CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-595

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics Review

NDA	21-595
Product Trade Name	Sanctura™
Active Ingredient	Trospium chloride
Formulation	Immediate release tablet
Strength	20 mg; twice daily dosing
Indication	Overactive bladder
Submission Dates	April 28, 2003; May 28, 2003; August 26, 2003; September 30, 2003; November 17, 2003; November 21, 2003; January 20, 2004; January 30, 2004; February 2, 2004; February 6, 2004; February 10, 2004, February 11, 2004; February 18, 2004; February 23, 2004; March 11, 2004; March 16, 2004; March 23, 2004; March 30, 2004; April 6, 2004; April 9, 2004; April 22, 2004; May 5, 2004; May 20, 2004
Sponsor	Indevus Pharmaceuticals, Inc.
Submission / Priority Type	Standard
Reviewer	Leslie Kenna, Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	DPE II

Briefing: Wednesday, January 28, 2003, 11:00 am – noon. Attendees: Hank Malinowski, John Hunt, Arzu Selen, Jennifer Schuh, Ameeta Parekh, Sandhya Apparaju, Mark Hirsch, Suresh Kaul, Don Stanski, Myong-Jin Kim, Stephan Ortiz, He Sun.

Executive Summary

Sanctura™ (trospium chloride) is an anticholinergic muscarinic receptor antagonist indicated for the relief of symptoms of overactive bladder (OAB) including urinary frequency, urgency, and urge incontinence. The sponsor is seeking approval for a 20 mg immediate-release oral tablet taken twice daily. It has been marketed in Germany since 1967 and as of December 2002, the drug is currently approved for marketing in nineteen countries in intravenous and oral formulations.

A. Recommendations

From an OCPB perspective, the application is acceptable given certain changes in the label (as indicated in the review).

B. Phase IV Commitments

None requested.

I. Table of Contents

II. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Trospium chloride is an anticholinergic muscarinic receptor antagonist whose quaternary amine structure is believed to restrict access to the central nervous system. Consequently, this new chemical entity is hypothesized to cause fewer adverse events than those associated with currently marketed treatments for OAB which do not carry a positive charge.

Trospium chloride faces numerous barriers to absorption as evidenced by an absolute bioavailability of 9.6% and a tmax of 5 to 6 hours. Approximately 20% of the drug may be eliminated from the systemic circulation into the gut by gut and/or biliary secretion. The drug's positive charge and its reported instability at pH>4 likely contributes to its low absorption. The apparent volume of distribution of trospium chloride is 395 liters (SD: 140). *Ex vivo* studies suggest that approximately 50 to 85% of drug is protein-bound at therapeutic concentrations.

Seventy percent of trospium chloride reaching systemic circulation is eliminated in the urine. Of this, 80% is eliminated as unchanged trospium. Thus, approximately 60% of trospium chloride is eliminated unchanged. Renal clearance exceeds glomerular filtration rate, suggesting that active renal secretion is a significant pathway of elimination for trospium chloride.

Three metabolites have been measured in clinical studies. Breakdown by an esterase to the inactive hydrolysis product azoniaspironortropanol is the major metabolic route of elimination. The mechanism for the production of the two minor metabolites has not been elucidated but cytochrome P450 isoenzymes are not predicted to play a significant role in elimination. Trospium exhibits dose linearity with AUC but not Cmax. Mean Cmax increases 3-fold and 4-fold with a doubling and tripling of the prescribed dose, respectively (from 20 mg to 40 mg or 60 mg).

Multiple dose studies suggest that there may be induction of trospium elimination with time in young subjects, perhaps via upregulation of renal transporters (e.g. cation transporters). However, drug accumulation occurs upon multiple dosing in elderly

subjects. High fat meals reduce exposure to trospium chloride by 84%. Trospium exhibits diurnal variation in pharmacokinetics; doses taken in the evening yield less exposure than those taken during the day. This may reflect an increase in gastric emptying time at night given that the drug is susceptible to absorptive barriers. There was no consistent effect of gender on trospium chloride.

Moderate to severe renal impairment was associated with a 1.8-fold increase in mean Cmax and a 4.2-fold increase in mean AUC relative to healthy subjects. Since only one dose strength is proposed for marketing, the sponsor proposes to reduce dosing frequency to address the increased exposure in renal impairment. The proposed dosing regimen in renal impairment is 20 mg QD at bedtime instead of 20 mg BID.

Moderate hepatic impairment (Child-Pugh 7-8) was associated with a 60% increase in mean Cmax, a 15% decrease in AUC, and a 50% increase in renal clearance relative to healthy subjects when a single oral dose of 40 mg trospium chloride was administered. The increase in Cmax with no change in AUC suggests that the liver's most important role may be in first pass metabolism. There is no information regarding the effect of severe hepatic impairment on the pharmacokinetics of trospium chloride, but the trend in Cmax, AUC, and renal clearance observed in subjects with Mild and Moderate Hepatic Impairment suggests that these parameters are correlated with the extent of hepatic function. No dosing adjustment has been recommended in hepatic impairment, however, caution is recommended when dosing to patients with moderate and severe hepatic impairment.

Drug interaction studies were not performed *in vivo*, however, preclinical metabolic studies suggest no significant interaction via competition for metabolism. Based on the drug's pharmacokinetic characteristics, renally secreted drugs may interfere with the elimination of trospium chloride. Such drugs, including pancuronium, vecuronium, disopyramide, procainamide, clonidine, neostigmine, metformin and amantadine, may increase exposure to trospium chloride. Trospium chloride may potentiate the anticholinergic action of other anticholinergic agents such as amantadine, tricyclic antidepressants, quinidine, antihistamines, and disopyramide. Similarly, it may decrease the efficacy of prokinetic agents (such as metoclopramide) or alter the absorption of any concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. An interaction with renally secreted cations, anticholinergics and beta-agonists would be of concern with regard to safety.

Efficacy was determined via two large pivotal trials and several supportive trials using the clinical endpoints of change in the average number of toilet voids per 24 hours and change in the number of urge incontinence episodes per 24 hours. In one of the pivotal trials, trospium demonstrated a statistically significant ($p<0.05$) improvement (i.e., decrease by 1 toilet visit per day) in average number of toilet voids per 24 hours at Week 12 when compared to placebo. In this trial, trospium demonstrated a statistically significant ($p<0.01$) improvement (i.e., decrease by 0.22) in the average number of urge incontinence episodes per 24 hours at Week 12 when compared with placebo. This

corresponds to a decrease of one incontinence episode in every 5 days. Refer to the medical officer's review for an in depth review regarding safety and efficacy.

The dose tested in pivotal trials—selected from the lowest tested in a dose escalation study of single doses—was chosen on the basis of the drug's adverse event profile. Adverse events correlated with exposure in renal impairment, hepatic impairment, age, and food effects studies.

Trospium chloride caused no significant change in Fridericia Corrected QT interval (QTcF) relative to placebo in a positively controlled study of the effect of both therapeutic and supratherapeutic doses of drug. In this study, Moxifloxacin was associated with a 5-10 msec increase in QTcF relative to placebo.

The proposed dosing regimen is a single 20 mg tablet taken orally twice daily (BID) at least one hour before meals (total daily dose 40 mg). Subjects with severe or moderate renal impairment are recommended to take 20 mg trospium chloride once daily at bedtime. Trospium chloride is recommended to be used with caution in subjects with moderate or severe hepatic impairment and in subjects with moderate or severe renal impairment. It is recommended that elderly subjects begin on a regimen of 20 mg BID trospium chloride but down-titrate to 20 mg QD dosing if tolerability issues arise.

In consultation with the Chemistry review team, a dissolution specification of Q=— in 30 minutes is recommended.

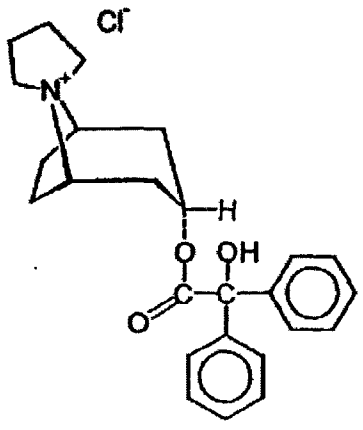
Since performing the pivotal clinical trial, there has been an addition of printing ink to the trospium chloride tablet. The ink provides a unique marking as required by US regulations. Dissolution comparison data (f1 and f2 testing) support the sponsor's claim that the to-be-marketed formulation of trospium chloride is equivalent to the clinical trial formulation.

III. Question Based Review

A. General Attributes

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the product?

Sanctura™ is a brownish-yellow, biconvex shaped, glossy coated tablet printed with black ink that contains 20 mg of the active ingredient, trospium chloride. The generic name for Sanctura™ is trospium chloride and its chemical name is spiro[8-azoniabicyclo[3,2,1]octane-8,1'-pyrrolidinium]-3-[(hydroxydiphenyl-acetyl)-oxy]chloride(1α, 3β, 5α)-(9Cl). The empirical formula of trospium chloride is $C_{25}H_{30}ClNO_3$. The structural formula of trospium chloride is represented in Figure 1. Its molecular weight is 427.97.



•Molecular formula: $C_{25}H_{30}NO_3Cl$

Figure 1. Structure of Trospium Chloride.

Trospium chloride is a fine, colorless to slightly yellow crystalline solid. The compound's solubility in various media are listed in Table 1.

Medium	Solubility
Water	Freely soluble (1 g / 2 mL)

Table 1. Solubility of Trospium Chloride.

Table 2 lists tablet ingredients by weight.

Constituent	Amount (mg) per tablet	Amount (kg) per batch
Trospium chloride	20.0	
Starch (wheat)		
Microcrystalline cellulose		
Lactose monohydrate		
Stearic acid		
Povidone		
Croscarmellose sodium		
Talc		
Colloidal silicon dioxide		
Purified water [2]		
Total Core Solids	70.0	

1

Table 2. Composition of the core tablet for trospium chloride 20 mg tablets.

What is the proposed mechanism of drug action and therapeutic indications?
Symptoms of overactive bladder (OAB)—urinary frequency, urgency, and/or urge incontinence—are attributed to involuntary contraction of the detrusor muscle primarily mediated via cholinergic muscarinic receptor stimulation. Trospium chloride is an anticholinergic muscarinic receptor antagonist which reduces smooth muscle tone in the urogenital and gastrointestinal tracts, thus allowing the detrusor to relax and improve its adaptation to the contents of the bladder.

Trospium's positively charged structure and *in vitro* studies suggest that trospium chloride does not cross the blood-brain barrier. It is hypothesized that its inability to access the central nervous system limits central effects such as dizziness, drowsiness, nervousness, and changes in cognitive function. Such central effects are adverse responses associated with currently marketed treatments for OAB which do not carry a positive charge.

What is the proposed dosage and route of administration?
The proposed dosing regimen is a single 20 mg tablet taken orally twice daily (BID) at least one hour before meals (total daily dose 40 mg). It is proposed that patients with severe renal impairment take a single 20 mg trospium chloride tablet once daily at bedtime.

B. General Clinical Pharmacology
What are the general pharmacokinetic characteristics of trospium chloride?
Absorption
Trospium chloride is slowly absorbed. Cmax occurs 5 to 6 hours after administration. Absolute bioavailability is low (mean: 9.6%) and exhibits considerable variability (range: 4%-16.1%). The drug's positive charge and its reported instability at pH>4 likely contribute to its low absorption. Considerable absorption occurs in the upper small intestine. High fat meals reduce exposure to trospium chloride. Figure 2 shows the concentration-time profile of a single 20 mg oral dose of trospium chloride.

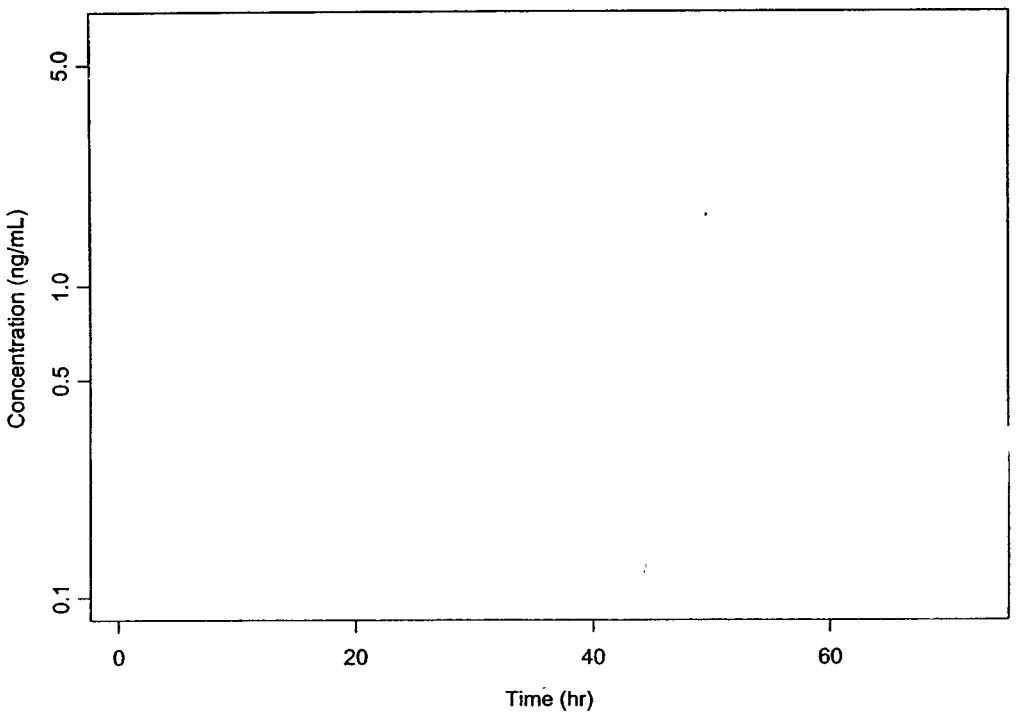


Figure 2. Plasma Concentration of Trospium Chloride After a Single 20 mg Oral Dose. Heavy-weight solid line shows the smooth through all data points. Dashed lines show the smooth through each individuals' data points.

Distribution

The apparent volume of distribution of intravenously dosed trospium chloride is 395 liters (SD: 140). *Ex vivo* studies suggest that approximately 50 to 85% of the drug is protein-bound at therapeutic concentrations. The nature of the proteins to which it is bound has not been reported. The plasma-to-whole blood ratio of trospium chloride was 1.6:1 when measured 0.75 hours post-dose.

Metabolism

Figure 3 illustrates the proposed metabolic elimination pathway for trospium chloride. Three metabolites have been detected in mass balance studies; two have been structurally characterized. Breakdown by an esterase to the inactive hydrolysis product azoniaspironortropanol is the major metabolic route of elimination. The mechanism for the production of the two minor metabolites has not been elucidated.

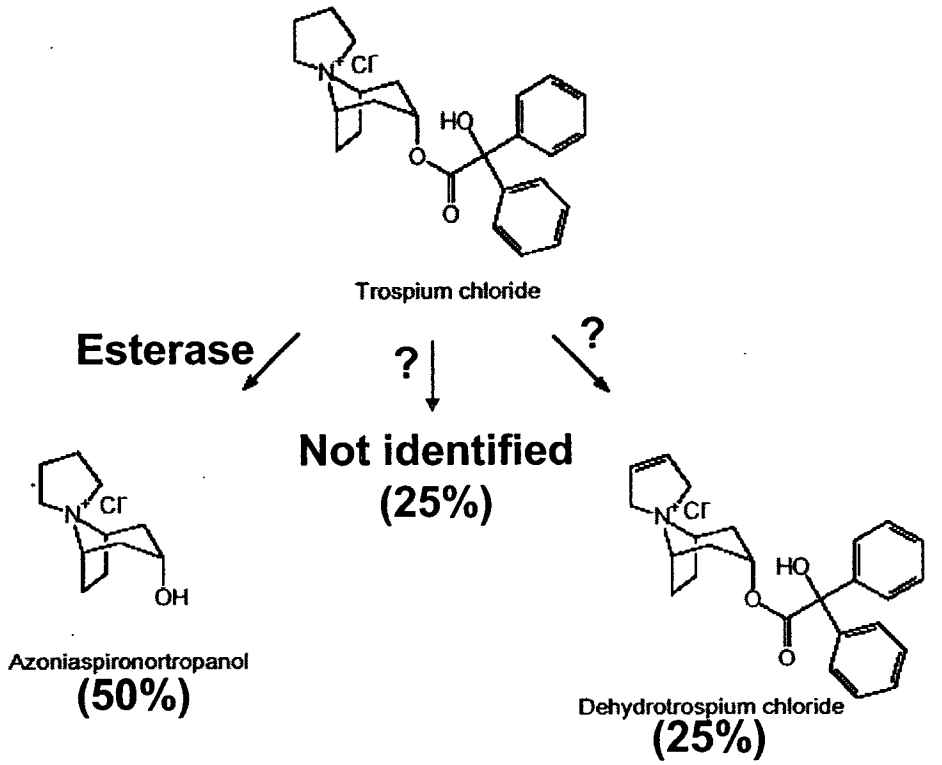


Figure 3. Proposed Biotransformation Pathway for Trospium Chloride.

No clinically relevant drug interactions resulting from competition with esterase metabolism are expected. Preclinical data suggest no clinically significant metabolism of trospium chloride by any Cytochrome P450 isoenzyme. Incubation of [^{14}C]-trospium chloride (10 μM) *in vitro* with human liver S9 fractions for 60 minutes yielded approximately 5% metabolites and 95% trospium chloride. The 50% inhibition concentration measured in *in vitro* interaction studies of CYP 1A2, 2C19, 2D6, 2E1, 3A4, 2A6, and 2C9 are reported in Table 3. Note that trospium chloride concentrations are expected to range from 1 to 20 ng/mL (. ——— .) in a therapeutic setting. The smallest IC50 value observed *in vitro* (for CYP 2D6) is approximately 1000 times greater than therapeutic trospium chloride concentrations.

