8 days of dosing.
*Based on reanalysis of pooled fecal waste and all remaining fecal matter from various sources, mass balance of radioactivity following a single oral dose 20 mg of 14C-trospium was established in this study. The overall recovery of drug-related radioactivity was 91% over 288 hours.
*Unchanged trospium appears to be actively secreted into urine.
*A total of 5.8% of total dose appeared as drug-related radioactivity in urine. Recovery of unchanged trospium in urine = 3.5% of total dose administered. (This was 60% of urinary recovery of drug-related radioactivity.)
*Mean renal clearance (29.07 L/hour) is greater than glomerular filtration rate (7.5 L/hour) and suggests active secretion of trospium into the urine.
*Approximately 74 to 80% of radioactivity measured in the quantifiable plasma samples could be attributed to metabolic products.
*Approximately 40% of radioactivity accounted for metabolites in urine
*Metabolic profiling in plasma could not be performed due to low levels of radioactivity recovered in plasma.
*A total of 8 adverse events were reported in 3 (50%) of the 6 subjects enrolled in the study.
*The most frequently reported adverse event was nausea, reported in 2 subjects (33%).
*Other adverse events reported included abdominal pain NOS (not otherwise specified), dyspepsia, loose stools, back pain, and chest wall pain, all reported in 1 subject (17%) each.
*All adverse events were assessed by the investigator as mild in intensity and all events resolved without sequelae.
*The disposition of trospium in plasma was multi-exponential with a terminal half-life of 20 hours.
*Unchanged trospium accounted for 21% to 33% of the total plasma radioactivity for the first 10 hours of sampling.

Study IP631-001
A Placebo-Controlled Trial of Trospium Chloride on QTc Interval in Healthy, Normal Subjects Following Steady-State and Single Oral Dosing

Summary

• This placebo controlled study investigated a supratherapeutic dose of trospium chloride (200 mg single dose) that covers the extreme exposures expected with renal impairment.
• Study has 18% power to detect a change in QTcF of 5 msec with a 5% error rate. Study did not include an active control.
• Mean increase of QTcF 5.6 msec for 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. 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. It is difficult to interpret these data given that subjects receiving the supratherapeutic trospium dose had a greater mean baseline value of QTcF than subjects receiving placebo or the therapeutic dose of trospium chloride.
• Subjects receiving the supratherapeutic dose of trospium chloride also had a mean negative change in QTcF from baseline.

Design

• Primary objective:
Compare the effects of the following therapeutic and supratherapeutic doses of trospium chloride on cardiac repolarization
Part I

20 mg BID for 5 to 7 days
40 mg BID for 5 to 7 days
Placebo for 5 to 7 days

Part II

20 mg single dose
200 mg single dose
Placebo single dose

• Secondary objective:
Compare the adverse event rate on the above regimens
• Multicenter, parallel group, randomized, double-blind, placebo-controlled study
• N=15 healthy, volunteers per treatment arm; 18-45 years; 60% female, 40% male
• 1 week washout between steady state and single dose periods

• Baseline: mean of seven (7) serial ECGs
• Multi-dose study:
-Subjects participated as outpatients; instructions on dosing with respect to meals given
-Dosing: 1 hour prior to meals
-Instructed to adhere to a low fat diet
-ECG measures taken on Day 6 at 0, 1, 3, 5, 7, 9 and 12 hours post-dose
• Single dose study:
-Subjects who received low dose in multi-dose study received low dose in single dose study
-Dosing: 1 hour prior to meals; low fat meals served
• Fridericia correction used

Critique of Study Design
• Study had 18% power to detect a change in QTcF of 5 msec with a 5% error rate
• Renal impairment is expected to yield the most extreme exposures in clinical practice. As the following table shows, there is a 2-fold change in Cmax and a 4.2-fold change in AUC in renally impaired versus healthy subjects.

	Cmax	AUC
40 mg renal impairment		233 (48.21-709.28)
40 mg healthy		55.6 (18.5-152)

Note that a 40 mg dose was tested in the renally impaired subjects but a 20 mg dose is proposed for clinical practice. To predict the worst-case exposures expected, dose linearity will be assumed for a 40 mg dose relative to a 20 mg dose. Thus, for a 20 mg trospium chloride dose to subjects with renal impairment, the expected Cmax is and the expected AUC is 120 ng*hr/mL. The following table shows the Cmax and AUC observed in the different arms of this study. The only subjects achieving these exposures were those who received a 200 mg single dose of trospium chloride.

	Cmax	AUC
20 mg BID		10.1
40 mg BID		25.5
20 mg single		5.7
200 mg single		204.2

Results
• Dose-dependent increase in heart rate
• The following table reports the baseline QTcF values. Note that the mean baseline value is higher in subjects receiving the supratherapeutic dose of trospium chloride than in subjects receiving the therapeutic dose.

	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)

Baseline QTcF For Each Study Arm.

• The following table reports the mean change in QTcF for each study arm of the single dose phase. Note that the wide confidence intervals make it difficult to detect a difference between placebo and trospium.

	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)

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.

• The following table reports the mean change in QTcF for each study arm of the multiple dose phase. Note that the wide confidence intervals make it difficult to detect a difference between placebo and trospium.

	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 (385.6,402.1)	-7.1 (-13.2,-1.1)

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.

• The following table reports the outlying values of QTcF observed during the single dose phase of the study.

	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

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.

• The following table reports the outlying values of QTcF observed during the multiple dose phase of the study.

	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

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.

• Note that there was a two-fold increase in the percent of subjects experiencing a change in QTcF from baseline (ΔQTcF) of 30 to 60 msec for those receiving the therapeutic dose of trospium chloride compared to those receiving placebo; 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.
• Note that 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. It is difficult to interpret these data given that subjects receiving the supratherapeutic dose had a higher baseline value of QTcF on average than subjects receiving placebo and the therapeutic dose of trospium chloride.

Study MP94D4.02

Investigation into the Pharmacokinetics of Trospium Chloride Following Single as Well as Multiple Oral Dosing of Two Different Trospium Chloride Containing Formulations in Young Healthy Volunteers

SUMMARY

1. The following differences were observed in the pharmacokinetics of TEST (40 mg QD) versus REFERENCE (20 mg BID) compound:
*AUC and Cmax were 8% and 18% higher, respectively, for the TEST versus REFERENCE compound under single dosing conditions.
*AUCss and Cmaxss were 40% and 105% higher, respectively, for TEST versus REFERENCE compound after multiple dosing.
*The large difference between Cmax at steady state reflects an increase in Cmax upon multiple dosing for the TEST compound but decrease upon multiple dosing with the REFERENCE product.
*Thirty six percent more (36%) of the test compound is excreted in urine than reference compound.

2. The following differences were observed with respect to gender:
*There was a gender difference in the mean AUC given single doses of either TEST or REFERENCE treatment.
*The mean Cmax did not appear to have a gender difference for TEST or REFERENCE products.
*The 90% confidence intervals overlapped for AUC and Cmax for males and females for single doses of TEST and REFERENCE products, however, the range was wide.
*Mean Css,max is greater in males than females for the TEST product. Mean Css,max is equivalent in males and females for the REFERENCE product.
*The 90% confidence intervals for AUCss and Cmax,ss between males and females after multiple dosing of TEST and REFERENCE products overlap, but the confidence intervals were wide.

3. The following adverse events were reported.
*An equivalent number of subjects suffered dry mouth on the TEST and REFERENCE compounds.
*More subjects reported pain in stomach (25%) on the TEST compound versus on REFERENCE (16.7%). There were more moderate events in subjects receiving the TEST product (4) versus subjects receiving the REFERENCE (2). A greater number of subjects experienced tachycardia (1 versus 0), accomodation difficulties (2 versus 0), micturition difficulties (6 versus 4), and dysopsia (2 versus 0) on the TEST product than on the REFERENCE product. More subjects experienced frequent miction (2 versus 1), dryness of eye (1 versus 0), and nausea (1 versus 0) on the REFERENCE product than on the TEST product.
*All of the adverse events disappeared after drug washout and without medical action.

PURPOSE

*Compare the plasma concentration versus time profile and urinary excretion of trospium chloride following oral doses of 40 mg ("TEST" product) QD and 20 mg ("REFERENCE" product) BID in healthy subjects. Note that the total daily dose is 40 mg for both the TEST and REFERENCE arms.
*Compare the pharmacokinetic parameters in males versus females.
*Compare the pharmacokinetic parameters for single versus multiple doses
*Mean Css,max is greater in males than females for the TEST product. Mean Css,max is equivalent in males and females for the REFERENCE product.
*Mean AUC,ss is equivalent in males and females for both the TEST and REFERENCE product.
*The 90% confidence intervals for AUCss and Cmax,ss between males and females after multiple dosing of TEST and REFERENCE products overlap, but the confidence intervals were wide.
*AUCss and Cmax,ss for the TEST product higher than for the REFERENCE product.

METHODS

Test Product

	Spasmo-lyt®-uno dragées	Spasmo-lyt® dragées
Contents	40 mg trospium chloride	20 mg trospium chloride
Lot number	960903/PGK	512286
Study lot number	7014103	7014103
Expiration	3/97	3/97

The sponsor has previously performed trials with 20 mg Spasmo-lyt® dragées dosed BID. The sponsor feels that the twelve (12) hour half life and 5-6 hour tmax of the compound would be better dosed once daily, thus, has developed a double size formulation containing 40 mg trospium chloride. The sponsor claims that the 40 mg dragee contains an unchanged ratio of active ingredient and excipients with respect to the 20 mg coated tablet.

Study Design

*Open, randomized, single-dose and multiple dose, two-way crossover pharmacokinetic study with a ten day washout period between the TEST versus REFERENCE studies.
*24 subjects (12 males and 12 females) aged 18 to 40 years
*Single-dose phase: 40 mg trospium chloride

Day 1	Two (2) 20 mg dragées dosed at 7 am two hours before breakfast

*Multiple-dose phase: 40 mg trospium chloride daily (20 mg dragées BID)

Days 3-7	One (1) 20 mg dragée dosed at 7 am half an hour before breakfast
	One (1) 20 mg dragée dosed at 7 pm half an hour before meal
Day 8	One (1) 20 mg dragée dosed at 7 am two hours before breakfast
	One (1) 20 mg dragée dosed at 7 pm two hours before meal

*Trospium Chloride blood levels determined until 216 hours (9 days) after the first dose.
*Urine samples collected until 48 hours after the first dose and 48 hours after the morning dose on Day 8.
*Subjects fasted from 9 pm until 7 am.
*Trough levels taken before each dose for the BID and QD dosing.
*Intensive sampling out to 48 hours after the single dose and following the Day 8 dose.
*Subjects remained under constant observation (AE monitoring) throughout the hospitalization

Assays

Blood plasma concentrations of trospium chloride:
Urine concentrations of total trospium:

Data Analysis

*Cmax, Cmin, tmax determined by inspection of data
*Terminal elimination slope determined by log-linear regression analysis of the concentrations appearing to be on a straight line on a log-linear plot. Each individual's data on each treatment was analyzed separately. The half life was computed using the formula: ln 2/terminal slope.
*AUC calculated using the trapezoidal rule

RESULTS

Table 1 shows that the mean AUC for the reference compound decreases upon multiple dosing.
The mean AUC for the TEST compound is the same for single and multiple dosing.
The mean AUC after single or multiple dosing of the TEST compound is greater than the AUC for the REFERENCE compound at steady state.
The mean Cmax for the TEST product is greater than the REFERENCE compound for both single and multiple dose regimens.
The Cmax incresases upon multiple dosing for the TEST compound but decreases upon multiple dosing with the REFERENCE product.
There was overlap between the 90% confidence intervals for estimates of AUC and Cmax for both the TEST and REFERENCE products, but the confidence interval on these estimates was wide.

Formulation	Characteristic	single dose	multiple dose	single/multiple dose
		Geometric mean and range corresponding to mean ± SD after logarithmic transformation		Point estimate (90 % confidence interval)
TEST (A)	AUC [h·ng/ml]	36.33 (20.80-63.47)	34.94 (22.48-54.32)	1.09 (0.91, 1.24)
	C_{max} [h]	4.46 [illegible]	4.90 [illegible]	0.95 (0.78, 1.17)
REFERENCE (B)	AUC [h·ng/ml]	32.97 (19.29-56.35)	24.04 (15.28-37.83)	1.39 (1.16, 1.60)
	C_{max} [h]	3.67 ([illegible]	2.41 [illegible]	1.52 (1.22, 1.87)

Table 1. Comparison of Single Versus Multiple Dose Parameter Estimates for the Test (40 mg dragee QD) and Reference (20 mg dragee BID) Products. Data from all subjects contributed to the analysis.

Table 2 shows that there is a significant difference in the relative bioavailability and rate of absorption for TEST versus REFERENCE products.
Under single dose conditions:
* Relative bioavailability = 108%
* Relative rate of absorption = 118%

Under multiple dose conditions:
* Relative bioavailability = 140%
* Relative rate of absorption = 205%

Characteristic	TEST (A)	REFERENCE (B)	TEST/REFERENCE
	Geometric mean and range corresponding to mean ± SD after logarithmic transformation		Point estimate (90 % confidence interval)
AUC(0-∞) [h·ng/ml]	36.33 (20.57-64.19)	32.97 (19.11-56.89)	1.08 (0.88, 1.33)
C_{max} [h]	4.46 (—	3.67 (—	1.18 (0.92, 1.54)
$AUC^{ss}_{168-192\,h}$ [h·ng/ml]	34.94 (22.29-54.78)	24.04 (15.14-38.17)	1.40 (1.20, 1.74)
C^{ss}_{max} [h]	4.90 (—	2.41 (—	2.05 (1.60, 2.45)

Table 2. Comparison of Test Versus Reference Product Parameter Estimates for the Single and Multiple Dose Studies. Data from all subjects contributed to the analysis. The steady state AUC is based on measurements between 168 and 192 hours after the first dose (between Study Day 7 and 8). Multiple dosing begins on Study Day 3. The elimination half life ranges from 7-15 hours, thus, subjects are expected to reach steady state by Day 7.

The following table shows the relative change in AUC and Cmax for the reference product: steady state relative to single dose.

	Change relative to Single Dose = (Single dose – Steady State) / Single Dose
Cmax	—
AUC	0.27

Table 3 compares the urinary excretion for TEST versus REFERENCE products.
There is thirty six percent more (36%) of the test compound excreted in urine than reference compound.

	Ae(0-48 hrs)	Ae(168-216 hrs)
TEST	1292.4 +/- 638.6	1405.6 +/- 544.1
REFERENCE	1093.0 +/- 512.8	1030.7 +/- 330.2
TEST / REFERENCE	1.18	1.36

Table 3. Cumulative Amounts of Total Trospium Excreted Into Urine. Means +/- standard deviation reported. Analysis based on the data from all subjects.

