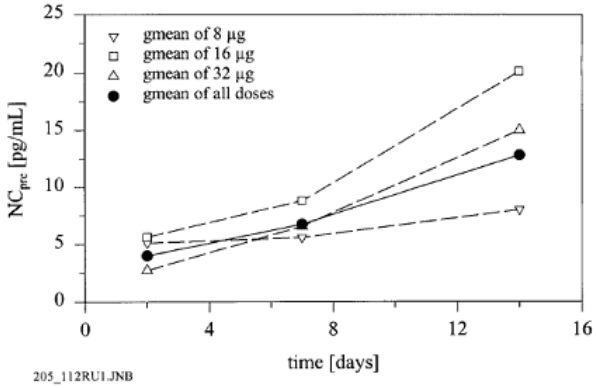


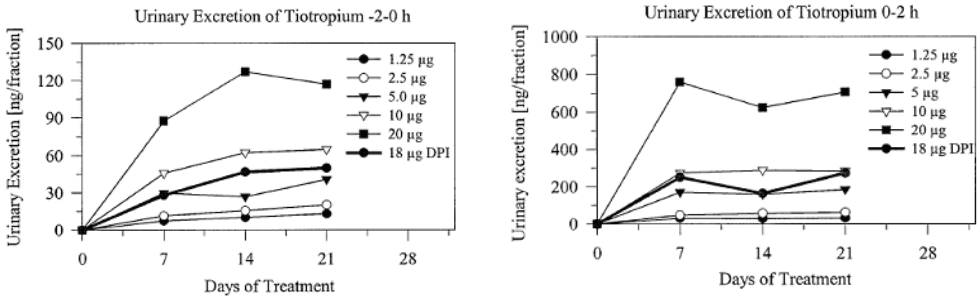
Figure 2. Geometric mean of trough tiotropium concentration before inhalation on day 2, 7 and 14 following 8, 16, and 32 µg once daily dose via the Respimat inhaler (version A3), normalized to the recommended dose of Spiriva Handihaler (18 µg)



According to the Handihaler data, the half-life after dry-powder inhalation was about 5-6 days, and pharmacokinetic steady state was reached after 2–3 weeks with no further accumulation. Change of device from Handihaler to Respimat will only affect absorption of the drug, it is not expected that it will affect drug elimination. In addition, tiotropium was rapidly absorbed in blood for both the Handihaler and Respimat device with T_{max} around 5 min. Therefore, it is reasonable to expect to that the half-life and time to steady state will be similar between the two devices. However, due to the limited sampling points, half-life of tiotropium delivered by Respimat could not be calculated. Since the last pharmacokinetic sampling time was on day 14, it was difficult to access when the pharmacokinetic steady state was reached.

The sponsor also claimed that that from day 7 onwards no change in tiotropium urinary excretion was observed in COPD patients (study 205.127), confirming that pharmacokinetic steady state was essentially reached by day 7. Figure 3 summarized the urinary excretion with time for all dose groups in study 205.127. According to $A_{e,-2-0\ h}$ data, it appeared that amount excreted in urine was still increasing after day 7. In addition, no plasma samples were taken in study 205.127. Along with the results in study 205.112, these data were not sufficient to support the claim that pharmacokinetic steady state was essentially reached by day 7.

Figure 3. Geometric mean of tiotropium urinary excretion with time after once-daily inhalation by Respimat device (days with reverse excretions pattern excluded)



2.3 Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety response?

1) Elderly

For data collected in the two Studies 205.249 and 205.250 with identical protocols, a pooled analysis was performed for tiotropium pharmacokinetics in special populations such as elderly patients. For the two tiotropium doses (5 and 10 µg) delivered by the Respimat inhaler, there was a trend towards lower $AUC_{0-4,ss}$ values in patients older than 70 years. The geometric mean $AUC_{0-4,ss}$ values for 5 µg and 10 µg tiotropium delivered with the Respimat inhaler were 18.7 pg·h/mL (CV: 97.5%) and 51.0 pg·h/mL (CV: 92.5%) in patients younger than 58 years; and declined to 16.9 pg·h/mL (CV: 121%) and 34.2 pg·h/mL (CV:78.9%), respectively, in patients older than 70 years. There were only slight differences observed in $AUC_{0-4,ss}$ values between patients younger than 58 years and patients at the age of 58 – 70 years. Similar trends were observed for C_{max}, which was 11.1 pg/mL (CV: 127%) and 31.1 pg/mL (CV: 93.5%) in patients younger than 58 years; and declined to 9.19 pg/mL (CV: 128%) and 17.3 pg/mL (CV: 79.7%) in patients older than 70 years. For 18 µg tiotropium delivered by the Handihaler, the $AUC_{0-4,ss}$ and C_{max} values were similar across the three different age groups.

Urinary excretion after inhalation of 5 µg and 10 µg tiotropium with the Respimat inhaler decreased from 11.1% (CV: 84.7%) and 11.6% (CV: 106%) of the inhaled dose in patients younger than 58 years to 7.71%

(CV: 94.7%) and 6.71% (CV: 66.0%) in patients older than 70 years, respectively. There was no difference between patients younger than 58 years and patients at the age of 58 to 70 years. When tiotropium was administered via the Handihaler, urinary drug excretion only decreased from 2.25% (CV: 55.7%) in patients younger than 58 years to 2.02% (CV: 95.9%) in patients older than 70 years. There was no difference in urine excretion of unchanged drug between patients younger than 58 years compared to patients at the age of 58 to 70 years.

The sponsor also cross-referenced to the approved labeling of Spiriva Handihaler (NDA (b) (4) Since tiotropium is predominantly eliminated by renal excretion, advanced age is associated with a decrease of tiotropium renal clearance. Study 205.133 evaluated age factor on PK of tiotropium in patients with COPD by using Spiriva Handihaler (18 mcg) for 14 days, and it was shown that renal clearance of tiotropium was significantly lower in the elderly patients (163 mL/min in COPD patients >70 years) compared with younger patients (326 mL/min in COPD patients <58 years). C_{5min} and AUC_{0-4h} were 59% and 43% higher in the elderly than the younger COPD patients on Day 14. However, age factor on the PK of tiotropium can not be confirmed due to inter- and intra-individual variability.

Since the effects of age on pharmacokinetics are mainly dependent on the drug substance rather than the inhalation device, and as the systemic exposure is comparable for Respimat 5 µg and Handihaler 18 µg, similar changes in terms of tiotropium plasma concentrations and drug clearance can be expected between the two devices in elderly populations. Therefore, the statements concerning the pharmacokinetics of tiotropium in geriatric patients in the label of Spiriva Handihaler will also be used for the label of Spiriva Respimat.

2) Pediatric patients

Pharmacokinetic data in subjects under an age of 18 years are not available. Spiriva Respimat is intended for use in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not normally occur in children. The safety and effectiveness of Spiriva in pediatric patients have not been established.

3) Race

The ethnicity factor was not analyzed, probably because of the highly biased race composition in the clinical trials. In study 205.112, all the subjects were Caucasians. In study 205. 249 and 205.250, 96 out of the 98 subjects with pharmacokinetic data were Caucasians.

According to the NDA submission package for Spiriva Handihaler, urinary excretion data in Study 205.201 indicated no clinically significant difference between Caucasian and African-American COPD patients. However, the majority of patients were Caucasians (95 Caucasians vs. 9 African-Americans), therefore, the ethnicity factor is not conclusively confirmed.

4) Renal impairment

For data collected in the two Studies 205.249 and 205.250 with identical protocols, a pooled analysis was performed for pharmacokinetics in special populations such as patients with renal impairment. An increase in tiotropium plasma concentrations was observed in COPD patients with impaired renal function in comparison to those with normal renal function. $AUC_{0-4,ss}$ values increased by 26% and 76% when comparing COPD patients with mild and moderate impaired renal function to those with normal renal function after inhalation of 10 µg tiotropium with the Respimat inhaler. A similar trend was observed for C_{max}. After inhalation of 10 µg tiotropium with the Respimat inhaler, C_{max} were 24.8 pg/mL (CV: 93.3%), 28.4 pg/mL (CV: 90.0%) and 42.9 pg/mL (CV: 101%) in patients with normal renal function and mild and moderate renal impairment, respectively. The other two dose groups, 5 µg via Respimat inhaler and 18 µg via the Handihaler inhaler, showed similar trends. The urinary excretion of tiotropium also changed with impaired renal function. Tiotropium excretion in urine decreased with a lower renal function. By comparing the ratio of urinary tiotropium excretion in moderate impairment patients to normal function patients, the decrease in tiotropium urinary excretion was more pronounced after inhalation of 5 µg tiotropium with the Respimat inhaler (0.538) and 18 µg with the Handihaler (0.470) than after inhalation of 10 µg with the Respimat inhaler (0.939).

The sponsor cross-referenced to the approved labeling of Spiriva Handihaler (NDA (b) (4) In NDA21-395, PK of tiotropium was compared in four different groups of subjects with normal to severe renal impairment following an intravenous dose of 4.8 µg of tiotropium (Study 205.134). And the result is summarized in Table 5. It was found that mild renal impairment (CrCl 50–80 mL/min) increased tiotropium plasma concentrations (39% increase in AUC_{0-4h} after intravenous infusion). In COPD patients with moderate to severe renal impairment (CrCl <50 mL/min), the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82% increase in AUC_{0-4h}).

Table 5. Geometric mean (% gCV) tiotropium pharmacokinetic parameters after intravenous infusion of 4.8 µg tiotropium to subjects with varying degrees of renal impairment.

	CL_{CR} [mL/min]		C_{max} [pg/mL]	$AUC_{0-4\,h}$ [pg.h/mL]	Ae_{0-4h} [% of dose]	$Ae_{0-\infty}$ [% of dose]	$t_{½}$ [days]	CL_{ren} [mL/min]
>80 mL/min	108	gMean	147	55.5	30.2	60.1	4.03	435
n=6		(%gCV)	(21.3)	(16.2)	(11.4)	(17.7)	(19.1)	(12.7)
50-80 mL/min	70.4	gMean	200	77.1	23.7	59.3	5.02	246
n=5		(%gCV)	(30.1)	(20.1)	(20.1)	(14.4)	(45.1)	(34.8)
30-50 mL/min	44.1	gMean	223	101	15.1#	39.9	3.96	124
n=7		(%gCV)	(26.5)	(29.8)	(31.4)	(34.5)	(32.3)	(29.9)
<30 mL/min	23.5	gMean	223	108	11.0*	37.4	5.95	85.7
n=6		(%gCV)	(17.5)	(27.3)	(14.6)	(10.2)	(29.3)	(35.5)

#: n=5, *: n=3

Since the pharmacokinetic properties in renal impairment populations are mainly dependent on the drug substance rather than the inhalation device, and as the systemic exposure is comparable for Respimat 5 µg and Handihaler 18 µg, similar changes in terms of tiotropium plasma concentrations and drug clearance can be expected between the two devices in renal impairment populations. Therefore, the statements concerning the pharmacokinetics of tiotropium in renal impairment patients in the label of Spiriva Handihaler will also be used for the label of Spiriva Respimat.

5) Hepatic impairment

No study was performed in patients with hepatic impairment. The sponsor cross-referenced to the approved labeling of Spiriva Handihaler (NDA (b) (4) Tiotropium was predominantly cleared by renal excretion (~74% of the dose is excreted unchanged in urine in healthy young subjects) and by simple non-enzymatic ester cleavage. Based on the low extent of overall metabolism of the drug (<30%), a clinically significant change due to hepatic dysfunction is not anticipated.

6) Pharmacogenetics

Tiotropium was predominantly cleared by renal excretion (~74%). Therefore, approximately 26% of the dose is expected to be eliminated by metabolism. In vitro data showed CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. No genotyping study was conducted in this NDA submission.