P450 Isoenzyme	Substrate	IC_{50} [mmol/L]
1A2	Caffeine	8.43 – 9.32
2C19	Mephenytoin	1.76 – 1.97
2D6	Dextromethorphan	0.020 – 0.051* 0.19 – 0.76**
2E1	Chlorzoxazone	14.96
3A4	Denitronifedipine	11.93 – 23.08
2A6	Warfarin	2.4 – 2.6
2C9	Coumarin	2.0 – 2.8

* Competitive inhibition constant of high affinity binding site.

** Competitive inhibition constant of low affinity binding site.

Table 3. Concentration of Trospium Chloride Yielding 50% Inhibition of P450 Enzyme Activity. Trospium chloride concentrations range from 1 to 20 ng/mL in a therapeutic setting. The smallest IC50 value observed *in vitro* (for CYP 2D6) is approximately 1000 times greater than therapeutic trospium chloride concentrations.

Metabolites comprise approximately 74 to 80% of the radioactivity measured in plasma samples.

Elimination

Figure 4 summarizes the results of two mass balance studies.

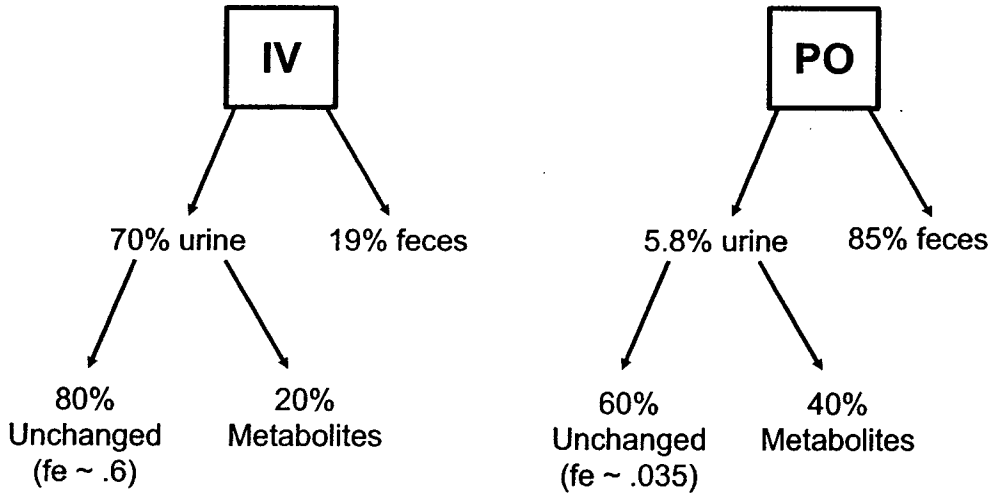


Figure 4. Results of Mass Balance Studies for Trospium Chloride. The elimination profile suggests that 20% of drug is eliminated via gut and/or biliary secretion, while 20 to 40% of absorbed drug is metabolized. Most (approximately 93%) is unabsorbed.

In a mass balance study using [^{3}H]-radiolabeled trospium chloride, approximately 90% of intravenously administered trospium chloride was recovered 168 hours post-dose. Of that, 71.4% was eliminated in urine (80% unchanged and 20% as metabolic products) and 19.4% was eliminated in feces. This suggests that 21.3% of drug (computed as 19.4%/(19.4%+71.4%)) is eliminated from the systemic circulation into the gut by gut and/or biliary secretion. It further suggests that between 16% to 37% of drug is

metabolized. That is, of the 90 mg recovered, it is known that twenty percent of the 71.4 mg excreted in urine appears as metabolites and anywhere from zero to all 19.4 mg excreted in feces may be metabolic products. Half of the metabolites in urine appeared as a single moiety—azoniaspironortropanol—while the remainder consisted of two unidentified molecules in equal proportions.

In a second mass balance study using ^{14}C-radiolabeled trospium chloride, ninety one percent (91%) of an orally administered 20 mg trospium chloride dose (dosed in the fasted state) was recovered within 288 hours of administration. Elimination was primarily via the fecal route. Of the 5.8% of total dose that was measured as drug-related radioactivity in urine, 60% was recovered as unchanged trospium chloride and 40% was recovered as metabolic products. Given that approximately 21.3% of drug reaching systemic circulation is predicted to be eliminated via gut or biliary secretion, since 5.8% of drug was eliminated via the kidneys, it is predicted that 7.25% of the administered drug was absorbed. According to mass balance studies, 93% of administered drug (computed as (91%-7.25%)/91%) is unabsorbed.

The disparity between the percent of drug eliminated unchanged in urine when dosed intravenously (80%) relative to when dosed orally (60%) may reflect absorptive phase mechanisms of elimination. Mean renal clearance (29.07 L/hour) is greater than glomerular filtration rate (7.5 L/hour), suggesting that trospium is actively secreted into the urine.

Figure 5 illustrates that intravenously administered trospium chloride exhibits three phases of elimination.

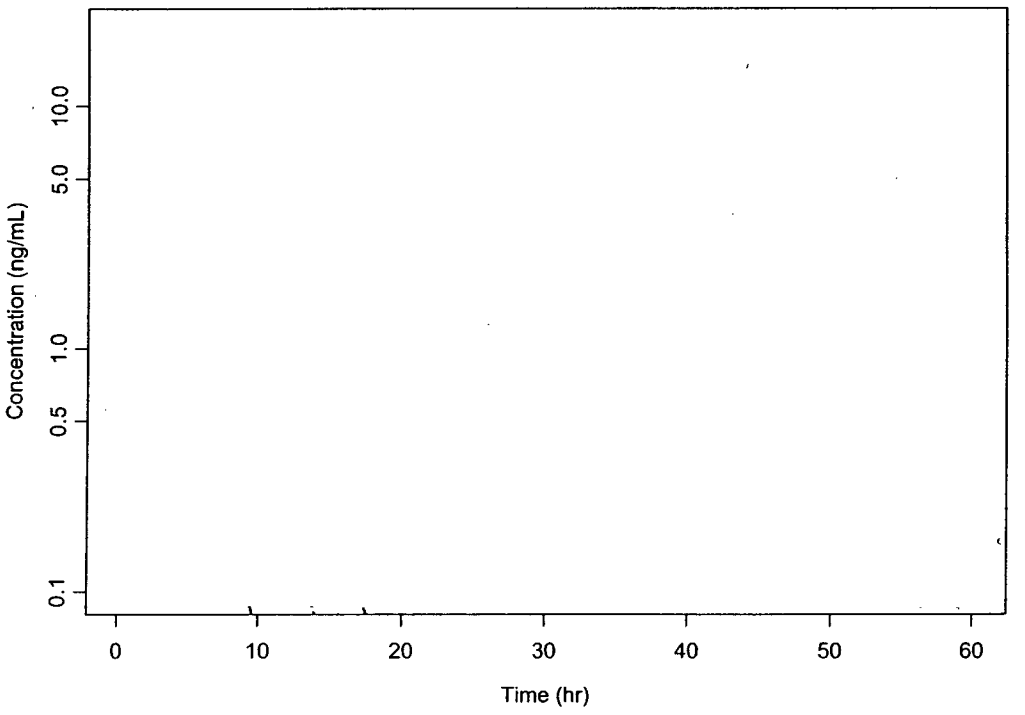


Figure 5. Plasma Concentration of Trospium Chloride After Intravenous Infusion of a Single 1.4 mg Dose in N=12 Subjects. Heavy-weight solid line shows the smooth through all data points. Dashed lines show the smooth through each individuals' data points.

What are the basic PK parameters?

Table 4 summarizes the PK parameters estimated in single dose studies of 20 mg trospium chloride in healthy volunteers. AUC ranged from 16.12 ng*hr/mL to 37.7 ng*hr/mL, while Cmax ranged from [redacted]. The half life ranged from 9.5 to 19.7 hours. Maximum concentration is achieved at approximately 5 hours, with a range of 2.5 to 7 hours. There is wide variability in each of these estimates. Between 4-7% of the dose was eliminated unchanged in urine—consistent with mass balance studies.

Although the data from these single dose studies suggest that elderly subjects have a higher clearance than young subjects, the opposite trend was observed during multiple dose studies. After ingestion of several doses in elderly subjects, Cmax and AUC were greater than that observed after a single dose. In contrast, at steady state, AUC and Cmax were reduced relative to that observed after a single dose in young subjects. This issue is addressed in greater detail later in this review.

	STUDY				
	MP94D4.02	MP94D2.05	IP631.006	MP94D2.11	MP94D2.10
Age	18-40	18-40	36-45	60-75	19-40
Gender	Male & Female	Male	Male	Male	Male
Dose	20 mg	20 mg	20 mg	20 mg	20 mg
$AUC_{0\rightarrow\infty}$ (ng*hr/mL)	37.46* (18.52)	37.7* (19.2)	27.38** (46.0)	16.12* (7.8)	36.4* (21.8)
Cmax (ng/mL)	4.6*	3.3*	1.14**	1.45*	3.45*
tmax (hr)		4.9* (1.4)	6***	4.8*** (2.5,7.0)	5.33* (1.2)
t½ (hr)		18.4* (11.5)	19.7** (24.9)	9.5*** (5.4,11.4)	18.33* (3.2)
$Ae_{0\rightarrow 72hrs}$ Dose (%)		7.0* (4.1)			4.06* (1.3)

***Mean (+/- SD)**
****Mean (CV%)**
*****Median (range)**

Table 4. Pharmacokinetic Parameter Estimates for Single Dose Studies in Healthy Subjects.

The sponsor's population PK model of data collected during an extension of the pivotal trial (discussed in greater detail later in this report) did not reveal age as a significant predictor of drug exposure. Data for that study were collected in subjects whose mean age was 60 with an interquartile range of 49 to 71 years. Subjects as young as 29 years and as old as 84 years contributed to the analysis.

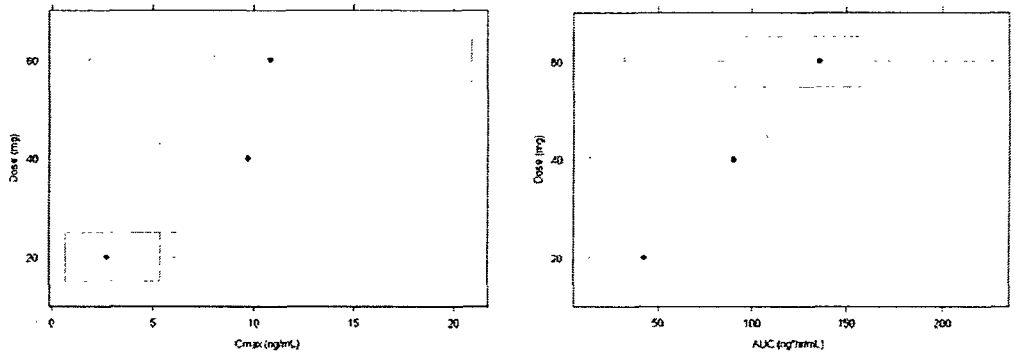
Are the PK parameters linear with respect to dose?

Dose linearity was investigated in a study of single 20 mg, 40 mg, and 60 mg trospium chloride doses in healthy males aged 18-40 years. The pharmacokinetic parameter

estimates listed in Table 5 and plotted in Figure 6 show that Cmax increases greater than dose proportionally. Mean Cmax increases 3-fold and 4-fold with a 2-fold and 3-fold increase in dose, respectively, while AUC, tmax, and Ae exhibit dose linearity across the range of exposures tested. The difference in half life for the 20 mg dose relative to all other doses tested was explained as resulting from too few points measured above the limit of quantitation with which to estimate the terminal slope. This is reflected in the wide confidence in estimates.

Dose [mg]	$AUC_{0-\infty}$ [ng x ml^{-1} x h]	C_{max} [ng x ml^{-1}]	t_{max} [h]	$t_{1/2}$ [h]	Ae_{0-72h}/dose [%]
20 p.o.	37.7 ± 19.2	3.3 ± 2.1	4.9 ± 1.4	18.4 ± 11.5	7.0 ± 4.1
40 p.o.	84.8 ± 39.2	9.7 ± 5.9	5.6 ± 0.7	12.1 ± 2.7	6.4 ± 3.3
60 p.o.	134.4 ± 58.9	14.0 ± 7.4	5.3 ± 1.2	12.5 ± 2.2	7.1 ± 3.8
1.4 i.v.	27.7 ± 6.4	17.5 ± 2.8	0.9 ± 0.1	12.0 ± 8.8	49.3 ± 9.4

Table 5. Pharmacokinetic Parameters of Trospium Chloride Measured in a Dose Proportionality Study.



(A) Cmax **(B) AUC**

Figure 6. Mean and Distribution of Exposure Estimates for Single 20 mg, 40 mg, and 60 mg Trospium Chloride Doses.

How do PK parameters change with time following chronic dosing?

Based on its accumulation index of 2 to 2.7, exposure is expected to increase with chronic dosing. However, as Table 6 shows, the sponsor's report on multiple dose studies suggest that elimination is induced with time—accumulation was less than predicted based on an assumption of linear pharmacokinetics with time. The results of these studies are conflicting, however, with respect to the extent of induction in young versus elderly subjects.

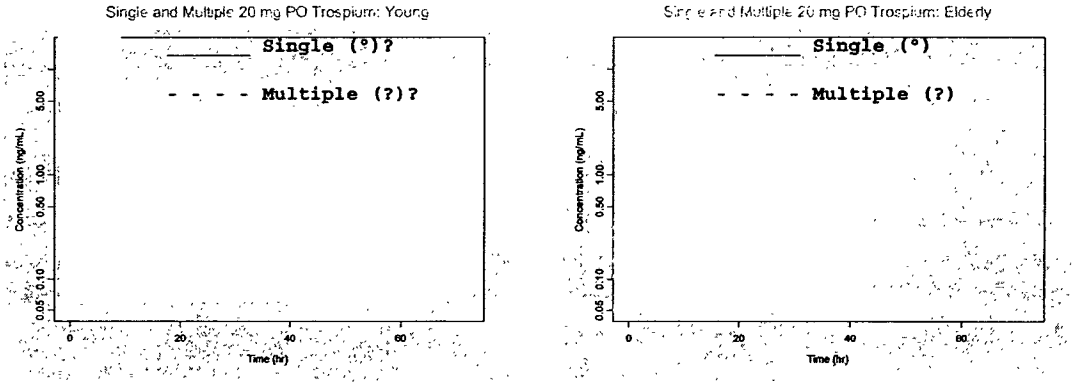
	Cmax	AUC
7 Day Study: Young	↓ 35%	↓ 50%
8 Day Study: Young	↓ 64%	↓ 73%
5 Day Study: Elderly	↑ 40%	↑ 7%

Table 6. Accumulation of Trospium Chloride in Three Multiple Dose Studies. Exposure increases less than expected based on an accumulation index of 2-2.7 for trospium chloride.

In one study of 12 healthy males aged 19 to 40 years, Cmax and AUC were reported to decrease 35% and 50%, respectively, after 7 days of dosing 20 mg trospium chloride BID

compared to drug exposure after a single 20 mg dose. In a study of 12 young males and 12 young females, Cmax and AUC were reported to decrease 64% and 73%, respectively, after 20 mg BID dosing of trospium chloride for 8 days relative to that after a single dose. Gender had no influence on the change in exposure with chronic dosing.

Figure 7 shows the reviewer's plot of data from the 7-day study in young subjects and the 5-day study in elderly subjects. Contrary to the sponsor's reported values in Table 6, Cmax and AUC appear to increase with multiple dosing in all subjects. However, the increase appears to be less for young subjects than elderly and, perhaps, less than that expected based on the accumulation index. Note that the plots are on the same scale to illustrate that there is greater variability in exposure for elderly subjects for both single and multiple doses.



(A) Young Subjects **(B) Elderly Subjects**

Figure 7. Plasma Concentrations Following a Single 20 mg Trospium Chloride Dose and Multiple Doses. (A) 20 mg Trospium Chloride BID for 7 Days in Young Subjects. (B) 20 mg Trospium Chloride BID for 5 Days in Elderly Subjects. The solid line shows the smooth through concentrations measured after a single dose (○). The dashed line shows the smooth through concentrations measured after multiple doses (Δ). Variability in exposure is greater in elderly subjects than young subjects for both single and multiple doses.

Given that trospium is not significantly eliminated by any CYP or any other inducible metabolic system and given that the drug is actively secreted by the kidney, the reduction in exposure with chronic dosing may reflect induction of renal cation transporters. A lesser induction of active renal elimination in the elderly may reflect an overall decrease in kidney function with age. The discrepancy among age groups might also be explained by the duration of the study. The study in elderly subjects was shorter than that in young subjects; perhaps 5 days was not enough time to develop steady state levels of trospium chloride and increased active secretion of drug.

Note that in all three of the chronic dosing studies, doses were administered in the fasted state, thus, food effects are not expected to contribute to the variability observed.

Do mass balance studies suggest that renal or hepatic elimination is significant?
As discussed earlier, mass balance studies suggest that renal elimination, primarily active renal secretion, is a significant pathway of elimination. The sponsor's population PK

model (discussed later in this review) revealed serum creatinine as a predictor of clearance.

What efficacy and safety information (e.g. biomarkers, surrogate endpoints, clinical endpoints) contribute to the assessment of clinical pharmacology and biopharmaceutic study data?

Efficacy was determined via two large pivotal trials and several supportive trials using clinical endpoints of change in the average number of toilet voids per 24 hours and change in the number of urge incontinence episodes per 24 hours. One of the pivotal trials was a multicenter, parallel, double-blind, placebo-controlled study to determine the effect of 20 mg trospium chloride versus placebo, given twice daily, on overactive bladder over a 12-week treatment period in a total of 523 subjects (262 received trospium chloride and 261 received placebo). The study enrolled a balanced distribution of subjects among the treatment arms. For the trospium cohort, median age was 63 years (range: 22 to 90 years), 77.5% of subjects were female and mean weight was 82.5 kg (SE: 1.4). Subjects with renal impairment were excluded from the study. Median creatinine clearance in subjects was 91.1 mL/min (interquartile range:). For inclusion in the study, overactive bladder was defined as an average of at least 10 micturitions per day, symptoms of urgency, and an average of at least one incontinence episode per day. These symptoms had to be present for six months before study enrollment.

