

**Drug Products: 20 mg trospium chloride**

• Treatment B

\_\_\_\_\_ Batch no: 827 976

• Treatment A and Treatment D

Spasmo-lyt \_\_\_\_\_

Batch no: 8391146

• Treatment C

Spasmo-lyt \_\_\_\_\_ )

Batch no: 8425149

**Methods**

- HPLC with \_\_\_\_\_ determination of concentrations.
- LOQ was ( \_\_\_\_\_ for trospium chloride.
- Test procedure: no difference if 90% CI  
 $0.5 < \text{mean(AUC test)/mean(AUC reference)} < 2.0$   
 $0.5 < \text{mean(Cmax test)/mean(Cmax reference)} < 2.0$

**Results**

- In period C, 4/8 subjects had Cmax values above LOQ
- In period C, 2/8 subjects had data to estimate a terminal half life
- For subjects with Cmax = LOQ:  
Cmax set to  $\frac{1}{2}$  LOQ, \_\_\_\_\_  
AUC set to 0.3 ng/mLhrs
- Summary statistics on tmax, tlast, MRTlast only computed on subjects who had data.  
No summary statistics on other parameters.
- Note that there were no corrections to the statistics for multiple comparisons.
- Table 1 reports the bioavailability evaluations for Spasmo-lyt (reference) to \_\_\_\_\_ (test).

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- Physical activity
- GI transit

Info from this study may identify opportunities to improve bioavailability via modified release formulations.

2. The following PK information has been gathered in young males 18-40 years of age.

- Poorly absorbed;  $F=10\%$
- After i.v. infusion, 49% excreted via kidneys as total trospium ( \_\_\_\_\_ ) within 72 hours.
- After p.o. dosing 20 mg to 60 mg, 6 to 7% total trospium recovered in urine within 72 hours.
- $t_{max} = 4$  to 5 hours for 20 mg trospium chloride
- Terminal  $t_{1/2} = 12$  hours
- Mean total clearance = 880 mL/min; renal clearance contributes 434 mL/min

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**Study MP94D2.10: Investigation of the trospium chloride plasma concentration/time profiles following single and multiple oral dosing with Spasmo-lyt® -Dragees in healthy volunteers**

**Summary**

- Tmax and Cmax decrease from 5.33 hours to 4.42 hours and from 3.45 ng/mL to 2.26 ng/mL, respectively, with steady state dosing (35% reduction).
- AUC and Ae/dose were 50-60% lower at steady state compared to the value observed after single dose administration, thus, accumulation not expected to occur upon multiple dosing
- Adverse event profile did not correlate with the lowered exposure at steady state:
  - 5/12 volunteers experienced adverse events after the single dose administration (primarily dry mouth)
  - 8/12 volunteers reported adverse events after steady state administration (primarily dry mouth, headache, and flatulence)
- T1/2 was equivalent for single and multiple dosing regimens (18.33 versus 19.42 hours, respectively). Steady state was likely to have been reached by Study Day 6.

**Objective**

To investigate the pharmacokinetics and urinary excretion of trospium chloride after single and multiple dosing of trospium chloride in man

**Design**

- Open, single center, single/multiple-dose (6 days), sequential parallel group design
- 9-day washout period between single dose and the first multiple dose
- N=12 healthy males, 19-40 years
- No food intake 10 hours prior to trial medication administration
- Test products
  - Trospium chloride 20 mg single oral tablet, Lot No. 4353060 (Period I),
  - Trospium chloride 20 mg oral tablet b.i.d., Lot No. 4353060 (Period II)
- Blood plasma concentrations of trospium chloride:
  - Period I: predose and up to 72 hours postdose; frequent sampling
  - Period II: predose and up to 192 hours postdose; trough and one full day sampling
- Urine concentrations of trospium chloride
  - Period I: predose and up to 72 hours postdose
  - 4 hour intervals to 48 hours, 6 hour intervals thereafter
  - Period II: subsequent to the last dose
- Noncompartmental pharmacokinetic analysis

**Results**

**1. Single-dose pharmacokinetics**

- Mean Tmax: 5.33 hours (range=3-7 hours; standard deviation=1.23 hours)
- Mean Cmax: 3.45 ng/mL (range=                      standard deviation=4.03 ng/mL)

| Period I                       | single dose: 20 mg                                      |                        |                        |                  |                               |
|--------------------------------|---|------------------------|------------------------|------------------|-------------------------------|
|                                | AUC <sub>0-∞</sub>                                      | C <sub>max</sub>       | t <sub>max</sub>       | t <sub>1/2</sub> | Ae <sub>(0-∞)</sub> /dose     |
|                                | 36.38 ± 21.8  | 3.45 ± 4.0             | 5.33 ± 1.2             | 18.33 ± 3.2      | 4.06 ± 1.3                    |
| Period II                      | multiple dose: 20 mg b.i.d. on days 1-5; 20 mg on day 6 |                        |                        |                  |                               |
|                                | SS<br>AUC <sub>(120-132)</sub>                          | SS<br>C <sub>max</sub> | SS<br>t <sub>max</sub> | t <sub>1/2</sub> | Ae <sub>(120-132)</sub> /dose |
|                                | 17.74 ± 5.5   | 2.26 ± 0.7             | 4.42 ± 1.6             | 19.42 ± 5.0      | 2.27 ± 0.8                    |
| Units                          | ng x ml <sup>-1</sup> x h                               | ng x ml <sup>-1</sup>  | h                      | h                | %                             |
| Ratio<br>period II<br>period I | 0.488   | 0.655                  | 0.829                  | 1.059            | 0.559                         |

## 2. Multiple dose pharmacokinetics

- Mean Tmax: 4.42 hours (range: 1.0-6.0 hours; standard deviation=1.56 hours)
- Mean Cmax: 2.26 ng/mL (range= \_\_\_\_\_ standard deviation= 0.73 ng/mL)
- AUC and Ae/dose were 50-60% lower at steady state compared to the value observed after single dose administration

## 3. Tolerability

- 5/12 volunteers experienced adverse events after the single dose administration (primarily dry mouth)
- 8/12 volunteers reported adverse events after steady state administration (primarily dry mouth, headache, and flatulence)
- Sponsor claims no serious adverse events were reported

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## Study MP94D2.11

### Open, Cross-Over, Four-Way, Two Sequence Study To Determine The Pharmacokinetic Profile Of Trospium Chloride In Elderly, Healthy Subjects With Single And Multiple Dose Administration Of Spasmo-lyt®, Stratified According To Sex And Hormone Replacement Therapy

#### Questions

- Significance of adverse event in — 07?
- Where are — 07's PK data?
- Significance of one subject with outlying relative bioavailability?

#### Summary

- After multiple dose administration, AUC and Cmax are 26% and 68%, respectively, higher in women without hormone replacement therapy than males. AUC and Cmax are equivalent between women taking hormone replacement therapy and males.
- Tmax, occurs earlier and half life is 40% greater in both female subgroups relative to males.
- Differences in response due to gender cannot be explained by weight.
- The average relative bioavailability calculated from AUC values for multiple dose administration relative to single dose administration 20 mg trospium chloride was 1.1 (90% CI: 0.85-1.35). In one subject— — 07—relative bioavailability was estimated as 6.47.
- No difference in urinary excretion observed for any of the strata.
- Note that 84.2% of subjects experienced dry mouth on the multiple dose regimen as compared to 38.9% after a single dose. Note also that a greater percent of subjects experienced obstipation, inability to micturate, blurred vision, difficulty swallowing, headache, nausea, vomiting, dizziness, and heart palpitation on the multiple dose regimen as compared to the single dose regimen.
- All adverse events reported in the single dose phase except for one moderate incident of dry mouth were of a mild nature.
- The adverse events reported during the multiple-dose period were approximately split as of a mild and of a moderate nature. There was one reporting of a strong incidence of dry mouth.
- One subject (— 07) discontinued the study due to a serious adverse event and required 15 days of hospitalization. The subject experienced vertigo, garbled speech, an increase in blood pressure that required administration of nifedipine, difficulty with micturation, vomiting, diarrhea, dry mouth, headache and sensitivity to light. The hypertension was improved, but not reversed, two days after hospitalization. The vertigo and unclear speech was present until 15 days after the last dose of study drug was administered. This subject was replaced and the subjects' data did not contribute to the PK analysis.

#### Objective

- Determine the pharmacokinetic parameters AUC, Cmax, tmax, t½, and MRT and evaluate safety and tolerability of single and multiple doses of Spasmo-lyt® (trospium chloride) in healthy elderly males and females (with and without hormone replacement therapy)



**\*\*Median value (range)**

**Pharmacokinetic Parameter Estimates.** Two values given because treatment studied in change-over fashion.

- The following table reports the PK parameters broken down by strata and by period. Note that it combines the data from the two periods in which the regimen was repeated in a given subject.

|                        | SINGLE DOSE       |                    |                    | MULTIPLE DOSE      |                     |                     |
|------------------------|-------------------|--------------------|--------------------|--------------------|---------------------|---------------------|
|                        | Males             | Females w/o HRT    | Females w/ HRT     | Males              | Females w/o HRT     | Females w/ HRT      |
| <b>AUC (ng*hr/mL)*</b> | 16.12<br>(7.8)    | 19.3<br>(15.12)    | 13.54<br>(7.4)     | 14.93<br>(5.02)    | 18.85<br>(10.21)    | 14.21<br>(3.56)     |
| <b>Cmax (ng/mL)*</b>   | 1.45<br>(0.4)     | 2.6<br>(3.0)       | 1.23<br>(0.8)      | 1.76<br>(0.6)      | 2.95<br>(1.9)       | 1.70<br>(0.5)       |
| <b>tmax (hr)**</b>     | 4.8<br>(2.5,7.0)  | 1.25<br>(1.0,3.0)  | 4.0<br>(2.0,5.5)   | 4.2<br>(2.0,6.4)   | 1.6<br>(0.5,3.5)    | 3.1<br>(1.3,7.1)    |
| <b>t½ (hr)**</b>       | 9.5<br>(5.4,11.4) | 11.7<br>(9.2,12.5) | 10.7<br>(4.4,19.3) | 10.3<br>(6.2,12.0) | 15.0<br>(10.9,16.8) | 14.8<br>(13.3,17.1) |

\*Mean value (standard deviation)

\*\*Median value (range)

**Pharmacokinetic Parameter Estimates.** Combines data from the two change-over periods.

Note that exposure (Cmax and AUC) is greater in females without HRT than females w/ HRT and males.

- Based on the previous table, the following table reports the relative change in parameters between single and multiple dosing.

|                        | MULTIPLE DOSE / SINGLE DOSE |                 |                |
|------------------------|-----------------------------|-----------------|----------------|
|                        | Males                       | Females w/o HRT | Females w/ HRT |
| <b>AUC (ng*hr/mL)*</b> | 0.93                        | 0.98            | 1.05           |
| <b>Cmax (ng/mL)*</b>   | 1.21                        | 1.13            | 1.38           |

\*Mean value (standard deviation)

\*\*Median value (range)

**Relative Change in Pharmacokinetic Parameter Estimates With Multiple Dosing.**

- The following table shows the parameters as estimated by pooling all strata for each of the two regimens (single and multiple dose).

|                        | SINGLE DOSE      | MULTIPLE DOSE    |
|------------------------|------------------|------------------|
| <b>AUC (ng*hr/mL)*</b> | 13.99<br>(63,59) | 15.00<br>(36,16) |
| <b>Cmax (ng/mL)*</b>   | 1.38<br>(73,61)  | 1.93<br>(44,22)  |
| <b>tmax (hr)**</b>     | 3.5<br>(72,77)   | 3.2<br>(90,60)   |
| <b>t½ (hr)*</b>        | 10.2<br>(36,42)  | 12.8<br>(28,22)  |

\*Geometric mean (interindividual, intraindividual CV%)

\*\*Arithmetic mean (interindividual, intraindividual CV%)

Note that body weight normalized C<sub>max</sub> and AUC values showed no reduction in variability. Sponsor claims there was no difference between strata for C<sub>max</sub> and C<sub>max,norm</sub> nor AUC and AUC<sub>norm</sub>.