In the NDA submission package for Spiriva Handihaler (NDA (b) (4) four subjects from study 205.222 were identified by their genotype. It was shown that AUC_{0-4h} was 33% higher in the 2D6 poor metabolizers compared to the 2D6 extensive metabolizers. Based on the low extent of overall metabolism of the drug (<30%) and low tiotropium plasma concentrations after 5 µg solution inhalation dose, along with the fact that the exposure is not directly linked to efficacy for a locally acting drug, PK change shown in 2D6 poor metabolizers does not warrant the lower dosing regimen.

7) Pregnancy and lactation

No adequate and well-controlled studies of tiotropium have been conducted in pregnant women. Spiriva should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8) Other human factors that are important to understand the drug's efficacy and safety

None

2.4 Extrinsic Factors

1. What extrinsic factors (drugs herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

The influence of above mentioned extrinsic factors on the PK and/or PD were not evaluated.

2. Drug-drug interactions

1) Is the drug a substrate of CYP enzymes?

The sponsor cross-referenced to the approved labeling of Spiriva Handihaler (NDA (b) (4) Since mass balance study was not conducted in human, tiotropium metabolism was investigated using *in vitro* studies. 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 (73.6% of an intravenous dose is excreted unchanged in the urine, leaving about 26% 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.

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

According to NDA (b) (4), *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations (1 µmol/L) does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4. Based on low plasma concentrations after 5 µg solution inhalation dose, tiotropium is not expected to inhibit these CYP450 in human.

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

According to NDA (b) (4), cyclosporine (competitive inhibitor of p-glycoprotein) did change tiotropium uptake in CaCo2 cells. Therefore, tiotropium does not appear to be a p-glycoprotein substrate.

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

The sponsor cross-referenced to the approved labeling of Spiriva Handihaler (NDA (b) (4) Since tiotropium renal clearance is higher than creatinine clearance, it is expected to be actively secreted by renal tubule. Therefore, interaction study was carried out to elucidate the effect of concomitant administration of tiotropium (iv infusion) with cimetidine (400 mg tid)/ranitidine (300 mg qd), which are also actively secreted by renal tubule (Study 205.222). However, no clinically significant interaction occurred between tiotropium and cimetidine or ranitidine.

2.5 General Biopharmaceutics

1. What are the solubility and permeability of tiotropium?

The aqueous solubility of the compound is about (b) (4) at room temperature, independent of pH. The drug substance is more soluble in polar organic solvents, such as methanol and dimethyl sulfoxide, but practically insoluble in non-polar solvents.

No study was conducted to determine the permeability of tiotropium. Tiotropium is a quaternary ammonium compound and was poorly absorbed from the gastrointestinal tract (oral bioavailability is about 2-3%), but was well absorbed from the lung. As per the sponsor suggested, the difference might be due to the fact that absorption via the gut requires penetration of several cell layers with tight junctions, while absorption via the lung is facilitated by the very few membranes that have to be penetrated to reach the systemic circulation. Therefore, tiotropium is expected to be a drug with poor permeability.

2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trials?

Three versions of the Respimat device (A3, A4 and A5) were used in the development program of Spiriva Respimat. The A3 device was used in all the Phase I and II trials; the A4 device was used in the six Phase III trials; and the A5 device is the inhalation device intended for marketing. (b) (4) The A5 inhaler is intended for use with a single cartridge for 30 days and differs from the A4 version only in so much as it has a locking mechanism that engages following the administration of the declared number of actuations, a turquoise cap color and an improved design of the dose indicator. The sponsor indicated that as agreed with the FDA no clinical bridging trials were conducted between the A4 inhaler, used in the Phase III trials, and the A5 inhaler, intended for marketing, because the two devices deliver identical doses of the same formulation and the changes to the A5 device do not influence the delivered volume, spray characteristics or concentration of delivered medication.

3. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The sponsor cross-referenced to NDA21-395. Oral solutions of tiotropium have an absolute bioavailability of 2–3%. The food effect on tiotropium absorption has not been studied. In the labeling for both Spiriva Handihaler and Spiriva Respimat, it is stated that (b) (4) Tiotropium is mainly absorbed into the systemic circulation via lung, and it has very poor oral bioavailability (about 2-3% for oral solution). Although food is not likely to affect the lung absorption, its effect on the oral absorption is not clear. Therefore, this statement should be deleted.

2.6 Analytical Section

1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Tiotropium was quantified by a validated LC-MS/MS assay method. A LC-MS/MS assay for determination of tiotropium plasma and urine concentration was submitted in NDA (b) (4), which was able to measure concentrations down to 5 pg/mL in human plasma and 10 pg/mL in human urine. Later the sponsor decided to lower the limits of quantification (LLOQ) to 2.5 pg/mL for plasma samples. Compared to the original method, the new method used the [D_3]-tiotropium as the internal standard, and a solid phase extraction step was included in the in the plasma sample preparation. In addition, a new LC-MS/MS system was used in the analysis. Besides these differences, the materials and methods remained the same. A revalidation of the modified calibration range was performed for the new method, and the results are summarized in Table 6.

The performance of the assay validation was acceptable as evidenced by QC sample precision and accuracy within ± 15%.

Table 6 Revalidation results of the tiotropium quantification by LC-MS/MS in human plasma

Parameter	Result
Calibrated range [pg/mL]	2.50 - 150
Defined LLOQ [pg/mL]	2.50
Linearity (mean r^2 of the std. curves)	0.99494
Precision (cv %) at the lowest calibrator (2.50 pg/mL)	12.72
Accuracy (bias %) at the lowest calibrator (2.50 pg/mL)	4.52
Precision (cv %) at the LLOQ QC (2.50 pg/mL)	8.38
Accuracy (bias %) at the LLOQ QC (2.50 pg/mL)	2.66

The sample analysis performance in individual study was summarized in Table 7; the results are acceptable as evidenced by QC sample precision and accuracy within ± 15%.

Table 7. Precision and accuracy of tiotropium quantification by LC-MS/MS in human plasma and urine

	205.102		205.127	205.249		205.250	
	Plasma	Urine	Urine	Plasma	Urine	Plasma	Urine
Precision (%)	8 8	6 4	4 1	13 4	8 2	7 9	6 2
Accuracy (± %)	3 3	5 6	11 5	6 8	6 2	9 4	1 3

3 Detailed Labeling Recommendations for Clinical Pharmacology Section

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 were dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

12.2 Pharmacodynamics

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 30–60 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 studies with SPIRIVA did not detect an effect of the drug on QTc intervals.

12.3 Pharmacokinetics

SPIRIVA RESPIMAT is administered as an inhalation spray. (b) (4) Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption

~~Following inhalation of the solution by young healthy volunteers, urinary excretion data suggest that approximately 33% of the inhaled dose reaches the systemic circulation.~~ (b) (4) ~~Food is not expected to influence the absorption of tiotropium for the same reason.~~ Oral solutions of tiotropium have an absolute bioavailability of 2–3%. The effect of food on tiotropium absorption has not been studied. At steady state, peak tiotropium plasma levels in COPD patients were 10.5-11.7 pg/mL when measured at 10 minutes, the first blood sampling time after administration of a 5 mcg dose via Spiriva Respimat. Steady state trough plasma concentrations were 1.49-1.68 pg/mL. ~~Maximum tiotropium plasma concentrations were observed five minutes after inhalation.~~

Distribution

(b) (4) 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 readily penetrate the blood-brain barrier.

(b) (4) *Metabolism*

The extent of (b) (4) 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.

Elimination

The terminal (b) (4) half-life of tiotropium is between 5 and 6 days following dry powder inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers (b) (4) . ~~After chronic once-daily inhalation of the inhalation solution by COPD patients, pharmacokinetic steady state was reached on day 7 with no accumulation thereafter.~~

(b) (4) *Population*

Geriatric ~~Patients~~

(b) (4)

(b) (4)

Hepatically impairmented Patients

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. (b) (4)

(b) (4)

(b) (4)

Gender and Race The effect of gender and race on the pharmacokinetics of Spiriva Respimat has not been studied.

Drug-Drug Interactions

Cimetidine and Ranitidine
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. Therefore, no clinically significant interaction occurred between tiotropium and cimetidine or ranitidine.

4 Appendix

4.1 Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21-936	**Brand Name**	Spiriva Respimat
OCPB Division (I, II, III)	II	**Generic Name**	Tiotropium Bromide Inhalation Spray
Medical Division	DPAP	**Drug Class**	Anticholinergic
OCPB Reviewer	Sandra Suarez-Sharp	**Indication(s)**	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
OCPB Team Leader	Wei Qiu	**Dosage Form**	solution
PM Reviewer		**Dosing Regimen**	Adults (b) (4) (b) (4) 2 sprays per nostril, twice daily
Date of Submission	November 16, 2007	**Route of Administration**	Oral Inhalation
Estimated Due Date of OCPB Review	May 2008	**Sponsor**	Boehringer Ingelheim
PDUFA Due Date	September 16, 2008	**Priority Classification**	10 months
Division Due Date	February 2007		

Clin. Pharm. 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**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				

multiple dose:	X	2		**Study 205.112/(U97-2426)**: A multiple increasing dose tolerance study after inhalant administration of 1 x 10 µg, 1 x 20 µg and 1 x 40 µg/24 h of BA 679 BR-BINEB for 14 days in healthy volunteers. **Study P98-3499:** This study was conducted to compare the lung deposition with the Respimat device vs conventional metered dose inhalers with and without spacer.
Patients-				
single dose:				
multiple dose:	x	3		**205.127 [U00-0077]:** Dose ranging study in COPD patients. **205.249 [U05-1949]:** Efficacy and safety comparison of tiotropium delivered by Respimat® and HandiHaler® in COPD patients. **205.250 [U04-2041]:** Efficacy and safety comparison of tiotropium delivered by Respimat® and HandiHaler® in COPD patients
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:				
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		**Study US5-2108/205.9991:** This consist of a pharmacokinetic meta-analysis for tiotropium bromide based on data obtained from patients with chronic obstructive pulmonary disease (COPD) was performed by combining plasma and urine data from studies 205.249 [U05-1949] and 205.250 [U04-2041].
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:				

Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
QTC STUDIES (PHASE 1)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	x	**6**		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. There are no comments to the sponsor at this time
QBR questions (key issues to be considered)		**1. Is the systemic exposure of tiotropium following administration of Spiriva Respimat similar to that after the administration of Spiriva Handihaler?** **2. Does renal impairment and age affect the pharmacokinetics of the drug?** **3. Is there a dose-response relationship following administration of Spiriva Respimat?**
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

4.2 Individual study summary

Study 205.112 (Report U97-2426)

Study Type: Safety, tolerability and pharmacokinetics in healthy volunteers (Phase I).

Title: A multiple increasing dose tolerance study after inhalant administration of 1 x 10 µg, 1 x 20 µg, and 1 x 40 µg,/24 h of BA 679 BR-BINEB for 14 days in healthy volunteers.

Objective: To evaluate the safety, tolerability and pharmacokinetics of different doses of tiotropium (8 µg, 16 µg, 32 µg tiotropium, corresponding to 10 µg, 20 µg, 40 µg tiotropium bromide monohydrate) administered via the Respimat® inhaler (version A3) in 36 healthy volunteers.

Study Design and Method: This was a placebo controlled, multiple dose rising study for 14-days. Totally 36 healthy male volunteers were recruited in the study, there were 9 subjects in each treatment group (placebo, 8 µg, 16 µg, 32 µg tiotropium). The Respimat device used in this study was version A3.

PK Sampling Time: Blood samples were taken before, 5 min and 20 min after the dose on day 1, 7 and 14. An additional blood sample was taken 24 hr after the dose on day1. Urine samples were take pr-dose and 0 hr, 0-4 hr, 4-8 hr, 8-24 hr after dose on day 1, 7 and 14.

Analytical Method: Plasma and urine samples were analyzed by HPLC-MS/MS. Limit of Quantification (LOQ) was 2.6pg/mL tiotropium in plasma and 11.9pg/mL tiotropium in urine. The assay precision and accuracy was 8.8% and ±3.3% in plasma, and 6.4% and ±5.6% in urine.

Data analysis: Because of the sparse sampling time, only limited PK parameters were calculated, including C_{max}, $AUC_{0\text{-}20\ min}$, $Ae_{0\text{-}4hr}$, $Ae_{0\text{-}8hr}$ and $Ae_{0\text{-}24hr}$.