In addition to the two co-primary endpoints assessed (change in the average number of toilet voids per 24 hours and change in the number of urge incontinence episodes per 24 hours), two secondary endpoints were considered, as well: (1) volume voided per toilet visit and (2) urgency.

Table 7 and Table 8 show the results of the primary analyses.

		Least squares means (SE)			
		Placebo	Trospium		P-Value
	Week	N=256	N=253		Model [a]
Baseline		12.93 (0.16)	12.74 (0.16)		0.4035
Change from baseline [b]	1	-0.81 (0.13)	-1.18 (0.13)		0.0509
	4	-1.07 (0.15)	-2.20 (0.15)		<0.0001
	12	-1.29 (0.17)	-2.37 (0.17)		<0.0001

[a] Model: change=center and treatment effects.

[b] A negative change score indicated improvement (i.e., decreased average number of toilet voids) from baseline.

SE=standard error, ITT=intent to treat, LOCF=last observation carried forward data set.

Table 7. Change in Average Number of Toilet Voids Per 24 Hours: Analysis of Variance.

		Averages		
		Placebo	Trospium	P-Value
	Week	N=256	N=253	Model [a]
Baseline		4.30	3.90	0.4637
Change from baseline [b]	1	-1.35	-1.40	0.1195
	4	-1.87	-2.02	0.0025
	12	-1.98	-2.20	0.0118

[a] Model: ranked change=center and treatment effects.
[b] A negative change score indicated improvement (i.e., decreased average urge incontinence episodes) from baseline.
ITT=intent to treat, LOCF=last observation carried forward data set.

Table 8. Change In Average Number Of Urge Incontinence Episodes Per 24 Hours: Averages With P-Values From Rank ANOVA.

Trospium demonstrated a statistically significant ($p<0.05$) improvement (i.e., decrease by 1 toilet visit per day) in average number of toilet voids per 24 hours at Week 12 when compared to placebo. Trospium demonstrated a statistically significant ($p<0.01$) improvement (i.e., decrease by 0.22) in the average number of urge incontinence episodes per 24 hours at Week 12 when compared with placebo. This corresponds to a decrease of one incontinence episode in every 5 days.

The results of the secondary analyses are provided in Table 9 and Table 10.

		Least squares means (SE)				
		Placebo		Trospium		P-Value
	Week	N=253		N=248		Model [a]
Baseline		156.62	(3.08)	155.09	(3.10)	0.7266
Change from baseline [b]	1 [c]	6.55	(2.31)	19.88	(2.33)	<0.0001
	4 [c]	8.45	(2.90)	29.96	(2.93)	<0.0001
	12	7.72	(3.05)	32.14	(3.08)	<0.0001

[a] Model: change=center and treatment effects.
[b] A positive change score indicated improvement (i.e., increased average volume voided per toilet void) from baseline.
[c] Denominator decreased by 1 patient for each treatment group at Weeks 1 and 4.
SE=standard error, ITT=intent-to-treat, LOCF=last observation carried forward data set.

Table 9. Change In Average Volume Voided (in mL) Per Toilet Void: Analysis Of Variance.

		Least squares means (SE)				
		Placebo		Trospium		P-Value
	Week	N=256		N=253		Model [a]
Baseline		1.77	(0.03)	1.77	(0.03)	0.8837
Change from baseline [b]	1	-0.01	(0.02)	-0.11	(0.02)	0.0033
	4	-0.06	(0.03)	-0.18	(0.03)	0.0041
	12	-0.04	(0.03)	-0.22	(0.03)	0.0001

[a] Model: change=center and treatment effects.
[b] A negative change score indicated improvement (i.e., decreased average urgency severity associated with toilet voids) from baseline.
SE=standard error, ITT=intent-to-treat, LOCF=last observation carried forward data set.

Table 10. Change In Average Urgency Severity Associated With Toilet Voids: Analysis Of Variance.

Trospium demonstrated a statistically significant improvement (i.e., increase by 24.42 mL) in average volume voided per toilet void at Week 12 when compared with placebo. The finding of a statistically significant increase in average volume voided for the trospium versus placebo group is consistent with anticholinergic relaxation of the detrusor muscle increasing maximum bladder capacity. Trospium was associated with a statistically significant improvement (i.e., decrease by 0.18) in average urgency severity associated with toilet voids at Week 12 when compared with placebo.

Refer to the medical officer's review for an in depth review regarding safety and efficacy.

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

A single strength of trospium chloride (20 mg) dosed twice daily in the fasted state was tested in the pivotal trial. This dose—the lowest tested in a single dose escalation study of 20 mg, 40 mg, 80 mg, 120 mg, 180 mg, 240 mg, and 360 mg—was selected on the basis of the drug's safety profile in terms of anticholinergic effects such as change in pupillary diameter, salivary flow and heart rate.

It is useful to note that dosing occurred 30 minutes after breakfast in the dose escalation study given that food has been shown to reduce exposure to trospium chloride (84% reduction in Cmax and 74% reduction in AUC). In the pivotal trials, trospium was taken one hour before meals, hence, the safety results for the 20 mg dose in the dose-escalation study may not represent the results expected clinically. Drug concentration was not measured during the dose-escalation study, thus, it is unclear how exposure after a particular dose in this trial relates to exposure following any of the same doses in the fasted state.

Figure 9 shows a dose-related decrease in salivary secretion across the range tested. The reduction in salivary flow to one third of baseline after doses of 180 and 360 mg correlates with a higher number of reports of dry mouth in this dose range (1/8 of subjects receiving 120 mg; 5/8 of subjects receiving 180 mg; 6/8 of subjects receiving 240 mg; and 7/8 of subjects receiving 360 mg reported dry mouth).

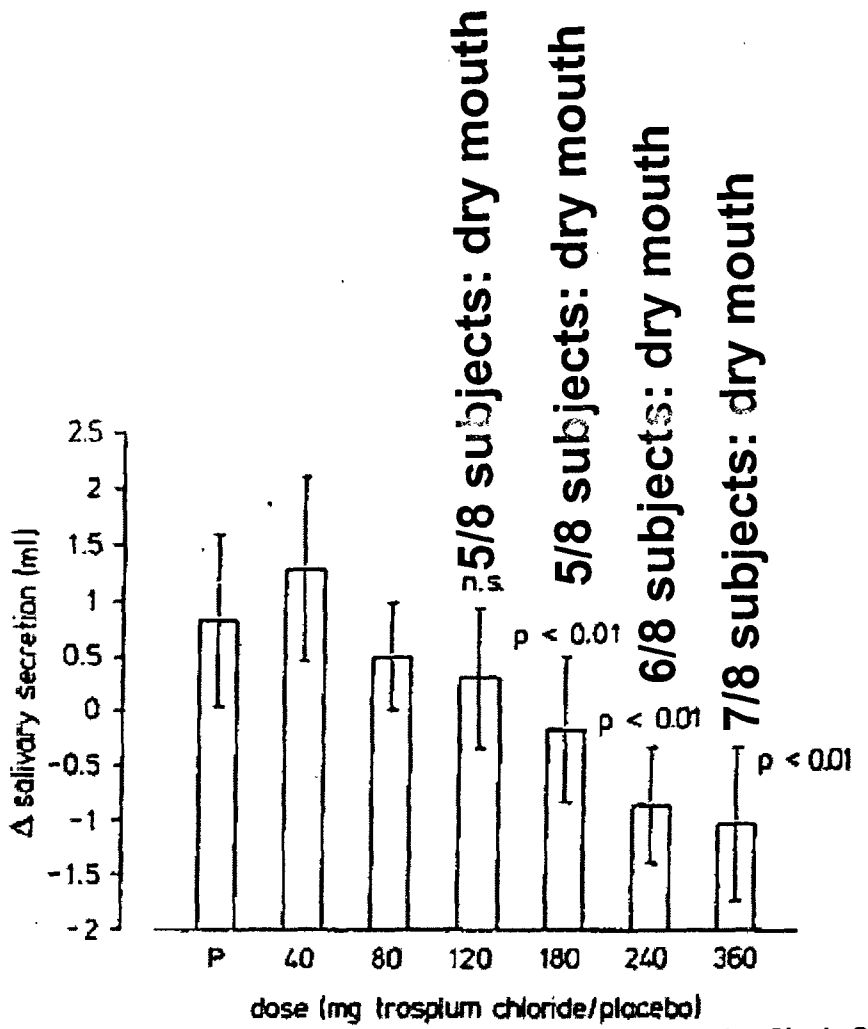


Figure 9. Changes of Salivary Secretion (mean +/- SD) Following Single Oral Administration of Trospium Chloride or Placebo (P). Placebo: N=15; 120 mg: N=9; 180 mg: N=9; 240 mg: N=9; 360 mg: N=8. A statistically significant change in salivary secretion was observed with doses exceeding 120 mg and correlated with reports of dry mouth.

Figure 10 and Table 11 show that change in heart rate is correlated with dose.

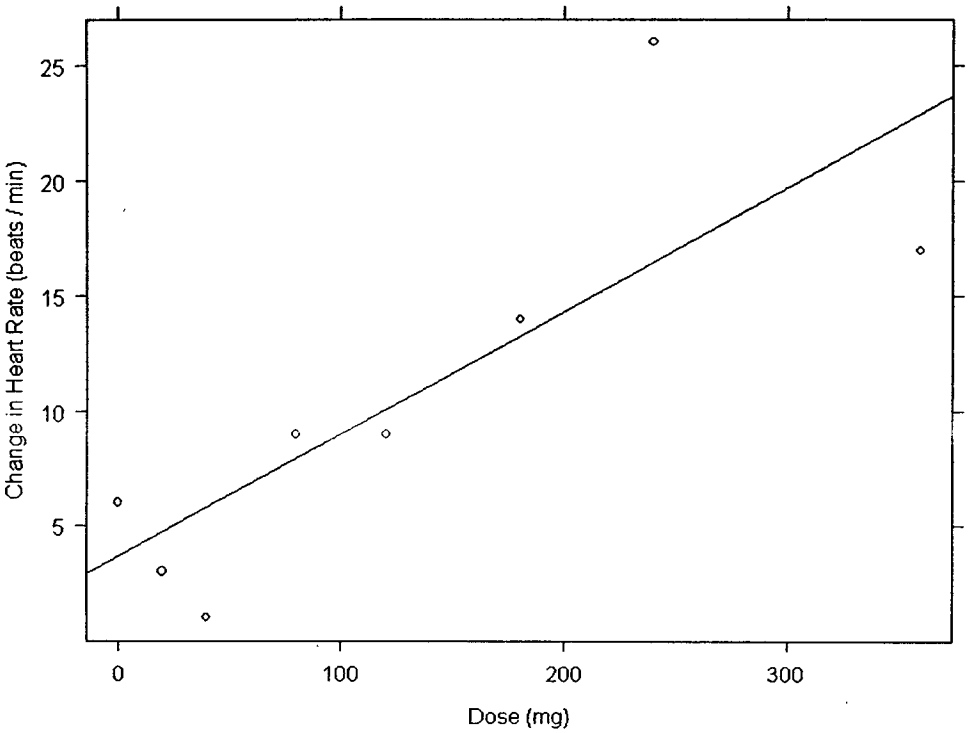


Figure 10. Heart Rate as a Function of Dose in the Dose Escalation Study. This may underestimate effect on heart rate at a given dose given that subjects were dosed in a fed state.

Treatment	Change in Heart Rate from Baseline (beats per minute)
Placebo	6
20 mg	3
40 mg	1
80 mg	9
120 mg	9
180 mg	14
240 mg	26
360 mg	17

Table 11. Effect of Single Doses of Trospium Chloride on Heart Rate. This may underestimate effect on heart rate at a given dose given that subjects were dosed in a fed state.

Additionally, a statistically significant and constant (not dose dependent) increase in pupillary diameter (1.5 cm) for doses greater than 120 mg was observed. Following treatment with 360 mg trospium, two volunteers had micturition difficulties lasting for 12 hours and 24 hours.

A study of the effect of food on the pharmacokinetics of a 40 mg single dose, where fed subjects had 80% less exposure than fasted subjects, offers further evidence in support of an exposure-response relationship for adverse events. Nine of twenty four fed subjects (37.5%) reported adverse events, while twenty one of twenty four fasted subjects (87.5%) reported adverse events. Dry mouth and headache were the most common adverse event

reported and all but two (moderate) adverse events were of a mild nature. One fed subject and one fasted subject reported events of moderate severity.

Similarly, a study of multiple dose pharmacokinetics in elderly subjects, where exposure increased with chronic dosing, 84.2% of subjects experienced dry mouth on the multiple dose regimen as compared to 38.9% after a single dose. In addition, a greater percent of subjects experienced an inability to micturate, blurred vision, difficulty swallowing, headache, nausea, vomiting, dizziness, "obstipation", and heart palpitation on the multiple dose regimen as compared to the single dose regimen. All but one adverse event (of a moderate nature) reported during the single dose phase were of a mild nature while half of the adverse events reported during the multiple-dose period were of a moderate nature. One subject discontinued the study due to a serious adverse event and required 15 days of hospitalization. The subject experienced vertigo, garbled speech, an increase in blood pressure that required administration of nifedipine, micturation difficulty, vomiting, diarrhea, dry mouth, headache and sensitivity to light. The hypertension was improved, but not reversed, two days after hospitalization. The vertigo and unclear speech was present until 15 days after the last dose of study drug was administered. Figure 11 shows that this subject had greater exposure than the average subject in the study.

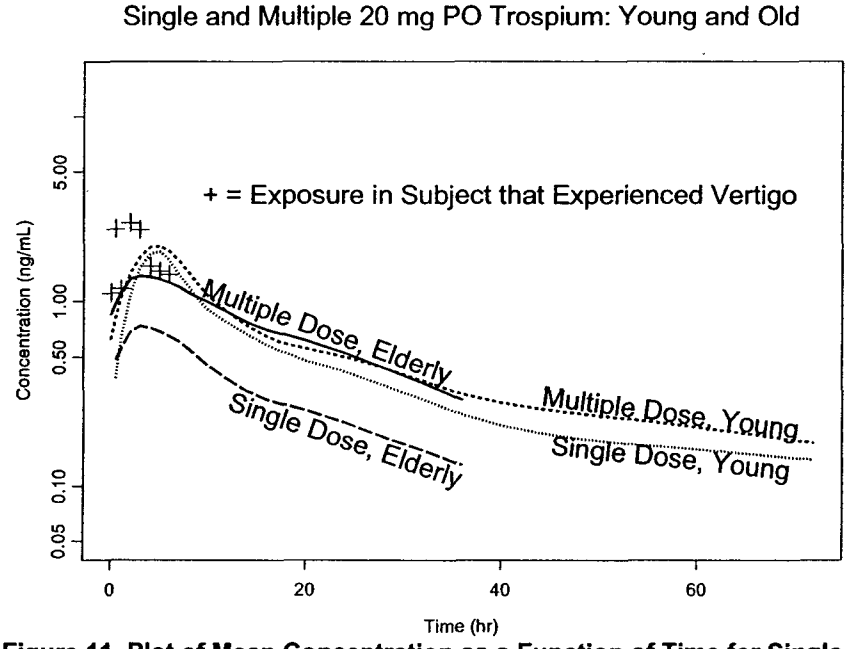


Figure 11. Plot of Mean Concentration as a Function of Time for Single and Multiple Dose Studies in Young and Elderly Subjects: Highlighting Excessive Exposure in an Elderly Subject Who Experienced Severe Adverse Events.

Note that vertigo and micturition difficulty was reported by subjects in another study of a single 40 mg trospium chloride dose administered to 16 healthy elderly volunteers. One subject experienced two episodes of vertigo occurring 8 hours (near tmax) and 23 hours

post-dose and lasting a total duration of 160 hours. The incidence of micturition difficulty reported by another subject occurred eleven hours post-dose and lasted for 6 hours.

The incidence of adverse events correlated with exposure in young subjects, as well. Specifically, 5 out of 12 volunteers experienced adverse events after a single 20 mg dose (primarily dry mouth), while 8 out of 12 volunteers reported adverse events after steady state administration (primarily dry mouth and headache).

What is the effect of trospium chloride on QT interval?

A prospectively designed, placebo-controlled study was conducted to evaluate the effect of therapeutic and supratherapeutic doses of trospium chloride on QT interval. The sponsor tested 20 mg and 200 mg single doses of trospium chloride and tested 20 mg BID and 40 mg BID regimens (dosed for 5 to 7 days) in a parallel study enrolling 15 subjects (males and females) per arm. Subjects were assigned either both supratherapeutic doses of trospium chloride tested (200 mg and then 40 mg BID) or both therapeutic doses tested (20 mg and then 20 mg BID) or placebo. The 200 mg single dose covers the extreme exposures expected with renal impairment.

Tables 12-16 summarize key results of the study.

	Baseline QTcF (95% CI)
Placebo	386.3 (379.9,392.8)
Trospium 20 mg BID/20 mg	384.4 (377.9,390.9)
Trospium 40 mg BID/200 mg	393.9 (385.6,402.1)

Table 12. Baseline QTcF For Each Study Arm. Note that the mean baseline QTcF is higher in subjects receiving the supratherapeutic dose of trospium chloride than in subjects receiving the therapeutic dose.

	Baseline QTcF (95% CI)	**Mean ΔQTcF from Baseline (95% CI)**
Placebo	386.3 (379.9,392.8)	-4.4 (-10.6,1.8)
Trospium 20 mg	384.4 (377.9,390.9)	1.2 (-6.1,8.4)
Trospium 200 mg	393.9 (385.6,402.1)	-9.6 (-16.9,-2.2)

Table 13. Mean Change in QTcF From Baseline For Each Arm in the Single Dose Study. Placebo corrected mean change in QTcF over baseline for the therapeutic dose of trospium chloride (20 mg) was +5.6 msec (computed as: 1.2 msec – (-4.4 msec)) and -5.2 msec for the supratherapeutic dose. The 200 mg dose covers exposures in renal impairment.

