CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
BRIEFING DOCUMENT

NDA	21-395
Drug Substance	Tiotropium bromide Inhalation Powder
Drug Product	Spiriva® Inhalation Powder
Strengths	18 μg per capsule
Route of Administration	Oral Inhalation
Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
Type of submission	NME, 1S
Date of submission	12/12/01
OCPB Division	DPE-II
Clinical Division	Pulmonary and Allergy Drug Products (HFD-570)

1. EXECUTIVE SUMMARY

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. The proposed dosage of tiotropium is inhalation of the contents of one capsule (18 μg of tiotropium cation), once daily, with the HandiHaler inhalation device.

Pharmacokinetic data for tiotropium were obtained from 15 clinical studies in a total of 600 subjects. In addition, many *in vitro* studies (metabolism pathways, stability of tiotropium, protein binding) were performed to support this NDA. Pharmacokinetic characteristics of tiotropium in humans are summarized below.

The absolute bioavailability of tiotropium after dry powder inhalation is 19.5% and negligible after oral administration (2-3%). The drug is extensively distributed in the body and has a volume of distribution of 32 L/kg. The apparent terminal elimination half-life is between 5 and 6 days. An approximate steady state is achieved within 2-3 weeks by inhalation of 18 μg dry powder inhalation capsules and steady state plasma concentrations are about two times higher than concentrations after a single dose. Tiotropium plasma concentrations after an 18 μg inhalation range in steady state between a minimum of 2-4 pg/mL and a maximum of 15-20 pg/mL. Tiotropium is eliminated by renal excretion (73.6% of dose as parent compound in young healthy subjects) with a renal clearance exceeding the creatinine clearance, which suggests an active secretion by the kidney. Some of the drug (<30%) undergoes nonenzymatic ester cleavage as well as metabolism. As expected for any mainly renally eliminated drug, there is an increase of systemic exposure in subjects with renal dysfunction and thus also a slight increase in advanced age. Drug-drug interactions by tiotropium on other drugs are not expected due to the low dose of 18 μg and the lack of cytochrome P450 inhibition by tiotropium shown

in *in vitro* studies. Since elimination of tiotropium by metabolism is minor, metabolic interactions of tiotropium are not expected.

During the drug development, the formulation was changed a few times (Phase I, II and III formulations). Also, the device that delivers the dry powder inhalation capsule was changed from the Inhalator Ingelheim (FO2) device to the HandiHaler device. Although a developmental formulation and device were used in dose-ranging studies, the to-be marketed formulation (Phase III formulation) and device (HandiHaler) were used in the Phase III studies and pivotal Phase I studies.

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3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The PK data for tiotropium were obtained in 15 clinical studies in a total of 600 subjects. In addition, many *in vitro* studies (7 reviewed) were performed to support this NDA.

Absorption: Tiotropium is a quaternary amine and it is not readily absorbed into the systemic circulation after oral administration of aqueous solutions as confirmed by the low bioavailability of 2-3% in young healthy subjects, while tiotropium showed an absolute bioavailability of 19.5% after dry powder inhalation in these subjects.

Plasma profiles of tiotropium showed a rapid absorption and distribution with t_{max} at 5 min post inhalation (first sampling time), then, tiotropium plasma concentrations declined rapidly and 2-4 hours after inhalation they are often no longer quantifiable. Geometric mean tiotropium plasma concentrations 5 minutes after a first inhalation (C_{5min}) of 18 µg were often below the limit of quantification (3-5 pg/mL), while observed C_{5min} of 17-19 pg/mL after multiple doses.

There was a trend to increased plasma concentrations with higher doses, which suggest the deviant behavior from the linear dose proportionality. However, the linearity of PK could not be confirmed due to insufficient data.

Distribution: 72% of tiotropium is bound to human plasma. The volume of distribution (V_{ss}) after a 14.4 µg intravenous infusion was 32 L/kg (205.105). This high V_{ss} indicates an extensive tissue binding of the drug.

Metabolism: Tiotropium is predominantly eliminated via renal secretion of unchanged drug (73.6% of dose as a parent drug was recovered in urine after intravenous infusion in healthy young male subjects). The fate of the remaining quarter of the dose in subjects is not exactly known.

Metabolism was investigated in *in vitro* studies and *in vivo* animal studies. *In vitro* studies indicated that (1) hydrolytic cleavage of the ester bond of tiotropium occurs non-ezamatically (converted to N-methylscopine and dithienylglycolic acid). (2) N-methylscopine and other metabolites (a variety of glutathione conjugates after oxidation of the thiophen ring system) were formed enzymatically via CYP 2D6 and probably CYP 3A4. (3) N-methylscopine and dithienylglycolic acid are pharmacologically inactive, and (4) high tiotropium concentrations of 1 µmol/L did not inhibit cytochrome P450 1A1, 1A2, 2B1, 2C9, 2C19, 2D6, 2E1, or 3A4.

Elimination: In healthy young male subjects, urinary excretion of unchanged drug accounted for 73.6% and 14.4% of the dose after an intravenous infusion and dry powder inhalation, respectively. Total clearance was 880 mL/min with a renal clearance (CLr) of 669 mL/min after intravenous infusion. CLr was 486 mL/min after inhalation. Renal clearance is greater than the creatinine clearance, which suggests that tiotropium under goes active renal secretion. It is not known which cation transporter is responsible for the active renal secretion but *in vitro* investigations in CaCo2 cells showed that it is probably not p-glycoprotein. Tiotropium excreted in urine after chronic once daily inhalation by COPD patients was about 7 % and the steady state was reached after 2-3 weeks in these patients. The terminal elimination half-life of tiotropium is between 5 and 6 days

following inhalation. The high renal clearance as well as the urinary recovery of about 73.6% (intravenous) as unchanged substance indicates that the long elimination half-life may be due to a slow redistribution process.

PK/PD relationship: None of the clinical studies related the responses (efficacy or safety) to the pharmacokinetics of tiotropium. An E_{max} model established from dose-response (FEV_1) relationship data obtained from Phase II studies was arrived to select the dose for Phase III studies. Time-response plots were made using the data from studies with a single escalating inhalation doses. A second peak was seen at around 24 hrs in these studies. The reason of this 2nd peak is not known, however, it does not appear to be due to pharmacokinetic characteristics of tiotropium (i.e., no active metabolites, no enterohepatic recirculation). It could be, as the sponsor suggested, due to circadian rhythm.

Pharmacokinetics in special populations

Gender effect: Male and female COPD and asthma patients showed no relevant differences in drug plasma concentrations or urinary excretion of tiotropium.