Results: Results of the PK parameters were summarized in Table 1.

After a single inhalation, maximum tiotropium plasma concentration was observed at 5 min after inhalation most of the time, then the drug concentration decrease rapidly. C_{max} were 4.23 pg/mL (37.8% CV), 12.5 pg/mL (28.9% CV), and 22.1 pg/mL (60.2% CV) at 8, 16, and 32 µg dose, which generally increased dose-proportionally. $AUC_{0\text{-}20min}$ could not be calculated in the 8 and 16 µg dose group due to high number of not quantifiable plasma concentration. $AUC_{0\text{-}20min}$ was 4.78 pg·hr/mL (51.4% CV) at 32 µg dose.

Tiotropium showed a two- to three-fold accumulation in plasma on day 14 after repeated once daily solution inhalation dosing, which was demonstrated in Figure 1. The geometric mean of the maximum tiotropium plasma concentration on day 7 appears to be about 2-fold of that on day 7; and appears to be less pronounced on day 14 compared to day 7 (about 1.5-fold). $AUC_{0\text{-}20min}$ also doubled on day 7 (10.4 pg·hr/mL, 59.4% CV) compared to day 1 (4.78 pg·hr/mL, 51.4% CV) at 32 µg dose, but appears to be less pronounced on day 14 compared to day 7 (about 1.5-fold at 16 and 32 µg dose, unchanged at 8 µg dose).

Figure 1. Geometric mean of tiotropium plasma concentration following once daily inhalation via the Respimat inhaler (version A3) at different doses (8 µg, 16 µg, 32 µg tiotropium), normalized to the recommended dose of Spiriva Handihaler (18 µg)

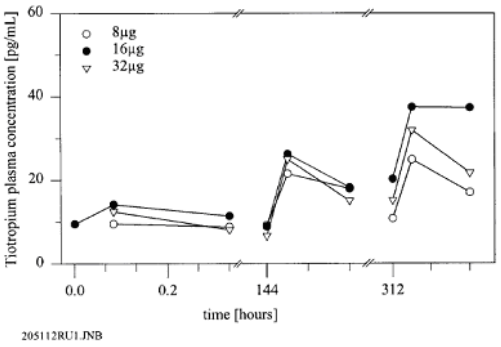


Table 1. Geometric mean (%CV) of tiotropium PK parameters following once daily inhalation (8 µg, 16 µg, 32 µg tiotropium) administered via the Respimat inhaler (version A3)in healthy male volunteers

Results of the noncompartmental pharmacokinetic evaluation standardized for all pharmacokinetic studies and expressed in tiotropium, not in tiotropium bromide monohydrate

		8.0 µg (n = 9)		16 µg (n = 9)		32 µg (n = 9)	
		gMean	% gCV	gMean	%gCV	gMean	% gCV
$C_{5min,\ day\ 1}$	[pg/mL]	4.23 (n = 6)	37.8	12.5 (n = 5)	28.9	22.1 (n = 8)	60.2
$AUC_{0\text{-}20min,day\ 1}$	[pg·h/mL]	NC		NC		4.78 (n = 7)	51.4
$C_{pre,\ day\ 7}$	[pg/mL]	4.05 (n = 4)	77.7	7.81 (n = 6)	27.5	11.7	50.6
$C_{5min,\ day\ 7}$	[pg/mL]	9.51	46.8	23.2 (n = 7)	23.7	44.2 (n = 8)	63.1
$AUC_{0\text{-}20min,day\ 7}$	[pg·h/mL]	3.74 (n = 4)	62.3	6.10 (n = 5)	22.0	10.4 (n = 7)	59.4
$C_{pre,\ day\ 14}$	[pg/mL]	4.75 (n = 7)	69.0	17.9 (n = 7)	34.5	26.7 (n = 7)	56.4
$C_{5min,\ day\ 14}$	[pg/mL]	11.0 (n = 8)	68.0	33.3 (n = 6)	33.1	56.5 (n = 7)	50.3
$AUC_{0\text{-}20min,day\ 14}$	[pg·h/mL]	3.64 (n = 5)	63.3	10.6 (n = 4)	17.8	14.4 (n = 5)	53.5
$Ae_{0\text{-}4h,\ day\ 1}$	(% of dose)	1.49	75.7	2.99	104	2.24	91.4
$Ae_{0\text{-}8h,\ day\ 1}$	(% of dose)	2.69	49.9	4.54	96.8	3.81	71.5
$Ae_{0\text{-}24h,\ day\ 1}$	(% of dose)	5.66 (n = 8)	36.1	8.41	61.1	6.45	55.2
$Ae_{0\text{-}4h,\ day\ 7}$	(% of dose)	4.54	43.6	7.62	59.5	6.82	64.0
$Ae_{0\text{-}8h,\ day\ 7}$	(% of dose)	7.21 (n = 2)	36.4	15.2 (n = 7)	32.5	15.8 (n = 4)	31.8
$Ae_{0\text{-}24h,\ day\ 7}$	(% of dose)	NC		29.1 (n = 7)	27.6	29.4 (n = 4)	28.7
$Ae_{0\text{-}4h,\ day\ 14}$	(% of dose)	5.41	38.1	7.69	47.6	7.40 (n = 8)	56.7
$Ae_{0\text{-}8h,\ day\ 14}$	(% of dose)	9.17	30.7	12.5	50.7	10.3 (n = 7)	52.9
$Ae_{0\text{-}24h,\ day\ 14}$	(% of dose)	20.1	25.5	24.5	34.0	21.3 (n = 6)	53.3

Source data: APPENDIX 15.9.3.3, TABLE PK6: 5
if not marked otherwise in the table the number of subjects was n = 9
NC not calculated

The geometric mean amount of tiotropium excreted in urine after 8, 16, and 32 µg dose was summarized in Table 2. For all dose groups, the tiotropium amount excreted in urine in 0-4 hr was approximately 20-30% of that in 0-24 hr on day 1, 7 and 14. And the amount excreted in urine was generally dose-proportional in all dose groups on day 1, 7 and 14. After a single inhalation, 5.66 % to 8.41 % of the inhaled dose was excreted unchanged in urine 24 hr after dose, while the number was about 29% on day 7 and 20.1% to 24.5% on day 14. It appears that tiotropium amount excreted in urine was similar between day 7 and day 14.

Table 2. Geometric mean of unchanged tiotropium amount excreted in urine within 0-4 hour and 0-24 hr following once daily inhalation via the Respimat inhaler (version A3) at different doses (8 µg, 16 µg, and 32 µg tiotropium)

Dose tiotropium cation	n	8.0 µg			16 µg			32 µg		
		[ng]	% gCV	% of dose	[ng]	% gCV	% of dose	[ng]	% gCV	% of dose
$Ae_{0-4h,day1}$	9/9/9	120	75.7	1.49	478	104	2.99	716	91.3	2.24
$Ae_{0-4h,day7}$	9/9/9	363	43.6	4.54	1220	59.6	7.62	2183	64.0	6.82
$Ae_{0-4h,day14}$	9/9/8	433	38.2	5.41	1230	47.6	7.69	2368	56.6	7.40
$Ae_{0-24h,day1}$	8/9/9	453	36.0	5.66	1345	61.1	8.41	2063	55.3	6.45
$Ae_{0-24h,day7}$	0/7/4	---	---	---	4657	27.6	29.1	9397	28.7	29.4
$Ae_{0-24h,day14}$	9/9/6	1612	25.6	20.1	3927	34.0	24.5	6800	53.4	21.3
ratio Ae_{0-4h} values										
day 7 / day 1			3.05			2.55			3.04	
day 14 / day 1			3.63			2.57			3.30	
day 14 / day 7			1.19			1.01			1.09	
ratio Ae_{0-24h} values										
day 7 / day 1			---			3.46			4.56	
day 14 / day 1			3.55			2.91			3.30	
day 14 / day 7			---			0.84			0.73	

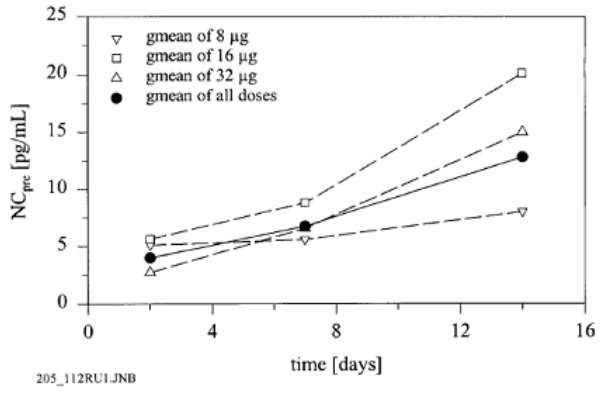
Source data: APPENDIX 15.9.3.3, TABLEs PK6: 5

Conclusions: Tiotropium was absorbed in systemic circulation quickly after inhalation via the Respimat device. Maximum plasma concentration was observed at 5 min after inhalation most of the time, which generally increased dose-proportionally. After repeated once daily solution inhalation dosing, tiotropium showed a two- to three-fold accumulation in plasma on day 14. The unchanged tiotropium amount excreted in urine was generally dose-proportional in all dose groups on day 1, 7 and 14. It appears that the unchanged tiotropium amount excreted in urine was similar between day 7 and day 14. Between 20.1% and 24.5% of the inhaled dose was excreted unchanged in urine on day 7 and 14.

Comments:

Because of the sparse sampling time, only limited PK parameters were calculated. The sponsor claimed only minor changes in tiotropium plasma concentrations and urinary excretion was observed after day 7, indicating that pharmacokinetic steady state was essentially achieved by day 7. According to the urine excretion data, the tiotropium amount excreted in urine was similar between day 7 and day 14. However, the plasma concentrations continued to increase between day 7 and day 14 according to Figure 1. More importantly, the trough drug concentration (C_{pre}) doubled between day 7 and day 14 at 16 and 32 µg dose groups (Figure 2), indicating the plasma steady state was not reached on day 7.

Figure 2. Geometric mean of trough tiotropium concentration before inhalation on day 2, 7 and 14 following 8, 16, and 32 µg once daily dose via the Respimat inhaler (version A3), normalized to the recommended dose of Spiriva Handihaler (18 µg)



According to the Handihaler data, the half-life after dry-powder inhalation was about 5-6 days, and pharmacokinetic steady state was reached after 2–3 weeks with no further accumulation. Change of device from Handihaler to Respimat will only affect absorption of the drug, it is not expected that it will affect

drug elimination. In addition, tiotropium was rapidly absorbed in blood for both the Handihaler and Respimat device with T_{max} around 5 min. Therefore, it is reasonable to expect to that the half-life and time to steady state will be similar between the two devices. However, due to the limited sampling points, half-life of tiotropium delivered by Respimat could not be calculated. Since the last pharmacokinetic sampling time was on day 14, it was difficult to access when the pharmacokinetic steady state was reached.

Tiotropium has very poor oral bioavailability (about 2-3%, NDA (b) (4) so drug amount absorbed in the GI tract could be ignored. It was known from a former study in NDA (b) (4) that after intravenous administration of 14.4 µg tiotropium, 73.6% of the dose is excreted unchanged in urine (205.105, NDA (b) (4)). The sponsor claimed since study 205.112 revealed that after inhalation between 20.1% and 29.4% of the inhaled dose was excreted unchanged in urine on day 7 and 14, it could be extrapolated that about 33% of the inhaled tiotropium dose reached the systemic circulation. This statement was not accurate since the extrapolation was based in the assumption that the pharmacokinetic steady state was reached by day 7, which could not be proved by the study results. In addition, the device used in this study was version A3, and no bioequivalence study has been conducted to compare the performance of this version and the final marketing version (A5). Therefore, the data was not sufficient to support the sponsor's claim.

Study 205.127 (Report U97-2426)

Study Type: Dose range finding study in COPD patients (Phase II).