	Baseline QTcF (95% CI)	**Mean ΔQTcF from Baseline (95% CI)**
Placebo	386.3 (379.9,392.8)	-1.5 (-9.2,6.3)
Trospium 20 mg BID	384.4 (377.9,390.9)	2.5 (-5.3,10.4)
Trospium 40 mg BID	393.9	-7.1

	(385.6,402.1)	(-13.2,-1.1)

Table 14. Mean Change in QTcF From Baseline For Each Arm in the Multiple Dose Study on Study Day 6. Placebo corrected mean change in QTcF over baseline for the therapeutic dose of trospium chloride (20 mg BID) was +4 msec (computed as: 2.5 msec – (-1.5 msec)) and -5.6 msec for the supratherapeutic dose. The 40 mg BID dose does not cover exposures expected in renal impairment.

	20 mg	200 mg	Placebo
30-60 msec increase	26.7% (8.9%)	6.7% (2.2%)	13.3% (2.2%)
>60 msec increase	0	0	0
>450 msec	0	0	0

Table 15. Outlying QTcF Values Observed in the Single Dose Study: Percent of Subjects (Percent of Observations). Note that no subject had a value of QTcF >450 msec at baseline.

	20 mg BID	40 mg BID	Placebo
30-60 msec increase	13.3% (4.8%)	6.7% (1.0%)	6.7% (1.9%)
>60 msec increase	0	0	0
>450 msec	6.7% (1.0%)	0	0

Table 16. Outlying QTcF Values Observed in the Multiple Dose Study on Day 6: Percent of Subjects (Percent of Observations). Note that no subject had a value of QTcF >450 msec at baseline.

A mean increase of 5.6 msec in Fridericia corrected QT interval was observed in subjects receiving the therapeutic dose of trospium chloride (20 mg single dose) after accounting for baseline and placebo response. There were twice as many subjects with outlying values of QTcF (30-60 msec change from baseline) among those receiving a therapeutic dose of trospium chloride (20 mg single dose or 20 mg BID) compared to those receiving placebo. Specifically, twenty seven percent (27%) of subjects receiving a single 20 mg trospium chloride dose had a ΔQTcF between 30-60 msec, compared to thirteen percent (13%) of subjects receiving a single dose of placebo. Thirteen percent (13%) of subjects receiving 20 mg trospium chloride BID had a ΔQTcF between 30-60 msec, compared to 7% receiving placebo.

No subject had an increase of 60 msec above baseline on any treatment arm.

Subjects receiving the supratherapeutic dose of trospium chloride had an equivalent number of outlying values as those receiving placebo during the multiple dose study and a fewer number of outlying values than those receiving placebo during the single dose study. Subjects receiving the supratherapeutic dose of trospium chloride also had a mean negative change in QTcF from baseline (decrease of 5.2 msec and 5.6 msec for the 200 mg single dose and the 40 mg BID dose, respectively). One challenge to the interpretation of these data is that subjects receiving the supratherapeutic trospium dose had a greater mean baseline value of QTcF than subjects receiving placebo (7.6 msec greater) or the therapeutic dose (9.5 msec greater) of trospium chloride. The result may be real—a supratherapeutic dose of trospium chloride may reduce QT interval, or it may reflect the tendency of regression to the mean to occur when subjects have different baseline values. Given that the study had only 18% power to detect a change in QTcF of

5 msec with a 5% error rate and given that it did not include an active control makes it difficult to rule out either possibility based on these data.

To support the lack of an effect of trospium chloride on QT interval, the sponsor used a population PK model (discussed in greater detail elsewhere in this report) to evaluate the strength of the correlation between drug exposure and safety sampling of QT interval. The sponsor claims that the population PK/PD model relating trospium chloride concentration and QT interval suggests no correlation between trospium exposure and QT interval. As explained in section of this review which evaluates the sponsor's population PK/PD model, several assumptions of the model limit its predictive utility.

The sponsor conducted an additional QT evaluation study employing placebo and positive controls. Study IP631-010 ("A Single Site Single-Blind Randomized Placebo and Positive Controlled, Parallel Designed Study of the Electrocardiographic Effects of Oral Trospium Chloride (20 mg BID Steady State and Supratherapeutic Levels) in Healthy Men and Women Volunteers: a Definitive or Thorough QT Trial") is a parallel study using both positive (400 mg Moxifloxacin QD) and placebo controls. Subjects either received a therapeutic dose of trospium (20 mg BID), or a supratherapeutic dose of trospium (depending on tolerability, 60 mg, 80 mg or 100 mg BID), or placebo (BID), or 400 Moxifloxacin QD for a total of 5 days. Triplicate ECGs were measured at each of 13 evaluation time points across 24 hours at Baseline, on Day 1, and on Day 5.

The highest exposure expected in a clinical setting is associated with dosing trospium chloride to subjects with severe renal impairment. Based on the pharmacokinetics of a single 40 mg dose in renally impaired subjects, subjects with severe renal impairment are predicted to have a Cmax of 5.5 ng/mL (range: [redacted] and an AUC of 120 ng*hr/mL (range: 24-355) after receiving a single 20 mg dose. The impact of such exposure on QT interval was investigated by dosing 80 mg BID trospium for 5 days. Some subjects could only tolerate up to 60 mg BID, while others were titrated up to 100 mg BID. Figure 12 and Figure 13, plots of measured trospium Cmax in each subject, show that a reasonable number of subjects (32 subjects out of 48) were exposed to trospium at a level expected in severe renal impairment on Study Day 5.

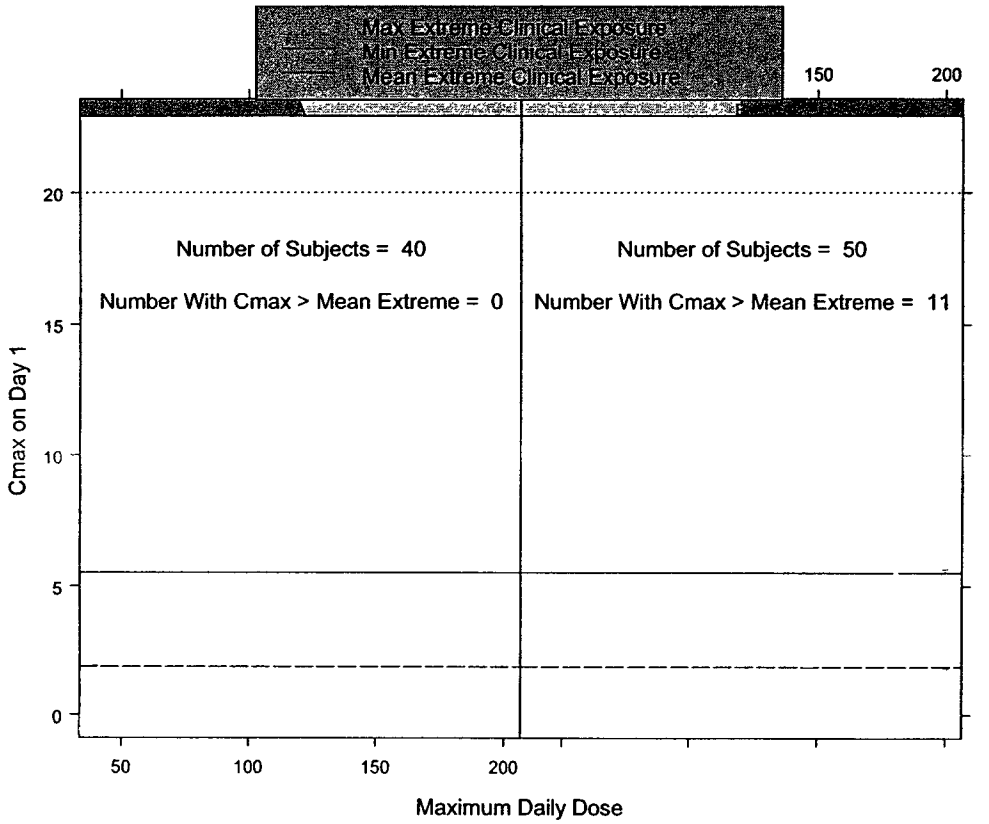


Figure 12. Maximum Exposure Achieved in Each Subject on Day 1 of the QT Evaluation Study. Treatment A = 20 mg BID Trospium for 5 days (therapeutic dose). Treatment B = 60 mg, 80 mg, or 100 mg Trospium BID for 5 days (supratherapeutic dose). Eleven of the fifty subjects (22%) receiving the supratherapeutic trospium dose had a Cmax value exceeding the average concentration expected after dosing 20 mg trospium to subjects with severe renal impairment (solid line: 5.5 ng/mL). The maximum concentration expected in subjects with severe renal impairment after receiving 20 mg trospium is 20 ng/mL (dotted line).

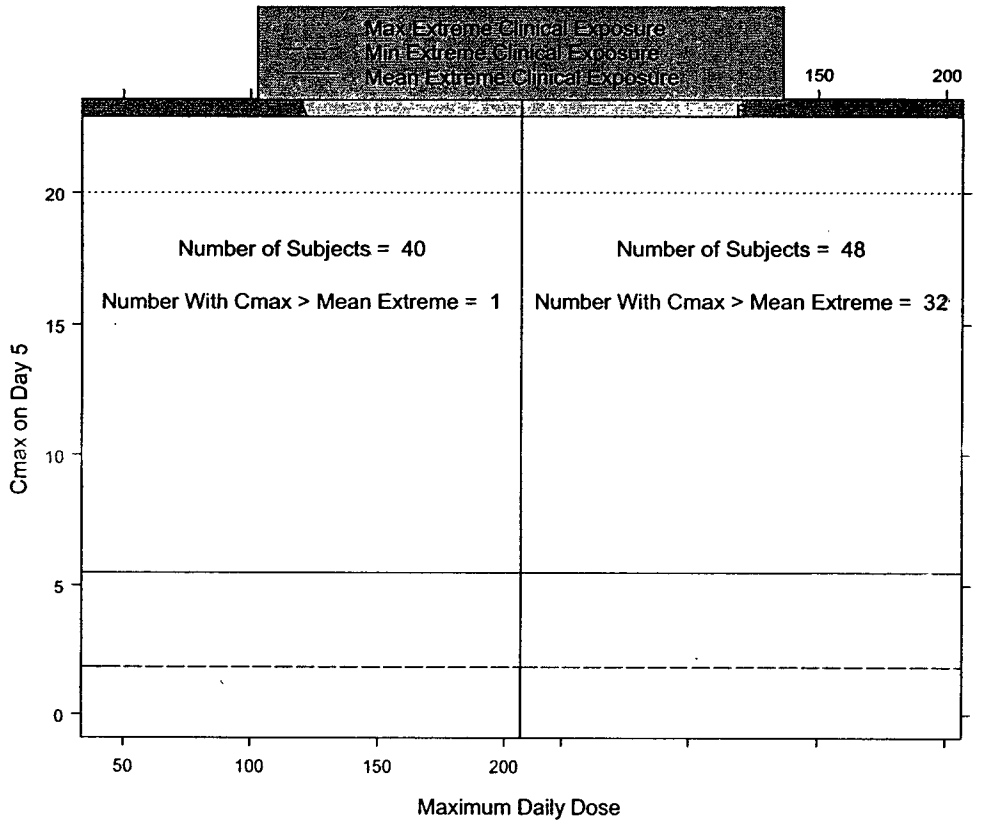


Figure 13. Maximum Exposure Achieved in Each Subject on Day 5 of the QT Evaluation Study. Treatment A = 20 mg BID Trospium for 5 days (therapeutic dose). Treatment B = 60 mg, 80 mg, or 100 mg Trospium BID for 5 days (supratherapeutic dose). Thirty two of the forty eight subjects (67%) receiving the supratherapeutic trospium dose had a Cmax value exceeding the average concentration expected after dosing 20 mg trospium to subjects with severe renal impairment (solid line: 5.5 ng/mL). All subjects receiving the supratherapeutic dose had a Cmax greater than the minimum value expected in renal impairment. Three subjects had Cmax between 15 ng/mL and 20 ng/mL. The maximum concentration expected in subjects with severe renal impairment after receiving 20 mg trospium is 20 ng/mL (dotted line).

Given that clinically relevant supratherapeutic exposures were reached on Study Day 5, the effect of trospium on QT interval will be considered with respect to this study day.

Trospium chloride caused a considerable increase in heart rate (HR). After 5 days of daily dosing, the supratherapeutic dose was associated with an average 20.6 bpm increase from baseline (95% CI=19.2,22.1 bpm), while the 20 mg dose was associated with a mean increase of 11.7 bpm (95% CI=9.3, 14). Moxifloxacin caused a 3.6 bpm change in HR whereas placebo was associated with a 2.6 bpm change. The change in heart rate supports using a correction method to evaluate the effect of drug on QT interval.

Figure 14 shows that placebo corrected change from baseline in Fridericia Corrected QT Interval (QTcF) for the supratherapeutic and therapeutic doses of trospium was -7.1 msec and a -2.8 msec, respectively, when the data across the entire study day were evaluated.

Moxifloxacin was associated with a 5.2 msec *increase* in QTcF during the same interval of time.

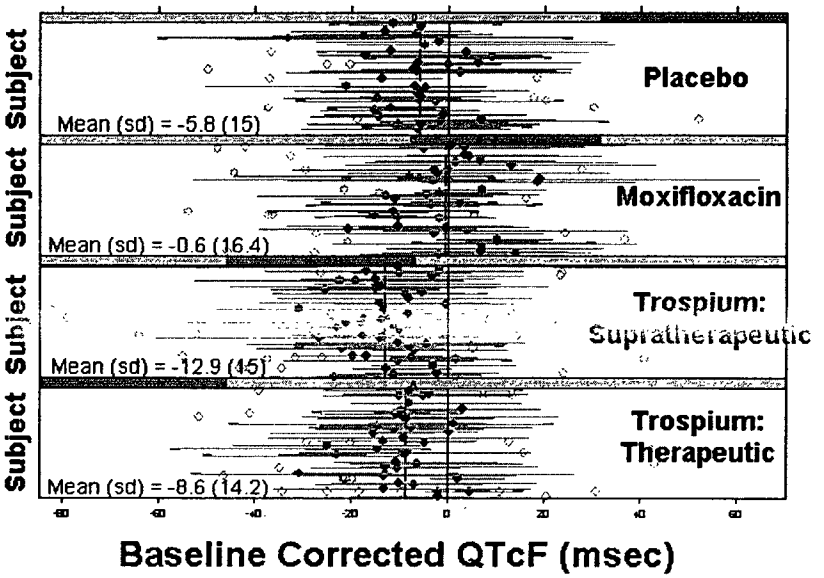


Figure 14. Baseline Corrected Mean Response on Study Day 5 for Each Subject. Each of the four panels shows the distribution of measures across a 24 hour period in each subject; each dot corresponds to the daily mean in each subject. The mean response for each treatment arm is illustrated by the vertical line in the plot and by the descriptive statistics listed. Placebo was associated with a -5.8 msec change in QTcF relative to baseline. Moxifloxacin was associated with a -0.6 msec change in QTcF relative to baseline. The placebo corrected change in baseline for the moxifloxacin treatment group was an increase of 5.2 msec (-0.6 – (-5.8)) in QTcF—a value consistent with previous results which suggests there was adequate study sensitivity. The placebo corrected change in QTcF from baseline for the supratherapeutic and therapeutic doses of trospium were -7.1 msec and -2.8 msec, respectively.

The effect of trospium on QT interval at Tmax (6 hours post-dose) is illustrated in Figure 15. Supratherapeutic and therapeutic doses of trospium are associated with a baseline corrected change of -12.92 and -7.87 msec in Fridericia corrected QT interval relative to

placebo, respectively.

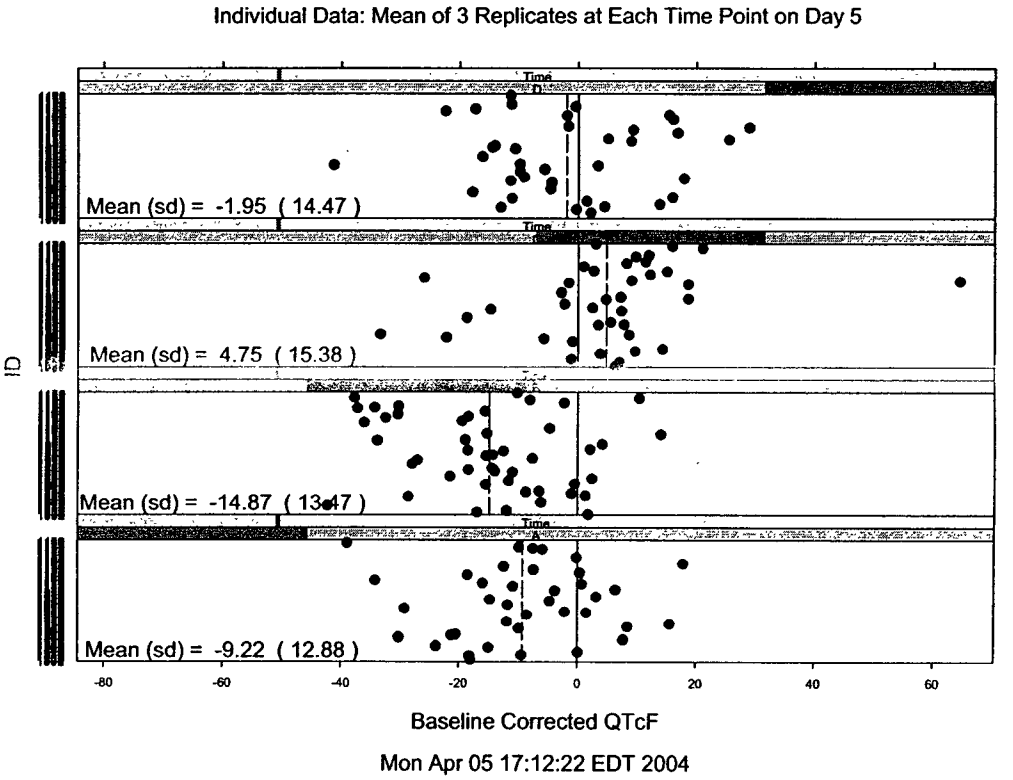


Figure 15. Baseline Corrected QTcF at Tmax on Study Day 5 for Each Subject. Each panel shows the distribution of measures at 6 hours post-dose in each subject; each dot corresponds to the mean of three replicate measures in each subject. The mean response for each treatment arm is illustrated by the vertical dashed line in the plot and by the descriptive statistics listed. The solid vertical line at zero demarcates the location of no effect. Placebo was associated with a -1.95 msec change in QTcF with respect to baseline. Moxifloxacin was associated with a 4.75 msec increase in QT interval relative to baseline. The placebo corrected change in baseline at Tmax for the supratherapeutic and therapeutic doses of trospium were -12.92 msec and a -7.87 msec, respectively.