Table 4 shows a comparison of pharmacokinetic parameters by gender for single doses of TEST or REFERENCE product.
*There was a gender difference in the mean AUC given single doses of either TEST or REFERENCE treatment. The 90% confidence intervals overlapped for AUC and Cmax for males and females for single doses of TEST and REFERENCE products, however, the range was wide.
*The mean Cmax did not appear to have a gender difference for TEST versus REFERENCE products.
*The mean Cmax differed between TEST and REFERENCE treatments for single doses.
This suggests a difference in absorption.
*The mean AUC was similar for TEST and REFERENCE treatments for single doses.
This suggests a similar CL/F.

TEST (A)	AUC(0-∞) [h·ng/ml]	C_{max} [ng/ml]	t_{max} [h]	HVD [h]	$t_{1/2}$ [h]
all subjects, (n=24)	41.77 ± 21.83	5.63 ± 3.90	3.17 ± 0.56	4.07 ± 1.28	9.37 ± 2.78
male subjects, (n=12)	37.56 ± 24.01	5.43 ± 4.73	3.25 ± 0.62	3.71 ± 1.19	9.07 ± 3.47
female subjects, (n=12)	45.98 ± 19.51	5.84 ± 3.05	3.08 ± 0.51	4.44 ± 1.31	9.67 ± 1.97

REFERENCE (B)	AUC(0-∞) [h·ng/ml]	C_{max} [ng/ml]	t_{max} [h]	HVD [h]	$t_{1/2}$ [h]
all subjects, (n=24)	37.46 ± 18.52	4.60 ± 3.05	3.13 ± 0.54	4.51 ± 1.42	11.67 ± 5.78
male subjects, (n=12)	33.78 ± 16.75	4.66 ± 3.51	3.00 ± 0.43	4.07 ± 1.48	10.42 ± 3.20
female subjects, (n=12)	41.15 ± 20.18	4.54 ± 2.67	3.25 ± 0.62	4.96 ± 1.26	12.91 ± 7.50

Table 4. Pharmacokinetic Parameters for Single Dose Administration of TEST and REFERENCE compounds. Mean +/- Standard Deviation Reported.

Table 5 shows a comparison of pharmacokinetic parameters by gender at steady state for TEST or REFERENCE product.

*Mean Css,max is greater in males than females for the TEST product. Mean Css,max is equivalent in males and females for the REFERENCE product.

*Mean AUC,ss is equivalent in males and females for both the TEST and REFERENCE product.

*The 90% confidence intervals for AUCss and Cmax,ss between males and females after multiple dosing of TEST and REFERENCE products overlap, but the confidence intervals were wide.

*AUCss and Cmax,ss for the TEST product higher than for the REFERENCE product.

TEST (A)	$AUC^{ss}_{168-192\,h}$ [h·ng/ml]	C^{ss}_{min} [ng/ml]	C^{ss}_{max} [ng/ml]	t^{ss}_{max} [h]	$t^{ss}_{1/2}$ [h]
all subjects, (n=24)	38.08 ± 15.08	0.46 ± 0.25	5.36 ± 2.12	2.88 ± 0.34	12.27 ± 5.10
male subjects, (n=12)	36.22 ± 14.23	0.40 ± 0.20	5.69 ± 2.25	2.92 ± 0.29	11.50 ± 3.02
female subjects, (n=12)	39.95 ± 16.29	0.52 ± 0.28	5.03 ± 2.03	2.83 ± 0.39	13.04 ± 6.63

REFERENCE (B)	$AUC^{ss}_{168-192\,h}$ [h·ng/ml]	C^{ss}_{min} [ng/ml]	C^{ss}_{max} [ng/ml]	t^{ss}_{max} [h]	$t^{ss}_{1/2}$ [h]
all subjects, (n=24)	26.61 ± 12.78	0.52 ± 0.23	2.69 ± 1.99	3.38 ± 2.32	12.27 ± 3.84
male subjects, (n=12)	25.19 ± 13.47	0.48 ± 0.24	2.84 ± 2.09	3.67 ± 3.31	12.70 ± 3.24
female subjects, (n=12)	28.03 ± 12.48	0.56 ± 0.23	2.94 ± 1.98	3.08 ± 0.29	11.84 ± 4.47

Table 5. Pharmacokinetic Parameters for Multiple Dose Administration of TEST and REFERENCE compounds. Mean +/- Standard Deviation Reported.

The following table shows the relative change in AUC and Cmax for steady state versus single dosing overall and by gender.

	Change relative to Single Dose = (Single dose – Steady State) / Single Dose		
	All Subjects	**Males**	**Females**
Cmax	(4.6-2.89)/4.6 0.37	(4.66-2.84)/4.66 0.39	(4.54-2.94)/4.54 0.35
AUC	(37.46-26.61)/37.46 0.29	(33.78-25.19)/33.78 0.25	(41.15-28.03)/41.15 0.32

Table 6 shows the incidence of adverse events for the TEST and REFERENCE products.
Note that the same percent of subjects reported dry mouth for the TEST and REFERENCE compounds. There were more events reported on the REFERENCE compound and of a more severe nature than for the TEST product. More subjects reported pain in stomach (25%) on the TEST compound versus on REFERENCE (16.7%). There were more moderate events in subjects receiving the TEST product (4) versus subjects receiving the REFERENCE (2). A greater number of subjects experienced tachycardia (1 versus 0), accomodation difficulties (2 versus 0), micturition difficulties (6 versus 4), and dysopsia (2 versus 0) on the TEST product than on the REFERENCE product. More subjects experienced frequent miction (2 versus 1), dryness of eye (1 versus 0), and nausea (1 versus 0) on the REFERENCE product than on the TEST product.
All of the adverse events disappeared after drug washout and without medical action.

Adverse Event	TEST 40 mg dragee QD			REFERENCE 20 mg dragee BID		
	Number (percent) subjects	**Number Mild Events**	**Number Moderate Events**	**Number (percent) subjects**	**Number Mild Events**	**Number Moderate Events**
Dry Mouth	21 (87.5%)	60	0	21 (87.5%)	70	4
Pain in Stomach	6 (25%)	5	4	4 (16.7%)	11	2
Accomodation Difficulties	2 (8.3%)	2	0	0	0	0
Micturition Difficulties	6 (25%)	6	0	4 (16.7%)	5	1
Dysopsia	2 (8.3%)	2	0	0	0	0
Abdominal Pain	1 (4.2%)	1	0	0	0	0
Tachycardia	1 (4.2%)	1	0	0	0	0
Frequent Miction	1 (4.2%)	1	0	2 (8.3%)	2	0
Dryness of Eye	0	0	0	1 (4.2%)	2	0
Nausea	0	0	0	1 (4.2%)	1	0

Table 6. Incidence of Adverse Events.

NOTES

Rationale for Study

Study MP94D4.02 was designed to answer questions brought up by the results of other studies (Study MP94D2.10, Study MP94D2.07, and Study MP94D2.08).
Study MP94D2.10 showed:
*Ae,ss, AUC, and Cmax lower after multiple dosing than after a single dose

Study MP94D2.07 showed:
*Food decreases bioavailability

Study MP94D2.08 showed:
*Effect of age on PK of TC
*No difference between elderly and young men
*Difference between elderly men and women

Study MP94D4.02 designed to examine whether food effects explain the difference in AUC for single versus multiple dosing.
Study MP94D4.02 also designed to determine if PK different between young men and women.

Study MP94T1.01

Investigation on Bioequivalence Following Multiple Dosing with Spamo-Urgenin® TC Dragees vs Spasmo-lyt® Dragees in Healthy Volunteers

SUMMARY

*The Test/Reference ratio for AUCss and Cmax,ss were between 0.8 and 1.25 and 0.7 and 1.42, respectively.
*AUCss=AUC of 12 hour dosing interval (120-132 hours)
*Bioavailability significantly higher during the day than at night

PURPOSE

*Clarify if two formulations of trospium chloride are bioequivalent
*Based on a multiple dose clinical trial; use plasma data
*Multiple dose design used to reduce intrasubject variability at steady state
*A previous single dose bioavailability study with two trospium chloride formulations (Spasmo-lyt® vs Spasmomex®) in N=24 healthy volunteers did not establish bioequivalence.
*The former study was based on cumulative renal excretion data up to 72 hours; urinary recovery was 0.52-7.19% of dose and there was large variability in individual test/reference ratios (CV=55.5%).

METHODS

Test Product

*2 Spasmo-lyt® Dragees or 4 Spasmo-Urgenin® TC Dragees total per day (40 mg/day)

*Spasmo-lyt® Dragee batch #341 219; Lot No. 4121049
*Spasmo-Urgenin® TC batch #545; Lot No. 4121048

Study Design

*Two way randomized crossover
*N=12 healthy males, 19-33 years
*B.I.D. dosing of 20 mg trospium chloride for 6 days (40 mg per day total)
*Steady state assumed at Days 5 and 6
*8 day washout
*Blood and urine sampling approximately every 2-3 hours for 48 hours.
* [redacted] and HPLC determination of trospium levels
*Assay sensitivity:
linear of quantitation between [redacted] trospium chloride
LOQ = [redacted]
CV% of within- and between- day precision: <6.9%
>90% trospium chloride removed by extraction

Data Analysis
*AUCss, Cmax,ss basis of bioequivalence assessment
*AUCss=AUC of 12 hour dosing interval (120-132 hours)

*Tmax and peak trough fluctuatation (%PTF) used as supportive data
*Definition:

%PTF = (Cmax-Cmin)*100/Cavg

*Testing hypothesis of bioequivalence: 90%CI by two one-sided Mann-Whitney-Wilcoxon test on ln-transformed data.

H1 (AUCss): $0.8 \leq \mu(T)/\mu(R) \leq 1.25$
$\mu(T)$ and $\mu(R)$ are the expected mean AUCss for Test and Reference of the time period 120 - 132 h (day 6)

and

H1 (Cmax): $0.7 \leq \mu(T)/\mu(R) \leq 1.43$
$\mu(T)$ and $\mu(R)$ are the expected mean Cmax for Test and Reference of the time period 120 - 132 h (day 6).

The a priori type 1 error is determined to be $\alpha = 0.05$ for all hypotheses.

RESULTS

day 6 (120 - 132 h)		AUCss [ng/ml.h] Test	AUCss [ng/ml.h] Ref	Cmax [ng/ml] Test	Cmax [ng/ml] Ref
valid n		12	12	12	12
mean		6.79	6.31	0.847	0.724
SD		2.856	2.619	0.4513	0.2659
SEM		0.824	0.756	0.1303	0.0768
95%-confidence interv. of mean	LB	4.98	4.65	0.560	0.555
	UB	8.61	7.97	1.133	0.893

Table 1. Statistics on Day 6 Parameter Measurements.

*Table 2 shows that the Test/Reference ratio for AUCss and Cmax,ss were bioequivalent with ranges between 0.8 and 1.25 and 0.7 and 1.42 for AUCss and Cmax,ss, respectively.

day 6 (120 - 132 h)		AUCss	Cmax
point estimate $\mu(T)/\mu(R)$		1.08	1.11
two-one-sided Mann-Whitney-Wilcoxon 90%-confidence interval	LB	0.96	—
	UB	1.19	1.28

Table 2. Statistics on Test/Reference Ratios at Day 6.

*Table 3 shows that there is a significant difference between bioavailability of the two formulations depending on the time of day that it is dosed.
*A greater amount of drug is absorbed during the day for both test and reference compounds.

	AUCss [ng/ml.h]		Cmax [ng/ml]	
	Test	Ref	Test	Ref
valid n	12	12	12	12
median day 6	5.945	5.575	0.680	0.64
median night 6	4.985	4.835	0.515	0.455
'difference of means'	-1.035	-0.87	-0.1875	-0.195
nonparametric 95%- LB	-1.65	-1.39	-0.32	-0.305
confidence interval UB	-0.705	-0.475	-0.12	-0.125

Table 3. Statistics on Effect of Time of Day on Bioavailability of Trospium Chloride.

The following table shows the relative change in AUC and Cmax for Day versus night dosing of the reference product.

	(Day-Evening)/Evening
Cmax	(0.64-0.455)/0.64 0.29
AUC	(5.575-4.835)/5.575 0.13

*Figure 1 shows the concentration-time profile for test and reference compounds on Day 6. Cmax appears to be greater for the test versus the reference product.

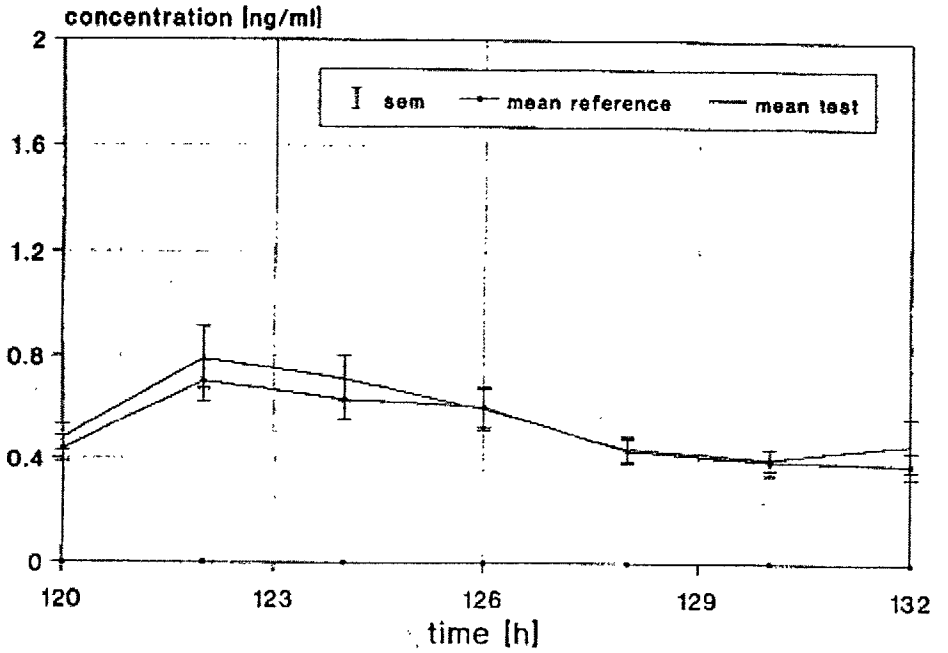

Figure 1. Mean Concentration-Time Profile of Test and Reference Compounds on Day 6.

* Figure 2 shows the mean concentration-time profile of test and reference compounds on Day 6 at night. Note the contrast with the Day 6 Day (Figure 1) profile. The night profile has a smaller Cmax.