- The following table illustrates the relative exposure to drug after multiple versus single doses in all subjects.

|                           | MULTIPLE DOSE / SINGLE DOSE |
|---------------------------|-----------------------------|
| AUC (ng*hr/mL)*           | 1.07                        |
| C <sub>max</sub> (ng/mL)* | 1.07                        |

- The following table shows the confidence intervals on C<sub>max</sub>.

| parameter                    | 90% confidence interval |             | point estimate |
|------------------------------|-------------------------|-------------|----------------|
|                              | lower bound             | upper bound |                |
| C <sub>max</sub> (n = 18)    | 1.11                    | 1.77        | 1.40           |
| C <sub>max</sub> (men)       | 0.91                    | 1.56        | 1.19           |
| C <sub>max</sub> (women hrt) | 0.72                    | 3.81        | 1.66           |
| C <sub>max</sub> (women)     | 1.03                    | 1.91        | 1.40           |

- The average relative bioavailability (reported below) calculated from AUC values for multiple dose administration relative to single dose administration 20 mg trospium chloride was 1.1 (90% CI: 0.85-1.35). In one subject—07—relative bioavailability was estimated as 6.47. This outlying value is the rationale for reporting of a nonparametric point estimate and confidence interval.

| parameter       | 90% confidence interval |             | point estimate |
|-----------------|-------------------------|-------------|----------------|
|                 | parametric              |             |                |
|                 | lower bound             | upper bound |                |
| AUC (n = 18)    | 0.85                    | 1.35        | 1.07           |
| AUC (men)       | 0.73                    | 1.24        | 0.95           |
| AUC (women hrt) | 0.54                    | 2.83        | 1.24           |
| AUC (women)     | 0.83                    | 1.32        | 1.05           |
| nonparametric   |                         |             |                |
| AUC (n=18)      | 0.86                    | 1.19        | 1.01           |

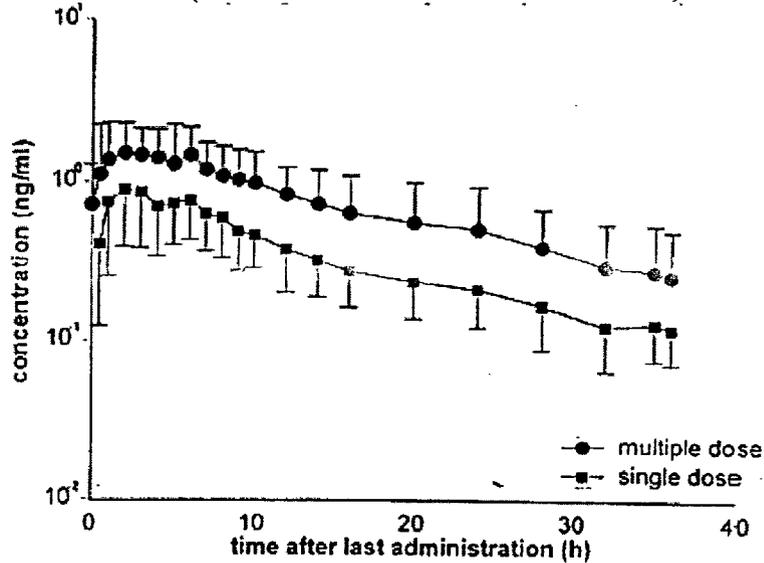
- The following table reports the PK parameters relative to those observed in males broken down by strata and by period. Note that it combines the data from the two periods in which the regimen was repeated in a given subject.

|                           | SINGLE DOSE |                 |                | MULTIPLE DOSE |                 |                |
|---------------------------|-------------|-----------------|----------------|---------------|-----------------|----------------|
|                           | Males       | Females w/o HRT | Females w/ HRT | Males         | Females w/o HRT | Females w/ HRT |
| AUC (ng*hr/mL)*           | 1           | 1.20            | 0.84           | 1             | 1.26            | 0.95           |
| C <sub>max</sub> (ng/mL)* | 1           |                 |                | 1             |                 |                |
| t <sub>max</sub> (hr)**   | 1           | 0.26            | 0.83           | 1             | 0.38            | 0.74           |
| t <sub>1/2</sub> (hr)**   | 1           | 1.23            | 1.13           | 1             | 1.46            | 1.44           |

\*For single dose administration, AUC and C<sub>max</sub> are 20% and 80%, respectively, higher in women without hormone replacement therapy than males. There is a 15% decrease in both AUC and C<sub>max</sub> for women taking hormone replacement therapy compared to males.

\*For multiple dose administration, AUC and C<sub>max</sub> are 26% and 68%, respectively, higher in women without hormone replacement therapy than males. AUC and C<sub>max</sub> are equivalent between women taking hormone replacement therapy and males.

- Overall results (combines data from males and females; w/ and w/o HRT):



Geometric Mean (+/- SD) of Plasma Concentrations Following Single and Multiple Doses; All Volunteers.

|   | AUC [ng·h/ml] | C <sub>max</sub> [ng/ml] | t <sub>max</sub> [h]<br>(arithmetic mean) | t <sub>1/2z</sub> [h] |
|---|---------------|--------------------------|---|-----------------------|
| <i>period A - single dose</i>                 |               |                          |   |                       |
| geometric mean                                | 13.99         | 1.38                     | 3.48                                      | 10.19                 |
| intraindividual coefficient of variation (CV) | 59%           | 61%                      | 77%                                       | 42%                   |
| interindividual CV                            | 63%           | 73%                      | 72%                                       | 36%                   |
| <i>period B - multiple dose</i>               |               |                          |   |                       |
| geometric mean                                | 15.00         | 1.93                     | 3.2                                       | 12.75                 |
| intraindividual coefficient of variation (CV) | 16%           | 22%                      | 60%                                       | 22%                   |
| interindividual CV                            | 36%           | 44%                      | 90%                                       | 28%                   |

- No difference in urinary excretion for any of the strata
- Results broken down by strata:

| Strata                      | C <sub>max</sub><br>[ng/ml] | t <sub>max</sub><br>[h] | AUC <sub>0-∞</sub><br>[ng*h/ml] | AUC<br>[ng*h/ml] | MRT<br>[h] | t <sub>1/2z</sub><br>[h] |
|-----------------------------|-----------------------------|-------------------------|---------------------------------|------------------|------------|--------------------------|
| men<br>(subject 1-6)        |                             |                         |                                 |                  |            |                          |
| Min                         |                             |                         |                                 |                  |            |                          |
| Max                         |                             |                         |                                 |                  |            |                          |
| GeoMean                     | 1.54                        | 4.90                    | 13.75                           | 15.21            | 12.58      | 7.55                     |
| CV                          | 0.71                        | 0.74                    | 0.74                            | 0.71             | 0.21       | 0.39                     |
| Mean                        | 1.82                        | 5.83                    | 16.63                           | 18.29            | 12.82      | 7.99                     |
| SD                          | 1.12                        | 3.71                    | 11.91                           | 13.30            | 2.79       | 2.90                     |
| Median                      | 1.66                        | 5.00                    | 12.66                           | 13.84            | 11.95      | 7.85                     |
| women hrt<br>(subject 7-12) |                             |                         |                                 |                  |            |                          |
| Min                         |                             |                         |                                 |                  |            |                          |
| Max                         |                             |                         |                                 |                  |            |                          |
| GeoMean                     | 1.06                        | 3.08                    | 13.82                           | 16.41            | 18.71      | 12.74                    |
| CV                          | 0.99                        | 1.10                    | 0.55                            | 0.48             | 0.34       | 0.36                     |
| Mean                        | 1.41                        | 4.01                    | 15.48                           | 17.93            | 19.60      | 13.47                    |
| SD                          | 1.16                        | 2.54                    | 8.36                            | 8.45             | 6.47       | 5.35                     |
| Median                      | 0.95                        | 4.50                    | 12.10                           | 15.15            | 18.85      | 11.75                    |
| women<br>(subject 13-18)    |                             |                         |                                 |                  |            |                          |
| Min                         |                             |                         |                                 |                  |            |                          |
| Max                         |                             |                         |                                 |                  |            |                          |
| GeoMean                     | 1.92                        | 1.20                    | 14.73                           | 17.34            | 16.21      | 12.33                    |
| CV                          | 1.09                        | 0.47                    | 0.68                            | 0.62             | 0.30       | 0.23                     |
| Mean                        | 2.90                        | 1.33                    | 17.84                           | 20.40            | 16.77      | 12.59                    |
| SD                          | 3.56                        | 0.82                    | 14.48                           | 15.27            | 4.60       | 2.80                     |
| Median                      | 1.67                        | 1.00                    | 14.04                           | 15.67            | 16.75      | 12.05                    |

Parameter Estimates During One of Two Single Dose Studies.

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| Strata                            | C <sub>max</sub> (ng/ml) | t <sub>max</sub> (h) | AUC <sub>Lz</sub> (ng*h/ml) | AUC (ng*h/ml) | MRT (h) | t <sub>1/2z</sub> (h) |
|-----------------------------------|--------------------------|----------------------|-----------------------------|---------------|---------|-----------------------|
| <b>men</b><br>(subject 1-6)       |                          |                      |                             |               |         |                       |
| Min                               |                          |                      |                             |               |         |                       |
| Max                               |                          |                      |                             |               |         |                       |
| GeoMean                           | 1.29                     | 3.18                 | 13.06                       | 14.60         | 14.55   | 10.12                 |
| CV                                | 0.42                     | 1.24                 | 0.36                        | 0.34          | 0.24    | 0.34                  |
| Mean                              | 1.38                     | 4.12                 | 13.73                       | 15.28         | 14.89   | 10.57                 |
| SD                                | 0.53                     | 2.27                 | 4.56                        | 4.95          | 3.41    | 3.23                  |
| Median                            | 1.27                     | 4.60                 | 13.98                       | 14.90         | 14.35   | 10.80                 |
| <b>women hr</b><br>(subject 7-12) |                          |                      |                             |               |         |                       |
| Min                               |                          |                      |                             |               |         |                       |
| Max                               |                          |                      |                             |               |         |                       |
| GeoMean                           | 0.94                     | 2.85                 | 6.51                        | 7.68          | 13.28   | 8.90                  |
| CV                                | 1.24                     | 1.22                 | 1.83                        | 1.73          | 0.92    | 0.97                  |
| Mean                              | 1.34                     | 3.75                 | 9.74                        | 11.29         | 15.85   | 10.91                 |
| SD                                | 1.19                     | 2.27                 | 6.90                        | 7.91          | 7.41    | 6.00                  |
| Median                            | 1.16                     | 4.00                 | 9.46                        | 11.39         | 16.60   | 9.63                  |
| <b>women</b><br>(subject 13-18)   |                          |                      |                             |               |         |                       |
| Min                               |                          |                      |                             |               |         |                       |
| Max                               |                          |                      |                             |               |         |                       |
| GeoMean                           | 1.79                     | 1.47                 | 13.26                       | 15.46         | 14.47   | 10.49                 |
| CV                                | 0.89                     | 0.74                 | 0.76                        | 0.68          | 0.27    | 0.33                  |
| Mean                              | 2.42                     | 1.83                 | 16.33                       | 18.73         | 15.18   | 10.94                 |
| SD                                | 2.49                     | 1.60                 | 13.06                       | 15.16         | 3.96    | 3.49                  |
| Median                            | 1.64                     | 1.00                 | 13.85                       | 14.58         | 14.85   | 10.17                 |

Parameter Estimates During Another of Two Single Dose Studies.