Figure 16 and Table 17 illustrate that trospium dosing was not associated with an increase in QTcF above that caused by placebo at any time during the study, while Moxifloxacin consistently caused an effect greater than placebo. The response on all arms approaches placebo response at 24 hours post-dose. This result is consistent with the given treatment causing the QT response observed.

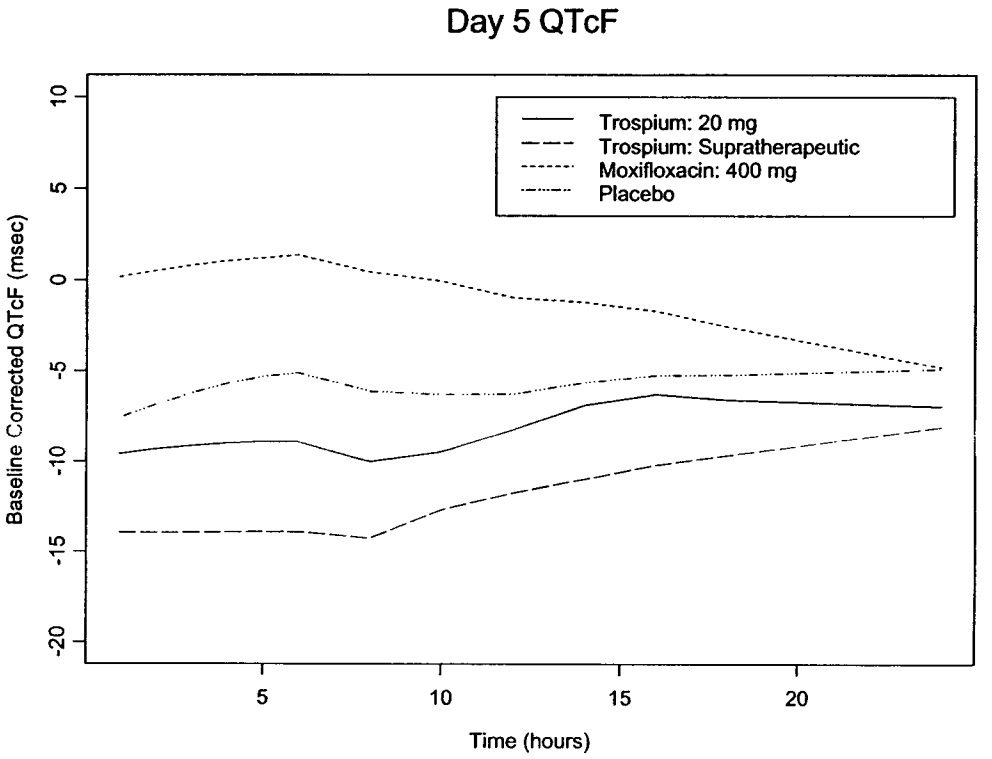


Figure 16. Smooth Through QTcF Measured Over 24 Hours in Each Treatment Arm.

	Trospium: 20 mg BID	Trospium: Supratherapeutic	Moxifloxacin 400 mg	Placebo
Time				
1	-9.91 (12.8)	-12.26 (11.3)	3.73 (17.3)	-10.57 (15.7)
2	-13.15 (13.8)	-16.01 (16.7)	0.036 (15.3)	-6.64 (13.8)
3	-5.46 (14.7)	-12.99 (12.1)	-2.24 (14.4)	-7.89 (12.1)
4	-8.07 (13.5)	-14.95 (13.8)	-2.07 (18.3)	-6.54 (15.4)
5	-7.89 (17.4)	-14.87 (18.6)	0.8 (19.8)	-3.91 (12.6)
6	-9.22 (12.9)	-14.87 (13.5)	4.75 (15.4)	-1.95 (14.5)
8	-7.67 (12.9)	-7.86 (12.8)	3.45 (14.8)	-3.96 (14.3)
10	-14.71 (13.7)	-22.73 (16.9)	-7.25 (16.2)	-13.20 (15.1)
12	-13.35 (14.4)	-11.96 (12.9)	-1.42 (14.7)	-4.57 (14.4)
14	-4.01 (11.6)	-5.67 (12.4)	3.37 (16.1)	-2.97 (17.1)
16	-2.42 (17.7)	-11.49 (14.9)	-6.27 (18.2)	-3.77 (14.7)
18	-4.93	-11.12	1.71	-1.91

	(9.7)	(13.6)	(13.3)	(14.9)
24	-10.79 (13.3)	-10.73 (17.7)	-6.74 (13.8)	-6.80 (17.4)

Table 17. Mean and Standard Deviation of Baseline Corrected Change in QTcF as a Function of Time on Day 5. Computation performed on the mean of each individual's measures—3 replicates taken.

Table 18 summarizes the effect of trospium chloride on heart rate, QTcF and individually corrected QT interval throughout the study. Given that drug concentration was at steady state on Day 5, this is the focus of discussion.

	Trospium 20 mg	Trospium 60,80,100 mg	Moxifloxacin 400 mg	Placebo
HR: Day 0 sd [1]	73.4 (10) (N=40)	72.4 (7.7) (N=49)	71.4 (8.5) (N=40)	73.3 (9.2) (N=40)
HR: Day 1 sd [2]	76.1 (10.5) (N=40)	86.2 (10) (N=49)	74.3 (9.2) (N=40)	75.4 (9.2) (N=40)
HR: Day 5 sd	84.7 (10.2) (N=40)	92.7 (8.8) (N=49)	75.0 (7.3) (N=40)	75.6 (8.4) (N=40)
ΔHR: Day 0→1 95% CI sd [1,2]	2.8 (1.5,4.0) (4) (N=40)	13.8 (12.1,15.5) (5.9) (N=49)	2.8 (1.3,4.3) (4.8) (N=40)	2.1 (0.8,3.5) (4.2) (N=39)
ΔHR: Day 0→5 95% CI sd [1,2]	11.7 (9.3,14) (7.2) (N=40)	20.6 (19.2,22.1) (4.9) (N=49)	3.6 (1.7,5.4) (5.8) (N=40)	2.6 (0.7,4.5) (5.9) (N=40)
Mean QT Day 0 sd [1]	375.2 (24.8) (N=40)	377.6 (20.1) (N=49)	378.6 (20.3) (N=40)	370.4 (21.7) (N=40)
Mean QT Day 1 sd [2]	365.3 (23.2) (N=40)	347.7 (21.9) (N=49)	374.1 (18.3) (N=40)	362.9 (18.5) (N=40)
Mean QT Day 5 sd [2]	349.1 (20.2) (N=40)	336.4 (19.1) (N=49)	371.7 (18.2) (N=40)	360.9 (16.8) (N=40)
ΔQT: Day 0→1 95% CI sd [1,2]	-9.8 (-12.7,-7.0) (9.0) (N=40)	-29.0 (-33.0,-26.7) (11) (N=49)	-4.5 (-7.5,-1.5) (9.4) (N=40)	-7.7 (-10.5,-4.9) (8.6) (N=40)
ΔQT: Day 0→5 95% CI sd [1,2]	-26.2 (-31.3,-21.1) (15.5) (N=40)	-42.0 (-44.7,-39.2) (9.5) (N=49)	-6.9 (-11.0,-2.8) (12.7) (N=40)	-9.8 (-14.1,-5.4) (13.4) (N=40)
Mn QTcI Day 0 sd [1]	398.0 (17.9) (N=40)	400.0 (15.5) (N=49)	400.3 (19.4) (N=40)	395.3 (20.0) (N=40)
Mn QTcI Day 1 sd [2]	392.4 (17.9) (N=40)	389.7 (19.2) (N=49)	400.0 (19.4) (N=40)	390.6 (18.7) (N=40)
Mn QTcI Day 5	389.0	388.4	399.5	388.8

sd [2]	(19.8) (N=40)	(19.8) (N=49)	(20.5) (N=40)	(18.0) (N=40)
ΔQTcI:Day 0→1 95% CI sd [1,2]	-5.6 (-7.1,-4.1) (4.6) (N=40)	-10.2 (-12.5,-7.9) (8.1) (N=49)	-0.3 (-1.9,1.2) (4.8) (N=40)	-4.8 (-6.2,-3.4) (4.4) (N=39)
ΔQTcI:Day 0→5 95% CI sd [1,2]	-8.1 (-10.4,-5.7) (7.1) (N=40)	-12.3 (-15.0-9.6) (9.2) (N=49)	-0.8 (3.5,1.9) (8.4) (N=40)	-6.1 (-8.7,-3.5) (8.0) (N=40)
Max ΔQTcI from Base >30 msec: Day 1 Day 5	 5 = 13% (N=40) 1 = 3% (N=38)	 1 = 2% (N=49) 1 = 2% (N=47)	 8 = 20% (N=40) 7 = 18% (N=40)	 5 = 13% (N=39) 5 = 13% (N=39)
Mn QTcF Day 0 sd [1]	397.5 (14.5) (N=40)	399.0 (12.3) (N=49)	398.3 (16.0) (N=40)	393.0 (16.5) (N=40)
Mn QTcF Day 1 sd [2]	391.4 (13.6) (N=40)	388.5 (13.7) (N=49)	397.9 (14.8) (N=40)	388.2 (15.3) (N=40)
Mn QTcF Day 5 sd [2]	388.5 (12.8) (N=40)	386.6 (13.0) (N=49)	397.7 (16.3) (N=40)	387.0 (13.9) (N=40)
ΔQTcF:Day 0→1 95% CI sd [1,2]	-6.0 (-7.4,-4.6) (4.3) (N=40)	-10.6 (-12.5,-8.6) (6.9) (N=49)	-0.4 (-2.0,1.2) (5.1) (N=40)	-4.9 (-6.2,-3.6) (4.1) (N=39)
ΔQTcF:Day 0→5 95% CI sd [1,2]	-8.5 (-10.7,-6.3) (6.8) (N=38)	-12.9 (-14.9,-10.8) (6.9) (N=47)	-0.6 (-3.2,2.0) (8.2) (N=40)	-5.8 (-8.2,-3.4) (7.4) (N=39)
Max ΔQTcF from Base >30 msec: Day 1 Day 5	 5 = 13% (N=40) 2 = 5% (N=38)	 1 = 2% (N=49) 1 = 2% (N=47)	 11 = 28% (N=40) 8 = 20% (N=40)	 3 = 8% (N=39) 6 = 15% (N=39)
New Outlier QT > 450 Day 1 Day 5 [6]	 4 = 10% (N=40) 1 = 3% (N=40)	 0 (N=49) 1 = 2% (N=49)	 7 = 18% (N=40) 2 = 5% (N=40)	 1 = 3% (N=39) 3 = 8% (N=40)
New Outlier QTcI > 450 Day 1 Day 5 [6]	 1 = 3% (N=40) 1 = 3% (N=38)	 1 = 2% (N=49) 1 = 2% (N=47)	 6 = 15% (N=40) 4 = 10% (N=40)	 2 = 5% (N=39) 3 = 8% (N=39)
New Outlier QTcF > 450 Day 1 Day 5 [6]	 2 = 5% (N=40) 1 = 3%	 NA (N=49) 1 = 2%	 5 = 13% (N=40) 1 = 3%	 NA (N=39) NA

	(N=38)	(N=47)	(N=40)	(N=39)
T Wave Abnormality:				
Day 1	2 = 5%	8 = 16%	1 = 3%	3 = 8%
Day 5	8 = 21%	9 = 19%	3 = 8%	4 = 10%
	(N=40)	(N=49)	(N=40)	(N=40)

Table 18. Summary of Response to Treatments in the 5 Day QT Evaluation Study.
All values are calculated from the mean of the mean of the three ECGs at each time point for each subject.
[1] Baseline values are the mean of the 13 serial ECGs on Day 0 (baseline) and only includes subjects with ECGs.
[2] For each follow-up time point, results are based on the mean of all ECGs taken on that day.
[3] A subject has had a bradycardic event if any heart rate value for that time point is < 50 bpm & represents
a >=25% decrease from baseline.
[4] A subject has had a tachycardic event if any heart rate value for that time point is > 100 bpm & represents
a >=25% increase from baseline.
[5]A subject has had a value that is an outlier at follow-up if any QT interval measure at the follow-up time point is > 500 msec while their baseline was <= 500 msec.
Treatments:
A = Trospium Cl 20 mg bid (recommended dose)
B = Trospium Cl 60, 80, 100 mg bid (supratherapeutic dose)
C = Moxifloxacin 400 mg qd (active control)
D = Placebo
[6] All values are calculated as the mean of three ECGs at each time point for each subject.

Although the baseline corrected results discussed above suggest that trospium causes a shortening of the QT interval, the non-baseline corrected results inTable 18 suggest that trospium neither shortens nor prolongs the QT interval. The mean QTcF on Day 5 for subjects receiving therapeutic and supratherapeutic doses of trospium (388.5 msec and 386.6, respectively) is similar to the mean QTcF for subjects receiving placebo (387.0). The standard deviation of these estimates is similar, as well. In contrast, on Day 5, Moxifloxacin was associated with a mean QTcF of 397.7 msec. Compared to placebo, on Day 5, Moxifloxacin was associated with a 10.1 msec increase in QT interval.

The discrepancy between baseline and non-baseline subtracted results suggests that there was a difference in baseline response for each treatment arm. Table 19 shows, however, that, on average, the treatment arms were equivalent at baseline.

Time Measured	Trospium: 20 mg BID	Trospium: Supratherapeutic	Moxifloxacin: 400 mg	Placebo
All measures over 24 hrs on Day 0	397.01 (18.54)	399.48 (16.91)	398.25 (19.81)	392.67 (20.18)
Measures at Tmax (6 hrs) on Day 0	395.0 (14.5)	397.2 (17.1)	396.8 (18.3)	389.7 (17.5)

Table 19. Mean QTcF at Baseline. Computation performed on the mean of all individual's measures—3 replicates taken. Results are shown for the mean over all baseline measures and for the mean of all baseline measures corresponding to Tmax for the drug.

Although no significant difference was observed in the mean baseline response, a difference was observed in the distribution of individual baseline measures. Figure 17 and Figure 18 show that there were more outlying QTcF measures for all treatments at baseline than were observed on Study Day 5. These outlying values wouldn't necessarily influence the overall mean QTcF at baseline, but could considerably influence the change from baseline computed for each subject. Figure 19, a plot of the distribution of each individual's standard deviation of QT measures sectioned by study day and treatment arm, is another way of showing that variability in each subjects' measures was greater at baseline than on any other study day.

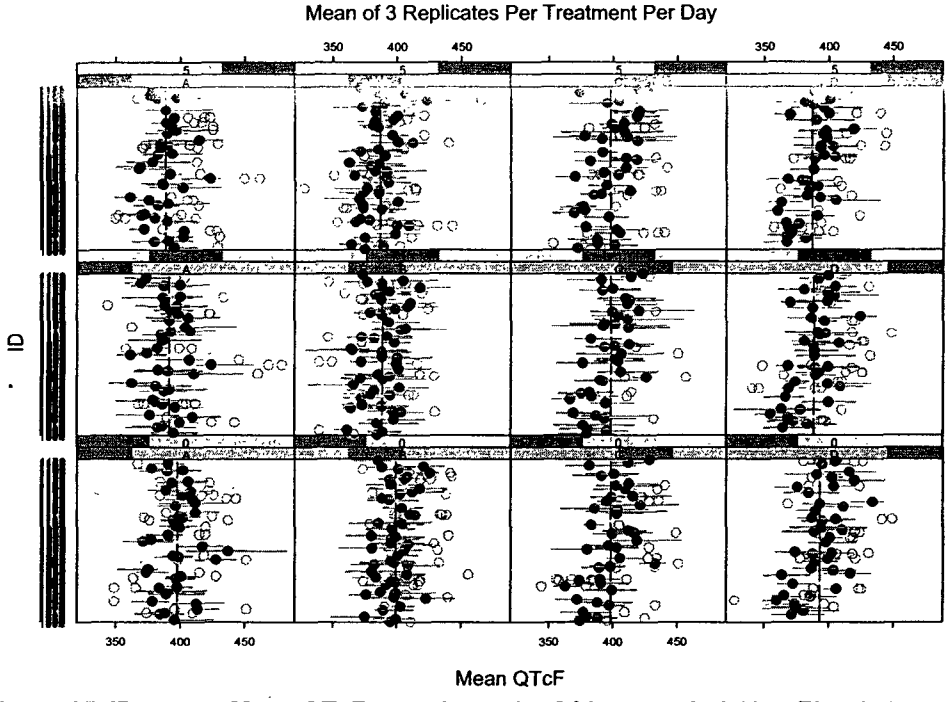


Figure 17. ID versus Mean QTcF over the entire 24 hour period. Key: Plots in top row: Day 5, middle row: Day 1, bottom row: Day 0; Plots in column 1: Trospium 20 mg, column 2: Trospium supratherapeutic dose, column 3: Moxifloxacin, column 4: Placebo. Note that the distribution of values is more variable in the bottom row (Day 0) than in the other rows (Day 1, Day 5).