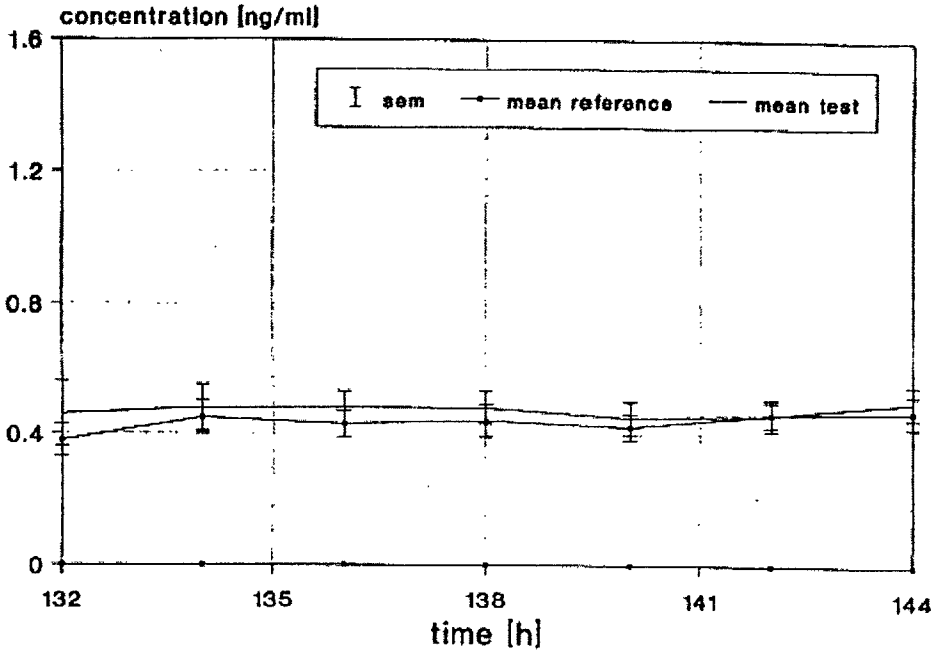

Figure 2. Mean Concentration-Time Profile of Test and Reference Compounds on Day 6 at night.

	Cmin [ng/ml]		Cmax [ng/ml]		tmax [h]		Cav [ng/ml]		AUCss [ng/ml*h]	
	reference	test	reference	test	reference	test	reference	test	reference	test
n	12									
mean	0.36	0.35	0.72	0.85	122.83	123.33	0.53	0.57	6.31	6.79
sd	0.17	0.13	0.27	0.45	1.34	2.87	0.22	0.24	2.62	2.86
sem	0.05	0.04	0.08	0.13	0.39	0.83	0.06	0.07	0.76	0.82
median	0.34	0.30	0.64	0.68	122.00	122.00	0.46	0.50	5.58	5.95
min.	0.09	0.14	0.41	0.48	122.00	122.00	0.28	0.32	3.40	3.79
max.	0.78	0.57	1.39	1.96	126.00	132.00	1.09	1.10	13.03	13.20

Table 4. Pharmacokinetic Parameters on Day 6.

Study MP94T2.01

Comparison of Bioequivalence of Two Different Trospium Chloride Containing Formulations in 24 Young Healthy Male Volunteers Following Multiple Oral Administration

SUMMARY

*For a total daily dose of 45 mg, Spasmo-lyt® was bioequivalent to the reference product (Spasmex®) after multiple dose administration with respect to AUCss and Cmax,ss.
*Bioequivalence assumed if the 90% CI of the ratios of Test/Reference do not exceed 0.8-1.25 for AUC and ——— for Cmax, respectively, using two one-sided t-tests under of the log transformed data with Wilcoxon tests.
*The products were not bioequivalent with respect to tss,max evening.
*Bioavailability differs for the night and day doses.
*According to a formal statistical test, steady state was not achieved in this study
*There was a similar incidence of adverse events for test and reference products
*Both test and reference products increased heart rate by approximately 12 beats per minute

PURPOSE

*Determine the relative bioavailability of the Spasmo-lyt® 30 mg tablet to the reference Spasmex® 30 mg film tablet during multiple dose administration at steady state.
*Steady state regimen uses 30 mg dosed in the a.m. and 15 mg dosed in the p.m.

METHODS

Products

*Test: p.o. trospium chloride Spasmo-lyt®; Batch No.: 011116; 45 mg / day total

*Reference: Spasmex®; Batch No.: 32843; 45 mg / day total

*30 mg in a.m. 15 mg in p.m.; evening dose is ½ tablet

Study Design

*Two way random crossover in N=24 healthy Caucasian males, 20-45 years
*Multiple dose (30 mg at 7 a.m. 15 mg at 7 p.m.) for 5 days
*No food taken -1 hour to +1 hour of dosing
*Sponsor justifies use of different dose in the evening than during the day under the assumption that urge and stress incontinence is more relevant during daytime activity than nighttime activity.
*Spasmex® is a marketed product using a 30 mg in a.m. 15 mg in p.m. regimen
*7 day washout
*Blood samples to 24 hours post-dose

Data Analysis

*

*Bioequivalence assumed if 90% CI of the ratios of Test/Reference do not exceed 0.8-1.25 for AUC and ——— for Cmax, respectively.

*Two one-sided t-tests under of the log transformed data with Wilcoxon tests
*Bioequivalence based on AUCss and Cmax,ss (last morning and evening dose, respectively)

BACKGROUND

*Mean pharmacokinetic parameters in healthy subjects:

- *TC poorly absorbed; F=10%
- *49% total trospium excreted by kidneys after iv infusion within 72 hours
- *Mean total clearance = 880 mL/min; CLrenal = 434 mL/min
- *Following p.o. dosing of 20-60 mg, 6-7% of total trospium is recovered in the urine within 72 hours.
- *Plasma Cmax: 3-7 hours for single 20 mg doses; terminal t½=10-14 hours.
- *Single dose studies:
  - Interindividual CV in AUC and Cmax: 70-100%
  - Intraindividual CV in AUC and Cmax: 65%
- *Multiple dose studies:
  - Interindividual CV in AUC and Cmax: 45%
  - Intraindividual CV in AUC and Cmax: 15-30%
- *20 mg dosed bid shows delayed and decreased absorption at night vs. day:
  - Cmax decreased 50% and AUC decreased 1/3

RESULTS

*Figure 1 shows the geometric mean trospium plasma concentrations for the test versus reference compounds. The products appear equivalent.

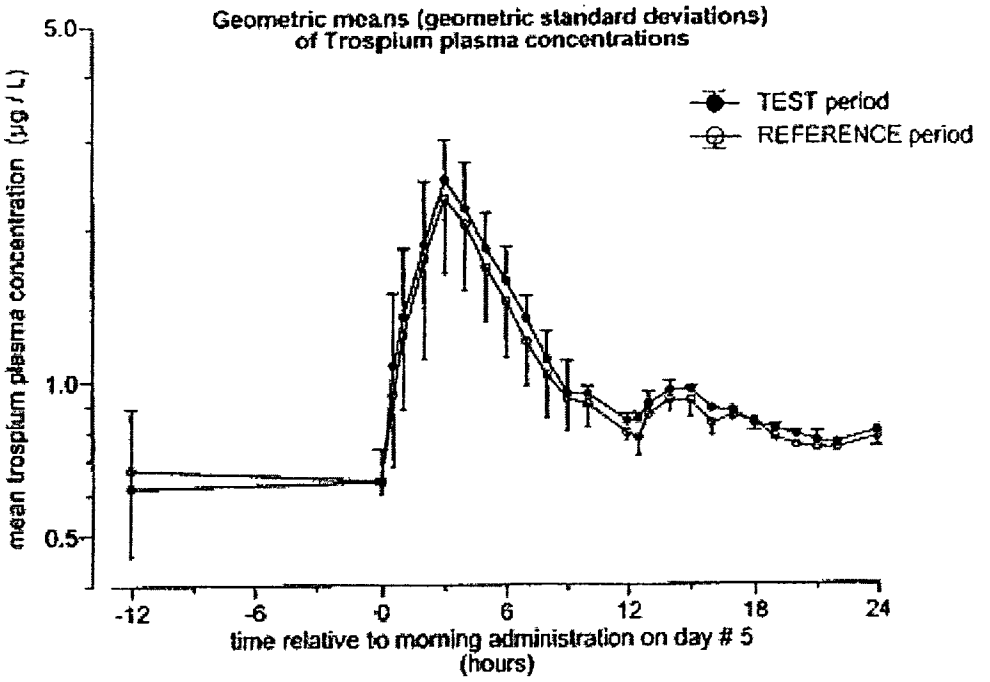

Figure 1. Geometric Mean Trospium Plasma Concentrations for the Test Versus Reference Compounds.

*Table 2 shows the statistics of AUCss and Cmax,ss comparisons. The products are bioequivalent by all metrics except tss,max evening.
*Bioavailability differs for the night and day doses.

parameter	test used	point estimate	90 % confidence interval
$AUC_{0-\tau,\ morning}$	t-test	1.0781	0.9745 – 1.1927
	Wilcoxon-test	1.0865	0.9597 – 1.2113
$Css_{max\ morning}$	t-test	1.0895	0.9520 – 1.2468
	Wilcoxon-test	1.1139	0.9226 – 1.2535
$AUC_{0-\tau,\ evening}$	t-test	1.0408	0.9735 – 1.1126
	Wilcoxon-test	1.0453	0.9721 – 1.1318
$Css_{max\ evening}$	t-test	1.0401	0.9752 – 1.1093
	Wilcoxon-test	1.0351	0.9606 – 1.1192

Table 2. Statistics of AUCss and Cmax,ss Comparisons for Spasmo-lyt versus Spasmex after 5 Days of Administration.

*Table 3 shows that according to formal hypothesis testing, steady state conditions were not reached in this study.
*Sponsor speculates that steady state was reached (drug has half life of 12 hours), but that the recumbent position of volunteers in the study center led to reduced absorption.

parameter	point estimate	confidence interval
$\mu_{Cssthrough\ morning\ day\ \#\ 5}$ / $\mu_{Cssthrough\ morning\ day\ \#\ 6}$ during intake of the TEST formulation	1.26	1.16 – 1.36
$\mu_{Cssthrough\ morning\ day\ \#\ 5}$ / $\mu_{Cssthrough\ morning\ day\ \#\ 6}$ during intake of the REFERENCE formulation	1.21	1.08 – 1.35
$\mu_{Cssthrough\ evening\ day\ \#\ 4}$ / $\mu_{Cssthrough\ evening\ day\ \#\ 5}$ during intake of the TEST formulation	1.35	1.17 – 1.56
$\mu_{Cssthrough\ evening\ day\ \#\ 4}$ / $\mu_{Cssthrough\ evening\ day\ \#\ 5}$ during intake of the REFERENCE formulation	1.18	1.00 – 1.39

Table 3. Test of Achievement of Steady State in the Study.

*61 Adverse events during the study—57 were mild, 4 were moderate in nature
*28 AEs during the test period and 33 during the reference period
*Equivalent number (9 each) of dry mouth reports for test and reference products
*8 subjects experienced dry mouth
*Based on measures taken at 4 hours post dose, heart rate increased approximately 12 beats per minute for both test and reference products on Day 5
*Accomodation problems in 2 and 3 volunteers

Study 51: The effect of cytochrome P450 1A2 with trospium chloride in vitro on the metabolism of caffeine.

Summary

• Approximately 9% inhibition of caffeine turnover at concentration > 2x most extreme in vivo

• Approximately 2% inhibition of caffeine turnover at clinically relevant concentrations in vivo

• Estimated IC50:

IC50 microsome #1 = 9317 +/- 3134 micromolar

IC50 microsome #2 = 8432 +/- 1918 micromolar

This is not considered to be clinically relevant given that concentrations in vivo are under 50 nM.

Methods

• Human liver microsomes from 2 different livers

• [Caffeine]: 500 micromolar (Km=500 micromolar)

• [Trospium chloride]: 37 – 3000 micromolar

• Caffeine metabolized by 1A2 to 1,7-dimethylxanthine and 1,3-dimethyxanthine by N-demethylation

• Quantity of 1,7-dimethylxanthine determined by HPLC

• NADPH regenerating system

Results

• For the highest trospium chloride concentration tested (3000 micromolar), the caffeine turnover was reduced 25%.

• Tabulation of relative effect on turnover:

Trospium Chloride Concentration (micromolar)	Microsome system #1 (% inhibition)	Microsome system #2 (% inhibition)
37	2.3	-0.007
111	8.9	8.2
333	18.2	18.4
1000	16.6	21.1
3000	25.2	24.1

• No effect on caffeine turnover for 37 and 333.3 micromolar trospium chloride detected.

• Relevant molar concentrations:

Molecular weight of trospium chloride: 427.97 g/mol

Worst case scenario: most extreme Cmax in renal impairment=

Cmax after 20 mg BID in healthy =

• Estimated IC50—based on straight line equation for Dixon plot (1/v = 1/v9 + m*l)

IC50 microsome #1 = 9317 +/- 3134 micromolar

IC50 microsome #2 = 8432 +/- 1918 micromolar

• Since concentration in vivo < 50 nM, CYP1A2 interaction not considered significant.

• Tabulated results

Sample designation	No.	Caf conc. /(µM)	TsCl conc. /(µM)	Protein conc. /(mg/ml)	NADPH regen. system	Response Metabolite A	Response Metabolite B	Conc. metabolite / (nM) A	Conc. metabolite / (nM) B	Turnover rate T (pmol/min/mgProtein) T_A	Turnover rate T (pmol/min/mgProtein) T_B	Mean $T_{A,B}$ / (pmol/min/mgP)	$T_{A,B}$ w.r.t Ref. / (%)
P3 t=0	1	500	0	2.188	yes	0.000		92		2.8			9
P3 TsCl:3000	2	500	3000	2.188	yes	0.007	0.008	723	743	22.0	22.6	22.3	76
P3 TsCl:1000	4	500	1000	2.188	yes	0.007	0.008	694	827	21.1	25.2	23.2	79
P3 TsCl:333	6	500	333.3	2.188	yes	0.008	0.008	765	810	23.3	24.7	24.0	82
P3 TsCl:111	8	500	111.1	2.188	yes	0.009	0.009	869	902	26.5	27.5	27.0	92
P3 TsCl:37	10	500	37	2.188	yes	0.010	0.010	978	967	29.8	29.5	29.6	101
P3 Reference	12	500	0	2.188	yes	0.010	0.010	940	992	28.6	30.2	29.4	100
P3 t=0	14	500	0	2.188	yes	0.000		79		2.4			8
P3 TsCl control	15	0	3000	2.188	yes	0.000		87		2.7			9
P20 t=0	16	500	0	1.931	yes	0.000		95		3.3			16
P20 TsCl:3000	17	500	3000	1.931	yes	0.003	0.004	359	408	12.4	14.1	13.2	74
P20 TsCl:1000	19	500	1000	1.931	yes	0.005	0.005	499	528	17.2	18.2	17.7	98
P20 TsCl:333	21	500	333.3	1.931	yes	0.006	0.006	564	556	19.5	19.2	19.3	107
P20 TsCl:111	23	500	111.1	1.931	yes	0.006	0.005	557	531	19.2	18.3	18.8	104
P20 TsCl:37	25	500	37	1.931	yes	0.005	0.005	530	518	18.3	17.9	18.1	101
P20 Reference	27	500	0	1.931	yes	0.003	0.002	548	493	18.9	17.0	18.0	100
P20 t=0	29	500	0	1.931	yes	0.000		72		2.5			14
P20 TsCl control	30	0	3000	1.931	yes	0.000		70		2.4			13

Caf = Caffeine, TsCl = Trospium chloride, t=0 = Incubation time of 0 min, A and B = Double incubations

Incubation of P3 and P20 human liver microsomes with caffeine and trospium chloride at varying inhibitor concentrations.