Age Effect: Renal clearance was significantly decreased to 326 mL/min in COPD patients with a geometric mean age of 53 years to 163 mL/min (50% decrease) in patients with an mean age of 74 years following 18 μg by inhalation. The decrease in urinary excretion was associated with an increase of AUC_{0-4h} values from 18.2 pg•h/mL (69% gCV) to 26.1 pg•h/mL (63% gCV) at the same time (~40% increase). However, a dose adjustment in advanced age is not considered necessary, because COPD patients of this age range are the target population, which was consequently studied regarding safety and efficacy.

Patients with renal impairment: Following an intravenous dose of 4.8 μg in healthy volunteers, tiotropium plasma concentrations increased with renal dysfunction with more pronounced changes in subjects with a CLcr < 50 mL/min; tiotropium AUC_{0-4h} were 39, 81 and 94% higher in mild (CLcr >50-80 mL/min), moderate (CLcr >30-50 mL/min), and severe (CLcr <30 mL/min) renal impairment when compared to control subjects. The effect of a renal insufficiency on tiotropium concentrations after inhalation in COPD patients was also evaluated in Study 205.117. Trough plasma concentrations (C_{-5min}) at steady state (Day 92) increased by about 10% and 27% in mild and moderate impairment, respectively, compared to patients with normal renal function. $C_{5min,ss\ (Day\ 92)}$ increased by 84% and 188% in mild and moderate impairment, respectively, compared to patients with normal renal function. Increase of plasma concentrations was associated with a decrease of 20% and 50% in $Ae_{0-24h,\ ss}$ mild and moderate renal impairment, respectively, compared to patients with normal renal function. Therefore, tiotropium should be used with caution in patients with renal impairment, especially those with moderate and severe impairment.

Patients with hepatic impairment: The effect of hepatic impairment was not studied in human. Tiotropium was predominantly cleared by renal elimination as a parent drug

(~70% in healthy young subjects), therefore, approximately 30% of dose (part of dose are degraded by ester cleavage) are expected to be eliminated as a metabolites. Thus, based on minor elimination by a metabolism route and low tiotropium plasma concentrations after 18 µg inhalation dose, a clinically significant effect due to hepatic dysfunction is not anticipated.

Effect of COPD and asthma: The effect of the pulmonary disease on the absorbed fraction of the inhaled dose is not exactly known, because this effect is hard to separate from the confounding effects of age and formulation on the urinary excretion.

Effect of different ethnicity: Urinary excretion data indicated no clinically significant difference between Caucasian (n = 95) and African-American (n = 9) COPD patients, however, the effect of different ethnicity was not conclusively determined since majority were Caucasians.

Drug-drug interactions: Less than 30% of tiotropium dose is expected to be metabolized by cytochrome CYP 2D6 and probably CYP 3A4. Therefore, potential interactions with the inhibitors of these two enzymes (e.g., quinidine, gestodene, ketoconazole) are expected. No clinical studies have been performed to evaluate these interactions. However, based on the low extent of overall metabolism of the drug (<30%) and low tiotropium plasma concentrations (0.01 and 0.05 nmol/L) after a dose of 18 µg dry powder inhalation, a clinically significant metabolic interaction is not anticipated. Higher tiotropium plasma concentrations are expected in the 2D6 poor metabolizers. Indeed AUC_{0-4h} was 33% higher in the poor 2D6 metabolizers (there were 4 subjects in the Study 205.222) in comparison to the extensive 2D6 metabolizers, however, this change does not warrant the lower dosing regimen. In addition, *in vitro* metabolic study showed that high tiotropium concentrations of 1 µmol/L did not inhibit cytochrome P 450 1A1, 1A2, 2B1, 2C9, 2C19, 2D6, 2E1, or 3A4 in human liver microsomes.
As many cationic drugs, tiotropium is actively secreted into urine, therefore, there is a possible interaction with drugs which are also actively secreted into urine. However, there were no clinically significant changes in pharmacokinetics of tiotropium when cimetidine (400-mg tid) or ranitidine (300 mg qd) was co-administered with tiotropium.

Food effect: Clinificantly significant food effects are not expected for this hydrophilic drug with its low oral bioavailability of 2-3%.

Formulation development: Formulation of a dry powder inhalation capsule was changed (Phase I, II and III formulation) along with inhalation devices during the drug development. Dose finding trial (Study 205.108) used a developmental formulation and device (i.e., Phase II formulation with FO2 device) was used, but the to-be marked formulation with the intended device (i.e., Phase III formulation with HandiHaler) was used in Phase III and pivotal Phase I studies. In Study 205.108, the urinary excretion was lower compared to that in Phase III study, such as Study 205.117 (approximately Ae_{0-24h} of 4.5 *vs*. 7% of dose).

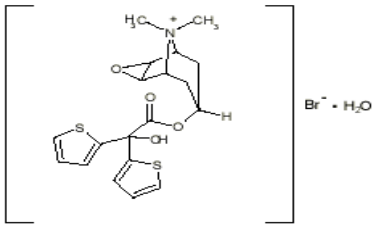
Analytical Methods: Tiotropium was quantified by the validated LC-MS/MS methods. The assay method was acceptable in terms of sensitivity and selectivity.

4. Question Based Review

4.1 General Attributes

4.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product? What is the proposed mechanism of drug action and therapeutic indications? What is the proposed dosage and route of administration?

SPIRIVA™ consists of a hard gelatin capsule containing a dry powder for use with the HandiHaler® inhalation device. Each hard gelatin capsule contains 18 μg tiotropium (equivalent to 22.5 μg tiotropium bromide monohydrate) blended with lactose monohydrate as the carrier. The drug substance, tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $C_{19}H_{22}NO_4S_2Br \bullet H2O$. It is sparingly soluble in water and soluble in methanol, and has the following structural formula:



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). Ipratropium bromide is currently on the market as a short acting (6 hours of duration of action) bronchodilator. Tiotropium bromide is intended for the long-term maintenance treatment of bronchospasm and dyspnea associated with COPD including chronic bronchitis and emphysema with one capsule inhalation powder once-daily dosing regimen.

4.1.2. What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., if disparate efficacy measurements or adverse event reports can be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?

Data from a study in asthma patients provided urinary excretion rates over a broader range of FEV_1 baseline values and suggested some minor influence of the disease severity on the urinary excretion (decreasing excretion with increasing severity). This effect was also evaluated in COPD patients of different disease severity. There was no

consistent effect of the decrease in lung function on tiotropium plasma concentrations or on the urinary excretion of tiotropium. Overall, the effect of the chronic pulmonary disease on the absorbed fraction of the inhaled dose is not exactly known, because this effect is hard to separate from the confounding effects of age on the urinary excretion.