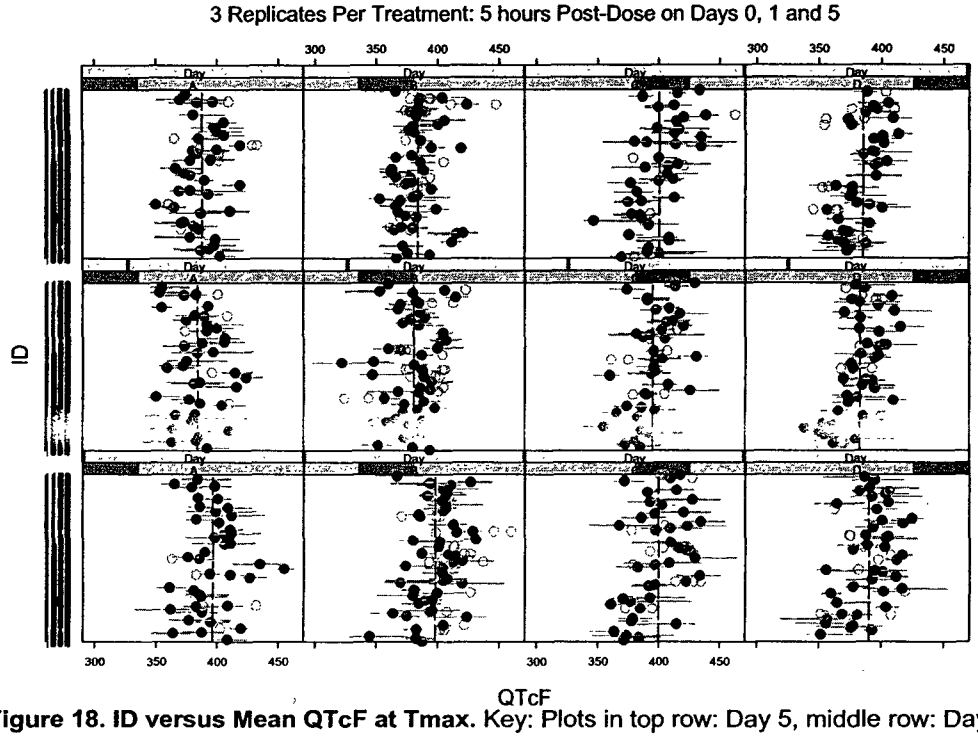


Figure 18. ID versus Mean QTcF at Tmax. Key: Plots in top row: Day 5, middle row: Day 1, bottom row: Day 0; Plots in column 1: Trospium 20 mg, column 2: Trospium supratherapeutic dose, column 3: Moxifloxacin, column 4: Placebo. Note that the distribution of values is more variable in the bottom row (Day 0) than in the other rows (Day 1, Day 5).

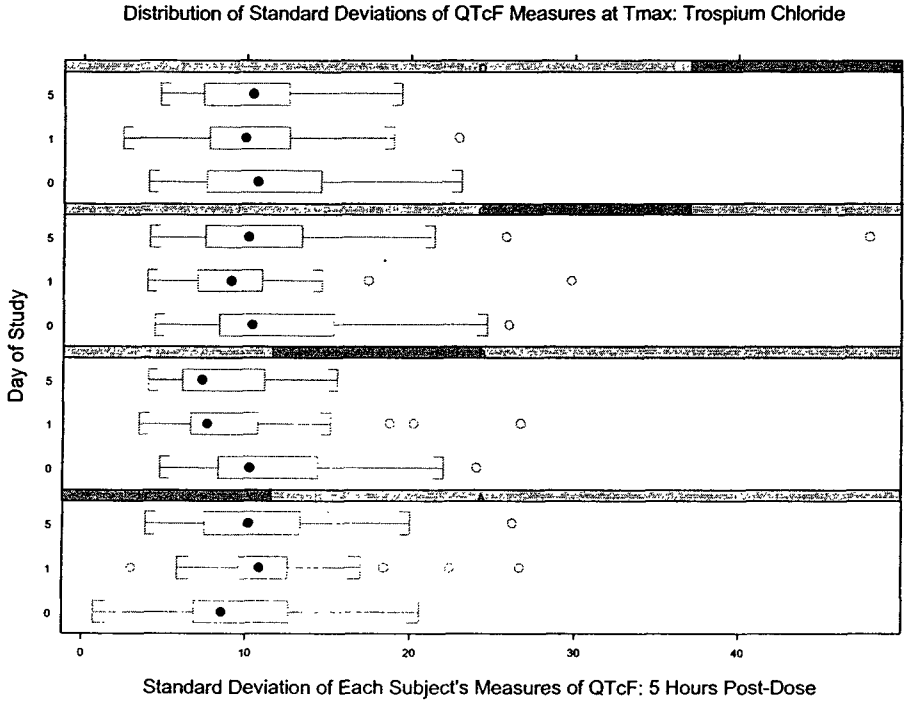


Figure 19. Boxplot of the Standard Deviation of Each Subject's Measures Taken at Tmax for Each Regimen on Study Day 0, Day 1, and Day 5. Key: Bottom panel: trospium 20 mg, second from the bottom: trospium supratherapeutic, third from the bottom: moxifloxacin, top plot: placebo. Within each panel, the bottom plot is the distribution on Day 0, the middle plot is the distribution on Day 1, and the top plot is the distribution on Day 5 (at steady state). The box indicates the interquartile range for the data; the whiskers indicate the limit of the most extreme measure within 1.5 times the interquartile range. Note that the interquartile range of the bottom bar (Day 0) in each panel is greater than the interquartile range on Day 1 or Day 5. This indicates that there was more interindividual variability on Day 0 than on other study days.

Note that there was no difference in the study protocol on the baseline day compared to Study Day 1 or Study Day 5 that could account for the difference in the distribution of responses. Thus, this may reflect random variability in the data.

To summarize, the mean QTcF in subjects receiving 20 mg trospium or supratherapeutic doses of trospium BID for 5 days was equivalent to subjects receiving placebo. Moxifloxacin was associated with a QTcF increase of 5-10 msec relative to placebo in this study, thus validating study sensitivity.

Evaluation of reported drug effect on heart rate offers further support for comparing non-baseline corrected responses on Study Day 5. Moxifloxacin is known to have no effect on heart rate. However, the baseline corrected value of heart rate makes it appear that moxifloxacin increases heart rate by 3.6 beats per minute on Study Day 5 relative to baseline. In contrast, mean heart rate in subjects receiving moxifloxacin is 75.0 (sd: 7.3) on Study Day 5—a value equivalent to the mean heart rate in subjects receiving placebo on Study Day 5 (75.6 beats/min; sd: 8.4). Subjects receiving 20 mg and supratherapeutic doses of trospium were observed to have a mean heart rate of 84 (sd: 10.2) and 92.6 (sd: 8.8), respectively, on study Day 5. This represents an increase of 9.1 beats/minute and 17.1 beats/minute, respectively.

Note that Table 18 shows that a greater number of subjects receiving trospium chloride experienced changes in their T wave morphology than subjects receiving moxifloxacin or placebo. T wave inversions were observed in 8 (21%) and 9 (19%) of subjects receiving 20 mg and supratherapeutic doses of trospium chloride, respectively, on Day 5, while 3 subjects (8%) receiving moxifloxacin and 4 subjects (10%) receiving placebo exhibited this response after 5 days of dosing.

In a formal consult from the Cardiorenal Division, the reviewer noted that T wave inversions may be caused by ischemia. Given that numerous clinical conditions are associated with T wave inversions, the clinical reviewer of this NDA researched the possibility and concluded that that was unlikely given that no subject with T wave inversions developed chest pain.

In a teleconference with the sponsor and their cardiovascular consultant, . the sponsor provided further evidence weighing against the possibility that trospium causes T wave inversions and/or ischemia. First, T wave inversions were not observed in three other clinical trials of trospium chloride. Second, the T wave inversions were not of a shape that is associated with ischemia.

C. Intrinsic Factors

What is the effect of renal impairment on the pharmacokinetics of trospium chloride?

Table 20 shows that moderate to severe renal impairment (CLcr: mean=15.3 mL/min/1.73 m^2; range 8.2 to 31.9 mL/min/1.73 m^2) was associated with a 1.8-fold increase in mean Cmax and a 4.2-fold increase in mean AUC relative to healthy subjects (CLcr: median= 85.0 mL/min/1.73 m^2; range 75 to 121 mL/min/1.73 m^2). Half life increased from a range of 5.5 to 50 hours to a range of 9.9 to 90 hours in renally impaired subjects versus healthy subjects. These data were collected in a study of a single oral dose of 40 mg trospium chloride administered to 12 males. This dose is twice the dose recommended in healthy subjects. Note that the study excluded patients receiving chronic dialysis. The results of this study are shown graphically in Figure 20.

Parameter	Mean (min-max)	
	Renally Impaired	Healthy
AUC (h·ng/mL)	233	55.6 (
Cmax (ng/mL)	10.9	5.96 (

Table 20. Exposure to a 40 mg Single Dose of Trospium Chloride.

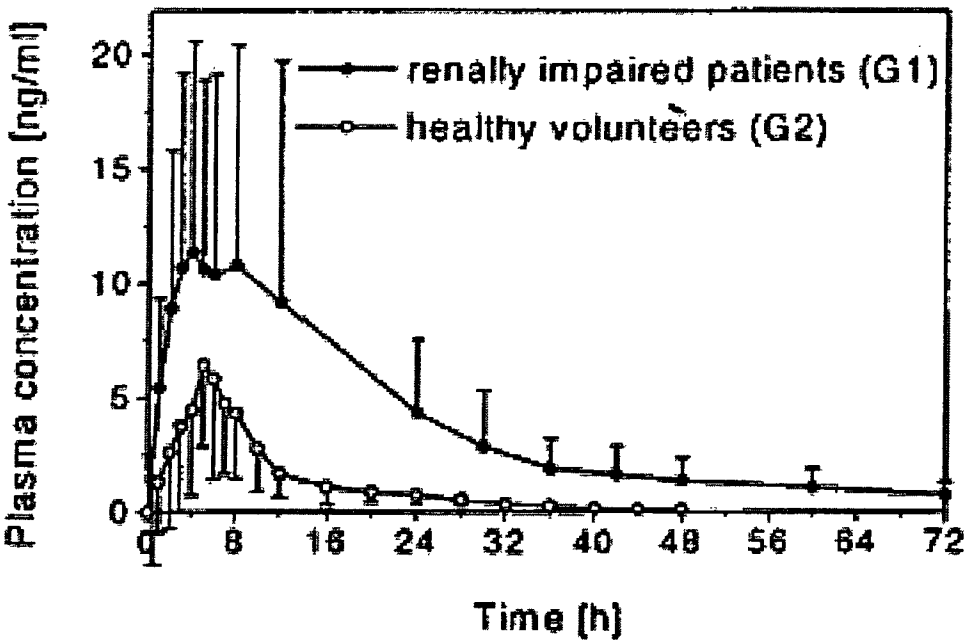


Figure 20. Mean Plasma Concentration Versus Time Curves (arithmetic mean +/- SD) of Trospium Chloride In Renally Impaired Patients (G1; N=12) and Healthy Volunteers (G2; N=12) After Single Dose Administration of 40 mg.

In this study, one renally impaired subject (8% of N=12) required diuretic rescue due to small urinary voiding. No healthy subject required such an intervention. However, two of the 12 renally impaired patients (17%) each reported a single adverse event, while six of the 12 healthy subjects (50%) reported 9 adverse events. Dry mouth was the most common complaint and no severe adverse events were reported.

Since one dose strength of trospium has been developed for the US market, the sponsor proposed to reduce dosing frequency to mitigate the increased exposure in renal impairment. The sponsor initially proposed to dose 20 mg QD in severe renal impairment.

Since AUC is increased 4.2-fold in severe renal impairment, reducing the dosing interval to one half the frequency in healthy subjects was expected to yield a 2-fold increase in AUC relative to that expected healthy subjects. To evaluate the safety of the doubled exposure expected in renal impairment, in addition to examining the safety data from the study of renally impaired subjects, safety and exposure data from former studies were reviewed. The studies were reviewed to identify studies yielding exposures expected in renal impairment. The exposure data reviewed are summarized in Table 21.

	Fasted?	Cmax	AUC
20 mg healthy (631-001)	YES		5.7
20 mg healthy (94D4.02)	YES		37.5
20 mg healthy (94D2.05)	YES		37.7
20 mg healthy (631.006)	YES		27.4
20 mg healthy (94D2.10)	YES		36.4
20 mg healthy (94D2.11)	YES		14.0
20 mg BID healthy (94D2.10)	YES		17.7
20 mg BID healthy (94D2.11)	YES		15.0
20 mg BID healthy (94T1.01)	NO		6.3
20 mg BID healthy (631-001)	YES		10.1
40 mg healthy (94D2.10)	YES		55.6 (18.5,152)
40 mg healthy (94D2.05)	YES		84.8
40 mg BID healthy (631-001)	YES		25.5
60 mg healthy (94D2.05)	YES		134.4
200 mg healthy (631-001)	YES		204.2
40 mg renal impairment	YES		233 (48.21-709.28)
20 mg renal impairment (prediction from 40 mg data)	YES		120 (24,355)

Table 21. Summary of Exposure Data in Clinical Trials.

Assuming that exposure to a 20 mg dose in renally impaired subjects is half the exposure to the tested 40 mg dose, one expects an AUC of 120 ng*hr/mL and a Cmax of 5.5 ng/mL after a single 20 mg dose. The above table shows that these values of Cmax and AUC were attained in a single dose study of 60 mg dosed to healthy subjects. Cmax (but not AUC) was covered by a 40 mg single dose (but not a 40 mg BID regimen) administered to healthy subjects. Table 21 shows that Study 94D2.05, a trial of 40 mg and 60 mg single doses, and Study 94D2.10, a trial of a 40 mg single dose, tested doses covering exposures predicted in renal impairment. Adverse event tables were not included in the study report for study 94D2.05, however, the sponsor reported that all 12 subjects in the study tolerated the drug. In Study 94D2.10, five of twelve volunteers experienced adverse events after the single dose administration, primarily dry mouth.

Recall that doses of up to 360 mg trospium chloride have been administered to healthy subjects in a dose escalation study. However, subjects in that study were dosed after a meal and a high fat breakfast has been shown to decrease Cmax by 84% and AUC by 74%. Since PK data were not collected in the dose escalation study, to make predictions based on the adverse event reports collected, exposure will be scaled to reflect the reduced exposure expected when dosing fed subjects. An estimate of the dose in this study which may reflect exposures in renal impairment is obtained as follows:

$0.16\ Cmax^{FASTED} = Cmax^{FED}$ (Known from the food effect study)

$Cmax^{FASTED} = 6.25\ Cmax^{FED}$

$0.26\ AUC^{FASTED} = AUC^{FED}$ (Known from the food effect study)

$AUC^{FASTED} = 3.8\ AUC^{FED}$

Therefore, based on this rough estimate, and based on the earlier prediction (Table 21) that Cmax and AUC in renally impaired subjects dosed 20 mg trospium in the fasted state may correspond to that expected when dosing 40 mg and 60 mg, respectively, to fasted healthy subjects:

Cmax for 40 mg dose in fasted state = Cmax for 6.25x40 mg dose in fed state
~ Cmax for 240 mg dose in fed state

AUC for 60 mg dose in fasted state = AUC for 3.8x60 mg dose in fed state
~ AUC for 240 mg dose in fed state

As discussed in the section on exposure-response, there was an increase in incidences of dry mouth and headache reported for doses greater than 120 mg. Vision disturbance was reported by subjects receiving the 240 mg dose. Micturition difficulty was reported by two subjects receiving doses greater than 240 mg. Blurred vision occurred once in the placebo group and four times in the trospium group following treatment with doses of 80 or 120 mg. Heart rate increased 9, 14, and 26 beats per minute above baseline for subjects receiving 120 mg, 180 mg and 240 mg trospium chloride, respectively.

Based on concerns that dosing QD to renally impaired subjects may not reduce exposure adequately, it was recommended that the sponsor also take advantage of the diurnal variability in exposure to trospium chloride to reduce exposure further. The recommendation was to consider dosing trospium once daily at bedtime. The sponsor performed a simulation study to evaluate this recommendation.

Specifically, the sponsor used estimates of Cmax, Tmax and T½ for 20 mg doses administered in the morning and in the evening obtained from fitting a one-compartment model with first order absorption and no lag time. Assuming renal impairment reduced volume 1.9-fold, reduced clearance 4.2-fold, and had no effect on absorption, the sponsor simulated pharmacokinetic profiles expected for different dosing regimens. The regimens simulated were: (1) Normal subject with 20 mg BID, (2) Renally impaired subject with 20 mg QD; morning dosing, (3) Renally impaired subject with 20 mg QD; evening dosing, (4) Renally impaired subject with 20 mg; every other day (QOD) morning dosing. Based on the simulations, the exposures achieved with once daily dosing in the

evening yield exposures closest to those in healthy subjects receiving 20 mg QD. The results of this simulation are reported in Figure 21.