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Study 52: The Effect of Cytochrome P450 2C19 with Trospium Chloride in Vitro on the Metabolism of S-(+)-Mephenytoin.

Summary

• Approximately 15% inhibition of caffeine turnover at clinically relevant concentration
• Estimated IC50 (with measures taken at only 2 concentrations)
IC50 microsome #1 = 1756.3 +/- 894 micromolar
IC50 microsome #2 = 1968.6 +/- 486.8 micromolar
This is not considered to be clinically relevant given that concentrations in vivo are under 50 nM.

Methods

• Human liver microsomes isolated from 2 livers
• Incubation at substrate concentration = 20 micromolar (Km value)
• Trospium chloride concentrations tested: 37, 333, 3000 nM
• S-(+)-Mephenytoin metabolized by CYP 450 2C19 to 4-hydroxymephenytoin
• 4-hydroxymephenytoin determined HPLC
• NADPH regenerating system

Results

• Trospium chloride peak in chromatogram was too high for 3000 micromolar sample to determine metabolite levels. These data not included in determination of IC50.
• Estimated IC50—based on straight line equation for Dixon plot (1/v = 1/v9 + m*I) & only relying on data for 333 and 37 micromolar trospium chloride
IC50 microsome #1 = 1756.3 +/- 894 micromolar
IC50 microsome #2 = 1968.6 +/- 486.8 micromolar
• Tabulation of relative effect on turnover:

Trospium Chloride Concentration (micromolar)	Microsome system #1 (% inhibition)	Microsome system #2 (% inhibition)
37	15	0
333	19	14
3000	7*	-3*

* Trospium chloride peak in chromatogram was too high for 3000 micromolar sample to determine metabolite levels. These data not included in determination of IC50.

• Since concentration in vivo < 50 nM, CYP2C19 interaction not considered significant.
• Tabulated results

Sample designation	No.	S-MP conc./(µM)	TsCl conc./(µM)	Protein conc./(mg/ml)	Response Metabolite	Metabolite conc. /(nM)	Turnover rate T / (pmol/min/mgP)	Mean T_M / (pmol/min/mgP)	T_M / (%) w.r.t Ref.
P11 I=0 1	1	20	0	3.11	0.021	62	0.33		
P11 Reference 1	2	20	0	3.11	0.226	1226	6.57		
P11 Reference 2	6	20	0	3.11	0.236	1271	6.81	6.45	100
P11 Reference 2	10	20	0	3.11	0.206	1115	5.98		
P11 TsCl 3000 1	3	20	3000	3.11	0.211	1133	6.07		
P11 TsCl 3000 2	4	20	3000	3.11	0.185	990	5.31	5.62	93
P11 TsCl 3000 3	5	20	3000	3.11	0.231	1245	6.67		
P11 TsCl 333 1	7	20	333	3.11	0.181	982	5.18		
P11 TsCl 333 2	8	20	333	3.11	0.184	981	5.26	5.21	81
P11 TsCl 333 3	9	20	333	3.11	Inferior sample	/	/		
P11 TsCl 37 1	11	20	37	3.11	0.191	1020	5.47		
P11 TsCl 37 2	12	20	37	3.11	0.201	1076	5.77	5.52	85
P11 TsCl 37 3	13	20	37	3.11	0.186	992	5.32		
P11 N=0 1	14	20	0	3.11	0.003	b.d.	b.d.	b.d.	0
P11 I=0 2	15	20	0	3.11	0.024	76	0.41	0.37	6
P11 TsCl contr.	16	0	3000	3.11	0.022	84	0.34	0.34	5
P13 I=0 1	17	20	0	3.14	0.069	330	1.75		
P13 Reference 1	18	20	0	3.14	0.271	1470	7.80		
P13 Reference 2	22	20	0	3.14	0.268	1454	7.72	7.80	100
P13 Reference 3	26	20	0	3.14	0.274	1486	7.89		
P13 TsCl 3000 1	19	20	3000	3.14	0.284	1545	8.20		
P13 TsCl 3000 2	20	20	3000	3.14	0.286	1555	8.31	8.07	100
P13 TsCl 3000 3	21	20	3000	3.14	0.268	1451	7.70		
P13 TsCl 333 1	23	20	333	3.14	0.229	1235	6.56		
P13 TsCl 333 2	24	20	333	3.14	0.238	1285	6.82	6.71	88
P13 TsCl 333 3	25	20	333	3.14	0.236	1274	6.76		
P13 TsCl 37 1	27	20	37	3.14	0.150*	1576	8.37		
P13 TsCl 37 2	28	20	37	3.14	0.254	1372	7.28	7.82	100
P13 TsCl 37 3	29	20	37	3.14	Inferior sample	/	/		
P13 N=0 1	30	20	0	3.14	0.011	6	0.03	0.03	0
P13 I=0 2	31	20	0	3.14	0.067	320	1.70	1.73	22
P13 TsCl contr.	32	0	3000	3.14	0.006	b.d.	b.d.	b.d.	0

S-MP = S-Mephenytoin, TsCl = Trospium chloride, I=0 = Incub. time of 0 min., N=0 = Incub. without NADPH-regenerating system, b.d. = below determination limit
* Sample contains twice the amount of internal standard

Incubation of Microsomes with S-(+)-mephenytoin and trospium chloride.

APPEARS THIS WAY
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Study 53: The effect of cytochrome P450 2D6 with trospium chloride in vitro on the metabolism of dextromethorphan.

Summary

• Trospium chloride is a competitive inhibitor of the CYP2D6 enzyme; competing with the substrate detromethorphan for the high affinity binding site.
• The Ci values (20 and 50 micromolar) are approximately 100-fold greater than that observed in vivo (50 nM).
• Sponsor claims that no clinically relevant inhibition expected in vivo.

Methods

• Human liver microsomes from 2 different livers
• Concentration of both trospium chloride and dextromethorphan varied

Substrate concentration:	0.4 - 2000 micromolar
Trospium chloride concentration:	37 – 3000 micromolar

• Dextromethorphan metabolized by human P450 2D6 to dextrorphan by O-demethylization.

Results

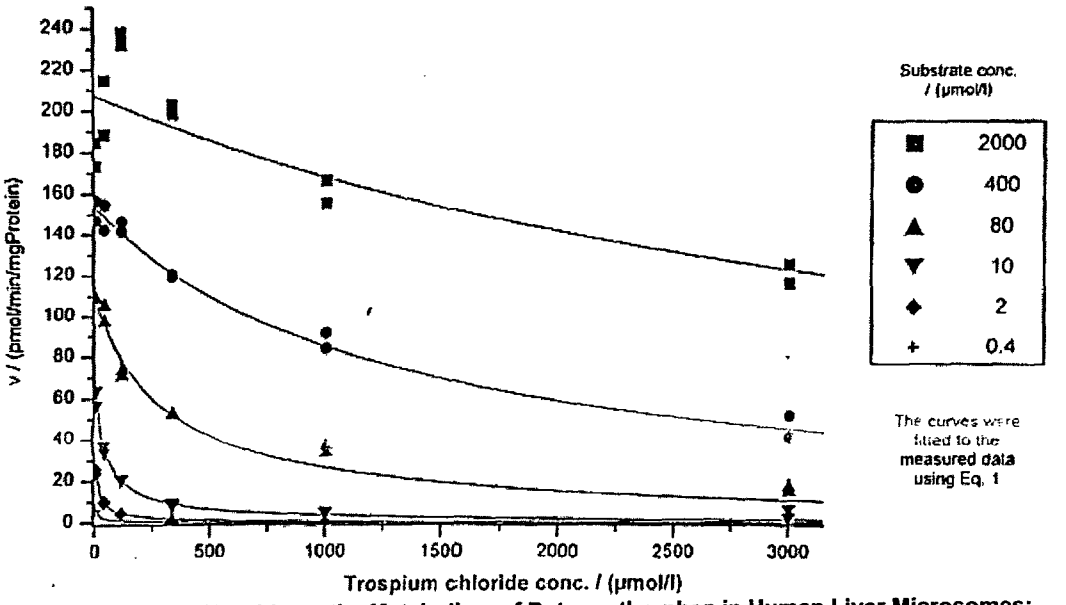
• Trospium chloride has a pronounced inhibitor effect on the high affinity binding site of CYP 2D6; reduction of turnover to 0% at substrate concentration = 4 micromolar and inhibitor concentration = 3000 micromolar or 1000 micromolar.
• For substrate concentration = 400 micromolar, turnover: 30-38%
• Data modeled by a model with terms for a low and a high affinity receptor binding site. Each had a competitive binding contant for inhibition.

$$v_0 = \frac{V_{max(1)}\,[S]}{C_{m(1)}\left(1 + \frac{[I]}{C_{i(1)}}\right) + [S]} + \frac{V_{max(2)}\,[S]}{C_{m(2)}\left(1 + \frac{[I]}{C_{i(2)}}\right) + [S]}$$

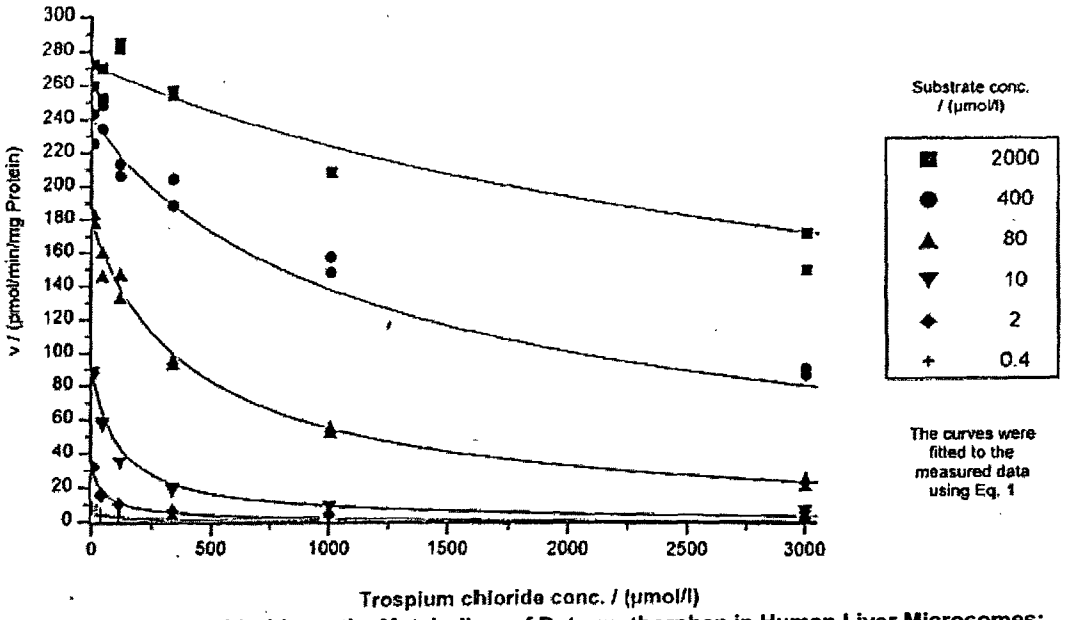
• Parameters of the inhibition model:

Microsomes	Binding site substrate	V_{max} nmol/min/mgProt	C_M µmol/l	C_i (inhibitor) µmol/l
P20	1 (high-affine) 2 (low-affine	98.7 141.8	6.7 605.9	20.2 760.9
P10	1 (high- affine) 2 (low-affine)	142.7 140.4	8.7 166.7	51.3 189.9

• Graphical display of results



Effect of Trospium Chloride on the Metabolism of Detromethorphan in Human Liver Microsomes: Liver #1.



Effect of Trospium Chloride on the Metabolism of Detromethorphan in Human Liver Microsomes: Liver #2.

• Tabulated results

[S] /µM	[I] /µM	$[M_A]$ /nM	$[M_B]$ /nM	$T_{A,B}$ /(pmol/min/mgProtein)		$T_{A,B}$ mean	T / %.
2000	3000	893	984	116	125	120	67
2000	1000	1200	1283	155	166	161	90
2000	333.3	1531	1564	198	203	200	112
2000	111.1	1835	1792	238	232	235	131
2000	37	1454	1657	188	215	201	113
2000	0	1339	1426	173	185	179	100
400	3000	394	316	51	41	46	30
400	1000	706	649	91	84	88	58
400	333.3	927	922	120	119	120	79
400	111.1	1093	1129	142	146	144	95
400	37	1186	1099	155	142	149	98
400	0	1134	1210	147	157	152	100
80	3000	134	118	17	15	16	15
80	1000	261	287	34	37	35	33
80	333.3	404	406	52	53	52	48
80	111.1	569	547	74	71	72	66
80	37	813	751	105	97	101	93
80	0	841	/	109	/	109	100
10	3000	52	21	6.7	2.7	4.7	8
10	1000	40	43	5.2	5.6	5.4	9
10	333.3	65	75	8.4	9.7	9.1	15
10	111.1	161	161	21	21	21	35
10	37	288	263	37	34	36	59
10	0	493	440	64	57	60	100
2	3000			0.0	0.0	0.0	0
2	1000	1.2	3.0	0.2	0.4	0.3	1
2	333.3	/	5.5	/	0.7	0.7	3
2	111.1	36	35	4.5	4.5	4.5	18
2	37	79	77	10	10	10	41
2	0	182	198	24	26	25	100
0.4	3000			0	0	0	0
0.4	1000			0	0	0	0
0.4	333.3			0	0	0	0
0.4	111.1			0	0	0	0
0.4	37			0	0	0	0
0.4	0	48	49	6.2	6.3	6.3	100

[S] = Dextromethorphan conc., [I] = Trospium chloride conc., [MA/B] = Conc. metabolite dextrorphan
indices A and B indicate double incubations

Incubation of Human Liver Microsomes with Dextromethorphan and Trospium Chloride at Varying Substrate and Inhibitor Concentrations: Microsome From Liver #1.