4.2. General Clinical Pharmacology

4.2.1 What is the basis for selecting the clinical-response endpoints (i.e., clinical or surrogate endpoints or biomarkers) and how are they measured in clinical pharmacology and clinical studies?

The clinical pharmacology of tiotropium was evaluated in 22 completed clinical trials (reviewed 15 studies which contained the PK). The tolerability and bronchoactive properties of tiotropium in relation to dose were evaluated in healthy volunteers, COPD patients and asthma patients.

Efficacy variables: Tiotropium is an anticholinergic bronchodilator. The effects of tiotropium is evidenced by improvements in FEV_1 (Forced Expiratory Volume in one second), FVC (Forced Vital Capacity), PEER (Peak Expiratory Flow Rate) or decrease in airway resistance (R_{aw}). In the clinical trials, the bronchodilator efficacy of inhaled tiotropium was primarily determined by trough FEV_1 response; defined as change from base line in trough FEV_1; trough FEV_1 was calculated as the mean of the two FEV_1 readings prior to the first administration of study medication and at the end of the dosing interval. Secondary endpoints include FVC, PEER, R_{aw}, PEFRs, COPD/asthma symptoms, physician's global evaluation, albuterol rescue use, oral and inhaled steroid use, theophylline use, the number of awakenings, Baseline and Transitional Dyspnea Index, and quality of life measures. To assess the quality of life, the Impact score from the St. George's Hospital Respiratory Questionnaire (SGRQ) was used.

Safety Measures: Adverse events, fluctuation in the patient's COPD/asthma symptoms, Clinical and laboratory tests, ECG and vital signs were monitored.

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

Only the parent compound, tiotropium, was measured in the plasma and urine. Tiotropium concentrations in plasma could only be measured up to 2 hrs post dose in most of the studies in healthy volunteers even with the adequate assay method (LC/MS/MS). This could be due to the high volume of distribution and the small dose. Therefore, PK parameters were estimated using the urine data. It should be noted that even urine data were not optimally collected in most of studies (e.g., urine was collected usually up to 4, 8, 24 hrs, not long enough compared to $t_{1/2}$ of 5-6 days). There is only one study (Study 205.105) that measured urine up to 25 days after tiotropium dose.

4.2.3. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

The sponsor conducted a dose-ranging study (Study 205.108) that was used to selct the dose for Phase III program (see section 4.2.3.4, page 9).

4.2.3.1. Based on PK parameters, what is the degree of linearity or non-linearity in the dose- concentration relationship?

Dose proportionality was evaluated using the data after iv infusion, oral administration and dry powder inhalation of tiotropium.

Intravenous doses: As shown in Table 1, there was a trend to increased urinary excretion after doses of 2.4, 4.8, 9.6 and 14.4 µg tiotropium. A similar trend was observed for plasma concentrations (Study 205.107).

Table 1. Geometric mean (% gCV): data from Study 205.107 after single iv infusion

Dose	2.4 µg	4.8 µg	9.6 µg	14.4 µg
$Ae_{0\text{-}24h}$ (% of dose)	39.3 (7)	42.0 (17)	46.0 (6)	54.3 (4)
C_{15min} (pg/mL)[a]	322.8 (9)	375 (16)	306 (24)	390 (22)

[a]Dose normalized to 14.4 µg

Oral doses: Tiotropium plasma concentrations were regularly below the limit of quantification and are therefore not discussed. Urinary excretion seemed to increase slightly with higher doses; 0.72%, 0.84%, 0.69% and 0.99% of dose were renally excreted over 24 hours for 8, 16, 32 and 64 µg respectively (Study 205.106).

Inhalation doses: The geometric mean urinary excretion data ($Ae_{0\text{-}4h}$) after a single and multiple doses are summarized in Table 2.

Table 2. Geometric mean % of tiotropium dose excreted unchanged in urine in the interval 0-4 h after dry powder inhalation by young healthy subjects

Study	Dose 8.8 µg	17.6 µg	35.2 µg	70.4 µg	108 µg	141 µg	282 µg
Single dose							
205.102	--	--	1.88	1.67	--	2.36	3.19
205.103	--	--	--	1.33	--	1.78	--
205.104	1.34	1.61	1.31	--	--	--	--
205.105	--	--	--	--	1.84	--	--
Multiple dose							
205.104	3.13	3.63	4.28	--	--	--	--
205.103	--	--	--	4.03	--	4.22	--

Note: multiple dose measured on Day 14 (Study 205.104) and 7 (Study 205.103)

As show in Table 2, there is a trend to higher urinary excretion after the higher doses. A similar trend was observed for urinary excretion, such as, 10.5%, 12.1% and 14.7% of the dose were excreted unchanged within 24 hours after doses of 8.8, 17.6 and 35.2 µg tiotropium measured on Day 14, respectively (Study 205.104). The reason(s) for this trend is not known. The sponsor speculates that an easier elimination could occur from

the binding sites (including muscarinic receptors) for the higher doses due to saturation of the binding sites. Dose proportionality within the therapeutic range cannot be determined due to insufficient data.

4.2.3.2. Do PK parameters change with time following chronic dosing?

No, the second once daily tiotropium inhalation dose (at a low dose range) generates consistently slightly higher AUC values than expected from the first dose (also seen it after intravenous infusion in Study 205.107). The reason for this finding is not know, however the sponsor suggested that this might be due to incomplete saturation of binding sites (including muscarinic receptors) after the first dose and a very slow dissociation constant of the tiotropium binding site complex. Once all binding sites are at least near to saturation, more tiotropium can escape from the tissue and the drug appears faster in the systemic circulation, which leads to higher systemic plasma concentrations. Urinary excretion indicated an accumulation by the factor 2-3 from first to the fourteenth inhalation.

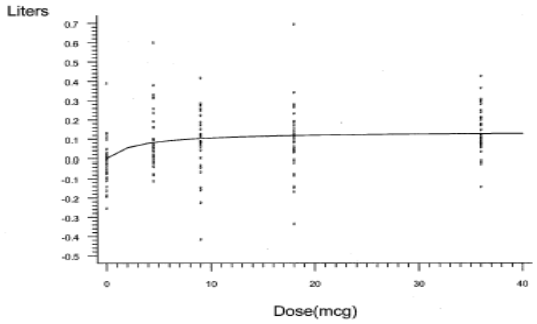
4.2.3.3. How long is the time to the onset and offset of the pharmacological response or clinical endpoint?

See Figure 2 on page 10 for study that measure pharmacodynamic endpoint (FEV_1).