Title: Pharmacodynamic and pharmacokinetic dose ranging study of tiotropium bromide administered via Respimat device in patients with chronic obstructive pulmonary disease (COPD): a randomized, 3-week multiple-dose, placebo controlled, intraformulation double-blind, parallel group study

Objective: To explore the pharmacodynamic and pharmacokinetic dose ranging of tiotropium bromide administered via Respimat device in patients with chronic obstructive pulmonary disease (COPD).

Study Design and Method: This was a randomized, 3-week multiple-dose placebo controlled, double-blind, paralleled group study in patients with chronic obstructive pulmonary disease (COPD). The objective of this pharmacodynamic and pharmacokinetic 3-week dose ranging study was to determine the optimal dose of Spiriva® Respimat in COPD patients. Five different doses of Spiriva Respimat (1.25, 2.5, 5, 10, 20 µg) were explored in this study, and the results was compared to that of Spiriva Handihaler (18 µg). The Respimat device used in this study was version A3.

PK Sampling Time: Urines samples were collected at -2 to 0 hr and 0 to 2 hr on day 7 ± 2; day 14 ± 2; day 21 ± 2. No blood samples were taken.

Analytical Method: Urine samples were analyzed by HPLC-MS/MS. Limit of Quantification (LOQ) was 10pg/mL tiotropium in urine. The assay precision and accuracy was 4.1% and ±11.5%, respectively.

Data analysis: $Ae_{-2\text{-}0hr}$ and $Ae_{0\text{-}2hr}$ were calculated.

Results

The primary efficacy variable was FEV1 and the primary endpoint was trough FEV1 after three weeks of therapy. The trough and average (over 4 hours post-drug administration) changes from baseline in both FEV1 and FVC on Day 21 are displayed in Table 1.The study revealed that 5 µg and 20 µg doses of tiotropium administered via the Respimat inhaler were effective in terms of trough FEV1 improvement after 21 days (152 and 146 mL, respectively), while the 10 µg response (130 ml) showed marginal statistical significance (p=0.06). The responses at 1.25 and 2.5 µg were not statistically significant compared to placebo. However, no clear dose-response relationship was demonstrated. The rank order of the response is 5 µg, 20 µg, then 10 µg. Based on the results of this study, a definite decision about the selection of the final tiotropium dose in the Respimat inhaler could not be made. Therefore, both 5 µg and 10 µg tiotropium were chosen for further investigation in the Respimat inhalation device in the Phase III program.

Table 1. Adjusted mean change of FEV1 from baseline in liters on Day 21 after once daily inhalation at various doses by Respimat or 18 µg by Handihaler

Device	Respimat®						HandiHaler®	
Dose (µg)	1.25	2.5	5	10	20	Pbo - R	18	Pbo - H
Total Randomized (N)	25	28	25	26	26	24	25	23
Trough FEV_1(L)	0.10	0.05	0.15*	0.13	0.15*	0.02	0.23**	-0.09
Average! FEV_1(L)	0.21*	0.18	0.30**	0.22*	0.30**	0.05	0.32**	-0.05
Trough FVC (L)	0.20	0.10	0.27	0.20	0.25	0.11	0.32**	-0.09
Average! FVC (L)	0.35	0.27	0.42*	0.36	0.51*	0.16	0.47**	-0.05

* Significantly different from placebo (* p <0.05, **p ≤0.001)
! Average over four hours post dose

Urinary excretion of unchanged tiotropium is summarized in Table 2. On some sampling days, several patients showed a higher excretion before inhalation than after inhalation. This is unexpected since the driving force for urine excretion is the drug plasma concentration, which is higher immediately after inhalation compared to pre-dose. Therefore, these data were excluded, and the result was re-summarized in Table 3.

Table 2. Comparison of geometric mean tiotropium Ae values [ng/fraction] after once daily inhalation at various doses by Respimat or 18 µg by Handihaler

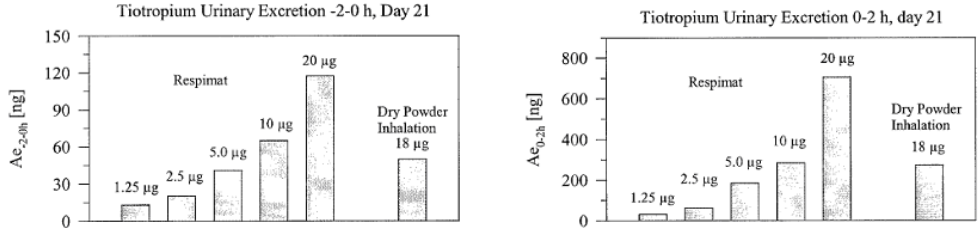
	Day 7 ± 2				Day 14 ± 2				Day 21 ± 2			
Dose (mcg)	2-h pre-dose gMean (% gCV)		2-h post-dose gMean (% gCV)		2-h pre-dose gMean (% gCV)		2-h post-dose gMean (% gCV)		2-h pre-dose gMean (% gCV)		2-h post-dose gMean (% gCV)	
RESPIMAT												
1.25												
N = 10	7.38	(50.4)	29.4	(64.9)	10.2	(82.1)	28.2	(88.1)	13.2	(79.8)	31.1	(106)
2.5	N = 8											
N = 9	11.5	(43.3)	47.3	(100)	27.6	(118)	53.2	(82.8)	23.4	(62.0)	50.9	(107)
5.0												
N = 10	29.9	(51.2)	170	(60.1)	35.4	(144)	167	(66.3)	48.0	(66.6)	185	(50.3)
10					N = 11		N = 10		N = 11		N = 11	
N = 12	45.8	(97.9)	273	(59.5)	62.3	(54.1)	241	(90.0)	74.1	(68.4)	283	(54.7)
20							N = 10					
N = 11	87.5	(88.4)	759	(75.0)	164	(144)	690	(98.4)	117	(135)	706	(104)
DRY POWDER INHALATION												
18					N = 8		N = 8		N = 8		N = 8	
N = 9	28.2	(83.4)	251	(63.2)	46.2	(58.5)	124	(121)	45.9	(86.6)	192	(140)

Table 3. Comparison of geometric mean tiotropium Ae values [ng/fraction] after once daily inhalation at various doses by Respimat or 18 µg by Handihaler, excluding days with reversed excretion pattern

	Day 7 ± 2				Day 14 ± 2				Day 21 ± 2			
Dose (mcg)	2-h pre-dose gMean (% gCV)		2-h post-dose gMean (% gCV)		2-h pre-dose gMean (% gCV)		2-h post-dose gMean (% gCV)		2-h pre-dose gMean (% gCV)		2-h post-dose gMean (% gCV)	
RESPIMAT												
1.25												
N = 10	7.38	(50.4)	29.4	(64.9)	10.2	(82.1)	28.2	(88.1)	13.2	(79.8)	31.1	(106)
2.5	N = 8				N = 6		N = 6		N = 8		N = 8	
N = 9	11.5	(43.3)	47.3	(100)	**15.7**	**(41)**	**56.0**	**(105)**	**20.3**	**(43.5)**	**62.3**	**(75.5)**
5.0					N = 9		N = 9		N = 9		N = 9	
N = 10	29.9	(51.2)	170	(60.1)	**27.0**	**(75.4)**	**159**	**(68.1)**	**40.8**	**(35.6)**	**185**	**(53.7)**
10					N = 10		N = 9		N = 10		N = 10	
N = 12	45.8	(97.9)	273	(59.5)	**62.4**	**(57.5)**	**289**	**(58.8)**	**64.8**	**(48.1)**	**284**	**(58.1)**
20					N = 10		N = 9					
N = 11	87.5	(88.4)	759	(75.0)	**127**	**(75.0)**	**624**	**(95.6)**	117	(135)	706	(104)
DRY POWDER INHALATION												
18					N = 7		N = 7		N = 7		N = 7	
N = 9	28.2	(83.4)	251	(63.2)	**46.8**	**(63.8)**	**164**	**(62.3)**	**49.9**	**(89.4)**	**273**	**(33.5)**

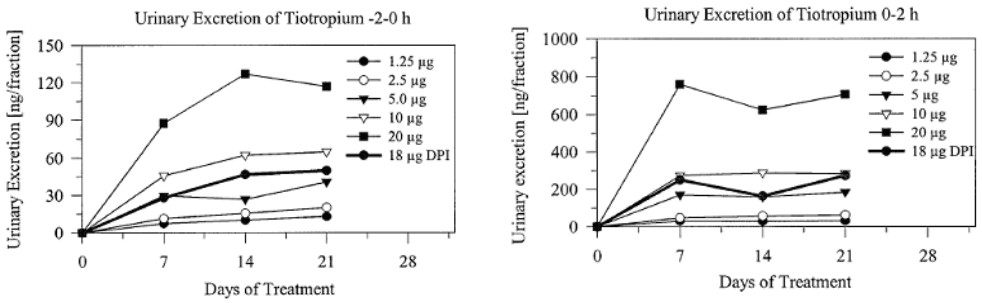
The results showed that tiotropium amount excreted in urine increased with increased dose in a dose-proportional way, which was also demonstrated in Figure 1. The amount excreted at -2 to 0 hr was much less than that at 0-2 hr. A comparable urine excretion was observed between 5 µg to 10 µg Spiriva Respimat and 18 µg Spiriva Handihaler, indicating a dose between 5 µg and 10 µg Spiriva Respimat may achieve a comparable systemic exposure as 18 µg Spiriva Handihaler.

Figure 1. Dose dependency of tiotropium $Ae_{-2\text{-}0hr}$ and $Ae_{0\text{-}2hr}$ at day 21 after once-daily inhalation by Respimat device (days with reverse excretions pattern excluded)



The sponsor claimed that from day 7 onwards no change in tiotropium urinary excretion was observed, confirming that pharmacokinetic steady state was essentially reached by day 7. Figure 2 summarized the urinary excretion with time for all dose groups. According to $A_{e,-2-0\ h}$ data, it appeared that amount excreted in urine was still increasing after day7. Along with the results in study 205.112, these data were not sufficient to support the claim that pharmacokinetic steady state was essentially reached by day 7.

Figure 2. Geometric mean of tiotropium urinary excretion with time after once-daily inhalation by Respimat device (days with reverse excretions pattern excluded)



Conclusions: By testing five different doses of Spiriva Respimat (1.25, 2.5, 5, 10, 20 µg) in COPD patients, no clear dose-response relationship was demonstrated. The study revealed that 5 µg , 10 µg and 20 µg doses were effective in terms of trough FEV1 improvement after 21 days, the rank order of the response was 5 µg, 20 µg, then 10 µg. Tiotropium amount excreted in urine increased with increased dose in a dose-proportional way, a dose between 5 µg and 10 µg Spiriva Respimat may achieve a comparable systemic exposure as 18 µg Spiriva Handihaler based on urine excretion data.

Comments: The study results were not sufficient to support the claim that pharmacokinetic steady state was essentially reached by day 7.

Study 205.249 and 205.250 (Report U05-1949 and U04-2041)

Study Type: Efficacy and safety studies in COPD patients (Phase III).

Title: A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Crossover Efficacy and Safety Comparison of 4-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, Tiotropium Inhalation Powder Capsule (18 µg) Delivered by the Handihaler in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Objective: To demonstrate non-inferiority of lung function response to at least one of the two doses of tiotropium inhalation solution (5 µg and 10 µg) delivered by the Respimat inhaler once-daily compared to 18 µg tiotropium inhalation powder capsule from the Handihaler once-daily at the end of the 4-week periods of randomized treatment

Study Design and Method: Both were randomized, double-blind, double-dummy, placebo-controlled, crossover efficacy and safety studies in patients with COPD. They were designed as controlled crossover studies including four treatment arms including tiotropium 5 and 10 µg delivered by the Respimat inhaler, tiotropium 18 µg delivered by Handihaler and placebo, separated by 4-week washout periods. The Respimat device used in this study was version A4.