[S] /µM	[I] /µM	$[M_A]$ /nM	$[M_B]$ /nM	$[M_A]^{corr}$ /nM	$[M_B]^{corr}$ /nM	$T_{A,B}^{corr}$ /(pmol/min/mgP)		$T_{A,B}^{corr}$ Mean	T^{corr} /%
2000	3000	1399	1583	1309	1503	149	171	160	80
2000	1000	/	1916	/	1826	/	208	208	78
2000	333.3	2322	2340	2232	2250	254	256	255	96
2000	111.1	2600	2568	2510	2469	285	281	283	106
2000	37	2481	2305	2371	2215	270	252	261	98
2000	0	2370	2485	2280	2395	259	272	266	100
400	3000	881	844	791	754	90	86	88	36
400	1000	1469	1389	1379	1299	157	148	152	65
400	333.3	1885	1744	1795	1654	204	188	196	84
400	111.1	1960	1903	1870	1815	213	205	210	90
400	37	2266	2150	2176	2060	248	234	241	103
400	0	2085	2222	1975	2132	225	243	234	100
80	3000	295	265	205	175	24	20	22	12
80	1000	559	540	469	450	54	51	52	29
80	333.3	894	928	804	838	92	95	94	52
80	111.1	1373	1250	1283	1160	146	132	139	77
80	37	1484	1367	1394	1277	159	145	152	85
80	0	1649	1688	1559	1598	177	182	180	100
10	3000	152	124	62	34	7.3	4.1	5.7	7
10	1000	165	164	75	74	8.9	8.6	8.8	10
10	333.3	253	263	163	173	19	20	19	22
10	111.1	/	352	/	302	/	35	35	40
10	37	604	588	514	498	59	57	58	66
10	0	867	847	777	757	89	86	87	100
2	3000	100	102	10	12	1.4	1.6	1.5	5
2	1000	123	120	33	30	4.0	3.6	3.8	12
2	333.3	139	138	49	48	5.8	5.7	5.7	18
2	111.1	175	172	85	82	9.9	9.5	9.7	31
2	37	226	218	136	128	16	15	15	48
2	0	366	364	276	274	32	31	31	100
0.4	3000	89	84	0	0	0.0	0.0	0.0	0
0.4	1000	106	/	18	/	2.0	/	2.0	27
0.4	333.3	113	106	23	16	2.6	1.8	2.2	30
0.4	111.1	118	115	28	25	3.2	2.8	3.0	40
0.4	37	117	119	27	29	3.1	3.3	3.2	42
0.4	0	148	164	58	74	6.6	8.4	7.5	100

[S] = Dextromethorphan conc., [I] = Conc. inhibitor trospium chloride, [M] = Conc. metabolite dextrorphan,
A and B indicate double incubations
* Correction of $[M_{A,B}]$ by 90 nmol/l is equivalent to turnover decrease of 10 pmol/min/mgP (cf. p. 9, 11)

Incubation of Human Liver Microsomes with Dextromethorphan and Trospium Chloride at Varying Substrate and Inhibitor Concentrations: Microsomes From Liver #2.

Study 54: The effect of cytochrome P450 2E1 with trospium chloride in vitro on the metabolism of chlorzoxazone.

Summary

• At 37 micromolar concentrations of trospium chloride, no effect on chlorzoxazone metabolism detected.
• At 111 micromolar concentration of trospium chloride, effect on metabolism was scarcely detectable.
• At trospium chloride concentrations of 333-3000 micromolar, there was a 15-18% decline in metabolism.
• IC50 values based on Dixon plot = 14857 +/- 5586 micromolar
• CYP 2E1 not expected to have a clinically relevant impact on disposition of trospium chloride.

Methods

• Microsomes from 2 human livers used
• Substrate concentration of 50 micromolar (Km value: 40-50 micromolar)
• Chlorzoxazone is metabolized by Cytochrome P450 2E1 to 6-hydroxychlorzoxazone

Results

• At 37 micromolar concentrations of trospium chloride, no effect on chlorzoxazone metabolism detected.
• At 111 micromolar concentration of trospium chloride, effect on metabolism was scarcely detectable.
• At trospium chloride concentrations of 333-3000 micromolar, there was a 15-18% decline in metabolism.
• IC50 values based on Dixon plot = 14857 +/- 5586 micromolar

• Tabulation of results

Sample designation	No.	Zo conc. /(µM)	TsCl conc. /(µM)	Protein conc. /(mg/ml)	NADPH regen. system	Response Metabolite / 10⁴ A	B	Conc. metabolite / (µM) A	B	Turnover rate T (pmol/min/mgProteins) T_A	T_B	Mean $T_{A,B}$ / (pmol/min/mgPr)	$T_{A,B}$ w.r.t. Ref / (%)
P21 N=0 1	1	50	0	0.420	no	10		b.d.		0			0
P21 I=0 1	2	50	0	0.420	yes	29		b.d.		0			0
P21 TsCl:3000	3	50	3000	0.420	yes	434	385	1746	1574	208	187	198	91
P21 TsCl:1000	5	50	1000	0.420	yes	395	410	1574	1639	187	195	191	89
P21 TsCl:333	7	50	333.3	0.420	yes	335	434	1308	1748	156	208	182	84
P21 TsCl:111	9	50	111.1	0.420	yes	369	385	1450	1573	174	187	180	84
P21 TsCl:37	11	50	37	0.420	yes	458	424	1843	1702	219	203	211	98
P21 Reference	13	50	0	0.420	yes	479	423	1924	1697	229	202	216	100
P21 N=0 2	14	50	0	0.420	no	24		b.d.		0			0
P21 I=0 2	15	50	0	0.420	yes	31		b.d.		0			0
P21 TsCl control	16	0	3000	0.420	yes	44		22		3			1
P3 N=0 3	17	50	0	0.438	no	29		b.d.		0			0
P3 I=0 3	18	50	0	0.438	yes	/		/		/			/
P3 TsCl 3000	19	50	3000	0.438	yes	377	364	1495	1439	171	164	167	82
P3 TsCl 1000	21	50	1000	0.438	yes	378	398	1498	1578	171	180	176	86
P3 TsCl 333	23	50	333.3	0.438	yes	362	409	1428	1635	163	187	175	85
P3 TsCl 111	25	50	111.1	0.438	yes	431	427	1730	1744	197	196	197	96
P3 TsCl 37	27	50	37	0.438	yes	458	410	1851	1641	211	187	199	97
P3 Reference	29	50	0	0.438	yes	482	429	1867	1722	213	197	205	100
P3 N=0 4	31	50	0	0.438	no	22		b.d.		0			0
P3 I=0 4	32	50	0	0.438	yes	28		b.d.		0			0
P3 TsCl control	33	0	3000	0.438	yes	17		b.d.		0			0

Zo = Chlorzoxazone, TsCl = Trospium chloride, N=0 = Incubation without NADPH-regenerating system, I=0 = Incubation time of 0 min, A and B = Double incubations
b.d. = below determination limit

Incubation of Human Liver Microsomes with Chlorzoxazone and Trospium Chloride at Varying Inhibitor Concentrations.

Study 55: The effect of cytochrome P450 3A4 with trospium chloride in vitro on the metabolism of denitronifedipine.

Summary

• For the highest trospium chloride concentration tested (3000 micromolar), the denitronifedipine turnover decreased to 90%.
• No effect on denitronifedipine turnover at 1000 micromolar concentration of trospium chloride.
• Estimated IC50 based on Dixon plot (for each of 2 microsomal systems):

IC50 microsome #1	23077 +/- 10315 micromolar
IC50 microsome #2	11928 +/- 5901 micromolar

• No clinically relevant effect on CYP 3A4 metabolism expected based on in vitro results.

Methods

• Microsomes from 2 human livers used
• Substrate concentration of 50 micromolar (Km value: 30-80 micromolar)
• Denitronifedipine is metabolized by CYP 450 3A4 to the pyridine derivative.

Results

• For the highest trospium chloride concentration tested (3000 micromolar), the denitronifedipine turnover decreased to 90%.
• No effect on denitronifedipine turnover at 1000 micromolar concentration of trospium chloride.
• Estimated IC50 based on Dixon plot (for each of 2 microsomal systems):

IC50 microsome #1	23077 +/- 10315 micromolar
IC50 microsome #2	11928 +/- 5901 micromolar

• No clinically relevant effect on CYP 3A4 metabolism expected based on in vitro results.
• Tabulation of results

Sample designation	No	DN conc. (µM)	TsCl conc. (µM)	Protein conc. (mg/ml)	NADPH regen. system	Response Metabolite A	Response Metabolite B	Conc. metabolite I (nM) A	Conc. metabolite I (nM) B	Turnover rate T (pmol/min/mgProtein) T_A	Turnover rate T (pmol/min/mgProtein) T_B	Mean $T_{A,B}$ (pmol/min/mgP)	$T_{A,B}$ w.r.t Ref. (%)
P3 N=0	1	50	0	0.437	no	0.030		292		33			10
P3 I=0	2	50	0	0.437	yes	0.011		102		12			4
P3 TsCl:3000	3	50	3000	0.437	yes	0.231	0.265	2310	2653	264	304	284	90
P3 TsCl:1000	5	50	1000	0.437	yes	0.282	0.271	2823	2711	323	310	317	100
P3 TsCl:333	7	50	333.3	0.437	yes	0.295	0.304	2948	3036	337	347	342	108
P3 TsCl:111	9	50	111.1	0.437	yes	0.264	[0.150]	2643	[1493]	302	/	302	96
P3 TsCl:37	11	50	37	0.437	yes	/	0.285	/	2853	/	326	326	103
P3 Reference	13	50	0	0.437	yes	0.274	0.278	2737	2784	313	319	316	100
P3 N=0	15	50	0	0.437	no	0.028		269		31			10
P3 I=0	16	50	0	0.437	yes	0.014		133		15			5
P3 TsCl Ref.	17	0	3000	0.437	yes	0.001		0		0			0
P20 N=0	18	50	0	0.386	no	0.030		290		38			29
P20 I=0	19	50	0	0.386	yes	0.011		97		13			10
P20 TsCl:3000	20	50	3000	0.386	yes	0.091	0.089	907	881	117	114	116	88
P20 TsCl:1000	22	50	1000	0.386	yes	0.104	0.103	1034	1023	134	133	133	101
P20 TsCl:333	24	50	333.3	0.386	yes	0.105	0.110	1047	1099	136	142	139	105
P20 TsCl:111	26	50	111.1	0.386	yes	/	0.106	/	1057	/	137	137	104
P20 TsCl:37	28	50	37	0.386	yes	0.138	0.247	1375	[2470]	178	/	178	135
P20 Reference	30	50	0	0.386	yes	0.108	0.097	1076	963	139	125	132	100
P20 N=0	31	50	0	0.386	no	0.030		298		39			30
P20 I=0	32	50	0	0.386	yes	0.012		117		15			11
P20 TsCl control	33	0	3000	0.386	yes	0.000		0		0			0

DN = Denitronifedipine, TsCl = Trospium chloride, I=0 = Incubation time of 0 min, N=0 = without NADPH, A and B = Double Incubations

Incubation of Human Liver Microsomes with Denitronifedipine and Trospium Chlorideat Varying Inhibitor Concentrations.

Study 56 Inhibitory effects of trospium chloride on cytochrome P450 enzymes in human liver microsomes.

Summary

• Sponsor submitted report to add information about CYP 2C9 and CYP 2A6 to the information already submitted on CYP profile.
• 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.
• Compared to therapeutic trospium chloride concentrations (<50 nM), the 1000-times higher competitive inhibition constant Ki suggests that the CYP 2D6 interaction is not clinically relevant.

Methods

• Publication submitted summarizing results of all CYP studies
• HPLC detection for all but 2A6; 2A6 determined by fluorescence spectroscopy

Results

• Tabulation of results

Cytochrome P-450 enzyme	Substrate (S) Metabolite (M) Internal standard (IS)	K_m value*/ (μM)	Protein concentration (mg/ml)
CYP2D6	S: dextromethorphan M: dextrorphan IS: none	4/1500 (two substrate binding sites)	0.4
CYP3A4	S: dehydronifedipine M: dehydronifedipine pyridine IS: 4-OH-dehydronifedipine	30-80	0.4
CYP1A2	S: caffeine M: paraxanthine IS: hydroxyethyltheophylline	100-600	2
CYP2E1	S: chlorzoxazone M: 6-OH-chlorzoxazone IS: phenytoin	30-10	0.4
CYP2C19	S: S-(+)-mephenytoin M: 4-OH-mephenytoin IS: phenytoin	20	4
CYP2C9	S: S-(−)-warfarin M: 7-OH-warfarin IS: 7-ethoxycoumarin	3-5	0.8
CYP2A6	S: coumarin M: 7-OH-coumarin IS: none	2	0.05

Cytochrome P-450 enzyme	Substrate and concentration used (μM)		v_0* (pmol/min./mg protein)	IC_{50} of trospium chloride* (mM)
CYP2D6	Dextromethorphan high affinity site	4	49/43	0.027/0.044
not known	Dextromethorphan low affinity site	1900	164/171	1.2/5.5
CYP3A4	Dehydronifedipine	50	327/145	23/12
CYP1A2	Caffeine	500	28.8/18.1	9.3/8.4
CYP2E1	Chlorzoxazone	50	195/197	15/∞
CYP2C19	S(+)-Mephenytoin	20	5.8/7.6	∞/∞
CYP2C9	S-(−)-Warfarin	5	0.37/0.50	3.6/2.4
CYP2A6	Coumarin	2	600/620	2.0/2.8

v_0, metabolite formation rates in absence of an inhibitor estimated using equation 1. IC_{50}, inhibitor concentration reducing metabolite formation rate by 50% at the given substrate concentration; * data pairs were obtained using human liver microsomes from two different donors.

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

Study 57: In vitro metabolism of [14C] trospium chloride in rat, dog, and human liver fractions.

Summary

- Together, the 2 metabolite peaks in human were less than 5% of the chromatogram
- Metabolism was not affected by the addition of sulfaphenazole

Methods

- Incubation of 10 micromolar [14-C]trospium chloride with human liver S9 preparations.
- Effect of CYP 2C9 studied by addition or lack of inclusion of sulfaphenazole (CYP 2C9 inhibitor).

Results

- After 60 minute incubation in liver S9, 96% [14-C] trospium chloride remaining
- Together, the 2 metabolite peaks in human were less than 5% of the chromatogram
- Metabolism was not affected by the addition of sulfaphenazole
- Metabolite Profile of [14-C] trospium chloride following 10 micromolar incubation in rat, dog and human liver S9.

	% Region of Integration								
Sample Type	P1[a] (15 min)[b]	P2 (21 min)	P3 (24 min)	P4 (26 min)	P5 (27 min)	P6 (28 min)	P7 (32 min)	P8 (34 min)	P9 (40 min)
Chemical Control	ND[c]	ND	ND	ND	ND	ND	ND	ND	100.00
Rat S9 T0	ND	ND	ND	ND	ND	ND	ND	ND	100.00
Rat S9 T60[d]	4.65	16.43	3.03	1.16	1.18	27.85	37.90	ND	7.82
Dog S9 T0	ND	ND	ND	ND	ND	ND	ND	ND	100.00
Dog S9 T60[d]	ND	ND	ND	ND	ND	ND	2.92	1.32	95.76
Human S9 T0	ND	ND	ND	ND	ND	ND	ND	ND	100.00
Human S9 T60[d]	ND	ND	ND	ND	ND	ND	3.41	0.38	96.22

a. Radioactive peak region.
b. Elution time.
c. ND: not detected.
d. Mean of n = 2.