4.2.3.4. Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Dose-Response relationship (Efficacy): A dose ranging study with a four-week multiple dose design (Study 205.108) showed that tiotropium administered once a day by oral inhalation via the FO_2 inhalation device over a range of doses (4.4, 8.8, 17.6 and 35.2 μg) was considered safe and effective. E_{max} model was fitted to the dose-response data (Figure 1). As shown in Figure 1, there is no apparent relationship (may be trends) between dose and response (FEV_1). Nevertheless, this study and two other dose-ranging studies (Study 205.119 and Study 205.120) provided support for a selection of 18 μg dose of titropium for the phase III program.

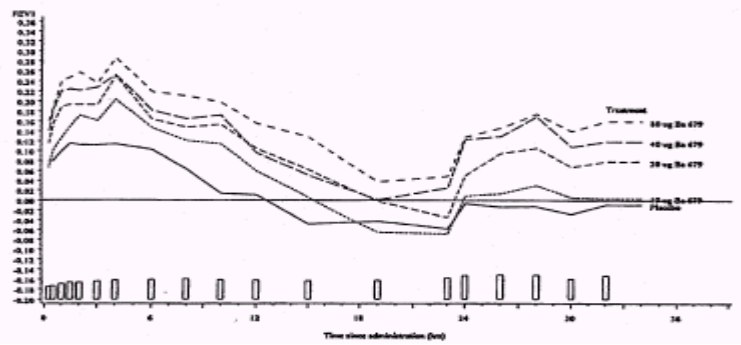
Figure 1. E_{max} Model of Dose-Response Data (205.108)



The relationship between the pharmacokinetics of tiotropium and the efficacy or safety variables was not explored in this submission. Safety parameters (see page 8 under 4.2.1 question) were measured at various times throughout the trial.

2nd Peak in Time-Response data: Approximately 24 hrs after a single dose inhalation of tiotropium, response (measured by mean FEV_1) was increased (2nd peak) in dose ranging studies (Figure 2). The 2nd peak was shown also in patients who received a placebo (smaller peak compared to the patients who received tiotropium). This 2nd peak could not be attributed to PK of tiotropium (no active metabolites, no enterohepatic recirculation) or to the intrinsic/extrinsic factors. It could be, as the sponsor suggested, due to the circadian rhythm.

Figure 2. Increase in Mean FEV_1 (L)



4.2.4. How does the PK of tiotropium in healthy volunteers compared to that in patients following dry powder inhalation? What are the basic PK parameters? Is this a high extraction ratio or a low extraction ratio drug?

Pharmacokinetics after intravenous doses: Tiotropium was infused in doses ranging from 2.4 to 14.4 µg over 15 minutes in healthy male subjects (Studies 205.105, 107 and 134). Tiotropium plasma concentrations at the end of the infusion (C_{max}) reached dose-normalized (to 18 µg) values of 320-440 pg/mL for 14.4 µg depending on the subject group tested. Study 205.105 provided the most complete pharmacokinetics of tiotropium among studies conducted (in this study, tiotropium was administered also by inhalation as well as orally): the mean (% gCV) values of volume of distribution (V_{ss}), total clearance, renal clearance, half-life and the residence time of tiotropium after 14.4 µg iv dose are of 32 L/kg (27.8% gCV), 880 mL/min (22.1% gCV), 669 mL/min (16.5% gCV), 5.7 days (26% gCV) and 50.6 hrs (31.5% gCV), respectively. Urinary excretion as an unchanged tiotropium was 73.6% in young healthy subjects after intravenous infusions and 14.4% after dry powder inhalation. Urinary excretion in the first 4 (or 24) hours was already 43.8% (53.6%) of the dose (thus 59% and 72% of the total urinary excretion are achieved within 4 hours and 24 hours). The long $t_{1/2}$ was not explained by the binding of tioptropium to erythrocytes, but expected due to binding of tioptropium to tissues.

Table 3. Geometric mean (% gCV) tiotropium PK parameters after intravenous infusion of 14.4 µg, dry powder (DP) inhalation of 108 µg or oral solution of 64 µg

tiotropium to different groups of twelve healthy male subjects,

			group comparison (n=12)					
			intraven. 14.4 µg		DP inhalation 108 µg		oral solution 64 µg	
		n	gMean	%gCV	gMean	%gCV	gMean	%gCV
C_{max}	[pg/mL]	11/11/12	378	25.4	65.4	58.0	2.35&	87.7
t_{max}		-/11/5	#	---	5 min	##	§ 2 h	§ 1-8 h
NC_{max}	[pg/mL] for 18 µg	11/11/12	473	25.4	10.9	58.0	0.66	87.7
AUC_{0-2h}	[pg.h/mL]	9/11/-	143	18.7	39.9	38.7	--	--
AUC_{0-4h}	[pg.h/mL]	9/11/-	161	19.4	61.7	34.1	--	--
AUC_{0-8h}	[pg.h/mL]	5/11/-	186	25.0	92.6	28.4	--	--
$NAUC_{0-2h}$	[pg.h/mL] for 18 µg	9/11/-	179	18.7	6.65	38.7	--	--
$NAUC_{0-4h}$	[pg.h/mL] for 18 µg	9/11/-	201	19.4	10.3	34.1	--	--
$NAUC_{0-8h}$	[pg.h/mL] for 18 µg	5/11/-	233	25.0	15.4	28.4	--	--
Ae_{0-4h}	[% of dose]	11/10/9	43.8	10.2	1.84	40.7	0.39	39.8
Ae_{0-8h}	[% of dose]	11/11/9	48.0	10.6	2.83	33.6	0.67	30.1
Ae_{0-24h}	[% of dose]	11/8/9	53.6	11.4	4.99	22.4	1.04	31.2
Ae_{0-96h}	[% of dose]	11/6/9	61.0	11.7	8.93	9.4	1.60	30.0
$Ae_{0-\infty}$	[% of dose]	11/9/9	73.6	13.7	14.4	7.8	--	--
F	[%]	(11)/9/9	--	--	19.5	--	2.6	
$CL_{r\,(0-4h)}$	[mL/min]	8/11/-	669	16.5	486	14.0	--	--
$t_{½}$	[h]	11/11/-	137	26.0	116	16.1	--	--
$t_{1/2}$	[days]	11/11/-	5.71	26.0	4.84	16.1	--	--
Parameters calculated from plasma concentrations that were obtained from urinary excretion data via renal clearance (only values > BLQ):								
$AUC_{0-\infty}$	[pg.h/mL]	8/9/-	273	22.1	518	16.6	--	--
$NAUC_{0-\infty}$	[pg.h/mL] for 18 µg	8/9/-	341	22.1	86.3	16.6	--	--
CL, CL/f	[mL/min]	8/9/-	880	22.1	3474	16.6	--	--
V_{ss}	[L]	8/-/-	2665	27.8	--	--	--	--
V_Z	[L/kg]	8/-/-	138	27.6	--	--	--	--
$MRT_{dis/tot}$	[h]	8/9/-	50.6	31.5	110	18.2	--	--

at the end of infusion (15 min),
always in the first plasma sampling 5 min post dose, § median and range
& values below 2.46 replaced by ½ this LOQ. Source data in U99-1315