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| Strata                            | C <sub>max</sub><br>[ng/ml] | t <sub>max2</sub><br>[h] | AUC <sub>t</sub><br>[ng*h/ml] | t <sub>1/2,z</sub><br>[h] |
|-----------------------------------|-----------------------------|--------------------------|-------------------------------|---------------------------|
| <b>men</b><br>(subject 1-6)       |                             |                          |                               |                           |
| Min                               |                             |                          |                               |                           |
| Max                               |                             |                          |                               |                           |
| GeoMean                           | 1.68                        | 3.04                     | 14.97                         | 12.94                     |
| CV                                | 0.37                        | 0.92                     | 0.37                          | 0.35                      |
| Mean                              | 1.77                        | 3.81                     | 14.86                         | 10.14                     |
| SD                                | 0.60                        | 2.44                     | 5.07                          | 3.21                      |
| Median                            | 1.76                        | 3.73                     | 15.20                         | 10.45                     |
| <b>women hr</b><br>(subject 7-12) |                             |                          |                               |                           |
| Min                               |                             |                          |                               |                           |
| Max                               |                             |                          |                               |                           |
| GeoMean                           | 1.64                        | 3.81                     | 13.98                         | 15.99                     |
| CV                                | 0.29                        | 0.60                     | 0.21                          | 0.18                      |
| Mean                              | 1.69                        | 4.41                     | 14.24                         | 16.20                     |
| SD                                | 0.46                        | 2.99                     | 2.95                          | 2.78                      |
| Median                            | 1.70                        | 3.52                     | 14.24                         | 17.30                     |
| <b>women</b><br>(subject 13-18)   |                             |                          |                               |                           |
| Min                               |                             |                          |                               |                           |
| Max                               |                             |                          |                               |                           |
| GeoMean                           | 2.52                        | 1.41                     | 16.99                         | 14.06                     |
| CV                                | 0.55                        | 1.65                     | 0.52                          | 0.25                      |
| Mean                              | 2.85                        | 2.27                     | 18.97                         | 14.41                     |
| SD                                | 1.70                        | 2.04                     | 10.82                         | 3.30                      |
| Median                            | 2.33                        | 1.78                     | 15.25                         | 14.25                     |

Parameter Estimates During One of Two Multiple Dose Studies.

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| Strata                             | $C_{max}$<br>[ng/ml] | $t_{max2}$<br>[h] | $AUC_t$<br>[ng·h/ml] | $t_{1/2,z}$<br>[h] |
|------------------------------------|----------------------|-------------------|----------------------|--------------------|
| <b>men</b><br>(subject 1-6)        |                      |                   |                      |                    |
| Min                                |                      |                   |                      |                    |
| Max                                |                      |                   |                      |                    |
| GeoMean                            | 1.68                 | 4.39              | 14.34                | 9.45               |
| CV                                 | 0.38                 | 0.42              | 0.37                 | 0.22               |
| Mean                               | 1.78                 | 4.69              | 15.13                | 9.63               |
| SD                                 | 0.68                 | 1.83              | 5.45                 | 2.10               |
| Median                             | 1.51                 | 4.52              | 13.15                | 9.31               |
| <b>women hrj</b><br>(subject 7-12) |                      |                   |                      |                    |
| Min                                |                      |                   |                      |                    |
| Max                                |                      |                   |                      |                    |
| GeoMean                            | 1.63                 | 2.21              | 13.76                | 14.28              |
| CV                                 | 0.36                 | 0.90              | 0.33                 | 0.18               |
| Mean                               | 1.71                 | 2.65              | 14.39                | 14.47              |
| SD                                 | 0.59                 | 1.35              | 4.80                 | 2.51               |
| Median                             | 1.59                 | 2.69              | 12.48                | 14.40              |
| <b>women</b><br>(subject 13-18)    |                      |                   |                      |                    |
| Min                                |                      |                   |                      |                    |
| Max                                |                      |                   |                      |                    |
| GeoMean                            | 2.67                 | 1.01              | 17.25                | 14.68              |
| CV                                 | 0.65                 | 0.68              | 0.49                 | 0.27               |
| Mean                               | 3.14                 | 1.17              | 19.00                | 15.13              |
| SD                                 | 2.26                 | 0.68              | 10.04                | 4.11               |
| Median                             | 2.33                 | 1.02              | 16.42                | 14.30              |

**Parameter Estimates During Another of Two Multiple Dose Studies.**

- Differences in response due to gender cannot be explained by weight.
- The following table reports some highlights of the adverse event report in terms of the percent of subjects experiencing the event.

|                        | SINGLE DOSE | MULTIPLE DOSE |
|------------------------|-------------|---------------|
| Obstipation            | 5.6         | 27.8          |
| Vomiting               | 0           | 5.3           |
| Nausea                 | 0           | 5.3           |
| Heart palpitation      | 0           | 11            |
| Diarrhea               | 5.6         | 0             |
| Dizziness              | 0           | 5.3           |
| Headaches              | 11          | 26.3          |
| Difficulty swallowing  | 0           | 5.3           |
| Blurred vision         | 0           | 11            |
| Dry mouth              | 38.9        | 84.2          |
| Skin dryness           | 16.7        | 10.5          |
| Acraturesis            | 0           | 5.3           |
| Swelling of the tongue | 0           | 5.3           |
| Dysphagy               | 0           | 5.3           |
| Inability to micturate | 0           | 5.3           |

Note that 84.2% of subjects experienced dry mouth on the multiple dose regimen as compared to 38.9% after a single dose. Note also that a greater percent of subjects experienced obstipation, inability to micturate, blurred vision, difficulty swallowing,

headache, nausea, vomiting, dizziness, and heart palpitation on the multiple dose regimen as compared to the single dose regimen.

All adverse events reported in the single dose phase except for one moderate incident of dry mouth were of a mild nature.

The adverse events reported during the multiple-dose period were approximately equally reported as a mild and moderate nature. There was one reporting of a strong incidence of dry mouth.

- The following narrative describes one serious adverse event reported. This subject (07) discontinued the study due to this adverse event and required 15 days of hospitalization. The subject experienced vertigo, garbled speech, an increase in blood pressure that required administration of nifedipine, difficulty micturating, vomiting, diarrhea, dry mouth, headache and sensitivity to light. The hypertension was improved, but not reversed, two days after hospitalization. The vertigo and unclear speech was present until 15 days after the last dose of study drug was administered. This subject was replaced and the subjects' data did not contribute to the PK analysis.

According to the randomization plan, volunteer 07 started with period B1 (multiple dose administration of 20 mg trospium chloride). For four days 20 mg trospium chloride twice a day (08:00 am and 08:00 pm) were administered to 07. The only observed adverse event was a weakly present dryness of the mouth. In the evening of day 4, 07 reported the occurrence of a mild diarrhea, a weakly present headache and tiredness. All observed disturbances of the state of health were considered as being non-serious and 07 could continue the study.

In the morning of day 5, 07 reported the diarrhea would no longer persist, but a clearly present dryness of the mouth.

The last dose of 20 mg trospium chloride was administered as planned. The first meal after study drug administration was lunch at 01:15 pm. At 02:00 pm 07 was not able to go to the toilet without help, because a strong vertigo had occurred. The blood pressure was 200 / 110 mmHg, the pulse rate 80 / min. The blood pressure was controlled repeatedly by the clinical subinvestigator, but no improvement was observed. 10 mg Adalat® (nifedipine) were administered orally and the blood pressure declined to 160 / 100 mm Hg. Though the blood pressure improved, the vertigo persisted. Still orientated, 07 additionally started to speak in an unclear manner. No other neurological abnormalities were observed.

At 04:15 pm the ambulance was informed because no improvement of the health status of 07 was observed. 07 started to feel sick and had to vomit after the ambulance arrived. She was directly transported to the emergency ward of the

After the arrival in the 07 reported that she still suffered from a diarrhea and that she had problems to micturate. Also an increased sensitivity to light was observed by her.

Blood analysis, including determination of trospium chloride levels, showed no relevant pathological findings or abnormalities.

Two days after hospitalization the sickness and the diarrhea disappeared. Hypertensive blood pressure values persisted, an improvement was reached after rheological therapy. The unclear speech and the vertigo showed a declining tendency. 07 left the hospital after 15 days (13.02.97). The symptoms have not resolved until now.

- Physical status of volunteer 07 at study entry:

| medical history          | medication                                 | hematology / clinical chemistry | general physical examination   |
|--------------------------|--|---------------------------------|--|
| 1993:<br>Cholecystectomy | hormone replacement therapy with Presomen® | no pathological findings        | blood pressure:<br>1 <sup>st</sup> examination: 180/100 (volunteer was upset)<br>2 <sup>nd</sup> examination after 10 min of rest: 130/80<br>No other pathological findings. |

• Other information on volunteer —07. The sponsor claims that it is improbable that this event was related to study drug.

The following diagnostics were carried out in volunteer —07 after the serious adverse event had occurred:

- Blood sampling: hematology, clinical chemistry
- electrocardiography
- abdominal ultrasonography
- cranial computed tomography
- transcranial Doppler ultrasonography
- Doppler ultrasonography of the A. carotis
- ophthalmological examination
- ENT consultation

Only the CCT, made by the neurologists, gave the impression of an ischemia of the right cerebellum. A hypertensive crisis with encephalopathical manifestation and an extended ischemic attack were discussed.

There was no evidence that the adverse event was related to the study medication, though it has to be considered that the hypertensive crisis could have been a result of the factors

1. stress, caused by the strange situation of the clinical study in an unfamiliar environment
2. volunteer subjectively felt uncomfortable because of the anticholinergic effects of trospium chloride.

An increase of the sympathetic tone might have been resulted in the induction of a hypertensive crisis, which could have lead to an ischemic insult of the cerebellum.

### Background

- Study MP94D2.10 showed that AUC decreased 2-fold at steady state in comparison to after a single dose ( $AUC_{\text{single dose}}: 36.38 \pm 21.8$ ,  $AUC_{\text{ss}}: 17.74 \pm 5.5$ ).
- Study MP94D2.08 showed that there was a large difference in PK between elderly men and women but no statistically relevant difference between young and elderly males.
- The present study (Study MP94D2.11) was designed to determine the PK of trospium chloride after single and multiple dose administration with respect to sex and hormone replacement therapy.

## **Study MP94D2.08**

### **Single-dose study on the pharmacokinetics of trospium chloride in 16 elderly healthy subjects for comparison to former data obtained in young subjects**

#### **Summary**

- Cmax is 35% reduced in elderly males compared and 64% reduced in elderly females compared to young males.
- AUC is equivalent between young and elderly males, but AUC is 40% reduced in elderly females relative to young males.
- Half life is 50% greater in elderly males and 80% greater in elderly females compared to young males. This was significantly different. (16.1 and 16.5 hours in elderly males and females, respectively, versus 10.5 hours in young males.)
- Sponsor claims that AUC and Cmax unaffected by age, however, there is large variability in estimates.
  - Cmax, AUC, and Ae are all approximately 45% lower in elderly females than males. This difference is significant and not explained by a difference in weight.
  - The terminal elimination t<sub>1/2</sub> did not differ significantly between elderly males and females. Cmax was a median of 5-6 hours post-dose.
  - Sponsor suggests that males may have enhanced bioavailability or a different volume of distribution may explain the difference in AUC and Cmax for males versus females. However, there are no data from a crossover study with intravenously and orally administered trospium chloride to young male and female volunteers. Difference does not appear to reflect a difference in metabolism as the level of metabolite similar in males and females.
- Eight episodes of adverse events were observed.
- Three subjects complained about headache, one subject about vomiting, one subject about vertigo, and one subject about problems urinating.