- Summary of the molecular masses observed in the radioactive regions in the chromatograms of trospium chloride incubated liver S9 samples.

Region	m/z	Species	Description
P1	440	Rat	Tri-hydroxylation of trospium chloride
P2	424	Rat	Di-hydroxylation of trospium chloride
P3	424	Rat	Di-hydroxylation of trospium chloride
P4	ND	Rat	unknown
P5	ND	Rat	unknown
P6	424	Rat	Di-hydroxylation of trospium chloride
P7	408	Rat, Dog, Human	Mono-hydroxylation of trospium chloride
P8	408	Dog, Human	Mono-hydroxylation of trospium chloride
P9	392	Rat, Dog, Human	trospium chloride

- Metabolite profile of [14-C] trospium chloride following 10 micromolar incubation in rat, dog and human liver microsomes, with and without sulfaphenazole, a CYP2C9 inhibitor.

Species	Sample Type	% Region of Integration								
		P1	P2	P3	P4	P5	P6	P7	P8	P9
Rat	With Inhibitor	3.45	19.64	1.96	0.40	ND	29.41	44.72	ND	0.41
		3.22	18.61	1.62	ND	ND	28.24	47.54	ND	0.77
	Without Inhibitor	5.41	23.01	2.83	0.68	ND	34.76	33.31	ND	ND
		5.53	25.26	2.37	ND	ND	36.38	30.45	ND	ND
Dog	With Inhibitor	ND	ND	ND	ND	ND	ND	3.66	1.59	94.74
		ND	ND	ND	ND	ND	ND	3.38	1.23	95.39
	Without Inhibitor	ND	ND	ND	ND	ND	ND	3.22	1.62	95.15
		ND	ND	ND	ND	ND	ND	3.55	1.10	95.35
Human	With Inhibitor	ND	ND	ND	ND	ND	ND	1.99	0.16	97.85
		ND	ND	ND	ND	ND	ND	2.65	0.42	96.93
	Without Inhibitor	ND	ND	ND	ND	ND	ND	2.87	ND	97.13
		ND	ND	ND	ND	ND	ND	2.98	ND	97.02

ND: Not determined

Study MP94D2.13

Pharmacokinetic-metabolic studies with [^{3}H]-trospium chloride in man
Part I: The excretion and plasma kinetics of radioactivity in man following a single intravenous administration of [^{3}H]-trospium chloride with and without pretreatment with non-radiolabelled trospium chloride;
Part II: Chromatographic analysis of the metabolite patter in plasma and urine after a single intravenous administration of [^{3}H]-trospium chloride with and without pretreatment with non-radiolabeled trospium chloride in man.

SUMMARY

• 89-93% recovery of drug
• Elimination plateaus at 120 hours post-dose
• Similar urinary excretion profile for the two groups
• By 168 hours, 71.4% (range: 70-75%) of dose excreted in urine for non-pretreated and 65.1% (range: 60-70%) excreted in urine for pretreated.
• By 168 hours, 19.4% (range: 16-22%) of dose excreted in feces for non-pretreated and 26.1% (range: 19-33%) excreted in feces for pretreated.
• 80% of radioactivity excreted as trospium chloride (57% of dose)
• 20% of radioactivity excreted as metabolites (14.3% of dose):
  10% excreted as azoniaspironortropanol
  10% excreted as two unknown metabolites
• There is a 9% reduction in excretion via the urine in subjects that are pretreated relative to those that are not pretreated with oral trospium chloride.
• There is a 35% increase in excretion via the feces in subjects that receive pretreatment with oral trospium chloride relative to those who only receive a single intravenous trospium chloride dose.
• More variability in profiles of subjects pretreated with p.o. trospium chloride than subjects that only receive an i.v. dose.
• No difference in CL or AUC for pretreated vs. non-pretreated

• 25% increase in half life with pretreatment reflects similar change in volume of distribution.

• Plasma protein binding determined *ex vivo* = 85% (fu=0.15)
• Plasma:whole blood ratio of non-volatile radioactivity was 1.6:1 at 0.75 hours post-dose.

PURPOSE

*Define the plasma and excretion kinetics of drug and related metabolites in man following single intravenous administration with or without pretreatment with trospium chloride twice daily for 7 days.

METHODS

Study Design

*Multicenter, uncontrolled, open label
*7 enrolled; 6 exposed to radiolabelled trospium
*Healthy males, 30-49 years
*All subjects received a single IV bolus injection of 1 mg trospium chloride
*Slow intravenous bolus over 30 seconds at 9 am
*3/7 subjects pretreated with 20 mg oral tablet (received nonradiolabeled 20 mg oral tablet of trospium chloride for 7 consecutive days before receiving labeled test compound.)
*3/7 subjects received labeled test compound only.
*Fasting from 11 pm the evening before radiolabelled dose until 4 hours post-dose.
*Urine and feces samples collected until at least 168 hours post-radiolabelled dose.
*Intense blood sampling until 120 hours post-dose.
*Drug level determined in blood and plasma.
Collection schedule:

Urine	0-3, 3-6,6-12,12-24,24-48,48-72,72-96,96-120,120-144,144-168 hrs
Feces	0-24,24-48,48-72,72-96,96-120,120-144,144-168 hrs
Blood	0.25,0.5,0.75,1,1.25,1.5,2,3,4,6,8,10,12,16,20,24,32,40,48,72,96,120 hrs

*Total reactivity measured in urine, feces and plasma.
*Non-volatile reactivity measured in plasma to determine the extent of exchange of tritium with body water.
*Non-volatile reactivity measured in whole blood to estimate the association of drug-related reactivity with blood cells.

Test Product

IV bolus 1 mg [3H]-trospium chloride solution in isotonic sterile saline
Concentration = 0.201 mg/g, code TRQ 7849
Nonlabelled trospium chloride (Lot number 47653)
Oral tablet 20 mg Spasmo-lyt® (Lot No. 512286): Used to pretreat 3 subjects

RESULTS

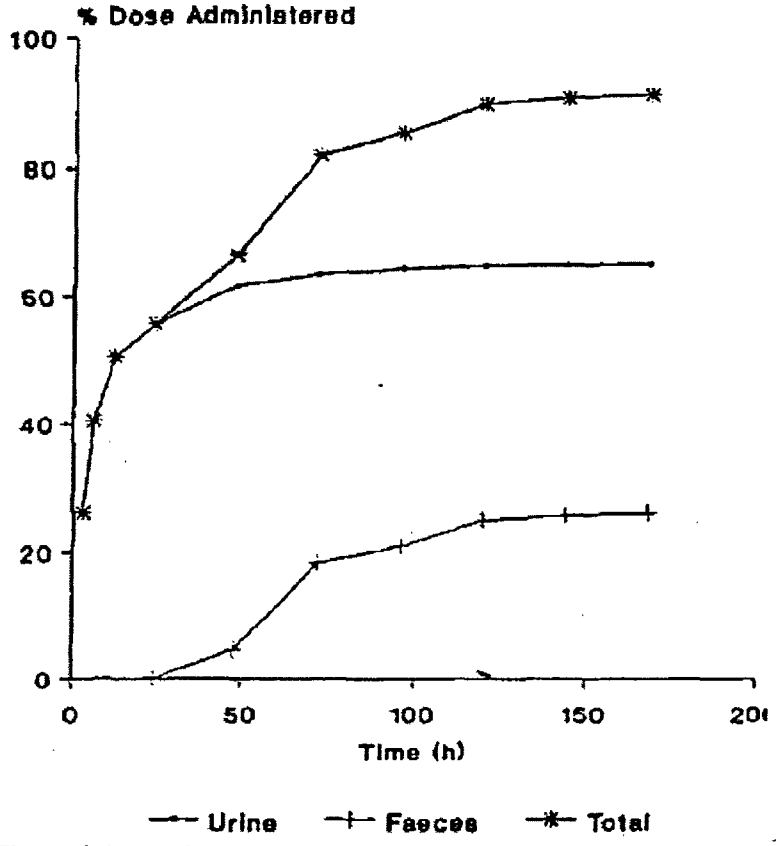


Figure 1. Mean Cumulative Excretion of Total Radioactivity Following Single Adminstration of 1 mg [3H]-Trospium Chloride to Three (N=3) Male Volunteers Pretreated with 20 mg Trospium Chloride Administered Orally BID For 7 Days.

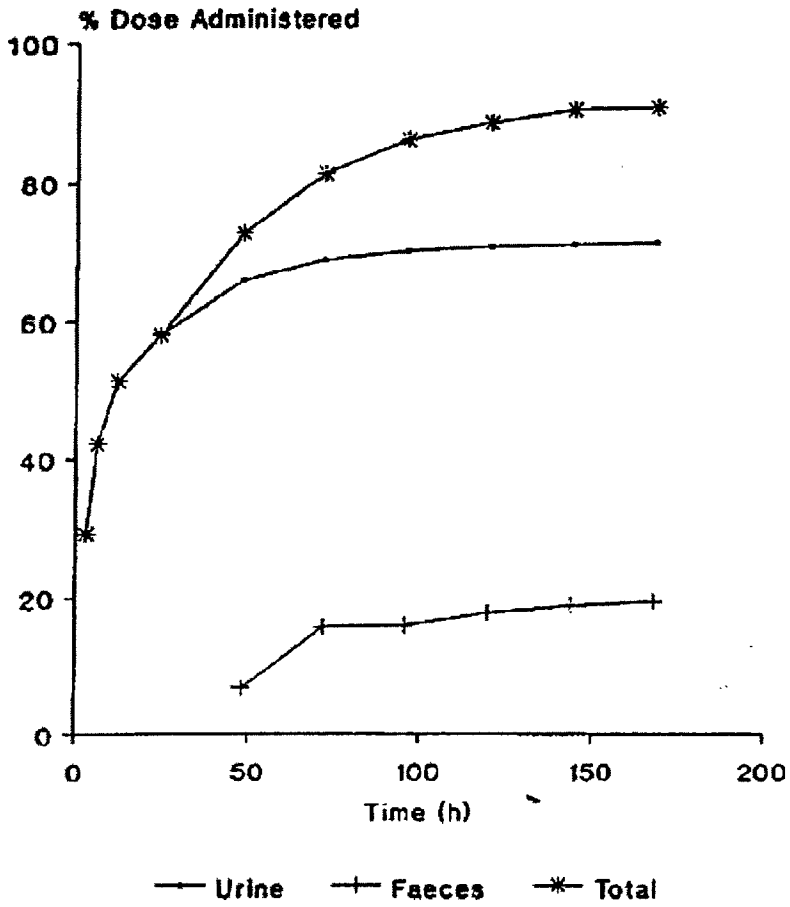


Figure 2. Mean Cumulative Excretion of Total Radioactivity Following Single Adminstration of 1 mg [3H]-Trospium Chloride to Three (N=3) Male Volunteers

*Note in Figure 1 and Figure 2: elimination plateaus at 120 hours post-dose

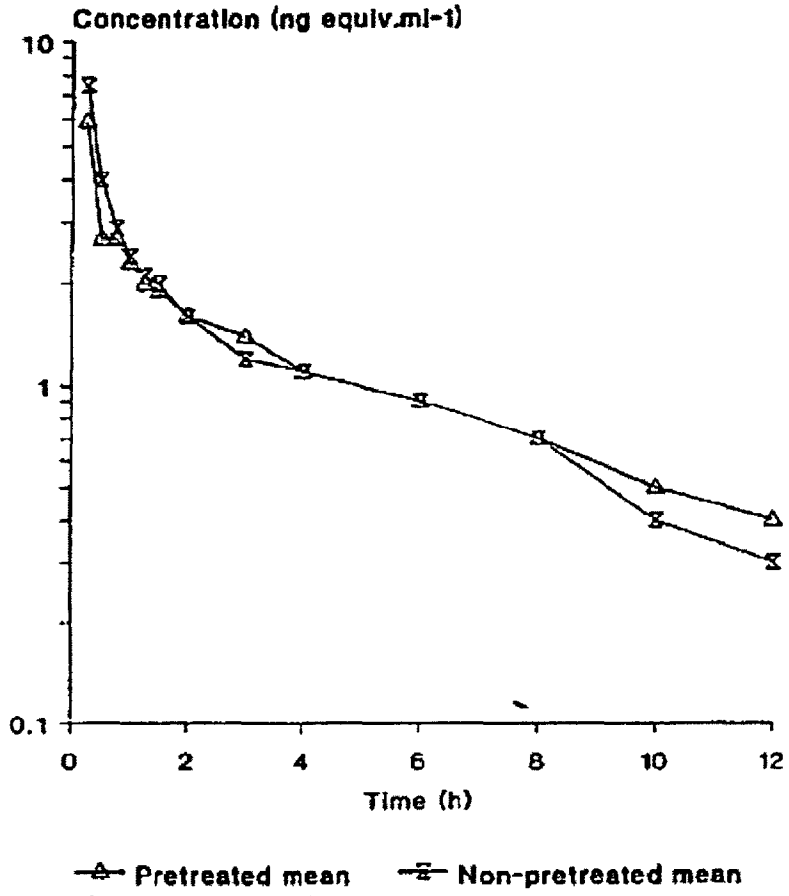


Figure 3. Concentration of Non-volatile Radioactivity in Plasma Following Single Intravenous Administration of 1 mg [3H]-Trospium Chloride to Male Volunteers With (N=3) or Without (N=3) Pretreatment with 20 mg Trospium Chloride Administered Orally BID for 7 Days.

*Note in Figure 3: Pretreatment with p.o. trospium chloride does not influence concentration time profile of an intravenous dose.