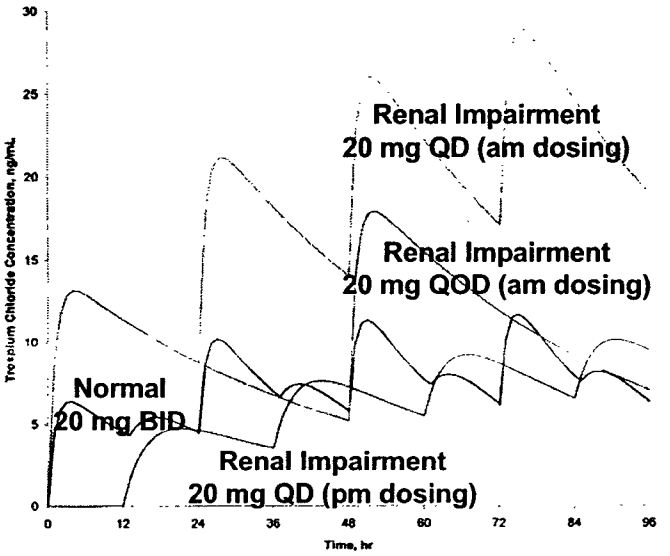


Figure 21. Simulation of Exposure in Renally Impaired Subjects for Different Dosing Regimens. The regimens simulated were: (1) Normal subject with 20 mg BID, (2) Renally impaired subject with 20 mg QD; morning dosing, (3) Renally impaired subject with 20 mg QD; evening dosing, (4) Renally impaired subject with 20 mg; every other day (QOD) morning dosing. Based on the simulations, the exposures achieved with once daily dosing in the evening yield exposures closest to those in healthy subjects receiving 20 mg QD.

The proposed recommendation is to dose trospium 20 mg once daily at bedtime to patients with severe and moderate renal impairment.

Note that "Patients with clinically significant renal disease" was an exclusion criterion in the pivotal trial.

What is the effect of hepatic impairment on the pharmacokinetics of trospium chloride?

Moderate hepatic impairment (Child-Pugh 7-8) was associated with a 60% increase in mean Cmax, a 15% decrease in AUC, and a 50% increase in renal clearance relative to healthy subjects when a single oral dose of 40 mg trospium chloride was administered. The increase in Cmax without a change in AUC suggests that the liver's most important role is in first pass metabolism. There is no information regarding the effect of severe hepatic impairment on the pharmacokinetics of trospium chloride. However, the trend in Cmax, AUC, and renal clearance observed in subjects with Mild and Moderate Hepatic Impairment (reported in the Table 22 and Figure 22 below) suggests that these parameters are correlated with the extent of hepatic function.

	Mild Impairment (Child-Pugh 5-6)	Moderate Impairment (Child-Pugh 7-8)
Cmax	1.1	1.6
$AUC_{0\rightarrow\infty}$	0.95	0.85
CL	1.1	1.2

CLrenal	1.1	1.5

Table 22. Ratio of Parameter Value Relative to Value Observed in Subjects With Normal Hepatic Function. Moderate hepatic impairment is associated with a 60% increase in Cmax and a 50% increase in renal clearance with administration of a single 40 mg oral trospium chloride dose.

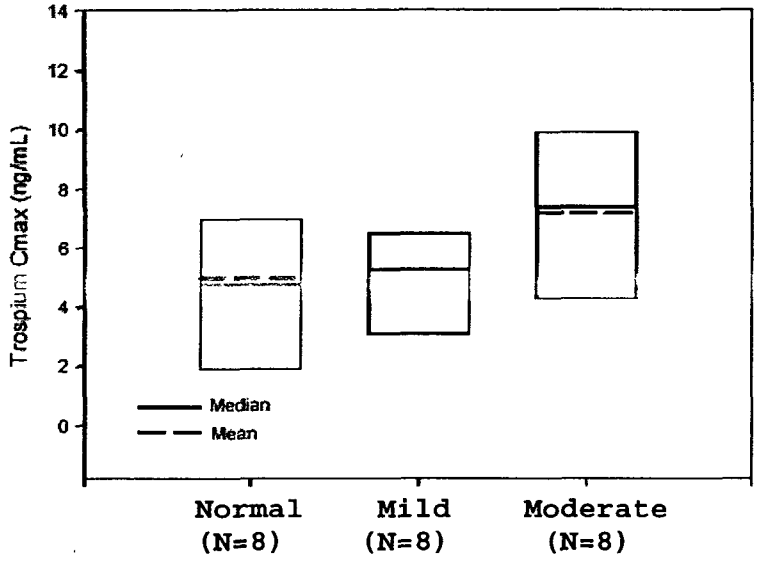


Figure 22. Boxplot of Cmax of Trospium Chloride Categorized by Hepatic Function (Normal Function, Mild Impairment, Moderate Impairment). The bottom of the box represents the 25th percentile and the top of the box represents the 75th percentile. Note that there is a greater mean and more variability in Cmax in subjects with moderate hepatic impairment compared to subjects with normal hepatic function.

Figure 23 represents renal clearance as categorized by hepatic function.

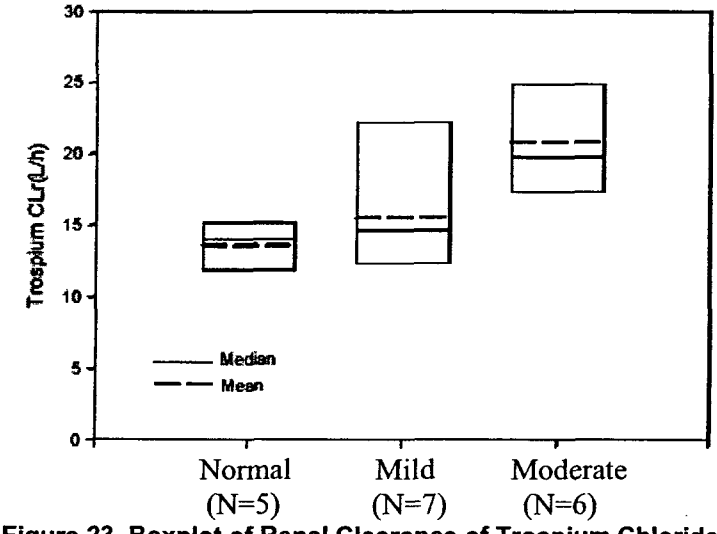


Figure 23. Boxplot of Renal Clearance of Trospium Chloride Categorized by Hepatic Function (Normal Function, Mild Impairment, Moderate Impairment). The bottom of the box represents the 25th percentile and the top of the box represents the 75th percentile. Note that renal clearance is greater in subjects with moderate hepatic impairment compared to normal subjects.

Total clearance appears unaffected by mild and moderate hepatic impairment as the decrease in hepatic elimination appears to be compensated for by renal elimination. It is unknown if this is the case with severe hepatic impairment. It is further unknown how the combination of renal impairment and hepatic impairment affects the elimination of trospium chloride.

The incidence of adverse events was greater in moderate hepatic impairment (87.5%) than mild hepatic impairment (37.5%) in comparison to subjects with normal hepatic function (25.0%). A total of 12 out of 24 subjects (50%) experienced 18 adverse events during the study; all were mild in severity. Gastrointestinal disorders (6 of 24 subjects [25.0%]) and nervous system disorders (6 of 24 subjects [25.0%]) were the most frequently reported adverse events.

What is the impact of gender on pharmacokinetics?
The data are conflicting regarding this question. When a single 40 mg trospium chloride dose was administered to 16 elderly subjects, Cmax and AUC were reduced by 44% and 45% in elderly females compared to elderly males. These differences were not explained by a difference in weight nor did it appear to reflect a difference in metabolism. Given that a large percent of elderly men have benign prostatic hypertrophy (BPH), the finding may reflect the difference in renal function for elderly males versus females.

When 20 mg trospium chloride was dosed BID for 4 days to 6 elderly (60 to 75 years) males, 6 elderly females taking hormone replacement therapy (HRT) and 6 elderly females not receiving HRT, AUC and Cmax were equivalent between women taking hormone replacement therapy and males. AUC and Cmax were 26% and 68%, respectively, higher in women without hormone replacement therapy than males. The differences in exposure due to gender were not explained by weight and no difference in urinary excretion was observed for any of the strata. This may be a spurious result reflecting the nature of low powered subgroup analyses. The studies were conducted in fasted subjects.

What is the effect of age on pharmacokinetics?
There are conflicting results regarding this question.

In single dose studies, age is inversely proportional to exposure. Figure 24 shows that exposure to a single 20 mg trospium chloride dose in elderly subjects was half that observed in young subjects. A comparison of the results from a single 40 mg trospium chloride dose study in 8 elderly males and 8 elderly females with the results of a single 40 mg dose trial in healthy young males showed that Cmax is 35% reduced in elderly males compared to young males and 64% reduced in elderly females compared to young males. AUC is equivalent between young and elderly males, but AUC is 40% reduced in elderly females relative to young males.

One possible mechanism for the reduced exposure in elderly subjects is a difference in gastric pH. Achlorhydria, a condition defined as the failure of the intragastric pH to fall to less than 4.0 under maximal stimulation[1], is more common in elderly than young

subjects. Given that the sponsor reports an instability of trospium chloride at pH > 4.0, increased degradation of drug in the gastrointestinal tract in elderly patients is consistent with clinical findings.

Although young subjects have greater exposure to drug after single doses, they have equivalent exposure at steady state as elderly subjects. A study of 20 mg trospium chloride dosed BID for 4 days to 18 elderly males and females revealed a 40% increase in Cmax for single versus multiple dose administration, while a chronic dosing study in young subjects revealed no significant change in exposure relative to that after a single dose. The lack of change in exposure with chronic dosing in young subjects is discussed elsewhere in this review as possibly reflecting inducible active renal secretion. The results of the single dose study may reflect a trade off between the relative contribution of absorptive barriers versus renal excretion to elimination in elderly subjects.

Elderly subjects in the pivotal trial (subjects aged 65-85 years) reported more adverse events (i.e. incidences of dry mouth, constipation, and abdominal pain) than young subjects. Additionally, in a single 20 mg dose study in elderly volunteers, one subject discontinued due to a serious adverse event and required 15 days of hospitalization. That subject experienced vertigo, garbled speech, an increase in blood pressure requiring administration of nifedipine, micturition difficulty, vomiting, diarrhea, dry mouth, headache and sensitivity to light. The hypertension was improved, but not reversed, two days after hospitalization. The vertigo and unclear speech was present until 15 days after the last dose of study drug was administered.

Given that mean exposure after steady state dosing of trospium in elderly subjects is expected to be equivalent to exposure in a young subjects, albeit, with greater variability, the incidence of adverse events may reflect a greater pharmacodynamic sensitivity to drug effects in the elderly. To determine if this was the case, the data from the elderly subject experiencing vertigo were investigated further. Figure 24 shows the mean plasma concentration data for young subjects receiving single and multiple doses and for elderly subjects receiving single and multiple doses. The individual measures of trospium concentration for the subject experiencing vertigo are plotted (with the plotting character "+"), as well. This plot shows that the elderly subject experiencing vertigo had levels of trospium that were above average in both young and elderly subjects. Thus, adverse events in this subject may have been influenced by pharmacokinetic and/or pharmacodynamic factors.

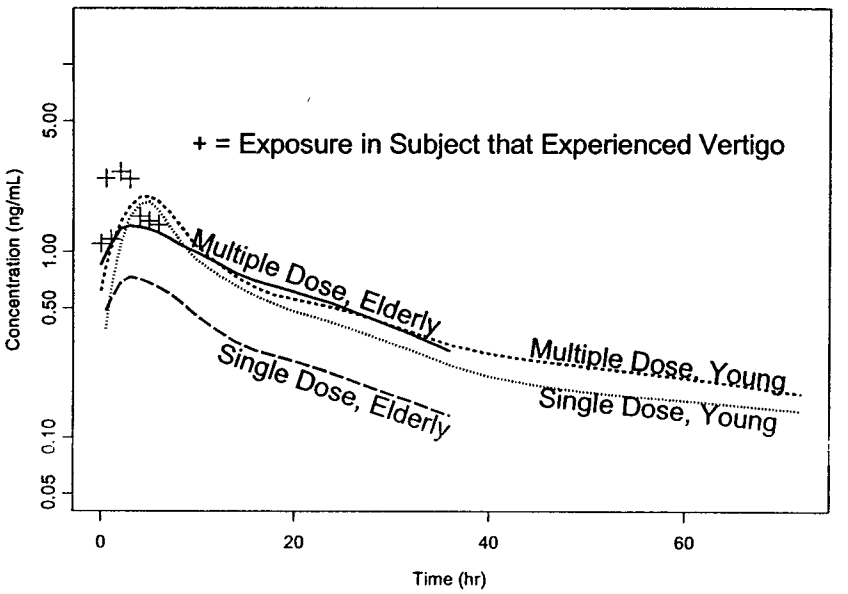


Figure 24. Exposure in Young and Elderly Subjects on Multiple and Single Dose Regimens: Highlighting Exposure in Elderly Subject Who Experienced Vertigo.

What is the effect of diurnal variability on trospium chloride?

Exposure is lower after evening doses than morning doses. The difference is less marked at steady state than after a single dose. A single dose study of 20 mg trospium chloride administered in a fasted state at 8 am and 8 pm to 8 healthy Caucasian males aged 20-40 years revealed a 33% reduction in AUC and a 59% reduction in Cmax when taken at night. A study of 20 mg trospium chloride dosed BID for 6 days to 12 healthy young males revealed a 13% reduction in AUC and a 29% reduction in Cmax. The diurnal effect may reflect a change in the rate of gastric emptying at night. Table 23 summarizes these results.

	Cmax	AUC
Single Dose Study	↓ 59%	↓ 33%
Multiple Dose Study	↓ 29%	↓ 13%

Table 23. Change in Exposure Following an Evening Dose Relative to Exposure Following a Morning Dose.

What is the inter- and intra- subject variability of PK parameters in volunteers and patients and what are the major causes of variability?

The sponsor provided a population PK analysis of data collected during an optional, nine month, open-label phase following the single pivotal clinical trial. Sparse sampling of PK was carried out on Study Day 1, Study Day 28, and Study Day 35 such that data were available in 19 subjects on Day 1, 46 subjects on Day 28, and 28 subjects on Day 135. The NONMEM data set included 179 samples from 81 subjects. Variables for NONMEM analysis included ID, visit number, gender, race, age, weight, height, BSA, BMI, dose time, dose amount, sampling time, trospium concentration, serum creatinine, creatinine clearance, SGPT, SGOT, and concomitant medications. Of the subjects enrolled, 70 were female and 17 were male; 77 were Caucasian, 1 was Asian, 5 were African American and 4 were American Indian. The sponsor investigated the effect of

including the following covariates in the model: metabolic inhibitors (CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A), metabolic inducers (CYP1A2, CYP2B6, CYP2C19 and CYP3A), and concomitant medications undergoing active renal secretion. Note that subjects with clinically significant renal disease or clinically significant bladder neck obstructions were excluded from the trial.

Table 24 lists the metabolic inhibitors, metabolic inducers and drugs eliminated by active renal secretion identified as concomitant medications administered within 3 days of trospium chloride dosing at Visits 1, 2 or 3.

Class of Compound	Specific compounds
CYP1A2 inhibitors	cimetidine, ciprofloxacin
CYP2C19 inhibitors	cimetidine, fluoxetine, lansoprazole, omeprazole, paroxetine
CYP2C9 inhibitors	fluvastatin, paroxetine, sertraline
CYP2D6 inhibitors	celecoxib, cimetidine, fluoxetine, paroxetine, sertraline
CYP3A4,5,7 inhibitors	cimetidine, ciprofloxacin, clarithromycin, diltiazem, erythromycin
CYP1A2 inducers	insulin, omeprazole
CYP2B6 inducers	phenobarbital
CYP2C19 inducers	prednisone
CYP3A4,5,7 inducers	phenobarbital, St. John.s wort
Drugs eliminated by active renal secretion	amantadine, cotrimoxazole, ciprofloxacin, famotidine, hydrochlorothiazide, metformin, methotrexate, miglitol, moexipril, penicillin, phenazopyridine, propoxyphene, ranitidine, triamterene, valaciclovir

Table 24. Drugs Taken by Subjects in the Population PK Study.

The sponsor reports that the best fitting population pharmacokinetic model for trospium chloride after 20 mg BID oral administration was a one-compartment model with first-order absorption, having serum creatinine, height and concomitant medication with a CYP2C9 inhibitor as covariates for apparent clearance (CL) and race as a covariate for the absorption rate constant (ka). The predictive ability of this population PK model was not improved by the addition of terms for age, sex, concomitant medication with a CYP450 modulator other than a CYP2C9 inhibitor, or concomitant medication with a drug eliminated by active renal secretion.

The model predicted that CL *increases* by 1.35-fold in the presence of concomitant medication with a CYP2C9 inhibitor, CL decreases with increasing levels of serum creatinine, and CL increases with height. The finding that serum creatinine is associated with trospium clearance was expected given that the drug is primarily eliminated by the kidneys. The finding that CYP2C9 inhibitors affect trospium CL is likely artifactual given that (1) the finding that an increase in clearance occurs with inhibition of CYP 2C9 metabolism lacks clinical relevance, (2) the parameter was estimated with large uncertainty, and (3) only 8% of the data records included in the analysis were associated with concomitant administration of CYP2C9 inhibitors.

The estimated value for oral clearance was 1170 L/hr in absence of concomitant medication with a CYP2C9 inhibitor for a typical patient of average height (163 cm) and average serum creatinine levels (0.9 mg/dL). The estimated value for the apparent volume of distribution (V) was 395 L. The distribution of ka across patients was best described using a bimodal distribution. The estimated value for ka was 0.033 /hr in the

majority of patients. A subset of patients (9%) had an increased value of ka of 0.175 /hr. Of the small proportion of the population that was non-Caucasian, ka was 2.54-fold higher. The limited data available in non-Caucasians in this extension of the pivotal trial was derived from a mix of Asian, African American and American Indian subjects. Therefore, it would be premature to conclusively state that racial differences exist in the rate of absorption.

These parameter estimates are consistent with those derived from one study of intravenously administered trospium chloride where volume was 292 L and clearance was 58.7 L/hr. The 20-fold difference in oral clearance relative to clearance represents the 7% bioavailability predicted by mass balance studies.

Figure 25 shows the agreement between the observed and model predicted trospium concentrations. It demonstrates that the model fit the data reasonably well for the few measured high concentrations, but had considerable misfit for low concentrations. The bulk of the observations were of low concentrations. The high concentration values, perhaps, yielded leverage on the fit. In a fast absorbing (high ka) subpopulation, the intersubject variability (coefficient of variation %) was 39.5%, 49.1%, 53.5%, and 60.6% for clearance, ka, AUC, and Cmax, respectively. In the slow absorbing (low ka) subpopulation, the intersubject variability (coefficient of variation %) was 59.9%, 36.9%, 73.9%, and 70.2% for clearance, ka, AUC, and Cmax, respectively. The apparent misfit in this plot and the physiologically irrelevant predictions generated by the model limit its utility as a predictive tool.