PK Sampling Time: Pharmacokinetic samples were collected at the end of each 4-week randomized treatment period (placebo, 5 µg Respimat, 10 µg Respimat and 18 µg Handihaler) in a subset of 98 out of 207 COPD patients. Plasma samples were collected before inhalation of test drug (within -1 hour prior to test drug inhalation), 10 min (±5 min), 60 min (±20 min) and 6 hours (±2 h) after test drug inhalation. Urine samples were collected before inhalation of test drug (-2 hours to just prior to test drug inhalation), 0-2 hours and 2-12 hours after test drug inhalation.

Analytical Method: Plasma and urine samples were analyzed by HPLC-MS/MS. Limit of Quantification (LOQ) was 2.5pg/mL tiotropium in plasma and 20pg/mL tiotropium in urine. The assay precision and accuracy was 13.4% and ±6.8% in plasma, and 8.2% and ±6.2% in urine for study 205.249. The assay precision and accuracy was 7.9% and ±9.4% in plasma, and 6.2% and ±1.3% in urine for study 205.250.

Data analysis: $AUC_{0\text{-}2,ss}$, $AUC_{0\text{-}4,ss}$, $AUC_{0\text{-}6,ss}$, $AUC_{0\text{-}tau,ss}$.$Ae_{\text{-}2\text{-}0hr}$, $Ae_{0\text{-}2hr}$ and $Ae_{0\text{-}12hr}$ were calculated.

Results:
Efficacious results showed the differences between each of the three active treatments and placebo were statistically significant ($p<0.0001$) for each of the two trials and for the pooled data. Pooling of the data demonstrated that both Respimat 5 µg and Respimat 10 µg doses resulted in statistically significant (at least at $p=0.03$) higher responses compared to Handihaler 18 µg for trough FEV1 (peak and $AUC_{0\text{-}3}$ after first dose and for trough, peak, $AUC_{0\text{-}3}$ and$AUC_{0\text{-}12}$ at day 29). These observed differences, although statistically significant, were nevertheless relatively small (range: 0.028-0.057 L).

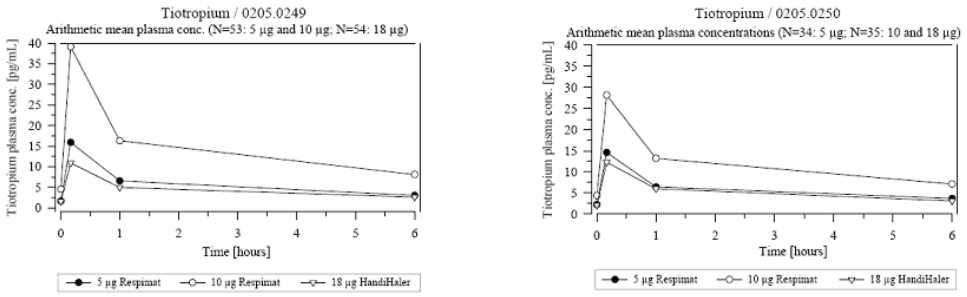
The comparability of the Respimat device to the Handihaler device was evaluated in these two studies in terms of systemic exposure at steady state in COPD patients. The descriptive statistics of plasma concentration and AUC are listed in Table 1 and average plasma concentrations are displayed in Figure 1. Based on limited blood sampling points, the systemic exposure after inhalation of 5 µg tiotropium via the Respimat inhaler appeared to be comparable to 18 µg tiotropium delivered by the Handihaler, whereas higher systemic exposure was obtained following inhalation of tiotropium 10 µg inhalation spray. Tiotropium 10 µg inhalation via the Respimat inhaler provided about two to three fold the systemic exposure as observed for tiotropium 5 µg inhalation via the Respimat inhaler and tiotropium 18 µg via Handihaler inhaler. The systemic exposure for 5 µg Spiriva Respimat and 18 µg Spiriva Handihaler were similar, so it can be concluded that the proportion of the dose deposited in the lungs is higher for the Respimat inhaler than for Handihaler. Dose proportionality was observed for the 5 µg and 10 µg doses of tiotropium delivered via the Respimat inhaler.

Table 1. Descriptive Statistics of Tiotropium Plasma Concentrations and AUCs in Steady State after Tiotropium 5 µg and 10 µg delivered by Respimat device and Tiotropium 18 µg delivered by Handihaler device at study 205.249 (left panel) and 205.250 (right panel)

	N	Gmean	% gCV	mean	% CV	median
Tio R 5						
predose	52	1.49	38.4	1.62	50.9	1.25
0.167 h	53	11.7	99.1	15.9	79.7	10.5
1.0 h	53	4.92	96.0	6.53	75.1	5.52
6.0 h	53	2.54	64.8	3.01	62.1	2.90
$AUC_{0\text{-}2,ss}$	52	12.5	88.9	16.2	70.9	13.0
$AUC_{0\text{-}4,ss}$	52	20.1	83.1	25.4	68.3	22.1
$AUC_{0\text{-}6,ss}$	52	26.1	77.4	32.4	66.0	28.9
$AUC_{\tau,ss}$	52	63.5	52.8	71.6	51.5	64.3
Tio R 10						
predose	53	3.03	102	4.50	116	3.17
0.167 h	53	29.2	104	39.1	74.7	31.6
1.0 h	53	12.1	111	16.3	69.1	12.3
6.0 h	53	6.34	83.4	8.08	72.6	6.33
$AUC_{0\text{-}2,ss}$	53	31.0	96.5	40.5	67.6	33.9
$AUC_{0\text{-}4,ss}$	53	49.9	94.7	64.8	67.4	56.5
$AUC_{0\text{-}6,ss}$	53	64.6	91.7	83.2	67.4	75.2
$AUC_{\tau,ss}$	53	148	83.2	190	74.7	150
Tio HH 18						
predose	54	1.37	37.1	1.53	81.8	1.25
0.167 h	53	7.77	106	10.9	86.8	7.64
1.0 h	53	3.84	86.9	4.93	67.7	3.78
6.0 h	54	2.10	68.8	2.58	70.5	1.25
$AUC_{0\text{-}2,ss}$	54	9.25	82.8	11.8	70.2	8.57
$AUC_{0\text{-}4,ss}$	54	15.4	77.9	19.3	68.1	14.2
$AUC_{0\text{-}6,ss}$	54	20.2	73.8	25.0	67.2	18.0
$AUC_{\tau,ss}$	54	52.2	53.5	59.8	59.9	41.8

	N	gmean	% gCV	mean	% CV	median
Tio R 5						
predose	34	1.68	71.3	2.25	113	1.25
0.167 h	34	10.5	114	14.6	83.0	11.3
1.0 h	34	5.08	83.4	6.45	71.3	5.07
6.0 h	34	2.70	89.9	3.70	92.7	2.76
$AUC_{0\text{-}2,ss}$	34	12.4	79.9	15.7	72.8	13.3
$AUC_{0\text{-}4,ss}$	34	20.5	78.4	25.8	73.4	20.1
$AUC_{0\text{-}6,ss}$	34	26.8	78.4	33.9	75.4	26.2
$AUC_{\tau,ss}$	34	67.4	69.9	84.2	80.9	62.8
Tio R 10						
predose	35	3.32	91.6	4.38	72.7	3.35
0.167 h	35	22.7	81.8	28.2	64.2	24.6
1.0 h	35	11.3	66.9	13.2	52.6	13.8
6.0 h	35	5.71	84.6	7.12	60.8	6.41
$AUC_{0\text{-}2,ss}$	35	27.3	68.1	32.0	53.9	32.1
$AUC_{0\text{-}4,ss}$	35	44.7	64.7	51.8	51.0	51.7
$AUC_{0\text{-}6,ss}$	35	58.1	63.9	67.1	50.2	71.4
$AUC_{\tau,ss}$	35	143	61.8	164	50.4	153
Tio HH 18						
predose	35	1.66	64.1	2.13	110	1.25
0.167 h	35	9.66	90.0	12.3	65.1	10.5
1.0 h	35	4.80	81.0	6.01	66.9	4.74
6.0 h	35	2.28	85.4	3.11	99.6	1.25
$AUC_{0\text{-}2,ss}$	35	11.6	74.8	14.1	61.1	12.2
$AUC_{0\text{-}4,ss}$	35	18.7	72.2	22.7	64.6	20.1
$AUC_{0\text{-}6,ss}$	35	24.2	71.0	29.5	68.9	26.4
$AUC_{\tau,ss}$	35	62.3	60.1	73.1	63.3	60.9

Figure 1. Tiotropium Plasma Concentrations in Steady State after Tiotropium 5 µg and 10 µg delivered by Respimat device and Tiotropium 18 µg delivered by Handihaler device at study 205.249 (left panel) and 205.250 (right panel)



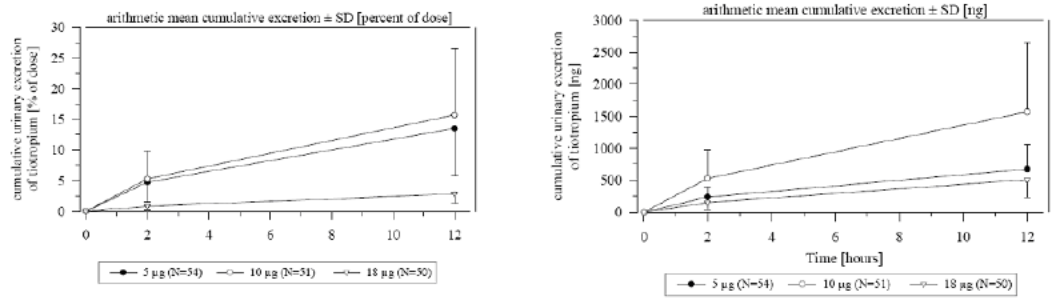
Urinary excretion samples were collected in fixed time intervals, i.e. -2-0 h, 0-2 h and 2-12 h. The descriptive statistics of average amounts and fractions excreted unchanged per collection interval are listed in Table 2 and average fractions excreted unchanged per collection interval are displayed in Figure 2. The amount excreted in urine for Respimat 10 µg was about two to three fold the as observed for Respimat 5 µg and Handihaler 18 µg, which was consistent with the plasma results. The urinary tiotropium excretion amount was comparable for the Respimat 5 µg dose and the Handihaler 18 µg dose. The urinary tiotropium excretion amount for the Respimat 5 µg dose is about half of amount for the tiotropium 10 µg dose, confirming dose proportionality for tiotropium delivered by the Respimat device.

Table 2. Descriptive Statistics of Urinary Excretion of Unchanged Tiotropium at Steady State after Tiotropium 5 µg and 10 µg delivered by Respimat device and Tiotropium 18 µg delivered by Handihaler device in study 205.249 (left panel) and 205.250 (right panel)

		Ae [ng]		fe [% of dose]	
	N	gmean	% gCV	gmean	% gCV
Tio R 5					
predose -2-0 h	54	35.5	104	0.710	104
postdose 0-2 h	54	189	85.3	3.77	85.3
postdose 0-12 h	53	561	73.4	11.2	73.4
Tio R 10					
predose -2-0 h	49	99.5	124	0.995	124
postdose 0-2 h	51	395	97.3	3.95	97.3
postdose 0-12 h	51	1230	84.2	12.3	84.2
Tio HH 18					
predose -2-0 h	49	25.7	89.1	0.143	89.1
postdose 0-2 h	50	110	109	0.614	109
postdose 0-12 h	49	428	73.4	2.38	73.4

		Ae [ng]		fe [% of dose]	
	N	gmean	% gCV	gmean	% gCV
Tio R 5					
predose -2-0 h	27	41.5	82.0	0.830	82.0
postdose 0-2 h	30	144	84.6	2.88	84.6
postdose 0-12 h	29	479	59.0	9.57	59.0
Tio R 10					
predose -2-0 h	30	74.4	82.5	0.744	82.5
postdose 0-2 h	31	290	77.9	2.90	77.9
postdose 0-12 h	31	892	79.1	8.92	79.1
Tio HH 18					
predose -2-0 h	28	33.8	69.9	0.188	69.9
postdose 0-2 h	32	126	84.4	0.701	84.4
postdose 0-12 h	32	410	65.7	2.28	65.7

Figure 2. Urinary Excretion of Unchanged Tiotropium at Steady State after Tiotropium 5 µg and 10 µg delivered by Respimat device and Tiotropium 18 µg delivered by Handihaler device in study 205.249 205.250 (data combined together). Left panel: Cumulative urinary excretion of tiotropium as percentage of dose; Right panel: Cumulative urinary excretion of tiotropium as absolute amount.