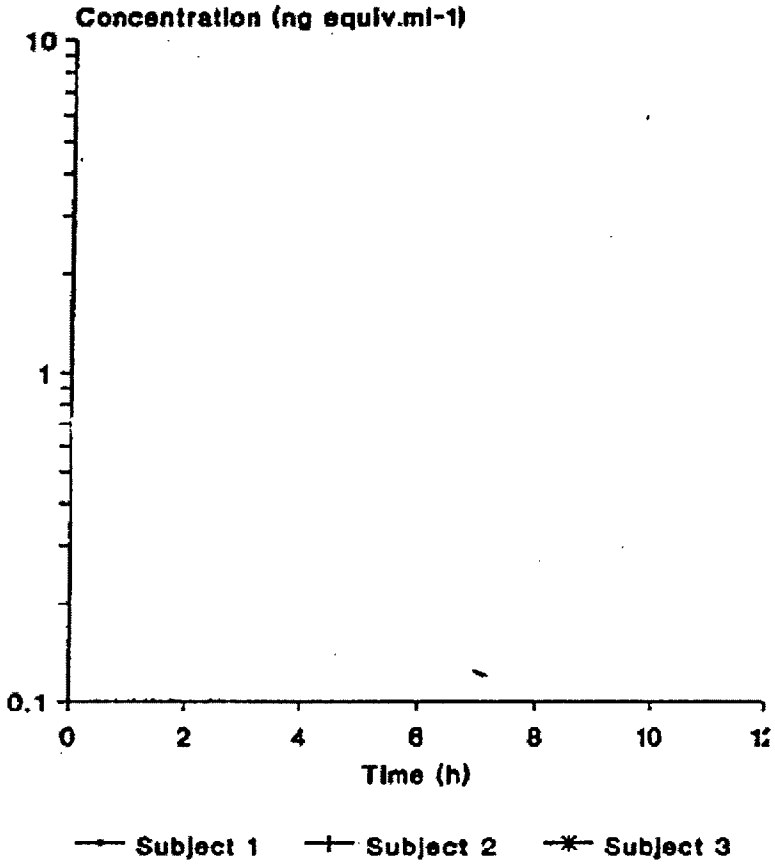


Figure 4. Administration of 1 mg [3H]-Trospium Chloride to Male Volunteers Pretreated with 20 mg Trospium Chloride Administered Orally BID for 7 Days.

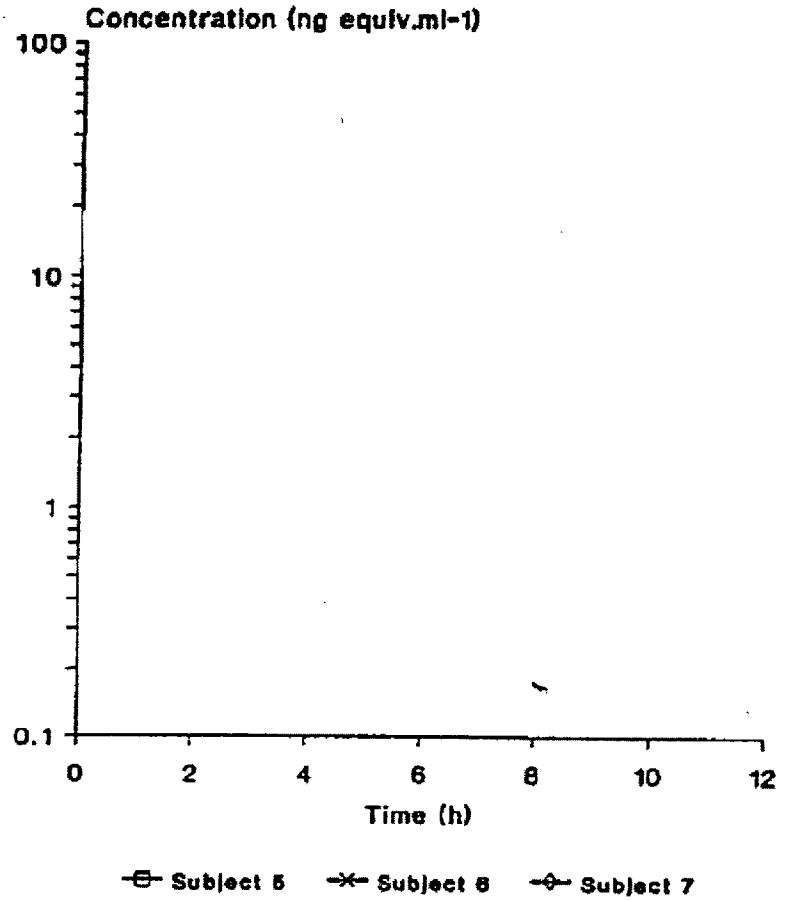


Figure 5. Concentration of Non-volatile Radioactivity in Plasma Following Single Intravenous Administration of 1 mg [3H]-Trospium Chloride to Male Volunteers.

*Note in Figure 4 vs. Figure 5: more variability in profiles of subjects pretreated with p.o. trospium chloride than subjects that only receive an i.v. dose.

	Pretreated	Non-Pretreated
$AUC_{0\to\tau}$ (ng*hr/mL)	15.11	15.52
$MRT_{0\to\tau}$ (hr)	3.69	3.33
$AUC_{0\to\infty}$ (ng*hr/mL)	17.76	17.5
$MRT_{0\to\infty}$ (hr)	6.1	5.00
t½ (hr)	4.99	4.08
V (mL)	360238	292089
CL (mL/hr)	58194	58651

Table 1. Comparison of Pharmacokinetic Parameters After a 1 mg Intravenous [^{3}H]-Trospium Chloride Dose for Subjects Pre-Treated for 7 Consecutive Days with 20 mg BID Trospium Chloride Versus Subjects Not Pre-Treated. **(From p. 41 of study report.)**

Note in Table 1:

*No difference in CL or AUC for pretreated vs. non-pretreated

*25% increase in half life with pretreatment reflects similar change in volume of distribution.

Time	Pretreated Group		Non-pretreated Group	
	Mean Urinary Excretion (% dose)	Mean A_e (%*)	Mean Urinary Excretion (% dose)	Mean A_e (%*)
3 h	26.30	40.4	29.26	41.0
6 h	40.63	62.4	42.26	59.2
12 h	50.53	77.7	51.41	72.0
24 h	55.74	85.7	58.13	81.4
48 h	61.69	94.8	66.04	92.5
72 h	63.50	97.6	68.96	96.5
96 h	64.34	98.9	70.24	98.3
120 h	64.77	99.5	70.88	99.2
144 h	64.96	99.8	71.21	99.7
168 h	65.07	100.0	71.43	100.0

Table 2. Amount of Radioactivity Excreted in Urine Expressed as a Percent of the Total Radioactivity Excreted in Urine Measured Following Single Intravenous Administration of 1 mg [3H]-Trospium Chloride to Male Volunteers With and Without Pretreatment With Non-Radiolabelled 20 mg Trospium Chloride.

*Note in Table 2: Similar urinary excretion profile for the two groups

• 89-93% recovery of drug as follows:

	Pretreated	Non-pretreated
Recovery in Urine	65.1% (60-70%)	71.4% (70-75%)
Recovery in feces	26.1% (19-33%)	19.4% (16-22%)

• More appears in feces of pretreated compared to non-pretreated
• Greater variability in parameters of pretreated versus non-pretreated
• Slow fecal excretion; 6-23% recovered by 72 hours
• Urinary excretion of drug plateaus by 168 hours post-dose for both pretreated and non-pretreated subjects

• By 168 hours, 71.4% (range: 70-75%) of dose excreted in urine for non-pretreated and 65.1% (range: 60-70%) excreted in urine for pretreated.
• By 168 hours, 19.4% (range: 16-22%) of dose excreted in urine for non-pretreated and 26.1% (range: 19-33%) excreted in urine for pretreated.
• 80% of radioactivity excreted as trospium chloride (57% of dose)
• 20% of radioactivity excreted as metabolites (14.3% of dose):
    10% excreted as azoniaspironortropanol
    10% excreted as two unknown metabolites
• See the following table for excretion characteristics

	Pretreated Excretion	Non-pretreated Excretion	Fold-change: pretreated / non-pretreated
Urine	65.1%	71.4%	0.91
Feces	26.1%	19.4%	1.35

• There is a 9% reduction in excretion via the urine in subjects that are pretreated relative to those that are not pretreated with oral trospium chloride.
• There is a 35% increase in excretion via the feces in subjects that receive pretreatment with oral trospium chloride relative to those who only receive a single intravenous trospium chloride dose.
• Plasma:whole blood ratio of non-volatile radioactivity was 1.6:1 at 0.75 hours post-dose.
• Plasma protein binding determined *ex vivo* = 85% (fu=0.15)

Study IP631-004
A Multicenter, Open-Label Study Of 20 Mg, Trospium Chloride, Twice-Daily, For Up To 9 Months To Characterize The Population Pharmacokinetics In Patients With Overactive Bladder Participating In The Open-Label Treatment Phase Of Study IP631-003.

Summary

• The best population pharmacokinetic model for trospium chloride after 20 mg b.i.d. oral administration was a one-compartment model with first-order absorption process. The distribution of KA was highly skewed and best described assuming a bimodal distribution.
• CL decreased with increasing serum creatinine levels. Findings that CL increased with increasing body size (height) and concomitant medication with CYP2C9 inhibitors are questionable, given the substantial uncertainty associated with parameter estimates.
• Although only 9% of the patients contributing to the analysis were non-Caucasian, a 2.54-fold increase in KA would be expected in these patients.
• Other evaluated patient demographics, including age and gender, markers of hepatic function or concomitant medication with CYP450 modulators other than CYP2C9 inhibitors or with drugs eliminated by active renal secretion did not demonstrate a significant impact on the pharmacokinetics of trospium chloride.
• The final covariate model was on average unbiased in predicting trospium concentrations; however, the model did not adequately describe the variability of trospium concentrations observed in this clinical trial. Extreme concentrations were not predicted well.
• Sponsor investigated the following covariates: metabolic inhibitors (CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4,5,7), metabolic inducers (CYP1A2, CYP2B6, CYP2C19 and CYP3A4,5,7), and concomitant medications undergoing active renal secretion. Sponsor did not investigate inhibitory effects of 2E1, 2C19 or 2A6.
• CYP 2C9 inhibitor as a covariate significantly improved model fitting. Sponsor claims this is likely an artifact given results of in vitro studies. Also, CL increased 1.35-fold—should have decreased with inhibition. 14 data records associated with CYP 2C9.
• There was no statistically significant correlation between the extent of exposure to trospium chloride and the occurrence of potentially clinically significant low or high ECG values. Increase in exposure to trospium chloride did not result in potentially clinically significant ECG abnormalities.
• Two subjects exhibited a prolonged QTcF interval on Day 1 or Day 28 (2% of all QTcF measurements in the pharmacokinetic population). Systemic exposure to trospium was comparable, on average, across patients exhibiting normal PR and QTcF intervals and patients presenting potentially clinically significant prolongation in PR and QTcF intervals, respectively. The sample size of patients with ECG abnormality was too limited to draw meaningful conclusions.

Objectives

• Characterize the population pharmacokinetic behavior of trospium chloride in patients with overactive bladder;

• Evaluate the potential effects of demographic variables, concomitant medications, and clinical pathology values on the pharmacokinetics of trospium chloride;
• Assess the performance of the population pharmacokinetic model in the prediction of trospium plasma concentrations; and
• Characterize the relationship between systemic exposure and ECG parameters (PR and QTcF intervals and heart rate).
• Missing demographics or laboratory measurements were imputed by using the population median if the covariate was continuous or the most frequent category if the covariate was categorical. If height and/or weight are missing for a patient, BSA and BMI were calculated based on imputed demographics. Similarly, if gender, age, weight and/or CCr are missing for patient, CLCr was calculated based on imputed demographics and laboratory measurements. No imputation was done if dosing date, dosing time, sampling date, sampling time, and/or trospium concentration were missing, and such records were excluded from the analysis.
• Prior to any modeling, plasma concentrations and sample times were examined for pharmacokinetic and dosing outliers. No formal tests for outliers were conducted. Outliers were identified by visual inspection of the data. A typical pharmacokinetic outlier was defined as an observation discordant from the bulk of the data within the same time interval.

Methods
• Population Pharmacokinetics of Twice Daily 20 mg Trospium Chloride in Patients with Overactive Bladder Participating in the Open-Label Treatment Phase of Study IP631-003
• 20 mg trospium chloride BID for 9 months open label treatment
• Sparse sampling for PK: on days 1, 28, 135
    Day 1 of open-label phase = Day 84 of treatment phase
        N=19 trospium chloride subjects
        3 PK samples: 0, 0.5-2, 2-6 hours post-dose
    Day 28 of open-label phase
        N=46
        2 PK samples: 0, 0.25-1 hour post-dose
    Day 135
        N=28
        1 PK sample 8 hours post-dose
• NONMEM data set included 179 samples from 81 subjects
• Demographics:
    77 Caucasian, 1 Asian, 5 African American, 4 American Indian
    17 male, 70 female
• ECG parameters (HR, QTcF)
• Inclusion criteria included
    -males or females; 18 years or older
    -OAB
    -negative pregnancy
• Exclusion criteria included
    -clinically significant renal disease
    -volume parameters specified

-patients with clinically significan bladder neck obstructions

• Variables for NONMEM analysis: ID, visit #, gender, race, age, weight, height, BSA, BMI, dosing time, amount, sampling time, trospium concentration, serum creatinine, creatinine clearance, SGPT, SGOT, concomitant medications.

• Handling of missing data:

Null values assigned to missing observations

Imputation of missing demographic variables

• Interindividual variability assumed log-normally distributed

• The 4 evaluation criteria described below were used to examine the model performance:

1. Given nested models, the objective function value (OFV) of the best model should be significantly smaller than the alternative model(s) based on the Likelihood Ratio test (LRT) at the pre-specified significance level of $p < 0.05$. Alternatively, for non-nested models, the model with the smallest Akaike information criterion (AIC) is chosen as the best model.

2. Goodness-of-fit parameters including a less systematic distribution of weighted residual plots and a decrease in 1.) standard error, 2.) correlation of the elements in the correlation matrix of the parameter estimates, 3.) inter-individual variability of the pharmacokinetic parameters, and/or 4.) residual error. The observed and predicted trospium concentrations from the preferred model are more randomly distributed across the line of unity (a straight line with zero intercept and a slope of one) than the base model.

3. The weighted residuals show less systematic distribution against covariates, e.g., patient weight, age, gender, race, and serum creatinine, for the preferred model.

The covariates included in the full model were sequentially removed in order to determine if all the covariates continued to provide significant influence on the population model.

4. The resulting reduced models were evaluated to determine if there was significant model degradation at a more stringent p-value of 0.005. Significance of the correlation term within the parameter covariance matrix was evaluated to determine if the parameter correlation term provided significant improvement to the final population model.

• The sensitivity of the final model to the model inputs was determined by sensitivity analysis. During this analysis, the value of the sampling times, covariates and plasma trospium concentrations were sequentially varied by ± 10% of the observed value assuming a uniform distribution, and the results were compared to the final covariate model.

• The performance of the final model to predict concentration values for patients not included in model parameter estimation was evaluated using an out-of-sample analysis

• One- and two-compartment population pharmacokinetic models with instantaneous, zero- or first-order absorption with or without lag time were subsequently compared by nonlinear mixed-effects modeling using first-order estimation method in order to identify the base structural model.