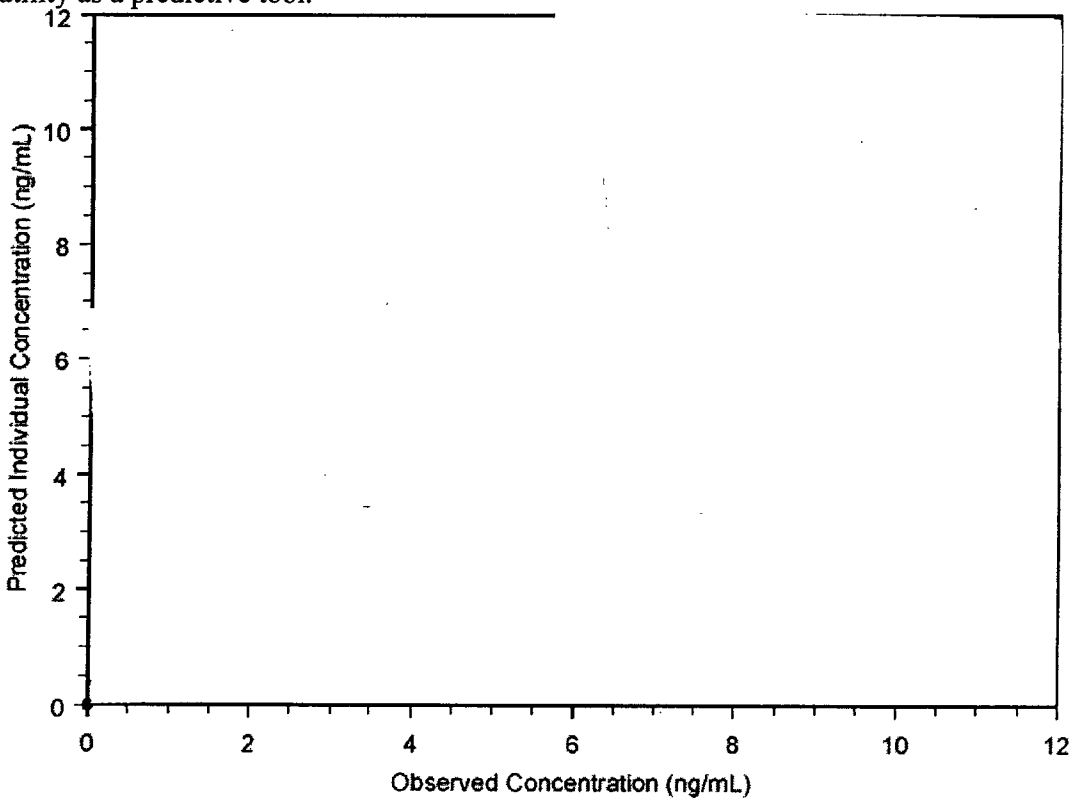


Figure 25. Predicted Versus Observed Concentrations of Trospium Chloride Based on the Sponsor's Population PK/PD Model.

In summary, the covariates serum creatinine, height, medication with a CYP 2C9 inhibitor, and race yielded the most significant reduction in variability in predictions of drug concentration from the sponsor's population PK model for trospium chloride. The model—based on data collected primarily in Caucasians and in a small group of subjects (N=81)—did not predict any of the clinically observed effects of age, gender or chronic dosing on exposure. Perhaps these observations in controlled studies of a short duration do not reflect trends occurring after steady state dosing. However, the model made one mechanistically unlikely prediction (inhibition of CYP 2C9 causes a 1.35-fold increase in clearance) which calls its utility into question.

What dosage adjustments (if any) are recommended for each of the following groups?
(i) Elderly
The higher incidence of adverse events reported in elderly versus young subjects in clinical trials could not be consistently attributed to exposure differences and may be related to the susceptibility of these subjects to anticholinergic side effects of the drug. In some clinical trials, patients were advised to titrate down to 20 mg QD in the event of intolerable side effects, however, efficacy data on this dose are sparse.

(ii) Gender
No dosing adjustment is recommended on the basis of gender.

(iii) Race
No dosing adjustment is recommended on the basis of race.

(iv) Renal impairment
Subjects with severe and moderate renal impairment are recommended to receive 20 mg trospium chloride once daily taken at bedtime.

(v) Hepatic impairment
No dosing adjustment is recommended in subjects with mild or moderate hepatic impairment. There is no information available to guide dosing in subjects with severe hepatic impairment or subjects with a combination of hepatic and renal impairment. Given that there was a 60% increase in Cmax in subjects with moderate hepatic impairment and may be greater in subjects with severe hepatic impairment, caution should be used in dosing to subjects with moderate or severe hepatic impairment.

D. Extrinsic Factors
What is the effect of a high fat meal on the pharmacokinetics of trospium chloride?
A high fat breakfast decreased Cmax 84% and reduced bioavailability 74% when a single 40 mg trospium chloride dose was administered to 12 young, healthy males. The results of this study are summarized in Table 25 and Table 26.

	AUC	Cmax	tmax	t½
Fed	20.1	[redacted]	3.29	15.7

	(12.6)	(1.17)	(1.57)	(5.46)
Fasted	87.2 (78.7)	(11.4)	5.00 (1.18)	16.47 (7.06)

Table 25. Pharmacokinetic Parameters (+/- Standard Deviation) Observed.

	mean (Fed) : mean (Fasted) (90% CI)
AUC	26% (21,29)
Cmax	16% (14,20)

Table 26. Summary of bioequivalence test parameters. The product failed to show equivalence for fed and fasted states with respect to all parameters tested.

In vitro basis to suspect in vivo drug-drug interactions?

The metabolism of trospium chloride was investigated *in vitro* using human liver preparations and human liver microsomes to assess the 50% inhibition concentration (IC50) for CYP 2D6, 3A4, 1A2, 2E1, 2C19, 2C9, and 2A6. The following table shows the IC50 values of trospium chloride with various probes of metabolic activity.

	Substrate	**Concentration of Substrate (micromolar)**	**IC50 of Trospium Chloride (micromolar)**
2D6	Dextromethorphan	0.4-2000	27
3A4	Denitronifedipine	50	11928 +/- 5901
1A2	Caffeine	500	8432 +/- 1918
2E1	Chlorzoxazone	50	14857 +/- 5586
2C19	S-(+)-Mephenytoin	20	1756.3 +/- 894
2C9	S-(-)Warfarin	5	2600
2A6	Coumarin	2	2000

Table 27. Effect of Trospium Chloride on Activities of Human Cytochrome P450 Enzymes at Km Substrate Concentrations.

Incubation of 10 micromolar [14-C]trospium chloride with human liver S9 preparations for 60 minutes yielded 2 metabolite peaks that were less than 5% of the chromatogram with the remainder as trospium chloride. Trospium chloride has negligible inhibitory effects on CYP3A4, 1A2, 2E1, 2C19, 2C9, and 2A6 but is a reasonably potent inhibitor of CYP 2D6 *in vitro*. Given that the highest trospium chloride concentration in a therapeutic setting (<50 nM) is 1000-times less than the competitive inhibition constant for CYP 2D6, this interaction is likely not clinically relevant.

The potential for trospium chloride to induce CYP enzymes has not been determined. The effect of trospium chloride on the disposition of other drugs has not been determined. The sponsor's population PK model based on an extension of the pivotal trial in 81 subjects suggests that only CYP 2C9 influences drug elimination. However, it predicted that inhibition of CYP 2C9 increases exposure to trospium—a mechanistically unlikely result which casts doubt on the predictive ability of the model. Renally secreted drugs were not predicted to interact with trospium chloride, however, subjects with renal disease were excluded from the pivotal trials in which the data for the population PK model were collected. Given the potential for active secretion of this compound, interactions may occur with drugs that are renally eliminated organic cations. Examples of such

compounds are pancuronium, vecuronium, disopyramide, procainamide, clonidine, neostigmine, metformin, and amantadine.

What other co-medications are likely to be administered to the target patient population?
Trospium chloride is likely to be dosed to elderly women. Since an aged population is prone to taking drugs for many indications, all possible drug interactions are considered here.

Renally excreted cations may interfere with the elimination of trospium chloride. Such drugs include pancuronium, vecuronium, disopyramide, procainamide, clonidine, neostigmine, metformin and amantadine.

Trospium chloride may potentiate the anticholinergic action of other anticholinergic agents such as amantadine, tricyclic antidepressants, quinidine, antihistamines, and disopyramide. Similarly, it may decrease the efficacy of prokinetic agents (such as metoclopramide) or alter the absorption of any concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

None of these interactions has been studied *in vivo* or *in vitro*.

E. General Biopharmaceutics
Based on BCS principles, in what class is this drug and dosage form? What solubility, permeability and dissolution data support this classification?
Trospium 20 mg is freely soluble in —— water. It is unstable at ——and solubility across the pH range has not been provided by the sponsor. Since the absorption is low, trospium cannot be classified as a High Permeability drug.

How do the dissolution conditions and specifications assure in vivo performance and quality of the product?
The sponsor proposed a dissolution limit set at NLT — released in — minutes. The recommended dissolution limit is Q=— in 30 minutes. The dissolution is performed in ———————— using USP apparatus 2 (paddle) at a rotation speed of — rpm. Table 28 shows the *in vitro* dissolution profile data for the batch used in the pivotal trial.

Vessel	% Release [a]			
	10 Min	20 Min	30 Min	40 Min
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
mean	39	74	88	91
% RSD	5.47	7.12	6.10	4.84

Table 28. Dissolution Data for Batch Used in the Pivotal Trial.

The amount of trospium chloride dissolved is determined by high-pressure liquid chromatography. The HPLC method is the same as that used for the assay, chromatographic purity, and content uniformity. Detection is by ultraviolet (UV) spectrophotometry at . The dissolution medium was selected based upon the chemical properties of the trospium chloride active pharmaceutical ingredient. Trospium chloride degrades in aqueous solutions above therefore, the dissolution medium was established to ensure drug stability during dissolution and sample analysis.

Is the proposed to-be-marketed formulation identical to the pivotal clinical trial formulation?

No. Since performing the pivotal clinical trial, there has been an addition of printing ink to the trospium chloride tablet. The ink provides a unique marking as required by US regulations. Based on dissolution comparison data (f1 and f2 testing), the sponsor claims that the to-be-marketed formulation of trospium chloride is equivalent to the clinical trial formulation.

Application of ink to the marketed tablet required slight processing modifications for the production of the US commercial supplies. The process change involves applying a

The sponsor provided bridging information (dissolution data) to support the equivalence of the tested and to-be-marketed formulations. Based on the calculated values of the quantities f1 and f2, the dissolution profile for printed (to-be-marketed) Trospium Chloride 20-mg tablets is claimed to be equivalent to the dissolution profile for unprinted (tested in the pivotal trial) Trospium Chloride 20-mg tablets. This conclusion holds for the dissolution media (. Note that the unprinted tablet was the reference, the criteria for "similar"

is f1 ranging from [redacted] and the range of f1 and f2 observed were [redacted], respectively. Table 29 lists the results of f1 and f2 testing.

	f1	f2	f2 [redacted]
[redacted]			

Table 29. Distance Measures for Trospium Chloride: Dissolution for Printed and Unprinted Tablets.

Table 30 lists the composition of the tablet coating.

Table 4-12 Composition of the tablet coating for Trospium chloride 20 mg tablets

Constituent	Amount (mg) per tablet:	Amount (kg) per batch:	Excess (%) [1]
Basic suspension			
Sucrose	[redacted]		
Talc			
Calcium carbonate			
Polyethylene glycol 8000			
Titanium dioxide			
Carboxymethylcellulose sodium			
Colloidal silicon dioxide			
Purified water [2]			
Color suspension			
Sucrose			
[redacted]			
Titanium dioxide			
Purified water [2]			
Printing			
[redacted]			
[redacted]			
[redacted]			
Total solids (coating)	60.0	[redacted]	[redacted]
Total solids (core + coating)	130.0	[redacted]	

[1] Excess to compensate for production loss during tablet coating; included in batch amounts.

[2] Removed during the process.

[3] As required per printing equipment.

[4] [redacted]

[5] Quantity includes excess amounts to compensate for production loss.

Table 30. Composition of Tablet Coating.

The sponsor reports that trospium chloride is unstable at pH above — Figure 26 illustrates the pH stability of trospium chloride as assessed by storing for — It shows that at — Celsius, 98% of trospium remains at . The sponsor may have other data supporting their statement that trospium is unstable at pH above —but they have not been submitted in the NDA.

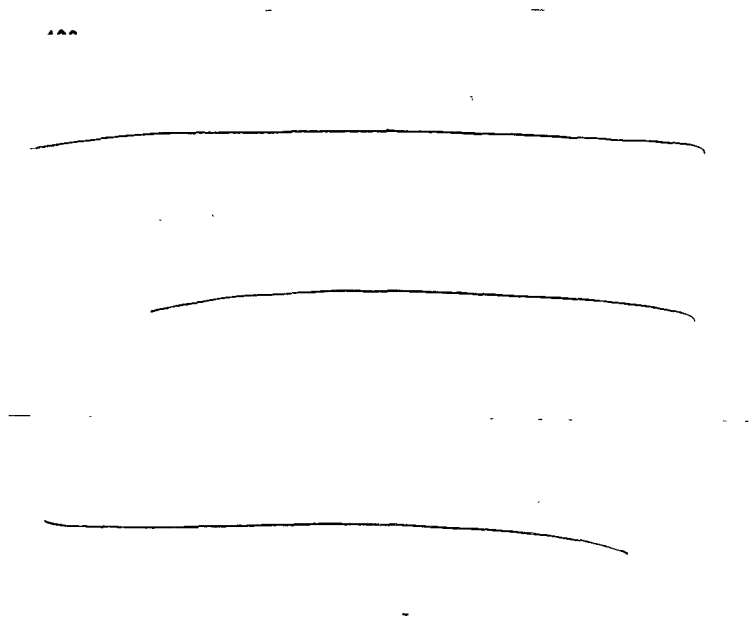
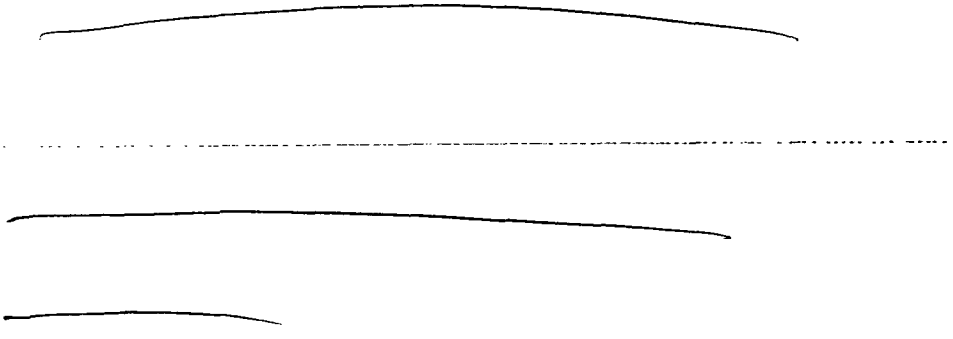


Figure 26. Degradation profile of trospium chloride in various pH buffer solutions following a storage time of — days. Note that % Trospium Chloride (TC) is indicated on the right-most y-axis and % is indicated on the left-most y-axis.

What bioanalytical methods are used to assess concentrations?



References

1. "Achlorhydria." Radebold, K. Editors: Greenwald, D., et. al. July 11, 2002. http://www.emedicine.com/med/topic18.htm

IV. Detailed Labeling Recommendations
Labeling has been discussed and mutually agreed upon with the sponsor.

V. Appendices

A. Package Insert
See approved labeling as submitted to DFS.

B. Individual Study Reviews
Study MP94D2.12
Pilot study to Describe the Gastrointestinal Absorption Pattern and Circadian Variations in the Pharmacokinetics of Enteral Trospium Chloride in Three Different Formulations

Summary
- Diurnal effect in bioavailability observed that is not due to difference in meals
- There was a 33% reduction in AUC and a 59% reduction in Cmax when dosed in the evening relative to dosing in the morning.
- It appears that considerable absorption occurs in the upper small intestine.
- t½ was 19.88 hours in this study
- Sponsor reports that it remains to be decided whether change in bioavailability at evening dose should affect strength of the evening dose.

Objective
- Identify the preferential absorption site from the gastrointestinal tract and the nature and extent of circadian variation of the p.o. bioavailability of trospium chloride.

Design
- Single-center, controlled, open, within-subject 4-way change-over design
- Change over design selected because within-subject variability smaller than between-subject variability
- Period balanced, randomly allocated sequences; 2 subjects per sequence
- N=8 healthy, Caucasian males aged 20-40 years
- Each of the 4 treatments evaluated in each of the N=8 subjects.
- 20 mg single doses in different formulations
- Oral (3 modes of administration) or rectal administration of trospium chloride
- 2 oral formulations and 1 rectal formulation dosed at 8 am; 1 oral formulation at 8 pm
- Subjects fasted from 10 hours before until 4 hours after dosing
- Meals at 4, 8, and 12 hrs post-dose
- Difference in position of subject

a.m. dose only:	Recumbent position from -0.5 to 2 hours after dosing
a.m. and p.m. dose:	Recumbent position from -0.5 to 4 hours (for meal)
	Recumbent position after meal until next dose period

- Washout of 7 days
- Blood drawn: -0.25,0.5,1,2,3,4,5,6,7,8,9,10,12,14,16,20,24,28,32,35,36 hours post-dose.
- Total fat content of 60 grams in meals as follows:

Hours after dosing	Fat content
4	18
8	9
12	33