Conclusions: Dose proportionality in systemic exposure and urine excretion was observed for the 5 µg and 10 µg doses of tiotropium delivered via the Respimat inhaler at steady state. Comparable systemic exposure and urine excretion was observed for tiotropium 5 µg inhalation via the Respimat inhaler and tiotropium 18 µg via Handihaler inhaler as steady state.

Comments: The sponsor claimed in the label that (b) (4) . Since only very limited plasma time points were taken in COPD patients (pre-dose, 10 min, 60 min, and 6 hr), the data was insufficient to support that (b) (4)

Study 205.9991 (Report U05-2108)

Study Type: A pharmacokinetic meta-analysis for tiotropium bromide based on data obtained from patients with chronic obstructive pulmonary disease (COPD) was performed by combining plasma and urine data from studies 205.249 [U05-1949] and 205.250 [U04-2041].

Title: A pharmacokinetic analysis for tiotropium bromide in chronic obstructive pulmonary disease (COPD) patients – A combined analysis of pharmacokinetic data obtained in studies 205.249 and 205.250

Objective: To analyze tiotropium plasma concentrations and urinary excretion data with regard to renal function and age.

Study Design and Method: Data from two clinical trials were available for the analysis. Trials 205.249 [U05-1949] and 205.250 [U04-2041] were designed as controlled crossover studies including the four treatment arms tiotropium 5 µg and 10 µg delivered by the Respimat inhaler, tiotropium 18 µg delivered by the Handihaler and placebo delivered by the Respimat inhaler and also the Handihaler according to the double-dummy design. The data set for the pharmacokinetic meta-analysis included data from 96 COPD patients.

PK Sampling Time: Pharmacokinetic samples were collected at the end of each 4-week randomized treatment period (placebo, 5 µg Respimat, 10 µg Respimat and 18 µg Handihaler) in a subset of 98 out of 207 COPD patients. Plasma samples were collected before inhalation of test drug (within -1 hour prior to test drug inhalation), 10 min (±5 min), 60 min (±20 min) and 6 hours (±2 h) after test drug inhalation. Urine samples were collected before inhalation of test drug (-2 hours to just prior to test drug inhalation), 0-2 hours and 2-12 hours after test drug inhalation.

Results:

Renal Impairment

The results of the meta-analysis for AUC, C_{max} and tiotropium plasma concentrations in different renal function groups are displayed in Table 1. $AUC_{0-4,ss}$ was chosen for comparison among different renal impairment groups because the statement in the package insert of SPIRIVA Handihaler refers to this pharmacokinetic parameter.

Table 1. Comparison of $AUC_{0-4,ss}$ [pg·h/mL] and $C_{max,ss}$ [pg/mL] of tiotropium after inhalation of 5 µg and 10 µg tiotropium with the Respimat inhaler and 18 µg with the Handihaler once daily for four weeks in patients with normal renal function (CLCR > 80 mL/min) and mild (CLCR 50 –80 mL/min) or moderate (CLCR 30 – 50 mL/min) impaired renal function

	normal renal function (CL_{CR} > 80 mL/min)		mild renal impairment (CL_{CR} 50 – 80 mL/min)		moderate renal impairment (CL_{CR} 30 – 50 mL/min)		Ratio gMean mild renal impairment / normal renal function	Ratio gMean moderate renal impairment / normal renal function
	gMean	% gCV	gMean	% gCV	gMean	% gCV		
				$AUC_{0-4,ss}$ [pg·h/mL]				
Tio R 5 µg	18.9 (N=46)	72.2	21.6 (N=36)	85.8	30.1 (N=4)	129	1.14	1.59
Tio R 10 µg	43.3 (N=49)	83.6	54.5 (N=33)	70.1	76.0 (N=5)	70.0	1.26	1.76
Tio HH 18 µg	14.2 (N=49)	68.4	20.0 (N=34)	77.9	23.0 (N=5)	110	1.41	1.62
				$C_{max,ss}$ [pg/mL]				
Tio R 5 µg	11.4 (N=46)	86.5	11.2 (N=36)	110	18.6 (N=4)	82.9	0.982	1.63
Tio R 10 µg	24.8 (N=49)	93.3	28.4 (N=33)	90.0	42.9 (N=5)	101	1.15	1.73
Tio HH 18 µg	6.95 (N=49)	91.8	10.7 (N=34)	96.4	12.7 (N=5)	145	1.54	1.83

An increase in tiotropium plasma concentrations was observed in COPD patients with impaired renal function in comparison to those with normal renal function. $AUC_{0-4,ss}$ values increased by 26% and 76% when comparing COPD patients with mild and moderate impaired renal function to those with normal renal function after inhalation of 10 µg tiotropium with the Respimat inhaler. A similar trend was observed for C_{max}. After inhalation of 10 µg tiotropium with the Respimat inhaler, C_{max} were 24.8 pg/mL (CV: 93.3%), 28.4 pg/mL (CV: 90.0%) and 42.9 pg/mL (CV: 101%) in patients with normal renal function and mild and moderate renal impairment, respectively. The other two dose groups, 5 µg via Respimat inhaler and 18 µg via the Handihaler inhaler, showed similar trends.

The results of the meta-analysis for the unchanged tiotropium dose excreted in urine in different renal function groups are displayed in Table 2. The urinary excretion of tiotropium also changed with impaired renal function. Tiotropium excretion in urine decreased with a lower renal function. By comparing the ratio of urinary tiotropium excretion in moderate impairment patients to normal function patients, the decrease in tiotropium urinary excretion was more pronounced after inhalation of 5 µg tiotropium with the Respimat inhaler (0.538) and 18 µg with the Handihaler (0.470) than after inhalation of 10 µg with the Respimat inhaler (0.939).

Table 2. Geometric means of cumulative fractions [percent of dose] ($fe_{0-12,ss}$) of tiotropium excreted in urine after inhalation of 5 µg and 10 µg tiotropium with the Respimat inhaler and 18 µg with the Handihaler once daily for four weeks in patients with normal renal function (CLCR > 80 mL/min) and mild (CLCR 50 - 80 mL/min) or moderate (CLCR 30 - 50 mL/min) impaired renal function

	normal renal function (CL_{CR} > 80 mL/min)		mild renal impairment (CL_{CR} 50 – 80 mL/min)		moderate renal impairment (CL_{CR} 30 – 50 mL/min)		Ratio gMean mild renal impairment / normal renal function	Ratio gMean moderate renal impairment / normal renal function
	gMean	% gCV	gMean	% gCV	gMean	% gCV		
Tio R 5 µg	12.1 (N=45)	68.1	9.29 (N=33)	63.8	6.51 (N=3)	106	0.768	0.538
Tio R 10 µg	11.5 (N=46)	80.7	10.5 (N=30)	93.6	10.8 (N=5)	56.3	0.913	0.939
Tio HH 18 µg	2.32 (N=45)	68.8	2.66 (N=31)	45.4	1.09 (N=5)	179	1.15	0.470

Age

The results of the meta-analysis for AUC values, C_{max}, and tiotropium plasma concentrations in different age groups are displayed in Table 3. For the two tiotropium doses delivered by the Respimat inhaler, there

was a trend towards lower $AUC_{0-4,ss}$ values in patients older than 70 years. The geometric mean $AUC_{0-4,ss}$ values for 5 µg and 10 µg tiotropium delivered with the Respimat inhaler were 18.7 pg·h/mL (CV: 97.5%) and 51.0 pg·h/mL (CV: 92.5%) in patients younger than 58 years; and declined to 16.9 pg·h/mL (CV: 121%) and 34.2 pg·h/mL (CV:78.9%), respectively, in patients older than 70 years. There were only slight differences observed in $AUC_{0-4,ss}$ values between patients younger than 58 years and patients at the age of 58 – 70 years. Similar trends were observed for C_{max}, which was 11.1 pg/mL (CV: 127%) and 31.1 pg/mL (CV: 93.5%) in patients younger than 58 years; and declined to 9.19 pg/mL (CV: 128%) and 17.3 pg/mL (CV: 79.7%) in patients older than 70 years. For 18 µg tiotropium delivered by the Handihaler, the $AUC_{0-4,ss}$ and C_{max} values were similar across the three different age groups.

Table 3. Comparison of $AUC_{0-4,ss}$ [pg·h/mL] and $C_{max,ss}$ [pg/mL] of tiotropium after inhalation of 5 µg and 10 µg tiotropium with the Respimat inhaler and 18 µg with the Handihaler once daily for four weeks in patients younger than 58 years, 58-70 years old and older than 70 years

	< 58 years		58-70 years		> 70 years		Ratio gMean patients 58-70 years / patients <58 years	Ratio gMean patients >70 years / patients <58 years
	gMean	% gCV	gMean	% gCV	gMean	% gCV		
				$AUC_{0-4,ss}$ [pg·h/mL]				
Tio R 5 µg	18.7 (N=17)	97.5	21.9 (N=54)	62.5	16.9 (N=16)	121	1.17	0.904
Tio R 10 µg	51.0 (N=17)	92.5	50.8 (N=57)	79.5	34.2 (N=14)	78.9	0.996	0.671
Tio HH 18 µg	15.8 (N=18)	67.6	17.0 (N=57)	78.9	16.1 (N=14)	81.4	1.08	1.02
				$C_{max,ss}$ [pg/mL]				
Tio R 5 µg	11.1 (N=17)	127	12.4 (N=54)	77.4	9.19 (N=16)	128	1.12	0.828
Tio R 10 µg	31.1 (N=17)	93.5	27.9 (N=57)	97.0	17.3 (N=14)	79.7	0.897	0.556
Tio HH 18 µg	7.80 (N=18)	93.4	8.93 (N=57)	100	7.72 (N=14)	110	1.14	0.990

The results of the meta-analysis of urinary tiotropium excretion in different age groups are displayed in Table 4. Urinary excretion after inhalation of 5 µg and 10 µg tiotropium with the Respimat inhaler decreased from 11.1% (CV: 84.7%) and 11.6% (CV: 106%) of the inhaled dose in patients younger than 58 years to 7.71% (CV: 94.7%) and 6.71% (CV: 66.0%) in patients older than 70 years, respectively. There was no difference between patients younger than 58 years and patients at the age of 58 to 70 years. When tiotropium was administered via the Handihaler, urinary drug excretion only decreased from 2.25% (CV: 55.7%) in patients younger than 58 years to 2.02% (CV: 95.9%) in patients older than 70 years. There was no difference in urine excretion of unchanged drug between patients younger than 58 years compared to patients at the age of 58 to 70 years.

Table 4. Geometric means of cumulative fractions [percent of dose] ($f_{e0-12,ss}$) of tiotropium excreted in urine after inhalation of 5 µg and 10 µg tiotropium with the Respimat inhaler and 18 µg with the Handihaler once daily for four weeks in patients younger than 58 years, 58 - 70 years old and older than 70 years

	<58 years		58-70 years		>70 years		Ratio gMean patients 58-70 years / patients <58 years	Ratio gMean patients >70 years / patients <58 years
	gMean	% gCV	gMean	% gCV	gMean	% gCV		
Tio R 5 µg	11.1 (N=13)	84.7	11.4 (N=55)	55.9	7.71 (N=14)	94.7	1.03	0.695
Tio R 10 µg	11.6 (N=15)	106	12.0 (N=54)	77.4	6.71 (N=13)	66.0	1.03	0.578
Tio HH 18 µg	2.25 (N=16)	55.7	2.45 (N=52)	68.4	2.02 (N=13)	95.9	1.09	0.898

Conclusions: There was a trend observed towards an increase in tiotropium plasma concentrations and a decrease in excretion of unchanged drug in urine in patients with impaired renal function. For the two tiotropium doses delivered by the Respimat inhaler there was a trend observed towards a lower systemic exposure to tiotropium assessed by $AUC_{0-4,ss}$ and C_{max} values in patients older than 70 years. For 18 µg tiotropium delivered by Handihaler the $AUC_{0-4,ss}$ and C_{max} values were found to be similar across the three different age groups. Tiotropium urinary excretion was decreased in patients older than 70 years compared to patients younger than 58 years for both devices.