#### **Objective**

- To compare pharmacokinetic parameter of the drug after oral administration to healthy elderly subjects of both sexes to corresponding data from a previous study in young subjects (Investigation on Dose Linearity and Absolute Bioavailability of Trospium Chloride Following Single Oral Dosing with Spasmo-lyt® Dragees in Healthy Volunteers; MP94D2.05)

#### **Design**

- Open, single center, single dose, single group uncontrolled design
- N=16 (8 males, 8 females) healthy subjects, 65-75 years
- Single 40 mg dose of p.o. trospium chloride
- Blood and urine sampled to 48 hours post-dose
- Meals

Day of administration:           fasted for breakfast; lunch at noon, supper at 7 pm

Day 3-4:                               includes breakfast with above meal schedule

#### **Drug Product**

\*Elderly males renally excrete 43% less drug and elderly females renally excrete 67% percent less drug than young males

- The following table summarizes the PK parameter estimates by sex.

|   | males       | females     | statistical significance |
|---|-------------|-------------|--------------------------|
| AUC <sub>0-∞</sub> [ng x h/ml]                    | 88.4 ± 28.8 | 48.9 ± 30.5 | p = 0.017                |
| C <sub>max</sub> [ng/ml]                          | 6.3 ± 3.0   | 3.5 ± 2.4   | p = 0.026                |
| t <sub>1/2</sub> [h]                              | 16.4 ± 3.2  | 17.3 ± 5.5  | p = 0.883                |
| Ae <sub>(0-48h)</sub> (total trospium) [% dose]   | 3.4 ± 1.7   | 2.0 ± 1.3   | p = 0.009                |
| Ae <sub>(0-48h)</sub> (trospium alcohol) [% dose] | 0.23 ± 0.3  | 0.16 ± 0.2  | p = 0.451                |
| ratio trospium alcohol [%]<br>total trospium      | 6.0 ± 4.2   | 7.1 ± 4.3   | p = 0.578                |

The following table summarizes the above changes relative to the value obtained in elderly males:

|                            | Elderly Males<br>(Study MP94D2.08) | Elderly Females<br>(Study MP94D2.08) |
|----------------------------|------------------------------------|--------------------------------------|
| C <sub>max</sub> (ng / mL) | 1                                  | 0.55                                 |
| AUC (ng * hr / mL)         | 1                                  | 0.55                                 |
| t <sub>1/2</sub> (hours)*  | 1                                  | 1.2                                  |
| Ae (micrograms)            | 1                                  | 0.59                                 |
| t <sub>max</sub> (hours)   | 1                                  | 1.1                                  |

Note that:

- An exact statistical comparison of the PK behavior of both age classes including a possibility of an interaction between factors would have required a control group of young females.
- Ae(0-48 h), AUC<sub>0-∞</sub>, and C<sub>max</sub> were significantly higher in elderly male subjects (1258 µg, 84.8 ng/mL.h, and 5.8 ng/mL, respectively) compared to elderly female subjects (671 µg, 39.9 ng/mL.h, and 2.9 ng/mL, respectively). Sex effect not explained by difference in weight.
- C<sub>max</sub>, AUC, and Ae are all approximately 45% lower in elderly females than males. This difference is significant and not explained by a difference in weight.
- The terminal elimination t<sub>1/2</sub> did not differ significantly between the sexes. C<sub>max</sub> was a median of 5-6 hours post-dose.
- The mean C<sub>max</sub> and Ae was 35% and 43% lower in elderly males than young males. There was no difference in AUC.
- No significant age dependent changes of mean Ae(0-48 h), AUC<sub>0-∞</sub>, and C<sub>max</sub> were demonstrated when comparing elderly male subjects to data of young male subjects. However, there was large variability in the estimates.
- Mean T<sub>1/2</sub>, was shorter in young male subjects (10.8 hours) compared to elderly male subjects (16.4 hours).
- Mean half life was not different between elderly males (16.12 hours) and elderly females (16.46 hours).
- The following table lists the pharmacokinetic parameters broken down by age and gender. Note that there is no PK information in young women.

| Pharmacokinetic Parameters |                            |                                  |                                 |                            |                                  |                                 |                            |                                  |                                 |
|----------------------------|----------------------------|----------------------------------|---------------------------------|----------------------------|----------------------------------|---------------------------------|----------------------------|----------------------------------|---------------------------------|
|                            | Young Men                  |                                  |                                 | Elderly Men                |                                  |                                 | Elderly Women              |                                  |                                 |
|                            | Ae <sub>0-12</sub><br>[μg] | AUC <sub>0-12</sub><br>[ng/ml·h] | AUC <sub>0-∞</sub><br>[ng/ml·h] | Ae <sub>0-12</sub><br>[μg] | AUC <sub>0-12</sub><br>[ng/ml·h] | AUC <sub>0-∞</sub><br>[ng/ml·h] | Ae <sub>0-12</sub><br>[μg] | AUC <sub>0-12</sub><br>[ng/ml·h] | AUC <sub>0-∞</sub><br>[ng/ml·h] |
| Mean                       | 2420.1                     | 78.75                            | 82.00                           | 1370.0                     | 79.00                            | 88.38                           | 809.0                      | 43.45                            | 48.88                           |
| SDev                       | 1298.8                     | 36.62                            | 37.16                           | 670.4                      | 26.72                            | 26.81                           | 512.9                      | 29.26                            | 30.52                           |
| CV%                        | 53.7                       | 46.5                             | 45.3                            | 48.9                       | 33.8                             | 30.3                            | 63.4                       | 67.3                             | 62.5                            |
| Min                        |                            |                                  |                                 |                            |                                  |                                 |                            |                                  |                                 |
| Med                        | 2150.6                     | 82.15                            | 89.99                           | 1045.5                     | 76.52                            | 85.26                           | 726.6                      | 35.44                            | 42.38                           |
| Max                        |                            |                                  |                                 |                            |                                  |                                 |                            |                                  |                                 |
| Geom                       | 2099.4                     | 65.87                            | 69.41                           | 1259.7                     | 75.13                            | 84.81                           | 671.2                      | 34.19                            | 39.85                           |

| Pharmacokinetic Parameters |                             |                      |                      |                             |                      |                      |                             |                      |                      |
|----------------------------|-----------------------------|----------------------|----------------------|-----------------------------|----------------------|----------------------|-----------------------------|----------------------|----------------------|
|                            | Young Men                   |                      |                      | Elderly Men                 |                      |                      | Elderly Women               |                      |                      |
| Subject                    | C <sub>max</sub><br>[ng/ml] | t <sub>max</sub> [h] | t <sub>1/2</sub> [h] | C <sub>max</sub><br>[ng/ml] | t <sub>max</sub> [h] | t <sub>1/2</sub> [h] | C <sub>max</sub><br>[ng/ml] | t <sub>max</sub> [h] | t <sub>1/2</sub> [h] |
| Mean                       | 9.73                        | 5.58                 | 10.81                | 6.31                        | 5.13                 | 16.38                | 3.54                        | 4.63                 | 17.30                |
| SDev                       | 5.92                        | 0.67                 | 2.82                 | 2.99                        | 0.99                 | 3.16                 | 2.42                        | 2.13                 | 5.45                 |
| CV%                        | 60.9                        | 12.0                 | 26.1                 | 47.4                        | 19.3                 | 19.3                 | 68.4                        | 46.1                 | 31.5                 |
| Min                        |                             |                      |                      |                             |                      |                      |                             |                      |                      |
| Med                        | 9.72                        | 6.00                 | 10.52                | 5.66                        | 5.00                 | 15.99                | 2.84                        | 5.50                 | 19.21                |
| Max                        |                             |                      |                      |                             |                      |                      |                             |                      |                      |
| Geom                       | 7.13                        |                      | 10.50                | 5.83                        |                      | 16.12                | 2.89                        |                      | 16.46                |

- Sponsor suggests that males may have enhanced bioavailability or a different volume of distribution may explain the difference in AUC and C<sub>max</sub> for males versus females. However, there are no data from a crossover study with intravenously and orally administered trospium chloride to young male and female volunteers. Difference does not appear to reflect a difference in metabolism as the level of metabolite similar in males and females.
- Eight episodes of adverse events were observed.
- Three subjects complained about headache, one subject about vomiting, one subject about vertigo, and one subject about problems urinating.
- One subject (subject 8) had a headache 4 hours post-dose; the second (subject 10) had a headache 10 hours post-dose, and the third (subject 12) had a headache 23 hours post-dose. Subject 10 also vomited 4 hours post-dose.
- Subject 9 had two episodes of vertigo; the first 8 hours post-dose, the second 23 hours post-dose. The total duration of vertigo was 160 hours.
- Subject 6 had difficulty urinating eleven hours post-dose. The symptom lasted for 6 hours.

### Background

- A previous PK study in man (MP94D2.05) showed linear dependence of C<sub>max</sub> and AUC in young male volunteers across 20 mg, 40 mg, 60 mg doses.
- Young male volunteers: t<sub>1/2</sub> ranges from 7.7 to 17.5 hours

## Study MP94D2.07

### A Single Dose Two-Way Crossover Investigation on the Pharmacokinetics of Trospium Chloride Under Fasting Conditions and After Concomitant Intake of a High-Fat Meal

#### Summary

- This study failed to demonstrate bioequivalence between the fed and fasted states.
- High fat breakfast intake reduced bioavailability 74% and reduced Cmax 84%.

#### Objective

- Determine influence of food intake (fed versus fasted) on single dose trospium chloride PK

#### Design

- Two-way crossover study, single dose (40 mg)
- N=12 healthy male volunteers on each arm (N=24 total), 21-35 years
- Fasted state versus immediately after high-fat breakfast
- Fasting state from 9 pm before study date. Single dose to all subjects at 7 am.
- Fed subjects: High fat breakfast at 6:30 am. Lunch at noon. Dinner at 7pm.
- Sampling times: 0,0.5,1,2,3,4,5,6,7,8,9,10,12,14,16,18,20,24,28,32,36,40,44,48 hrs
- High fat meal content (fed subjects, study day 1):

|                  | Protein (g) | Fat (g) | Carbohydrate (g) |
|------------------|-------------|---------|------------------|
| <b>Breakfast</b> | 23          | 75      | 64               |
| <b>Lunch</b>     | 51          | 28      | 57               |
| <b>Dinner</b>    | 22          | 41      | 58               |
| <b>Total</b>     | 96          | 144     | 179              |

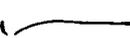
- Meal content after first study day (fasted and fed subjects)

|                  | Protein (g) | Fat (g) | Carbohydrate (g) |
|------------------|-------------|---------|------------------|
| <b>Breakfast</b> | 15          | 41      | 70               |
| <b>Lunch</b>     | 51          | 28      | 57               |
| <b>Dinner</b>    | 22          | 41      | 58               |
| <b>Total</b>     | 88          | 110     | 185              |

#### Drug Product

- Test A: Fed condition
  - Two 20 mg film-coated tablets (Spasmo-lyt); (40 mg trospium chloride)
  - Lot no. 341219, study lot no. 6033082
- Test B: Fasted condition
  - Two 20 mg film-coated tablets (Spasmo-lyt); (40 mg trospium chloride)
  - Lot no. 341219, study lot no. 6033082

#### Methods

- Plasma measurement via 

- Statistical bioequivalence parameters:  
AUC<sub>0→∞</sub>, Cmax, and HVD (half value duration; hours)
- No food interaction accepted if:  
80% < Nonparametric 90% CI of median<sup>TEST</sup>/median<sup>REFERENCE</sup> AUC<sub>0→∞</sub> < 125%  
and  
70% < Nonparametric 90% CI of median<sup>TEST</sup>/median<sup>REFERENCE</sup> HVD < 143%
- HVD (time span for which plasma concentration exceeds ½Cmax) is regarded as a more reliable characteristic of controlled-release formulations. Used here although immediate release formulation of tiroprium chloride.
- Reason for use of HVD  
In Study MP94D2.10—a single dose study—the majority of subjects had plateau like concentration patterns. Sponsor says this behaved more like a controlled-release formulation.

### Results

A summary of the bioequivalence test parameters are reported in Table 1. This study failed to demonstrate bioequivalence between the fed and fasted states. Thus, food intake is expected to influence drug absorption.

|      | mean (Fed) : mean (Fasted)<br>(90% CI) |
|------|--|
| AUC  | 26%<br>(21,29)                         |
| Cmax | 16%<br>(14,20)                         |
| HVD  | 131%<br>(110,152)                      |

**Table 1. Summary of bioequivalence test parameters.** The product failed to show equivalence for fed and fasted states with respect to all parameters tested.

|        | AUC            | Cmax | tmax           | t½              |
|--------|----------------|------|----------------|-----------------|
| Fed    | 20.1<br>(12.6) | —    | 3.29<br>(1.57) | 15.7<br>(5.46)  |
| Fasted | 87.2<br>(78.7) | —    | 5.00<br>(1.18) | 16.47<br>(7.06) |

**Table 2. Pharmacokinetic Parameters (+/- Standard Deviation) Observed.**

The following summarizes the adverse events observed.