Pharmacokinetics after inhalation: Tiotropium was rapidly absorbed after inhalation regardless the inhalation device used in any studies. The earliest blood sample was always scheduled 5 minutes after inhalation and this plasma sample contained with a few exceptions always the highest tiotropium concentration (C_{max}) of the complete profile, suggesting a very rapid absorption. Then, tiotropium concentrations fell rapidly afterwards in an polyexponential (the sponsor used 4-5 compartment model) manner and were usually not quantifiable after 2 to 8 hours post inhalation, while urinary excretion was quantifiable for days after a single inhalation. Urinary excretion rates declined polyexponentially until they reached an apparent terminal elimination phase at about 96 hours post dose. Urinary excretion after a single dose ($Ae_{0-\infty}$) was 14.4% (7.8% gCV) for a dose of 108 µg in Study 205.105. This was the only study which collected urine long enough for a reliable calculation. The terminal elimination half-life was 4.84 days in the Study 205.105 and geometric mean values ranged from 5 to 7 days in other studies. The pharmacokinetic parameter values from Study 205.105 are shown in Table 3.

PK parameters from individual studies following a single and multiple doses of tiotropium by inhalation in healthy subjects and patients with COPD or asthma are summarized in Table 4.

Table 4. Tabular overview of geometri mean (% gCV) PK parameters of individual single or multiple dose tiotropium studies after inhalation doses in healthy subjects (shaded area) and patients with COPD or asthma (C_{5min} and AUC_{0-2h} are dose normalized to 18 µg).

Study	Dose (µg)	C_{5min} (pg/mL)	AUC_{0-2h} (pg•h/mL)	Ae_{0-4h} % of dose	Ae_{0-24h} % of dose	CLr (mL/min)	$t_{1/2}$ (days)
Single Dose							
205.103	*70.4*	*8.61 (63)*	*6.4 (64)*	*1.33 (54)*	-	-	-
	141	*13.7 (75)*	*9.4 (58)*	*1.78 (62)*	-	-	-
205.104	*8.8*	-	-	*1.34 (35)*	*3.30 (27)*	-	-
	17.6	*15.1 (94)*	-	*1.61 (65)*	*4.64 (48)*	-	-
	35.2	*6.9 (32)*	-	*1.31 (50)*	*3.70 (6)*	-	-
205.105	*108*	*10.9 (58)*	*6.65 (39)*	*1.84 (41)*	*4.99 (22)*	*486 (14)*	*4.8 (16)*
205.108	8.8	-	-	-	-	-	-
	17.6	6.53 (44)	-	-	-	-	-
	35.2	10.07 (80)	-	-	-	-	-
205.120	8.8	-	-	0.85 (89)	-	-	-
	17.6	-	-	1.50 (55)	-	-	-
	35.2	7.52 (21)	-	1.70 (27)	-	-	-
	70.4	8.57 (56)	-	1.69 (25)	-	-	-
205.133	18[a]	4.87 (69)	5.99 (28)	0.61 (143)	-	-	-
	18[b]	7.06 (83)	8.12 (46)	0.66 (66)	-	-	-
205.201	18	-	-	0.53 (66)[c]	-	-	-
	36	-	-	0.92 (105)[c]	-	-	-
Multiple Dose							
205.103	*70.4*	*16.4 (49)*					
	141	*25.4 (57)*					
205.104	*8.8*	*16.2 (50)*	-	*3.13 (50)*	*10.5 (26)*		*5.8 (23)*
	17.6	*25.1 (58)*	-	*3.63 (39)*	*12.1 (20)*		*7.7 (31)*
	35.2	*16.5 (16)*	*16.4 (7)*	*4.28 (25)*	*14.7 (14)*	*407 (8)*	*6.0 (21)*
205.108	8.8	13.5 (39)[d]			4.8 (28)[d]		
	17.6	7.68 (36)[d]			3.97 (48)[d]		
	35.2	18.31(35)[d]			4.75 (38)[d]		
205.117	18	15.3 (63)[e]	-	2.02 (52)[c]	6.63 (66)	-	-
		19.2 (73)[f]		1.46 (82)[c]	7.01 (38)		
		16.1 (72)[g]		1.32 (54)[c]	6.95 (45)		
		19.0 (45)[h]		0.98 (77)[c]	7.43 (59)		
205.133	18[a]	9.63 (142)	10.8 (84)	1.97 (74)	-	326 (60)	5.5 (29)
	18[b]	15.3 (60)	15.7 (67)	1.42 (89)	-	163 (93)	6.5 (29)
205.201	18	-	-	1.19 (122)[c]	-	-	-
	36	-	-	2.15 (61)[c]	-	-	-

[a]Younger patients (45-58 yrs age) [b]Older patients (69-80 yrs age) [c]Ae_{0-2h}
[d]day 22 [e]40-49 yrss [f]50-59 yrs [g]60-69 yrs [h]>69 yrs

Single dose: Geometric mean tiotropium plasma concentrations 5 minutes after (C_{5min}) a single 17.6 µg dose in healthy young male subjects were 14.8 pg/mL (94.3% gCV) in Study 205.104 and 10.9 pg/mL (58% gCV) in Study 205.105. In COPD patients, calculated C_{5min} of tiotropium was 4.9-7.1 pg/mL (69-83% gCV) after a single dose (Study 205.133).

Urinary excretion of tiotropium were 1.61% of dose (64.8% gCV) in the interval 0-4 h and 4.64% (47.6% gCV) in the fraction 0-24 h in Study 205.104, while those values in Study 205.105 were 1.84% (40.7% gCV) and 4.99% (22.4% gCV), respectively. In COPD patients, urinary excretion of tiotropium showed lower values with 0.61-0.66% in the 4 h interval (Study 205.133).