Comments:
Tiotropium is mainly eliminated by renal excretion. After intravenous administration of tiotropium bromide, approximately 74% of the administered dose was excreted unchanged in urine (NDA (b) (4) U99-1315), suggesting that impaired renal function might affect the pharmacokinetics of tiotropium. This hypothesis was confirmed by a study conducted in patients with renal impairment (NDA (b) (4) U00-1289).
These two studies (205.249 and 205.250) were not specifically designed to evaluate special pharmacokinetic populations such as patients with impaired renal function and the elderly. Therefore, it was difficult to assess a possible effect of renal impairment or age on the pharmacokinetics of tiotropium on the basis of the limited data. However, since the pharmacokinetic properties in special populations are dependent on the drug substance rather than the inhalation device, and as the systemic exposure is comparable for Respimat 5 µg and Handihaler 18 µg, similar changes in terms of tiotropium plasma concentrations and drug clearance can be expected between the two devices in these special populations. Therefore, the statements concerning the pharmacokinetics of tiotropium in special populations included in the label of Spiriva Handihaler will also be used for the label of Spiriva Respimat.

Study P98.3499

Study Type: Literature reference.

Title: Newman SP, Brown J, Steed KP, Reader SJ, Kladders H. Lung deposition of fenoterol and flunisolide delivered using a novel device for inhaled medicines: Comparison of Respimat with conventional metered-dose inhalers with and without spacer devices. Chest 1998; 113: 957-963

Objective: To compare the lung disposition of fenoterol and flunisolide administrated by Respimat device from the metered dose inhalers (MDIs) with or without spacer.

Study Design and Method: This was a randomized, three-way crossover study. Radio-labeled fenoterol and flunisolide were administrated by Respimat device, and metered dose inhalers (MDIs) with or without spacer in healthy, non-smoking volunteers. Lung deposition of the drugs was as assessed by γ-scintigraphy.

Results: About 39% of the fenoterol dose and 45% of the flunisolide dose delivered by the Respimat device was deposited in the lungs.

Comments: The sponsor claimed the lung deposition in this study was assessed by γ-scintigraphy, which primarily depends on the inhaler and formulation characteristics (aqueous for both fenoterol and tiotropium) and not on drug substance characteristics. Therefore, the study results could be extrapolated to tiotropium. In the proposed label by the sponsor, it was stated that (b) (4) . However, the data submitted was not sufficient to support such a statement. The physical-chemical characteristics of drug may also affect of the lung deposition for the same device. Actually, the percentage of dose deposited in the lungs was different between the two test drugs in this study (39% for fenoterol and 45% for flunisolide). In addition, the sponsor claimed the device version in this study was A3. But no bioequivalence study has been conducted to compare the performance of this version and the final marketing version (A5). So the current data was inadequate to support such a claim in the label. The sponsor may consider conduct a similar by using Spiriva Respimat to make the statement. Moreover, determination of lung disposition by using the pharmacoscintigraphic method is generally not acceptable since radio-labeling of the drug substance may affect disposition of the drug. Therefore, this statement should be deleted.

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

/s/

Yun Xu
7/31/2008 03:50:39 PM
BIOPHARMACEUTICS

Wei Qiu
7/31/2008 03:53:29 PM
BIOPHARMACEUTICS

Clinical Pharmacology Review

"Spiriva Respimat"

NDA	**21-936**
Sponsor:	**Boehringer Ingelheim Pharm. Inc.**
Type:	**NDA filing meeting package**
Drug:	**Tiotropium Bromide**
Submission date:	**November 16, 2007**
Submission assigned:	**November 27, 2007**
Draft review:	**December 12, 2007**
Reviewer:	**Sandra Suarez-Sharp, Ph.D.**

INTRODUCTION

Spiriva Respimat inhalation spray contains tiotropium bromide, a specific muscarinic acetylcholine receptor antagonist. Tiotropium bromide monohydrate was approved by the Agency on January 30, 2004 for use as inhalation powder with the HANDIHALER inhalation device (dry powder inhaler) under NDA 21-395. Spiriva Handihaler (18 µg tiotropium) is indicated for the long-term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. In the Present submission Spiriva Respimat is being proposed for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The recommended dosage of Spiriva Respimat is two inhalations (2 x 2.5 mcg) once-daily.

This reviewer's Comments

The table below summarizes the overall content of the clinical pharmacology information provided by the sponsor to support the request for the approval of this NDA. The sponsor has submitted a reviewable package for this NDA and therefore, there are no filing issues.

Study Title/Description	Tabular listing/ PK summary	Analytical method	PK parameters	Statistical analysis
Study 205.112/(U97-2426): A multiple increasing dose tolerance study after inhalant administration of 1 x 10 µg, 1 x 20 µg and 1 x 40 µg/24 h of BA 679 BR-BINEB for 14 days in healthy volunteers.	√	√	√	√
Study 205.127 [U00-0077]: Pharmacodynamic and pharmacokinetic dose ranging study of tiotropium bromide administered via Respimat® device in patients with chronic obstructive pulmonary disease (COPD): a randomized, 3-week multiple-dose placebo controlled, double-blind, parallel group study.	√	√	√	√
Study 205.249 [U05-1949]: A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Crossover Efficacy and Safety Comparison of 4-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, tiotropium Inhalation Powder Capsule (18 µg) delivered by the HandiHaler® in Patients with Chronic Obstructive Pulmonary Disease (COPD).	√	√	√	√

Study 205.250 [U04-2041]: Efficacy and safety comparison of tiotropium delivered by Respimat® and HandiHaler® in COPD patients.	√	√	√	√
Study US5-2108/205.9991: This consist of a pharmacokinetic meta-analysis for tiotropium bromide based on data obtained from patients with chronic obstructive pulmonary disease (COPD) was performed by combining plasma and urine data from studies 205.249 [U05-1949] and 205.250 [U04-2041].	√	**NA**	√	√
Study P98-3499: This study was conducted to compare the lung deposition with the Respimat device vs conventional metered dose inhalers with and without spacer.	**NA**	√	√	√

RECOMMENDATION

The Office of Clinical Pharmacology, the Division of Clinical Pharmacology 2 (DCP2) has reviewed the NDA 21-936 package for filing submitted on November 16, 2007. The OCP/DCP2 is aware of the pharmacokinetic studies that the sponsor submitted to the NDA. The NDA is filaeble from a CPB standpoint. There are no comments to the sponsor at this time.

Sandra Suarez-Sharp, Ph.D.
Senior Clinical Pharmacology Reviewer, DCP2, OCP

Concurrence:

Wei Qiu, Ph. D.
Acting Team Leader, DCP2, OCP

cc:
HFD-570 Div., Raggio, Lee, Chowdhury, Michelle
HFD-870 Sahajwalla, Doddapaneni, Qiu, Suarez-Sharp

BACKGROUND

Drug Substance

The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1α, 2ß, 4ß, 5α, 7ß)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$] nonane bromide monohydrate (Figure 1). 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.

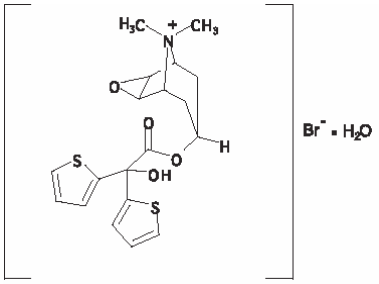


Figure 1. Structural formula for Tiotropium Bromide

Molecular Weight: 490.4
Molecular formula: $C_{19}H_{22}NO_4S_2Br \bullet H_2O$.

Drug Product

The tiotropium inhalation solution for use with the RESPIMAT device is a sterile aqueous solution of tiotropium bromide monohydrate and two excipients, benzalkonium chloride (BAC), and edetate disodium (EDTA). One dose (2 actuations) of Spiriva Respimat provides a delivered dose (b) (4) of solution) from the mouthpiece of 5 µg of tiotropium (which is equivalent to 6.25 µg of tiotropium bromide monohydrate). Spiriva® Respimat® Inhalation Spray has the following composition:

Table 1. Composition of Spiriva® Respimat®

Name of Ingredient	Function	Reference to Standards	Per dose 1 (Label Claim) (mg)	Percentage Formula (g/100ml)	Per cartridge [4] (mg)
Tiotropium [2]			0.005		(b) (4)
corresponds to Tiotropium bromide monohydrate	Drug substance	In house standard			(b) (4)
Benzalkonium chloride [3]	Preservative	NF			
Edetate Disodium	Stabilizer	USP			
(b) (4) Hydrochloric acid	(b) (4)	NF			
Water for injection		USP			
					(b) (4)
Total weight			(b) (4)	100.0	(b) (4)

(b) (4)

Product Development

The sponsor stated that three versions of the Respimat device (A3, A4 and A5) were used in the development program of Spiriva Respimat. According to the sponsor, all versions are identical in performance and materials in contact with the drug solution and all three versions of the inhaler have the same nozzle type and are identical in terms of aerodynamic performance of the emitted aerosol sprays.

The A3 device was used in all the Phase I and II trials; the A4 device was used in the six Phase III trials; and the A5 device is the inhalation device intended for marketing. (b) (4) The A5 inhaler is intended for use with a single cartridge for 30 days and differs from the A4 version only in so much as it has a locking mechanism that engages following the administration of the declared number of

actuations, a turquoise cap color and an improved design of the dose indicator. The sponsor indicated that as agreed with the FDA no clinical bridging trials were conducted between the A4 inhaler, used in the Phase III trials, and the A5 inhaler, intended for marketing, because the two devices deliver identical doses of the same formulation and the changes to the A5 device do not influence the delivered volume, spray characteristics or concentration of delivered medication.

Clinical Studies Included in the Present Submission

The Clinical Development Program for Spiriva Respimat consisted on ten Phase I, II and III trials (see table below).

Phase	Trial No	Study Objective and Design	Dosing	No. and Type of Subjects	Duration
I	205 112 (U97-2426)	Safety and tolerability + PK Multiple increasing doses, pl-c, rand	10µg, 20µg, 40µg tiotropium bromide monohydrate o.d. vs. pl via RESPIMAT	36 Healthy subjects	14 days
I	205 138 (U99-1355)	Safety and tolerability after ocular administration pl-c	0.02µg, 0.04µg, 0.08µg, 0.16µg, 0.28µg, 0.40µg tiotropium vs. pl	48 Healthy subjects	Single doses
II	205 127 (U00-0077)	Dose-ranging + PK md, rand, d-b, pg, pl-c and act-c	1.25µg, 2.5µg, 5.0µg, 10.0µg, 20.0µg, tiotropium via RESPIMAT vs. pl vs. Tio HH18 o.d.	202 COPD	3 weeks
II	205 248 (U02-1222)	Safety and tolerability sd, rand, d-b, pl-c, 4-way c-o	Respimat pl (pH=2.7) Respimat pl (pH=3.4) Respimat pl (pH=3.7) vs. CFC-MDI pl	34 Asthmatic	Single doses
III	205.249 (U05-1949) 205.250 (U04-2041) Pooled data (U05-2161) Pooled PK data (U05-2108)	Non-inferiority of tiotropium in RESPIMAT vs. HANDIHALER +PK md, rand, d-b, d-d, pl-c, act-c, c-o, 4 4-week periods	5µg, 10µg, tiotropium via RESPIMAT vs. pl vs. Tio HH18 o.d.	131 (205.249) 76 (205.250) COPD	4 weeks
III	205.251 (U04-3400) 205.252 (U04-3343) Pooled data (U05-2162)	Comparison of efficacy/safety of tiotropium in RESPIMAT to IB md, rand, d-b, d-d, pg, pl-c, act-c	5µg, 10µg tiotropium via RESPIMAT o.d. vs. pl vs. 36µg IB via pMDI q.i.d.	361 (205.251) 358 (205.252) COPD	12 weeks
III	205.254 (U05-2112) 205.255 (U05-2113) Pooled data (U05-2249)	Efficacy, safety of tiotropium in RESPIMAT vs. pl md, rand, d-b, pg, pl-c	5µg, 10µg tiotropium vs. pl via RESPIMAT o.d.	983 (205.254) 1007 (205.255) COPD	48 weeks
IIIb	205 392 (U07-3356)	Retrospective vital status data collection for prematurely withdrawn patients from 205.254 & 205.255	5µg, 10µg tiotropium vs. pl via RESPIMAT o.d.	456 COPD	48 weeks + 30 days

act-c: active-controlled, d-b: double-blind, c-o: cross-over, d-d: double-dummy, IB: ipratropium bromide, md: multiple dose, o.d: once daily, pg: parallel group, PK: pharmacokinetics, pl: placebo, pl-c: placebo controlled, q.i.d.: four times daily, rand: randomised, sd: single dose, Tio HH 18: tiotropium powder 18⌈g via HANDIHALER

Clinical Pharmacology Studies

The pharmacokinetics of Spiriva® Respimat® was evaluated in four clinical trials which used two different versions of the Respimat® inhaler (see Table 2).