- Nine (9) of twenty four fed subjects (37.5%) had adverse events
- Twenty one (21) of twenty four fasted subjects (87.5%) had adverse events
- Dry mouth and headache were the most common adverse event
- All but two (moderate) adverse events were of a mild nature.

## Study MP94D2.05

### A Study on Dose Linearity and Absolute Bioavailability of Trospium Chloride Following Single Oral Dosing with Spasmolyt® Doses in Healthy Volunteers

#### Summary

- Large standard deviation in C<sub>max</sub> and AUC
- Equivalence of C<sub>max</sub> and AUC for 20, 40, and 60 mg doses by virtue of inability to reject the null hypothesis of their equivalence at p<.05
- Mean absolute bioavailabilities for oral doses of 20, 40, and 60 mg were 9.6%, 10.8%, and 12%, respectively. These values are higher than expected based on previous studies.
- Wide variability in absolute bioavailability (range: 2.6%-26.5%) across all doses tested
- Absolute bioavailability for 20 mg dose: 9.6% (range: \_\_\_\_\_)
- The sponsor reports mean absorption rates for oral doses of 20, 40, and 60 mg were 14.6%, 13.2%, and 14.3%, respectively.
- Information on assay sensitivity and selectivity provided

#### Objective

- Demonstrate the linear dependence of AUC and C<sub>max</sub> for up to 3 times the therapeutic dose.
- Intravenous dose included to allow determination of absolute bioavailability.
- To investigate the pharmacokinetics and urinary excretion of trospium chloride after oral and intravenous administration of trospium chloride in man
- To calculate the absolute bioavailability of trospium chloride released from the test formulation

#### Design

- Single center, randomized, single-dose, 4-way crossover design
- Healthy male volunteers; >18 to <40 years
- Oral doses of trospium chloride: 20 mg, 40 mg, 60 mg
- Intravenous trospium chloride: 1.4 mg infused over 1 hour
- 1 week washout
- Study period: July 17, 1994-August 13, 1994; Germany
- Sponsor claims to use a more sensitive analytic technique ( \_\_\_\_\_ with \_\_\_\_\_ with CV and inaccuracy of <10%.)

Former assay was \_\_\_\_\_ was unable to quantitate levels <0.1 ng/mL.

- Urine analyzed by \_\_\_\_\_ HPLC
- Intense sampling of blood and urine until 72 hours post-dose

#### Drug Product

- 1, 2, or 3 film coated 20 mg tablets [lot no. 341219]
- One single intravenous dose: 1.4 mg trospium chloride [lot no. 419538]

#### Results

##### 1. Dose proportionality

- Table 1, Table 2, Table 3, and Table 4 show various pharmacokinetic parameters as reported by the sponsor. Note that only non-compartmental analyses were performed.

| Dose [mg] | AUC <sub>0-∞</sub> (ng x ml <sup>-1</sup> x h) | C <sub>max</sub> (ng x ml <sup>-1</sup> ) | t <sub>max</sub> [h] | t <sub>1/2</sub> [h] | Ae <sub>0-∞</sub> /dose [%] |
|-----------|--|---|----------------------|----------------------|-----------------------------|
| 20 p.o.   | 37.7 ± 19.2                                    | 3.3 ± 2.1                                 | 4.9 ± 1.4            | 18.4 ± 11.5          | 7.0 ± 4.1                   |
| 40 p.o.   | 84.8 ± 39.2                                    | 9.7 ± 5.9                                 | 5.8 ± 0.7            | 12.1 ± 2.7           | 6.4 ± 3.3                   |
| 60 p.o.   | 134.4 ± 58.9                                   | 14.0 ± 7.4                                | 5.3 ± 1.2            | 12.5 ± 2.2           | 7.1 ± 3.8                   |
| 1.4 i.v.  | 27.7 ± 6.4                                     | 17.5 ± 2.8                                | 0.9 ± 0.1            | 12.0 ± 8.8           | 49.3 ± 9.4                  |

Table 1. Arithmetic mean (+/- SD).

Note in Table 1:

- Sponsor reports that longer t<sub>1/2</sub> in Dose=20 mg p.o. group (18.4 hours) relative to higher doses likely “an accidental outcome” due to “difficulties in fitting the extremely low concentrations in the 20 mg dosing group to a straight line”
- Large standard deviation in C<sub>max</sub> and AUC

| Subject no. | Dose of trospium chloride and route of administration |            |            |   |
|-------------|---|------------|------------|---|
|             | 20 mg p.o.  | 40 mg p.o. | 60 mg p.o. | 1.4 mg i.v.                                 |
|             | Cl <sub>l</sub> / F = dose / AUC <sub>0-∞</sub>       |            |            | Cl <sub>l</sub> = dose / AUC <sub>0-∞</sub> |
| 1           |   |            |            |   |
| 2           |   |            |            |   |
| 3           |   |            |            |   |
| 4           |   |            |            |   |
| 5           |   |            |            |   |
| 6           |   |            |            |   |
| 7           |   |            |            |   |
| 8           |   |            |            |   |
| 9           |   |            |            |   |
| 10          |   |            |            |   |
| 11          |   |            |            |   |
| 12          |   |            |            |   |
| Mean        | 11.60   | 12.53      | 9.83       | 0.68  |
| ± SD        | 6.564   | 12.721     | 7.217      | 0.198                                       |
| CV [%]      | 56.6  | 101.5      | 73.4       | 22.5  |

Table 2. Oral clearance of trospium chloride.

Note:

- Large standard deviation in CL/F

| Subject no. | Dose of trospium chloride and route of administration            |            |            |  |
|-------------|--|------------|------------|--|
|             | 20 mg p.o.   | 40 mg p.o. | 60 mg p.o. | 1.4 mg i.v.  |
|             | V <sub>l</sub> / F = dose / AUC <sub>0-∞</sub> x K <sub>el</sub> |            |            | V <sub>l</sub> = dose / AUC <sub>0-∞</sub> x K <sub>el</sub> |
| 1           |  |            |            |  |
| 2           |  |            |            |  |
| 3           |  |            |            |  |
| 4           |  |            |            |  |
| 5           |  |            |            |  |
| 6           |  |            |            |  |
| 7           |  |            |            |  |
| 8           |  |            |            |  |
| 9           |  |            |            |  |
| 10          |  |            |            |  |
| 11          |  |            |            |  |
| 12          |  |            |            |  |
| Mean        | 17791  | 14095      | 10832      | 814  |
| ± SD        | 16822  | 15894      | 8961       | 514.8  |
| CV [%]      | 94.6   | 112.8      | 82.7       | 63.2   |

Table 3. Volume normalized to bioavailability for trospium chloride.

Note:

- Large standard deviation in V/F

Table 4 shows the dose-proportionality calculations for AUC and Cmax.

|            | AUC <sub>0-∞</sub> /Dose | Cmax/Dose |
|------------|--------------------------|-----------|
| 20 mg p.o. | 1.89                     | 0.165     |
| 40 mg p.o. | 2.12                     | 0.243     |
| 60 mg p.o. | 2.24                     | 0.233     |

Table 4. Dose proportionality of parameters.

The sponsor claims that there is linearity in the pharmacokinetic parameters explored. The sponsor claims that the AUC and Cmax are equivalent for 20 mg, 40 mg, and 60 mg by virtue of the inability to reject the null hypothesis of their equivalence at  $p < .05$ . There was large standard deviation in estimates.

Figures 1-3, plots of the individual and mean plasma concentration profiles for 20, 40, and 60 mg single doses of trospium chloride, respectively, illustrate the variability in exposure between subjects.

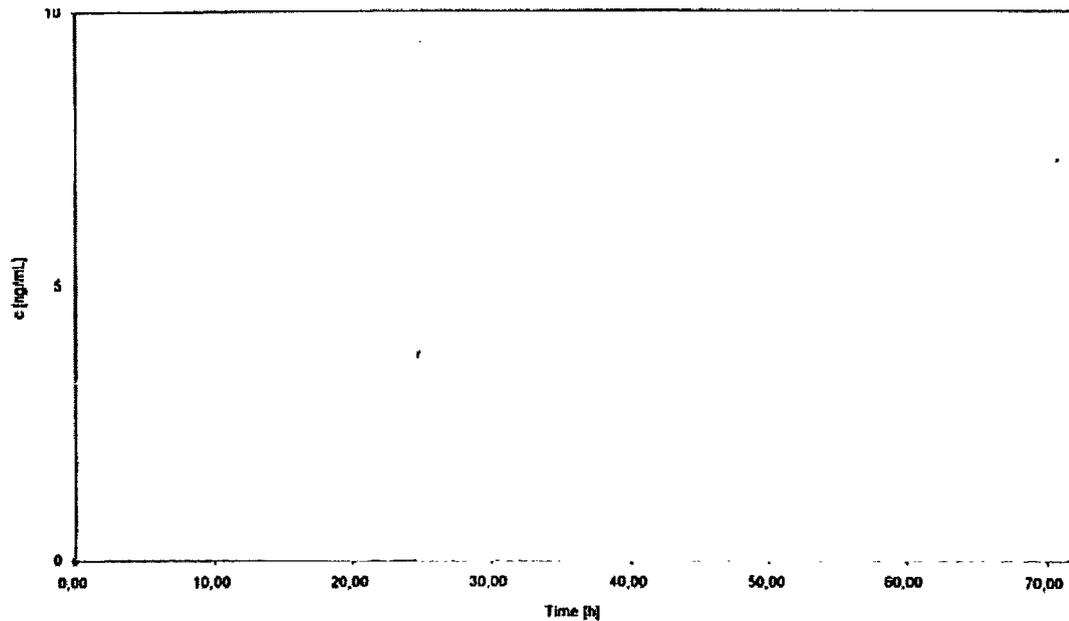
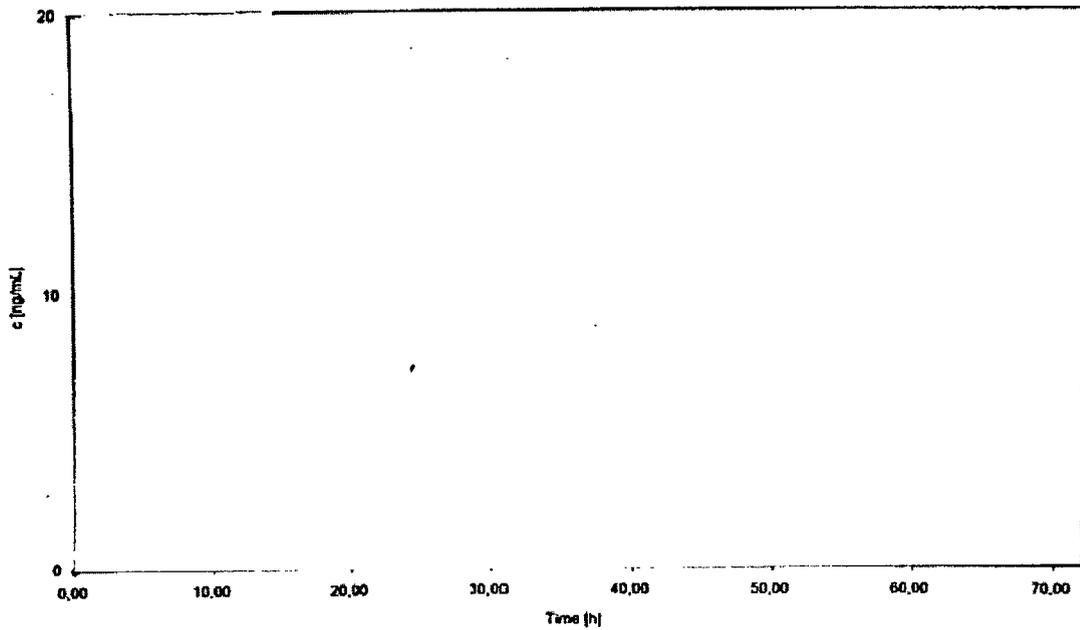
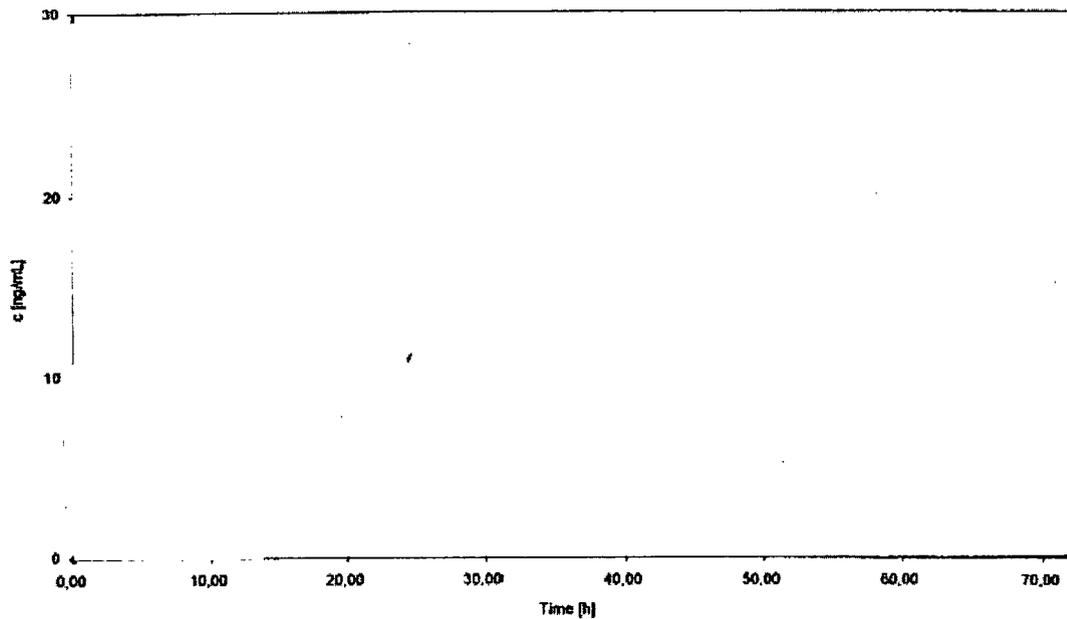