A comparison of Ae_{0-4h} (1.84%) and Ae_{0-24h} (4.99%) values with the total urinary excretion (14.4%) in Study 205.105 showed a different behavior in contrast to the excretion after an intravenous dose. About 12.8% (= 1.84/0.144) and 34.7% (= 4.99/0.144) of the total excretion was complete 4 and 24 hours after inhalation. This is much less than for infusion with 59.5% and 72.8% for the same time intervals. There was therefore a clear difference in tiotropium disposition between intravenous infusion and inhalation. The reason is not known, however, as the sponsor suggested, this could be due to a more pronounced tissue binding sites in the lung after inhalation. The fraction of an intravenous infusion, which gets access to lung tissue is smaller and the load for the kidney becomes much higher, which results in a faster excretion. The longer mean residence time of 110 h (18.2% gCV) after inhalation *vs* 50.6 hours (31.5% gCV) after infusion fits in this view.

Multiple doses: Pharmacokinetic profiles after 7 (Study 205.103 and 133) or 14 days (Study 205.104 and 133) were investigated in Phase I studies. Urinary excretion in asthma patients was also studied after 21 days in Study 205.201. The following results are summarized based on these studies:

- The accumulation factor did not exceed the 2-3 despite a terminal elimination half-life of 5-7 days and a once daily dosing regimen. This suggests that long terminal elimination half-life is not dominant (Study 205.103). It was shown that there was no further accumulation with continued tiotropium inhalation (e.g. over weeks and months). Peak as well as trough plasma concentrations and urinary excretion remained approximately constant over months once a steady state was achieved (Study 205.117).
- Based on $t_{1/2}$ of 5-7 days, steady state conditions are expected to be reached 3-5 weeks of continued treatment and such a long treatment time was only reached in the 4-week Study 205.108 and the 1-year safety and efficacy studies (Study 205.114/117). However, the scatter in the data does often not allow differentiating between data after 7 and 14 days treatment. Thus approximate steady state conditions is achieved after 7-14 days treatment.
- Geometric mean tiotropium concentrations in healthy subjects 5 minutes after a 17.6 µg tiotropium dose given for 14-days inhalation were 24.6 pg/mL (58% gCV) after a 17.6 µg tiotropium dose given for 14-days (Study 205.104). Corresponding values in COPD patients were 9.63 pg/mL (142% gCV) and 15.3 pg/mL (60.0% gCV) in younger (mean 53 years of age) and older patients (mean 74 years of age), respectively (Study 205.133). In COPD patients (Study 205.117), C_{5min} and C_{-5min} (trough) at true steady state conditions (e.g., measurements on Day 50 or 92) were about 18.6 and 5.8 pg/mL, respectively. 24-h urine samples at steady state conditions (Day 50) showed 7.01% of dose (62.6% gCV) for female and 7.12% of dose (38.2% gCV) for male patients were excreted in urine (Study 205.117). Therefore, this data

suggests that steady state conditions are not much different from the status achieved within 2 weeks of treatment.

- Urinary excretion of tiotropium in healthy subjects reached 3.63% of dose (39.1% gCV) in the interval 0-4 h after two weeks and 12.1% of dose in the interval 0-24 h (Study 205.104). Corresponding values in COPD patients for the interval 0-4 h were 1.42% (88.7% gCV) to 1.97% (74.4% gCV) in older and younger patients of Study 205.133, respectively.

Absolute bioavailability: Absolute bioavailability was 19.5% after an inhalation (Study 205.105). The respective value for an oral dose is between 2% and 3%. This means that about 17% of the inhaled dose reached the lung, while up to 83% were swallowed (assume full bioavailability from the lung).

Overall summary: Tiotropium is a quaternary amine and it is not readily absorbed into the systemic circulation. This was confirmed by the low bioavailability of 2-3% for oral solutions in young healthy subjects, while tiotropium showed an absolute bioavailability of 19.5% in these subjects. Urinary excretion of unchanged drug was 73.6% and 14.4% ($Ae_{0-\infty}$) of the dose after an intravenous and inhalation dose respectively in healthy subjects and 7% (Ae_{0-24h}) after inhalation of tiotropium in COPD patients. The drug has a high volume of distribution of 32 L/kg, a total clearance of 880 mL/min and a terminal elimination half-life of 5-6 days. The renal clearance of tiotropium (669 mL/min after an iv dose) exceeds the creatinine clearance, which suggests the presence of active secretion into kidney tubules. After multiple administration, (approximate) steady state was reached after 2-3 weeks with an accumulation factor of about two to three. Pharmacokinetics linearity of tiotropium could not be confirmed due to insufficient data.

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 (Table 3). Absorption of the drug could be affected by the Disease State (COPD/asthma), however, it is not exactly known, because this effect is hard to separate from the confounding effects of age on the urinary excretion.

4.2.5. Does mass balance suggest renal or hepatic the major route of elimination?

A mass balance study of tiotropium in humans was not conducted. The sponsor stated that this was not possible due to the combination of analytical problems and the PK characteristics of tiotropium (i.e., large V_{ss}, long $t_{1/2}$, metabolism play a minor role in the excretion of tiotropium, inhalation route of administration, etc.). However, following iv infusion 73.6% of the dose is excreted in urine as unchanged drug. The remaining 25% of the dose undergo nonenzymatic hydrolysis and CYP 450 metabolism (see section 4.4.2, page 17).

4.3 Intrinsic Factors

4.3.1 What are the relevant covariates that influence the pharmacokinetic variability of tiotropium?

Pharmacokinetics in elderly subjects with COPD: Study 205.133 evaluated age factor on PK of tiotropium in patients with COPD, and the results are summarized in Table 5. Renal clearance of tiotropium was significantly lower in the elderly patients (163 mL/min) compared with younger patients (326 mL/min). C_{5min} and AUC_{0-4h} were 59% and 43% higher, respectively, in the elderly than the younger COPD patients (Day 14). However, age factor on the PK of tiotropium can not be confirmed due to the confounding factor of old age (compromised renal function). Table 6 lists multiple dose pharmacokinetic parameters in subjects of various age groups.