Table 2. Clinical Pharmacology Studies in the Spiriva® Respimat® Program that included Pharmacokinetic Assessments

Trial [report no.]	Respimat® Inhaler Version	Study Description
205.112 [U97-2426]	A3	Multiple increasing dose tolerance study in healthy volunteers
205.127 [U00-0077]	A3	Dose ranging study in COPD patients
205.249 [U05-1949]	A4	Efficacy and safety comparison of tiotropium delivered by Respimat® and HandiHaler® in COPD patients
205.250 [U04-2041]	A4	Efficacy and safety comparison of tiotropium delivered by Respimat® and HandiHaler® in COPD patients

Study 205.112: It was a sequential, parallel group, multiple increasing dose tolerance study after inhalation of 8 µg, 16 µg and 32 µg tiotropium with the BINEB device (an early version of the Respimat® device) (A3) inhaler for 14 days in 36 healthy volunteers. According to the sponsor, between 20.1 and 29.4% of the inhaled dose was excreted unchanged in urine. Tiotropium showed a two- to three-fold accumulation in plasma after repeated once daily dosing. Pharmacokinetic steady state was essentially achieved by Day 7. Tiotropium plasma concentrations and urinary excretion data suggested dose proportionality for tiotropium administered via the Respimat® inhaler within the dose range 8 µg to 32 µg tiotropium.

Study 205.127: It was a parallel group, multiple-dose, dose-ranging study conducted over a period of three weeks in 202 COPD patients. Doses of 1.25 µg, 2.5 µg, 5.0 µg, 10 µg and 20 µg tiotropium administered via the Respimat® inhaler (version A3) were compared to tiotropium inhalation powder capsules given via the HandiHaler® device (18 µg) and placebo. According to the sponsor, results showed that 5 µg and 20 µg tiotropium administered via the Respimat® inhaler were effective doses in terms of trough FEV1 improvement after 21 days. However, no clear dose response relationship was demonstrated, as the rank order of the Respimat® responses was 5 µg, 20 µg, and 10 µg tiotropium, with a significant difference from the placebo Respimat® obtained with 5 µg and 20 µg of tiotropium.

The amount of tiotropium excreted unchanged in urine after inhalation of 18 µg tiotropium via the HandiHaler® ranged between the urinary excretion of tiotropium after inhalation of 5 µg and 10 µg tiotropium via the Respimat® inhaler. The sponsor stated that based on the results of this Phase II dose ranging study, a definite decision about the selection of the final tiotropium dose for use with the Respimat® inhaler could not be made. Therefore doses of 5 µg and 10 µg tiotropium (corresponding to 2.5 µg and 5.0 µg tiotropium per puff delivered by the Respimat® inhaler) were selected for further investigation in Phase III.

Studies 205.249 and 205.250: These two studies were conducted to assess the comparability of the tiotropium bromide inhalation spray formulation (Respimat®) to the tiotropium inhalation powder formulation (HandiHaler®) in terms of systemic exposure at steady state in COPD patients. Trials 205.249 and 205.250 were designed as controlled crossover studies and included the four treatment arms tiotropium 5 µg and 10 µg delivered by the Respimat® inhaler, tiotropium 18 µg delivered by HandiHaler® and placebo. According to the sponsor, the pharmacokinetic results of the two studies

indicated comparable systemic exposure between the 5 µg tiotropium dose delivered by the Respimat® inhaler and the 18 µg tiotropium dose delivered by the HandiHaler® (see Figure 1).

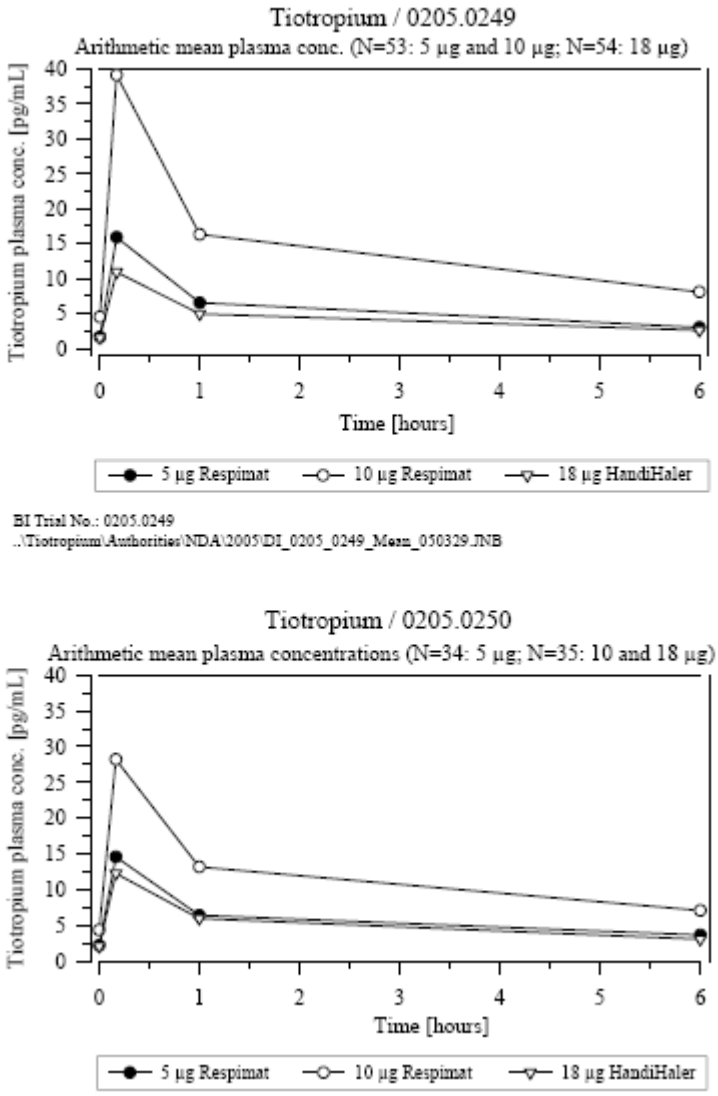


Figure 1. Arithmetic mean drug plasma concentration-time profiles of tiotropium after inhalation of 5 µg and 10 µg tiotropium with the Respimat® inhaler and 18 µg tiotropium with the HandiHaler® once daily for four weeks in studies 205.249 (upper graph) and 205.250 (lower graph).

This submission also includes the study reports for the following pharmacokinetic analysis:

Study US5-2108/205.9991: This consist of a pharmacokinetic meta-analysis for tiotropium bromide based on data obtained from patients with chronic obstructive pulmonary disease (COPD) was performed by combining plasma and urine data from

studies 205.249 [U05-1949] and 205.250 [U04-2041]. For tiotropium bromide delivered by the Respimat inhaler no studies were performed in special populations such as patients with impaired renal function or elderly patients. In the present report tiotropium plasma concentrations and urinary excretion data are analyzed with regard to renal function and age.

According to the sponsor, there was a trend observed towards an increase in tiotropium plasma concentrations and a decrease in excretion of unchanged drug in urine in patients with impaired renal function. Concerning the analysis of the plasma and urine data of the study population with regard to age, the two tiotropium doses delivered by the Respimat inhaler showed a trend towards lower values for AUC0-4,ss with advancing age. Urinary excretion of tiotropium showed a decrease with advancing age. There was a trend observed towards an increase in tiotropium plasma concentrations and a decrease in excretion of unchanged drug in urine in patients with impaired renal function. The sponsor concluded that it was difficult to assess a possible effect of renal impairment on the pharmacokinetics of tiotropium on the basis of the limited data.

Study P98-3499: It was a study conducted to compare the lung deposition of flunisolide and fenoterol with the Respimat device vs conventional metered dose inhalers with and without spacer. According to the sponsor, (b) (4) The sponsor believes that this finding can be extrapolated to Spiriva Respimat. The results of this study come from the following published journal article: Newman SP, Brown J, Steed KP, Reader SJ, Kladders H. Lung deposition of fenoterol and flunisolide delivered using a novel device for inhaled medicines: Comparison of Respimat® with conventional metered-dose inhalers with and without spacer devices. Chest,1998;113:957-963.

Sponsor's Proposed Clinical Pharmacology Labeling

Most of the clinical pharmacology proposed labeling is part of the currently marketed Spiriva Handihaler.

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-936	**Brand Name**	Spiriva Respimat
OCPB Division (I, II, III)	II	**Generic Name**	Tiotropium Bromide Inhalation Spray
Medical Division	DPAP	**Drug Class**	Anticholinergic
OCPB Reviewer	Sandra Suarez-Sharp	**Indication(s)**	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
OCPB Team Leader	Wei Qiu	**Dosage Form**	solution
PM Reviewer		**Dosing Regimen**	Adults (b) (4) 2 sprays per nostril, twice daily
Date of Submission	November 16, 2007	**Route of Administration**	Oral Inhalation
Estimated Due Date of OCPB Review	May 2008	**Sponsor**	Boehringer Ingelheim
PDUFA Due Date	September 16, 2008	**Priority Classification**	10 months
Division Due Date	February 2007		

Clin. Pharm. 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**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				

multiple dose:	X	**2**		**Study 205.112/(U97-2426**): A multiple increasing dose tolerance study after inhalant administration of 1 x 10 µg, 1 x 20 µg and 1 x 40 µg/24 h of BA 679 BR-BINEB for 14 days in healthy volunteers. **Study P98-3499:** This study was conducted to compare the lung deposition with the Respimat device vs conventional metered dose inhalers with and without spacer.
Patients-				
single dose:				
multiple dose:	**x**	**3**		**205.127 [U00-0077]:** Dose ranging study in COPD patients. **205.249 [U05-1949]:** Efficacy and safety comparison of tiotropium delivered by Respimat® and HandiHaler® in COPD patients. **205.250 [U04-2041]:** Efficacy and safety comparison of tiotropium delivered by Respimat® and HandiHaler® in COPD patients
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:				
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**		**Study US5-2108/205.9991:** This consist of a pharmacokinetic meta-analysis for tiotropium bromide based on data obtained from patients with chronic obstructive pulmonary disease (COPD) was performed by combining plasma and urine data from studies 205.249 [U05-1949] and 205.250 [U04-2041].
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:				

Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
QTC STUDIES (PHASE 1)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	x	**6**		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable. There are no comments to the sponsor at this time
QBR questions (key issues to be considered)		**1. Is the systemic exposure of tiotropium following administration of Spiriva Respimat similar to that after the administration of Spiriva Handihaler?** **2. Does renal impairment and age affect the pharmacokinetics of the drug?** **3. Is there a dose-response relationship following administration of Spiriva Respimat?**
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Sandra Suarez
7/8/2008 11:22:08 PM
BIOPHARMACEUTICS

Wei Qiu
7/10/2008 11:39:54 AM
BIOPHARMACEUTICS