Figure 1. Individual (N=12) and Mean Plasma Concentration Profile for Trospium Chloride After a Single 20 mg Oral Dose.

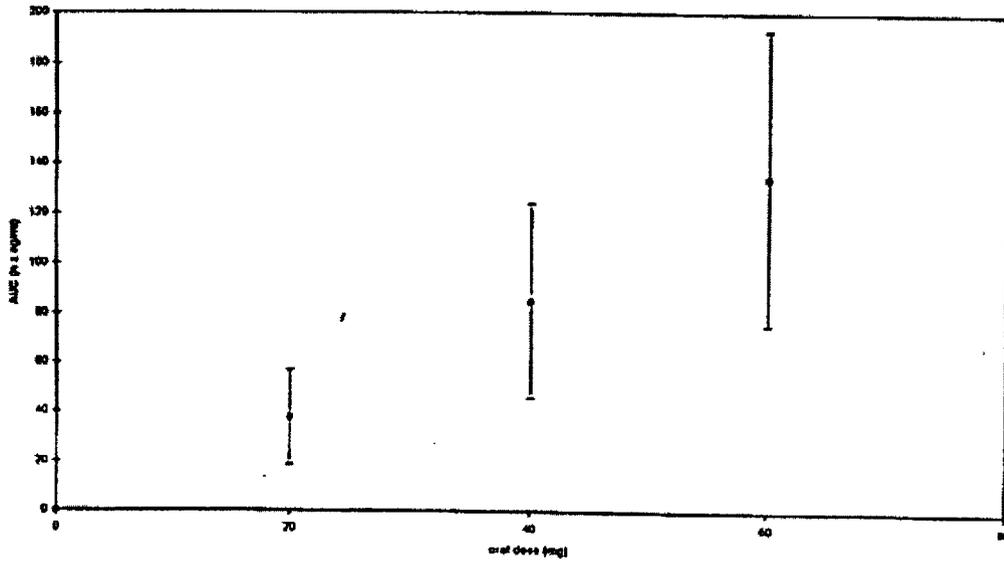


**Figure 2. Individual (N=12) and Mean Plasma Concentration Profile for Trospium Chloride After a Single 40 mg Oral Dose.**



**Figure 3. Individual (N=12) and Mean Plasma Concentration Profile for Trospium Chloride After a Single 60 mg Oral Dose.**

Figure 4, the plot of mean and standard deviation (N=12) in AUC as a function of DOSE, illustrates the linearity of this parameter.



**Figure 4. Mean and Standard Deviation of AUC as a Function of Trospium Chloride Dose.**

**2. Absolute Bioavailability**

- Computed relative to 20 mg p.o. dose
- Wide interindividual variability (range: 2.6%-26.5%)

The sponsor reports mean absolute bioavailabilities for oral doses of 20, 40, and 60 mg were 9.6%, 10.8%, and 12%, respectively.

The sponsor reports that mean absorption rates for oral doses of 20, 40, and 60 mg were 14.6%, 13.2%, and 14.3%, respectively.

| Subject no. | Dose of trospium chloride and route of administration |         |                          |         |                          |         |                          |
|-------------|---|---------|--------------------------|---------|--------------------------|---------|--------------------------|
|             | 20 mg p.o.  |         | 40 mg p.o.               |         | 60 mg p.o.               |         | 1.4 mg i.v.              |
|             | AUC <sub>0-∞</sub> /20mg                              | abs. BA | AUC <sub>0-∞</sub> /20mg | abs. BA | AUC <sub>0-∞</sub> /20mg | abs. BA | AUC <sub>0-∞</sub> /20mg |
| 1           |   |         |                          |         |                          |         |                          |
| 2           |   |         |                          |         |                          |         |                          |
| 3           |   |         |                          |         |                          |         |                          |
| 4           |   |         |                          |         |                          |         |                          |
| 5           |   |         |                          |         |                          |         |                          |
| 6           |   |         |                          |         |                          |         |                          |
| 7           |   |         |                          |         |                          |         |                          |
| 8           |   |         |                          |         |                          |         |                          |
| 9           |   |         |                          |         |                          |         |                          |
| 10          |   |         |                          |         |                          |         |                          |
| 11          |   |         |                          |         |                          |         |                          |
| 12          |   |         |                          |         |                          |         |                          |
| Mean        | 37.68   | 9.61    | 42.39                    | 10.78   | 44.79                    | 11.97   | 395.16                   |
| ± SD        | 19.184  | 4.536   | 19.585                   | 5.230   | 19.649                   | 6.500   | 91.972                   |
| CV (%)      | 50.9  | 47.2    | 46.2                     | 48.5    | 43.9                     | 54.3    | 23.3                     |

**Table 3. Mean and individual values of absolute bioavailability for trospium chloride. Normalized (to 20 mg dose) AUC values and absolute bioavailability (AUC p.o./AUCi.v. for normalized areas).**

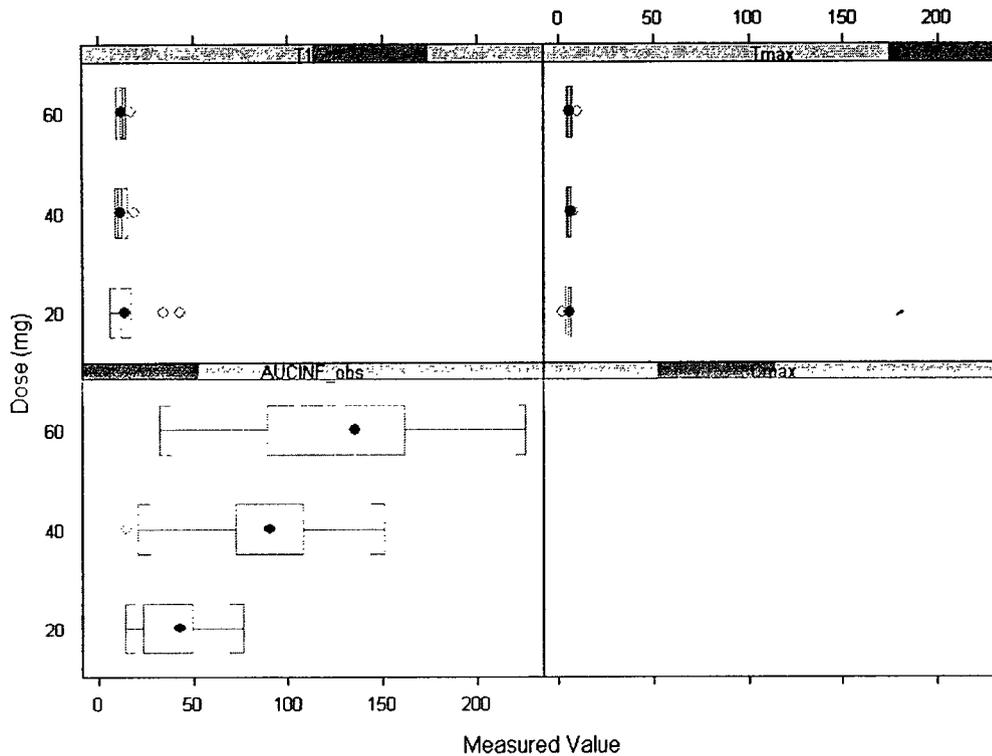
| Subject no. | Dose of trospium chloride and route of administration |            |            |             |
|-------------|---|------------|------------|-------------|
|             | 20 mg p.o.  | 40 mg p.o. | 60 mg p.o. | 1.4 mg i.v. |
|             | AUC <sub>0-∞</sub>                                    |            |            |             |
| 1           |   |            |            |             |
| 2           |   |            |            |             |
| 3           |   |            |            |             |
| 4           |   |            |            |             |
| 5           |   |            |            |             |
| 6           |   |            |            |             |
| 7           |   |            |            |             |
| 8           |   |            |            |             |
| 9           |   |            |            |             |
| 10          |   |            |            |             |
| 11          |   |            |            |             |
| 12          |   |            |            |             |
| Mean        | 37.68   | 84.77      | 134.37     | 27.66       |
| ± SD        | 19.184  | 39.169     | 58.946     | 6.438       |
| CV (%)      | 50.9  | 46.2       | 43.9       | 23.3        |

Table 4. Values of AUC<sub>0-∞</sub>. Note that <sup>1)</sup> indicates that AUC calculated to tlast.

|       | Oral                   |       |       | Intravenous |
|-------|------------------------|-------|-------|-------------|
|       | 20 mg                  | 40 mg | 60 mg | 1.4 mg      |
|       | <b>C<sub>max</sub></b> |       |       |             |
| mean  | 3.3                    | 9.7   | 14.0  | 17.5        |
| sd    | 2.1                    | 5.9   | 7.4   | 2.8         |
| range |                        |       |       |             |
|       | <b>AUC</b>             |       |       |             |
| mean  | 37.7                   | 84.8  | 134.4 | 27.7        |
| sd    | 19.2                   | 39.2  | 58.9  | 6.4         |
| range |                        |       |       |             |

Table 5. Mean, standard deviation, and range in exposure.

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### 3. Tolerability

- Sponsor claims the study medication was tolerated by all (12/12) subjects.

#### Comments

- This is a fairly old study, as evidenced by the following:  
 “For pharmacokinetic calculation of time dependent trospium plasma concentration values in man, the TOPFIT Pharmacokinetic and Pharmacodynamic Data Analysis System for the PC (Version 2.0), published by G. Heinzel, R. Woloszczak, and P. Thomann was used.. The software was installed on an QT 80486 Personal Computer (50 MHz).”
- Metrics of linearity are computed relative to the 20 mg dose only.