Table 5. Geometric mean PK parameters in elderly (69-80 yrs) and young (45-58 yrs) patients

		elderly patients		young patients		
		gMean	95% CI	gMean	95% CI	
Day 1						ratio
C_{5min}	pg/mL	7.06	3.68-13.6	(4.87)	2.71-8.74	(1.45)
AUC_{0-4h}	pg h/mL	(13.7)	(10.4-18.0)	(11.2)	(9.34-13.4)	(1.22)
Ae_{0-4h}	% of dose	0.661	0.384-1.14	0.606	0.224-1.64	1.09
CL_{ren}	mL/min	(141)	83.2-239	(162)	62.9-417	(0.870)
Day 7						ratio
C_{5min}	pg/mL	13.2	6.76-25.8	11.6	4.86-27.7	1.14
AUC_{0-4h}	pg h/mL	21.8	14.3-33.3	17.9	10.7-29.9	1.22
Ae_{0-4h}	% of dose	1.42	0.936-2.15	1.61	0.704-3.68	0.882
CL_{ren}	mL/min	194	113-333	268	136-527	0.724
Day 14						ratio
C_{5min}	pg/mL	15.3	9.27-25.3	9.63	3.58-25.9	1.59
AUC_{0-4h}	pg h/mL	26.1	15.5-43.9	18.2	10.1-32.8	1.43
Ae_{0-4h}	% of dose	1.42	0.713-2.83	1.97	1.05-3.68	0.721
CL_{ren}	mL/min	163	79.9-333	326	193-550	0.500
Overall						ratio
$t_{½}$	days	6.5	4.93-8.57	5.5	4.16-7.27	1.18

Note: (1) Elderly = mean age of 74 years (range 69-80 years); Young = mean age of 53 years (range 45-58 years). (2) Drug plasma concnetrations below 5 pg/mL (LOQ) were replaced by ½ the LOQ to calculate PK parameters. Parameter values with a high incidence of replaced values were set into brackets.

Table. Multiple dose tiotropium pharmacokinetic parameters (geometric means) for dry powder inhalation and different age groups

study	age [yrs] *	dose	n	C_{5min} [pg/mL]	%gCV	C_{2h} [pg/mL]	%gCV	Ae_{0-4h} [% of dose]	%gCV	Ae_{0-24h} [% of dose]	%gCV
205.105	28-42	108	-/-/-/9	--	--	--	--	--	--	14.4 &	8
205.104	24-45	17.6 $	2/-/5/5	25	58	--	--	3.63	39	12.1	20
205.104	24-45	35.2 $	3/4/5/5	17	16	4.4	22	4.28	25	14.7	14
205.117#	40-49	18	7/9/-/6	15	63	7.9	30	--	--	6.63	66
205.133	45-58	18	12/12/12/-	10 §	142	4.0 §	68	1.97	74	--	--
205.117#	50-59	18	20/24/-/23	19	73	8.2	52	--	--	7.01	38
205.117#	60-69	18	38/39/-/42	16	72	7.8	42	--	--	6.95	45
205.133	69-80	18	13/13/13/-	15 §	60	5.7 §	69	1.42	89	--	--
205.117#	70-85	18	19/24/-/28	19	45	12	48	--	--	7.43	59

§: BQL replaced by ½ BQL
&: single dose, to strengthen the data base for young subjects, $Ae_{0-\infty}$, corresponds to Ae_{0-24h} in steady state
$: normalized to a 18 µg dose
#: data for Day 50
* range

Pharmacokinetics in subjects with renal impairment: 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 (Study 205.134). The results are summarized in Table 7.

The effect of a renal insufficiency on tiotropium plasma concentrations after inhalation was also evaluated in Study 205.117 (COPD patients). Trough tiotropium plasma concentrations (C_{-5min}) at steady state (Day 92) increased by about 10% and 27% in mild and moderate impairment, respectively, compared to patients with normal renal function. $C_{5min,ss\ (Day\ 92)}$ increased by 90% and 188% in mild and moderate impairment, respectively, compared to patients with normal renal function. Increase in tiotropium plasma concentrations was associated with a decrease of $Ae_{0-24h,\ ss}$ 0.3% and 33% in mild and moderate renal impairment, respectively, compared to patients with normal renal function. Therefore tiotropium should be used with caution in patients with renal impairment, especially those with moderate and severe impairment.

Table 7. 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]	$t_{1/2}$ [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

Pharmacokinetics in subjects with hepatic impairment: No study was performed in patients with hepatic impairment. Tiotropium was predominantly cleared by renal elimination as a parent drug (~70% of the dose is excreted in urine in healthy young subjects), therefore, approximately 30% of dose are expected to be eliminated as metabolites. Tiotropium was degraded by nonenzymatic ester cleavage (U98-2865). Also, tiotropium was metabolized by CYP 2D6 and probably by CYP 3A4. Therefore, there is possible interaction with drug(s) that are substrate of CYP 2D6 and 3A4, such as quinidine and ketoconazole, and concern for CYP 2D6 poor metabolizers. Four subjects from the study 205.222 were identified (by genotype). AUC_{0-4h} was 33% higher in the poor 2D6 metabolizers in comparison to the extensive 2D6 metabolizers.

However, overall, based on the low extent of overall metabolism of the drug (<30%) and low tiotropium plasma concentrations (0.01 and 0.05 nmol/L) after 18 µg dry powder inhalation dose, a clinically significant change due to metabolic interaction or hepatic dysfunction is not anticipated. Similarly, PK change shown in poor 2D6 metabolizers does not warrant the lower dosing regimen.

Pharmacokinetics in subjects of different human races: 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.

PK in Pediatric patients: Pharmacokinetic data in subjects under an age of 18 years are not available. Tiotropium inhalation powder was intended for the maintenance treatment of bronchospasm and dyspnea associated with COPD including chronic bronchitis and emphysema. Since the disease being treated is typically found in older patients, the lack of data in subjects with an age of less than 18 years is not considered to be an issue.

4.4 Extrinsic Factors

4.4.1. What are the extrinsic factors (drugs, herbal products, diet, smoking, and alcohol) influence exposure and/or response of tiotropium?

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

4.4.2. Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Some of the administered dose (<30%) of tiotropium is metabolized by cytochrome CYP 2D6 and probably CYP 3A4. Therefore, there may be potential interactions with inhibitors of these two enzymes (e.g., quinidine, gestodene, ketoconazole). No clinical studies have been performed to evaluate the interactions. However, based on the low extent of overall metabolism of the drug (<30%) and low tiotropium plasma concentrations (between 0.01 and 0.05 nmol/L) after a dose of 18 µg by dry powder inhalation, clinically significant metabolic interaction is not anticipated.

Since mass balance study in human was not conducted, metabolism was investigated using *in vitro* studies (and *in vivo* animal studies). *In vitro* metabolism of tiotropium was investigated in human liver microsomes and in liver microsomes from mice, rats, and dogs to compare the metabolic pattern between species (U99-1348). The results from this study are summarized as follows:

- Ba 679 BR is metabolized by CYP resulting in the formation of N-methylscopine. The site of metabolic attack was the dithienylglycolie acid moiety.
- The metabolic pathways leading to the metabolites observed *in vitro* are oxidation in the thiophene ring systems, glutathione conjugation and oxidative cleavage of thiophene ring systems.
- Enzymatic cleavage of the ester linkage either by esterases or by CYP does not occur.
- Use of enzyme specific chemical inhibitors (e.g., ketoconazole, quinidine), recombinant CYPs, and correlation analysis showed the involvement of CYP 3A4 (minor) and CYP 2D6 (dominant) the metabolism of Ba 679 BR.
- These principal pathways were also observed with rat and human hepatocytes.
- Metabolism is marginal in rat lung microsomes compared to rat liver microsomes.