Results

• Best fitting population pharmacokinetic model for trospium chloride after 20 mg b.i.d. oral administration was a one-compartment model with first-order absorption, in which the estimated value for apparent clearance (CL) was associated
with or affected by serum creatinine levels, body size (height) and concomitant medication with a CYP2C9 inhibitor, and the estimated value for absorption rate constant (KA) was associated with or affected by race and followed a bimodal distribution.
• The population pharmacokinetic model was not improved with 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 estimated value for CL 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).
• CL increased by 1.35-fold in the presence of concomitant medication with a CYP2C9 inhibitor.
• Estimated CL decreased with increasing levels of serum creatinine and increased with increasing body size (height).
• The finding that renal function, as represented by serum creatinine levels in this model, affects trospium CL was expected given that the drug is predominantly eliminated unchanged in urine.
• The findings that CYP2C9 inhibitors and height affect trospium CL are questionable, most likely artifactual and lack clinical relevance given the large uncertainty of the parameter estimates. Also, only 8% of the data records included in the analysis were associated with concomitant administration of CYP2C9 inhibitors.
• The estimated value for the apparent volume of distribution (V) was 395 L.
• The distribution of KA across patients was skewed and 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. Although only a small proportion of the population was non-Caucasian, KA for that segment of the population was 2.54-fold higher than for the Caucasian population.
• Table of parameter estimates:

Table A - Summary of Trospium Chloride NONMEM Population Parameter Estimates – FOCE/Interaction		
Parameter	Estimate ± SE	95 % Confidence Interval
Apparent clearance, CL (L/hr) [Θ(1) * (1+Θ(8)*CYP3) * (HTCM/163)**Θ(9) + (CRE-0.9)*Θ(7)]		
Θ(1) (L/hr)	1170 ± 93.0	930 – 1410
Θ(7)	-1580 ± 539	-2968 – -192
Θ(8)	0.349 ± 0.227	-0.236 – 0.934
Θ(9)	3.19 ± 1.88	-1.65 – 8.03
Apparent volume of distribution, V (L) [Θ(2)]		
Θ(2) (L)	395 ± 140	34.4 – 755.6
Absorption rate constant, KA (/hr) Sub-population 1: [Θ(3)*(1+Θ(6)*RACE)] Sub-population 2: [Θ(4)*(1+Θ(6)*RACE)]		
Θ(3) (/hr)	0.175 ± 0.0332	0.0895 – 0.2605
Θ(4) (/hr)	0.0330 ± 0.00438	0.0217 – 0.0443
Θ(6)	1.54 ± 0.460	0.355 – 2.725
Proportion of patients in sub-population 1, p(1) [Θ(5)]		
Θ(5)	0.0915 ± 0.0464	-0.0280 – 0.2110

Abbreviations: CYP3 is intake of CYP2C9 inhibitors within 3 days of administration of trospium chloride, coded as 0=No and 1=Yes, HTCM is patient height (cm), CRE is serum creatinine (mg/dL), and race is coded as 0=Caucasian and 1=non-Caucasian.

• Summary of Trospium Chloride POSTHOC estimates listed below for 2 patient subsets (subset on KA value):

Table B - Summary of Trospium Chloride NONMEM POSTHOC Individual Patient Parameter Estimates			
	Sub-population 1 (n=10)	Sub-population 2 (n=77)	All Patients (n=87)
CL (L/hr) *Mean ± SD*	1201 ± 474	1552 ± 929	1512 ± 894
Range			
Median	1231	1361	1308
V (L) *Typical value*	395	395	395
KA (/hr) *Mean ± SD*	0.283 ± 0.139	0.0369 ± 0.0136	0.0652 ± 0.0917
Range			
Median	0.176	0.0330	0.0330
AUC(0-τ) (ng*hr/mL) *Mean ± SD*	18.5 ± 9.90	17.6 ± 13.0	17.7 ± 12.6
Range			
Median	14.9	13.5	14.0
Css (ng/mL) *Mean ± SD*	1.54 ± 0.825	1.47 ± 1.08	1.47 ± 1.05
Range			
Median	1.24	1.12	1.17
Cmax (ng/mL) *Mean ± SD*	4.06 ± 2.46	1.71 ± 1.20	1.98 ± 1.57
Range			
Median	4.01	1.37	1.43
Note: Because the distribution of KA was highly skewed, the model for KA included a mixture of two distinct log-normal distributions. Assignment of the patients to sub-population1 or sub-population 2 was done by NONMEM during model fitting. Pharmacokinetic parameters were set to the typical parameter estimates for patients that did not contribute to the population pharmacokinetic analysis.			

• As measured by the condition number, the final population pharmacokinetic model for trospium chloride was considered fairly stable. The base model and final model had a condition number of 7.14 and 16.96, respectively, upon FOCE/Interaction minimization.
• The final population pharmacokinetic model for trospium chloride was relatively sensitive to changes in model inputs, including observed plasma trospium concentration, serum creatinine level, presence of concomittant medications with CYP2C9 inhibitors, height, and race.
• The predictability of the final covariate model for trospium chloride was evaluated by the out-of-sample approach based on standardized mean prediction error (SMPE). For unbiased estimates, SMPE has an expected value of 0 and a standard deviation of 1. The SMPE had a mean of 3.91 with a 95% confidence interval of 2.78 to 10.6. The t-test showed that the average SMPE was not significantly different from zero (p=0.2574), demonstrating that the predictions of trospium concentrations using the final covariate model were on average unbiased. The standard deviation of mean SMPE had a mean of 19.5 with a 95% confidence interval of 1.18 to 41.3 using a bootstrap resampling technique with 10,000 iterations.
• The t-test showed that the standard deviation of SMPE was significantly different from 1 ($p < 0.0001$), indicating that the model did not adequately describe the variability of the concentrations. The observed trospium concentrations ranged from [redacted] in this study, however the predicted concentrations ranged from [redacted] The final model failed to predict extreme concentrations well.
• The relationship between systemic exposure (Cmax, Css and AUC(0-τ)) and ECG parameters (PR and QTcF intervals and heart rate) was explored using logistic and linear regression analyses. There was no statistically significant correlation between the extent of exposure and the occurrence of potentially clinically significant low or high ECG values. Increase in exposure to trospium chloride did not result in potentially clinically significant ECG abnormalities.
• Two subjects exhibited a prolonged QTcF interval on Day 1 or Day 28 (2% of all QTcF measurements in the pharmacokinetic population). Systemic exposure to trospium was comparable, on average, across patients exhibiting normal PR and QTcF intervals and patients presenting potentially clinically significant prolongation in PR and QTcF intervals, respectively. The sample size of patients with ECG abnormality was too limited to draw meaningful conclusions.
• Information on model selection

Table 8.	Summary of Base Model Development – Structural Model				
Model	Model Description	Modeled Parameters			OFV
		Thetas	Etas	Epsilons	
1CIV1 – Model 1	1-compartment, instantaneous absorption	2	1	1	397.290
1CPO1 – Model 2	1-compartment, first-order absorption	3	1	1	377.801
1CPO2 – Model 3	1-compartment, first-order absorption, lag time	4	1	1	377.801
1CPO3 – Model 4	1-compartment, zero-order absorption	3	1	1	379.612
1CPO4 – Model 5	1-compartment, zero-order absorption, lag time	4	1	1	394.746
2CIV1 – Model 6	2-compartment, instantaneous absorption	4	2	1	367.261
2CPO1 – Model 7	2-compartment, first-order absorption	5	2	1	335.869
2CPO2 – Model 8	2-compartment, first-order absorption, lag time	6	2	1	*
2CPO3 – Model 9	2-compartment, zero-order absorption	5	2	1	341.789
2CPO4 – Model 10	2-compartment, zero-order absorption, lag time	6	2	1	**

* *OFV not reported - Minimization terminated*
** *OFV not reported – R-matrix singularity*

Supporting Data: *Page:*

Exhibit 1: Summary of Base Model Development *page 143*

Based upon the OFV, models with a distinct absorption phase (Models 2-5 and 7-10) performed better than models based on instantaneous absorption (Models 1 and 6), which would be expected based upon the study design. Inclusion of a lag time of absorption failed to improve the goodness of fit (Models 3 and 5) or could not reach satisfying convergence (Models 8 and 10). Models with first-order absorption rate constant also performed better than models with zero-order absorption rate constant (Models 4 and 9) on the basis of the OFV. Model 7 performed significantly better than Model 2 based on the OFV. However, inspection of the correlation matrix of parameter estimates indicated a significant level of correlation among parameter estimates for Model 7, as well as an extremely high value of the estimate of inter-individual variability for V. Model 2 was therefore preferred on the basis of the principle of parsimony.

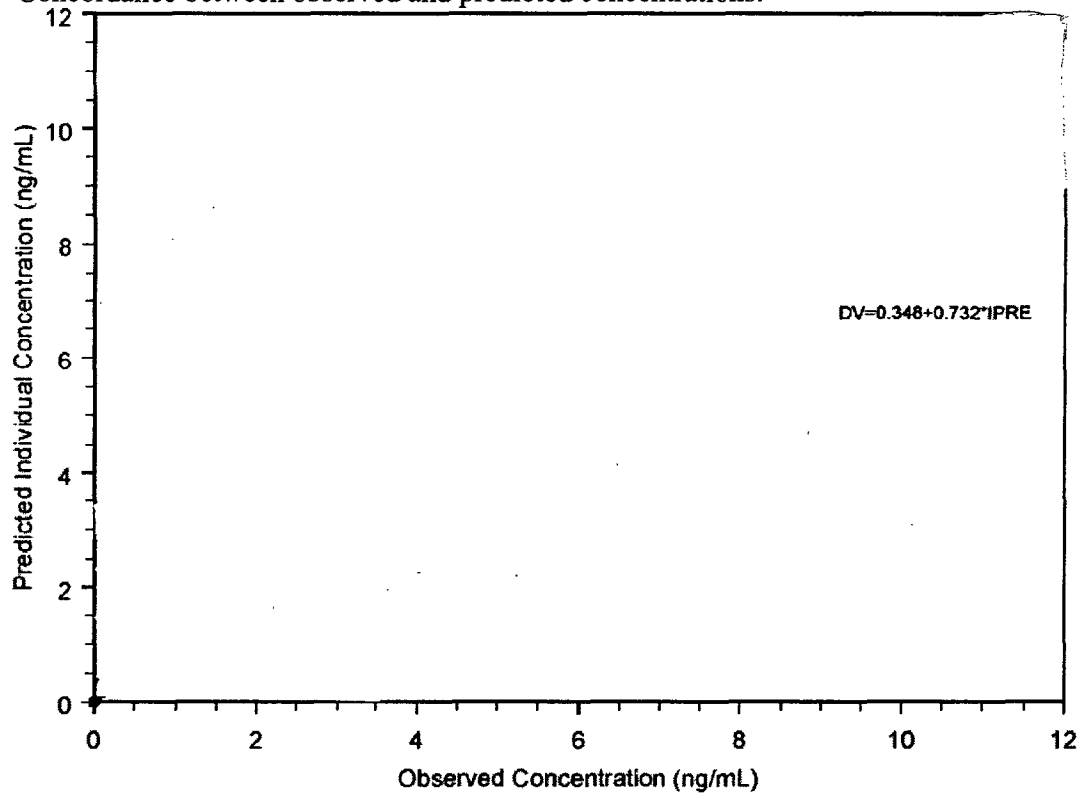
• Sponsor investigated the following covariates: metabolic inhibitors (CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4,5,7), metabolic inducers (CYP1A2, CYP2B6, CYP2C19 and CYP3A4,5,7), and concomitant medications undergoing active renal secretion. Sponsor did not investigate inhibitory effects of 2E1, 2C19 or 2A6.

• The following metabolic inhibitors and inducers and drugs eliminated by active renal secretion were identified as concomitant medications administered within 3 days of administration of trospium chloride at Visits 1, 2 or 3:

-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.

• Concordance between observed and predicted concentrations:



C. Consult Review (including Pharmacometric Reviews)

Refer to Cardiorenal consult reviews on DFS.

D. Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information

NDA Number	21-595	Brand Name	Tropaxa™
OCPB Division (I, II, III)	DPE II (HFD 870)	Generic Name	trospium chloride
Medical Division	DRUDP (HFD 580)	Drug Class	antispasmodic, antimuscarinic
OCPB Reviewer	Leslie Kenna, Ph.D.	Indication(s)	overactive bladder
OCPB Team Leader	Ameeta Parekh, Ph.D.	Dosage Form	20 mg tablet
		Dosing Regimen	20 mg tablet twice a day
Date of Submission	April 28, 2003	Route of Administration	oral
Estimated Due Date of OCPB Review		Sponsor	Indevus Pharmaceuticals
PDUFA Due Date	February 23, 2004	Priority Classification	1S
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			Electronic submission
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	7		
Blood/plasma ratio:	X	2		
Plasma protein binding:	X	2		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	10		
multiple dose:	X	5		
Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:	X	2		
fasting / non-fasting multiple dose:	X	2		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		
In-vivo effects of primary drug:				
In-vitro:	X	7		
Subpopulation studies -				
ethnicity:	X	1		
gender:	X	3		
pediatrics:				
geriatrics:	X	2		
renal impairment:	X	1		
hepatic impairment:				
PD:				
Phase 2:	X	2		
Phase 3:	X	5		
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2		
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:				
Data sparse:	X	1		
II. Biopharmaceutics				
Absolute bioavailability:	X	2		

Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics	X	1		
Pediatric development plan				
Literature References	X			
Total Number of Studies		20		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		• Sponsor should provide data relevant to the Human Pharmacology and Bioavailability/Bioequivalence section in SAS transport file format. The studies of specific interest are MP94D2.13 MP94D2.05, MP94D2.10, MP94D4.02, MP94D2.07, MP94D2.12, MP94D2.08, MP94D2.11, MP94D2.02, IP631-004, MP194/68, and MP194/26. • The population PK study (IP631-004) suggests a potential interaction between trospium chloride and CYP 2C9 inhibitors. The significance of this result will be a review issue. The need for a drug-drug interaction study to investigate the result further will also be a review issue. • An investigation of the effect of trospium chloride on QT interval was provided. Whether or not the results are significant will be a review issue. • Bridging information linking the clinical trial and to-be-marketed formulations has been provided.
QBR questions (key issues to be considered)	• Dose proportionality • Change in PK parameters with chronic dosing • Food effects • Influence of renal impairment • Drug interactions (e.g. CYP2C9 inhibitors) • Interaction with renally eliminated drugs • Gender effects • Chronopharmacokinetics • Exposure-response of trospium chloride • Effect on QT interval	
Other comments or information not included above	To verify the metabolites observed in the mass balance study using [^{3}H]-trospium chloride, sponsor is conducting a second human mass balance study using [^{14}C]-trospium chloride. Sponsor will present the results of this study in the 120-day safety update.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Leslie Kenna
5/26/04 04:44:41 PM
BIOPHARMACEUTICS

Ameeta Parekh
5/27/04 07:27:07 AM
BIOPHARMACEUTICS
I concur