### 4. Assay Validation

|                                      |       |       |       |       |        |
|--------------------------------------|-------|-------|-------|-------|--------|
| Trospium chloride added [ng/ml]      | 10    | 25    | 50    | 100   | 250    |
| Mean trospium chloride found [ng/ml] | 10.33 | 24.53 | 49.27 | 99.54 | 251.28 |
| $\Delta$ [%]                         | 3.30  | -1.88 | -1.46 | -0.46 | 0.51   |
| $\pm$ SD                             | 0.554 | 1.033 | 2.293 | 3.879 | 3.988  |
| CV [%]                               | 5.36  | 4.21  | 4.65  | 3.90  | 1.59   |
| n                                    | 50    | 50    | 50    | 50    | 50     |

Accuracy and Precision of Assay for Trospium Chloride in Human Urine.

|                                      |        |
|--------------------------------------|--------|
| Trospium chloride added [ng/ml]      | 50.0   |
| Mean trospium chloride found [ng/ml] | 49.34  |
| $\Delta$ [%]                         | - 1.32 |
| $\pm$ SD                             | 2.641  |
| CV [%]                               | 5.36   |
| n                                    | 50     |

Quality Control Analysis for Assay of Trospium Chloride in Human Urin

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## **Study MP94D2.02 Pharmacokinetics and Bioavailability of Trospium Chloride in Patients with Renal Impairment in Comparison with Healthy Volunteers after Administration of an Oral Dose of 40 mg**

### **Summary**

- Renally impaired subjects: median CL<sub>Cr</sub> = 12.2 mL/min/1.73 m<sup>2</sup>, range: 8.2, 31.9
- Healthy subjects: median CL<sub>Cr</sub> = 85 mL/min/1.73 m<sup>2</sup>, range: 75, 121
- 1.8-fold increase in C<sub>max</sub> for renally impaired
- 4.2-fold increase in AUC for renally impaired
- 35% reduction in amount excreted in renally impaired subjects
- Range on t<sub>max</sub> differs considerably for renally impaired (1 to 12 hours) versus healthy (4 to 7 hours).
- Range on t<sub>1/2</sub> differs considerably for renally impaired (9.9 – 90 hours) versus healthy (5.5 to 50 hours).
- One renally impaired subject (8.3% of subjects) required rescue with a diuretic as a result of minimal urinary voiding.

### **Objective**

- PK, Bioavailability, and tolerability in N=12 with moderate and severe renal impairment versus N=12 young healthy volunteers

### **Design**

- 2 Study centers; Healthy patients in German site, renally impaired patients at Polish site
- Open, parallel group
- Single 40 mg dose administration in fasted state
- N=12 Healthy males: 18-40 years of age
- N=12 Renally impaired males: CL<sub>Cr</sub><40 mL/min/1.73 m<sup>2</sup>
- Demographics: only evaluated in Central European males, mismatch in age for healthy versus renally impaired (18-40 years versus 18-70 years, respectively)
- Excluded renal transplant patients and patients receiving chronic dialysis
- Excluded females
- Required a low protein diet
- Blood sampling scheme:
  - Healthy 0,0.5,1,2,3,4,5,6,7,8,10,12,16,20,24,28,32,36,40,44,48 hours
  - Renally Impaired 0, 1,2,3,4,5,6, 8, 12, 24, 30, 36, 42, 48, 60,72 hours
- Urine sampling scheme:
  - 0-8, 8-16, 16-24, 24-36, 36-48, 48-60, 60-72 hours

### **Drug Product**

- Two 20 mg trospium chloride tablets; Batch no. 512286

### **Methods**

- Plasma quantification of trospium chloride via \_\_\_\_\_
- Urine quantification of total trospium (trospium chloride and trospium alcohol) via HPLC with fluorescence detection.

**Results**

- Table 1 summarizes the creatinine clearance of patients in this study.

|   | <b>Renally Impaired</b> | <b>Healthy</b> |
|---|-------------------------|----------------|
| <b>Mean</b><br>(mL/min/1.73 m <sup>2</sup> )    | 15.3                    | 93.3           |
| <b>SD</b><br>(mL/min/1.73 m <sup>2</sup> )      | 7.4                     | 16.9           |
| <b>Median</b><br>(mL/min/1.73 m <sup>2</sup> )  | 12.2                    | 85.0           |
| <b>Min,Max</b><br>(mL/min/1.73 m <sup>2</sup> ) | 8.2,31.9                | 75,121         |

Table 1. Creatinine Clearance of Subjects.

- Figure 1 shows the creatinine clearance and age of patients in this study.

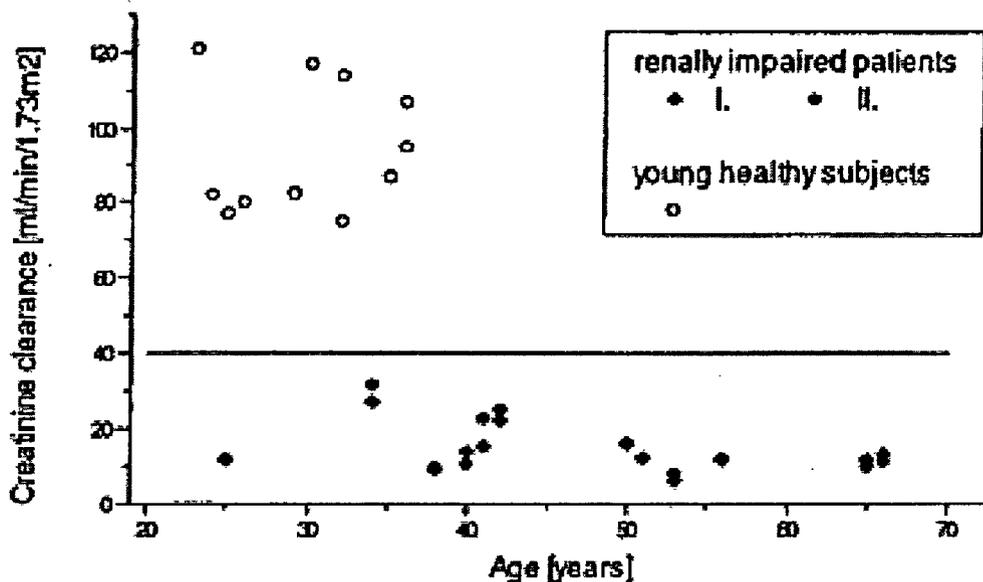


Figure 1. Creatinine Clearance for Subjects in Study.

- Table 2 summarizes the PK in renally impaired subjects.

Note in Table 2:

- Wide variability in PK parameters; greater variability in renal impaired patients
- Range on t<sub>max</sub> and t<sub>1/2</sub> differs considerably for renally impaired versus healthy.
- 35% reduction in amount excreted in renally impaired subjects
- Although difference in A<sub>e</sub> and t<sub>max</sub> not statistically significant, the wide variability suggests that this study may not have been adequately powered to detect a difference.

|  | <b>Renally Impaired</b> | <b>Healthy</b> | <b>Fold Change Impaired:Healthy</b> | <b>Statistically Significant?</b> |
|--|-------------------------|----------------|-------------------------------------|-----------------------------------|
|  |                         |                |                                     |                                   |

|   |                  |                  |      |     |
|---|------------------|------------------|------|-----|
| <sup>a</sup> AUC <sub>0→∞</sub><br>(ng*hr/mL) | 233.1<br>(195.4) | 55.61<br>(68.9)  | 4.2  | Yes |
| <sup>a</sup> Cmax<br>(ng/mL)                  | 10.90<br>(93.4)  | 5.96<br>(60.4)   | 1.8  | Yes |
| <sup>b</sup> tmax<br>(hr)                     | 4.51<br>(3.27)   | 5.25<br>(0.75)   | 0.86 | No  |
| range<br>(hrs)                                | 1 to 12          | 4 to 7           | NA   | NA  |
| <sup>b</sup> t <sub>1/2</sub><br>(hr)         | 33.32<br>(24.63) | 15.19<br>(12.30) | 2.2  | Yes |
| range   |                  |                  | NA   | NA  |
| <sup>a</sup> Ae <sub>0→72</sub><br>(μg)       | 789.2<br>(72.1)  | 1199.3<br>(57.0) | 0.66 | No  |

**Table 2. Pharmacokinetics in Renally Impaired versus Healthy Volunteers.**

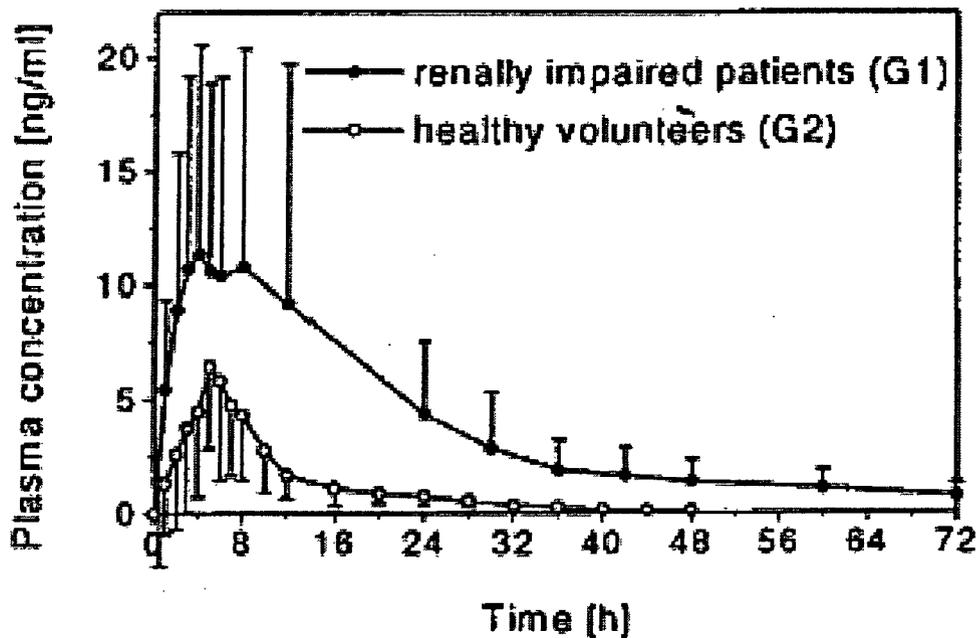
<sup>a</sup>Geometric mean (CV%) for AUC, Cmax, and Ae.

<sup>b</sup>Arithmetic mean (SD) for tmax and t<sub>1/2</sub>.

- Figure 2 shows the concentration-time profile of trospium chloride in trial participants.