Stability of tiotropium bromide in plasma was evaluated *in vitro*. Tiotropium bromide is stable in acidic aqueous solutions (pH 2). The hydrolytic cleavage becomes more rapid with increasing pH and had a hydrolysis half-life of 17 h at 37 °C in pH 7.4 plasma as well as in 0.1 M phosphate buffer pH 7.25 (U91-0236). The hydrolysis of the ester bond was temperature-sensitive, as the rate of hydrolysis was threefold lower at 25°C (U91-0236).

The possible involvement of esterases as well as the possible species specificity of tiotropium cleavage in plasma was investigated in EDTA-plasma of mice, rats, dogs, rabbits and humans (U98-2865). Neither physostigmine, paraoxon, PMSF nor PCMB (esterase inhibitors) influenced the hydrolysis of tiotropium bromide. BEA 2108 BR, a structurally related compound to tiotropium bromide, had also no effect on tiotropium bromide hydrolysis. The results indicated that plasma esterase enzymes did not contribute to the hydrolysis of tiotropium bromide. This study showed that hydrolytic cleavage of the ester bond of tiotropium (formed to N-methylscopine and dithienylglycolic acid) was occurred in plasma, therefore, it occurred via nonenzymatic reaction. Inhibition of CYPP450 by tiotropium was investigated (U97-2651). The results showed that tiotropium (used concentrations of 1 µmol/L) did not inhibit cytochrome P 450 1A1, 1A2, 2B1, 2C9, 2C19, 2D6, 2E1, or 3A4 in human liver microsomes.

In summary, metabolism plays a minor role in the elimination of the drug from the body (73.6% renal excretion of unchanged drug after an iv dose). It showed that hydrolytic cleavage of the ester bond of tiotropium occurred in plasma (formed to N-methylscopine and dithienylglycolic acid). A (minor) amounts are metabolized by the cytochrome CYP 450 2D6 and probably CYP 450 3A4 involving the formation of N-methylscopine and a variety of glutathione conjugates after oxidation of the thiophen ring system.

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

In vitro study showed that high tiotropium concentrations of 1 µmol/L did not inhibit cytochrome P 450 1A1, 1A2, 2B1, 2C9, 2C19, 2D6, 2E1, or 3A4 (U97-2651) in human liver microsomes.

4.4.4. Are there other metabolic/transporter pathways that may be important?

Interactions via p-glycoprotein: Tiotropium may be secreted into the gastrointestinal tract (like in animals) as well as active secretion into the kidney, then, there is possible interactions with p-glycoprotein (i.e., p-glycoprotein may inhibit tiotropium secretion into gut and the renal proximal tubulus). Thus it was investigated in CaCo 2 cells *in vitr*o, whether ciclosporine (well known competitive inhibitor of p-glycoprotein) did change tiotropium uptake in CaCo 2 cells or not. No effect was found, thus, it appears that tiotropium is not dependent on p-glycoprotein to be transported to the kedney (U00-1350).

Interactions via renal elimination: Since tiotropium is expected to be actively secreted by the renal tubule (because tiotropium renal clearance is relevantly high compared to the

creatinine clearance), 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 (Study 205.222). As shown in Table 8, no clinically significant interaction occurred between tiotropium and cimetidine or ranitidine.

Table 8. Summary of geometric mean (% gCV) PK parameters

		with cimetidine			tiotropium alone			Point	90% CI
Tiotropium 14.4 µg		gMean	%gCV	n	gMean	%gCV	n	estimate	
AUC_{0-4h}	pg.h/mL	304	26.0	6	253	23.3	6	1.20	1.03-1.4
C_{max}	pg/mL	664	26.8	6	635	10.6	6	1.05	0.8-1.37
Ae_{0-96h}	% dose	47.2	15.5	5	48.2	14.8	5	-	-
CLr	mL/min	277	26.4	5	355	19.6	5	-	-
Tiotropium 14.4 µg		with ranitidine			tiotropium alone			Point estimate	90% CI
		gMean	%gCV	n	gMean	%gCV	n		
AUC_{0-4h}	pg.h/mL	254	19.6	12	256	19.4	12	0.99	0.9-1.08
C_{max}	pg/mL	596	24.1	12	683	16.3	12	0.87	0.73-1.04
Ae_{0-96h}	% dose	50.4	11.1	11	50.6	9.7	11	-	-
CLr	mL/min	343	28.0	11	342	25.7	11	-	-

4.5 General Biopharmaceutics

4.5.1. Based on BCS principle, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The aqueous solubility of the compound is about 25 mg/ml 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. 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. Moreover, a variety of efficient transporters in the gut pump drugs out of the cells in the gut lumen thereby eliminating the drug from the body and reducing net absorption. Since tiotropium is inhalation route of administration, dissolution is not relevant.

4.5.2. Has the proposed commercial formulation and device been adequately linked to the Phase III clinical trial formulation and device?

Tiotropium was administered in several formulations throughout the clinical development including intravenous infusions, oral solutions, and solutions for dispersion by a piezoelectric device as well as by dry powder inhalation from inhalation capsules.

Inhalation solution was administered via piezoelectric dispersion (Study 205.101), BINEB (Study 205.112) or RESPIMAT device (205.127). Dry powder inhalation was administered via Inhalator Ingelheim (FO2 device) or HandiHaler device.

During the development, the contents of dry powder inhalation capsule were changed (Phase I, II and III formulation). Dry powder inhalation capsule with Phase III formulation is the to-be marketed formulation and this will be delivered by the HandiHaler device. The to-be marketed formulation with the HandiHaler device was used in pivotal clinical trials, such as 205.105, 114/117, 133, 139 (on going study) and 201.

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

Food effect was not evaluated, however, it is expected not significant since this hydrophilic drug has low oral bioavailability of 2-3% and the drug will be administered by inhalation route.

4.6 Analytical

4.6.1. Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Tiotropium was quantified by the validated LC-MS/MS assay method. This validated LC-MS/MS assay for tiotropium after ion pair extraction was able to measure concentrations down to 5 pg/mL in human plasma and 10 pg/mL in human urine. The performance of the assay during study sample analysis was acceptable as evidenced by QC sample precision and accuracy within ± 15%.