Note in Figure 2:

- Higher concentration in renally impaired patients at all time points relative to healthy.
- At least 2 elimination phase slopes



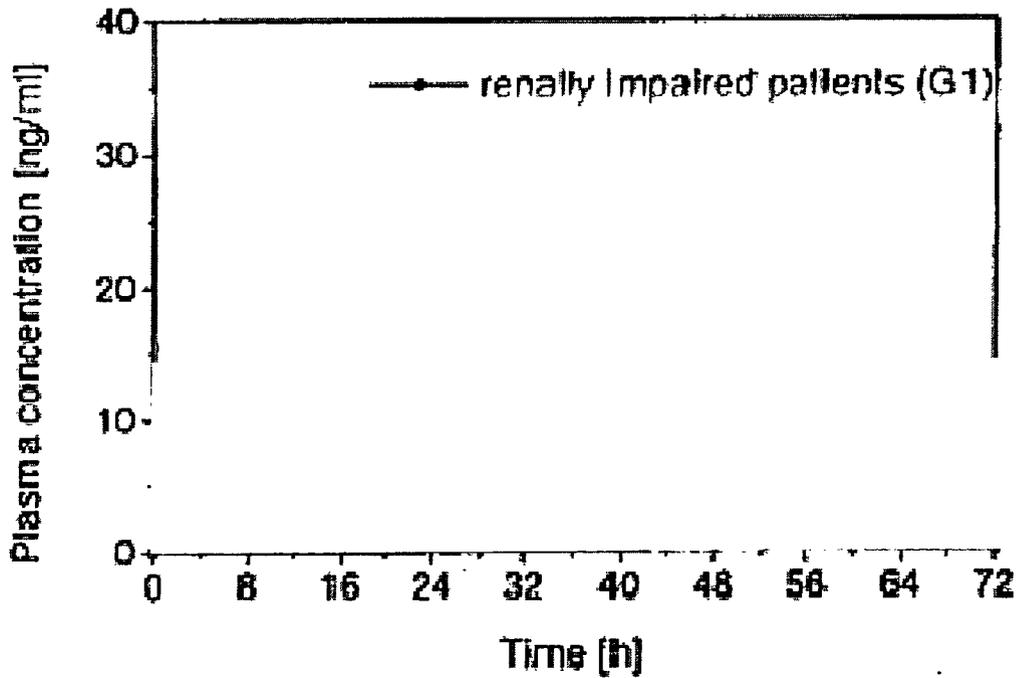
**Figure 2. Mean Plasma Concentration Versus Time Curves (arithmetic mean +/- SD) of Trospium Chloride In Renally Impaired Patients (G1; N=12)**

**and Healthy Volunteers (G2; N=12) After Single Dose Administration of 40 mg.**

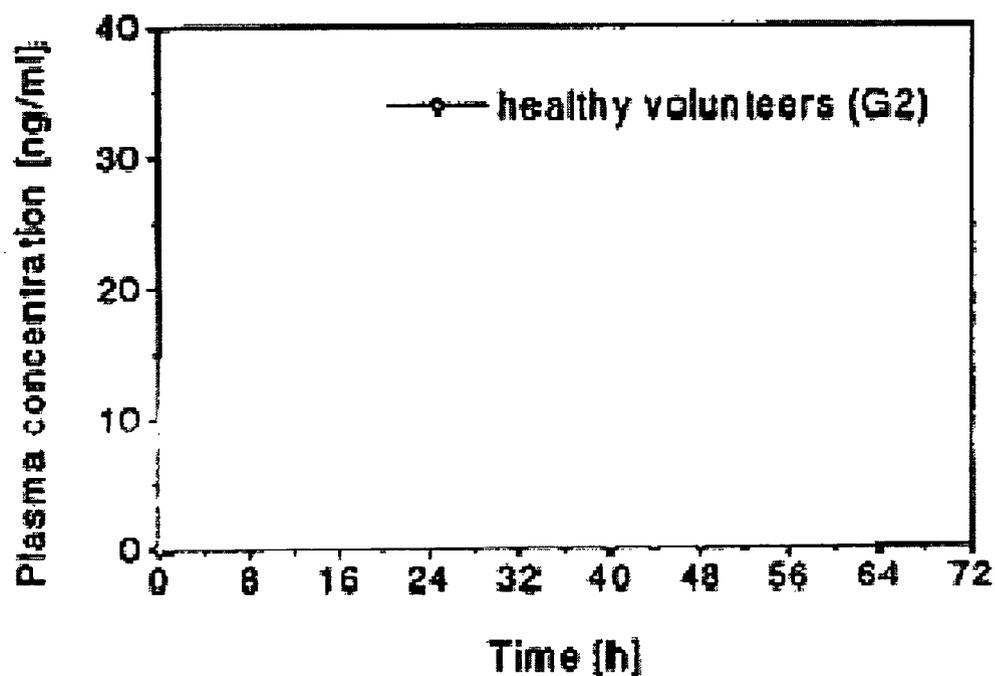
- Figure 3 and Figure 4 show the individual concentration-time profiles for renally impaired and healthy subjects, respectively.

Note in Figure 3:

- One subject has a much later  $T_{max}$  and higher  $C_{max}$  than the other eleven subjects.



**Figure 3. Individual Plasma Concentration Vs. Time Curves of Trospium Chloride in Renally Impaired Patients (N=12) After Single Dose Administration of 40 mg.**



**Figure 4. Individual Plasma Concentration Vs. Time Curves of Trospium Chloride in Healthy Volunteers (N=12) After Single Dose Administration of 40 mg.**

- Figure 5 shows the cumulative excretion data collected in this study.

Note in Figure 5:

- Renal excretion is more rapid and more extensive in healthy volunteers

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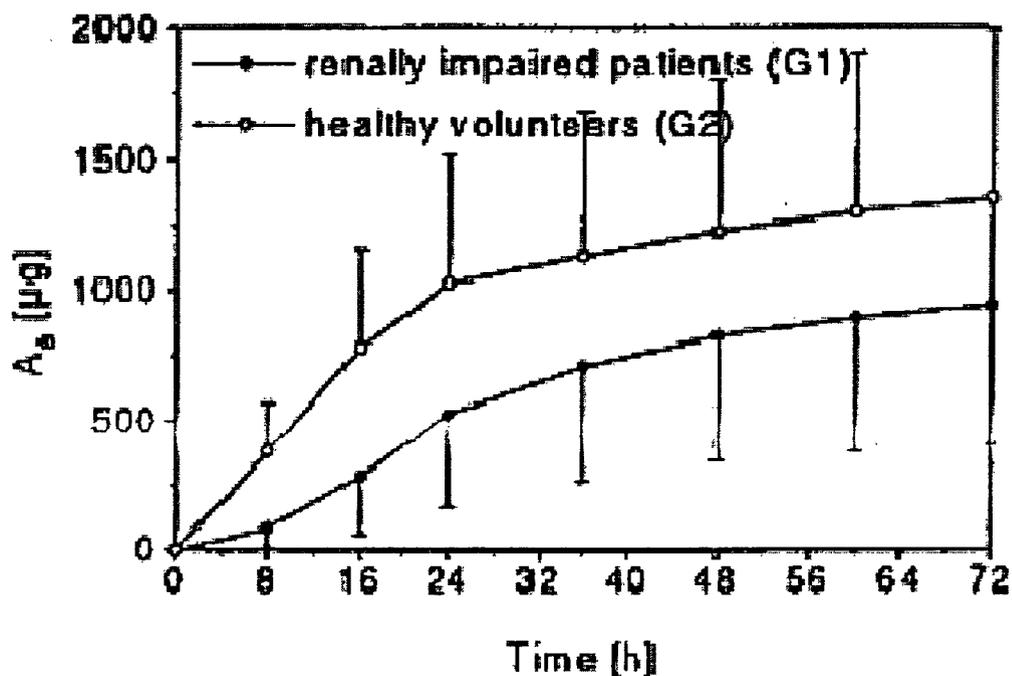


Figure 5. Mean Cumulative Urinary Excretion Vs. Time Curves (Arithmetic Mean  $\pm$  SD) of Trospium Chloride in Renally Impaired Patients (N=12) and Healthy Volunteers (N=12) After Single Dose Administration of 40 mg.

- Figure 6 and Figure 7 plot individual renal excretion data.

Note in Figure 6 and Figure 7:

- Wide interindividual variability in renal excretion.

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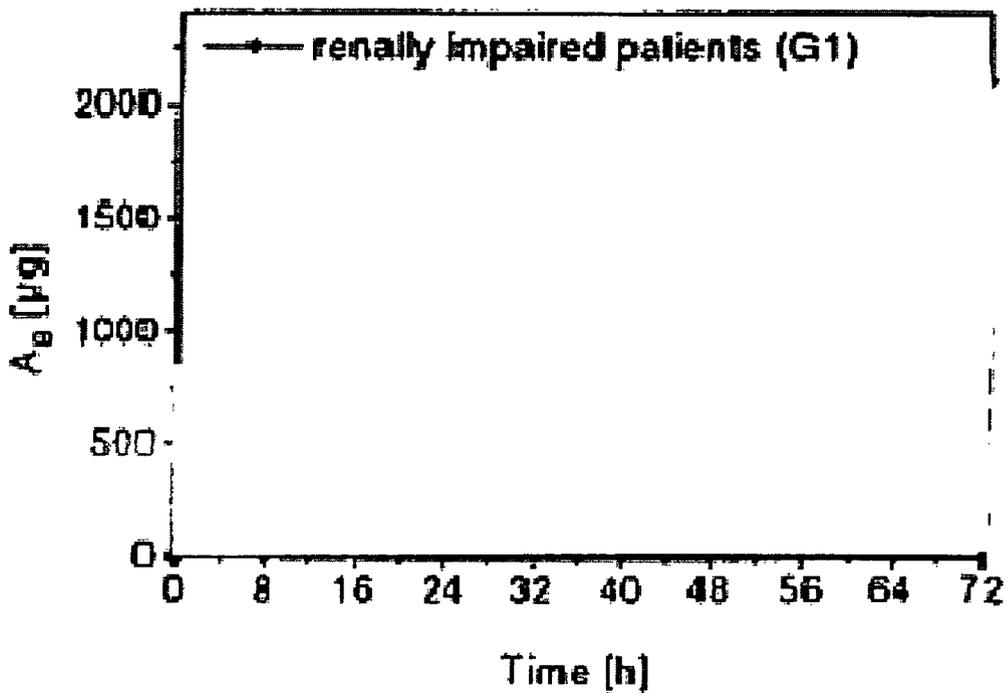


Figure 6. Individual Cumulative Urinary Excretion Vs. Time Curves of Trospium Chloride in Renally Impaired Patients (N=12) After Single Dose Administration of 40 mg.

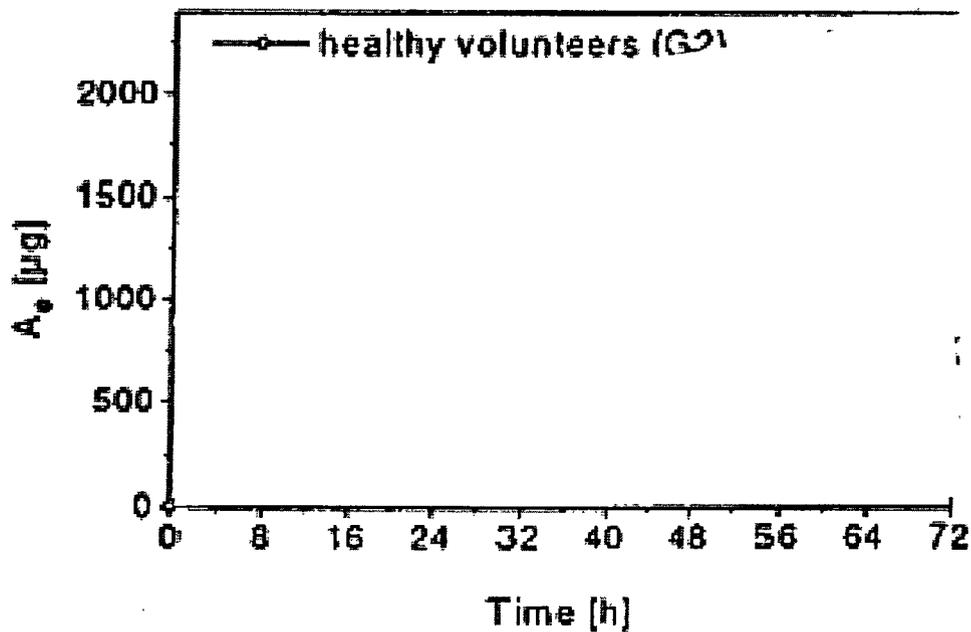


Figure 7. Individual Cumulative Urinary Excretion Vs. Time Curves of Trospium Chloride in Healthy Subjects (N=12) After Single Dose Administration of 40 mg.

- Table 3 shows the incidence of adverse events.

Note in Table 3:

- One subject (8%) of renally impaired subjects required a diuretic rescue due to small urinary voiding. No healthy subject required such an intervention.
- The healthy and renally impaired subjects were studied at different sites.
- Two of the 12 renally impaired patients (17%) reported 1 AE each.
- Six of the 12 healthy subjects (50%) reported 9 AEs; mostly dry mouth.
- No severe AEs.

| Adverse Event group                     | No. of AEs by intensity |          |        |       | No. of subj. with AEs (%) |
|---|-------------------------|----------|--------|-------|---------------------------|
|   | Mild                    | Moderate | Severe | Total |                           |
| <b>Renally impaired patients (n=13)</b> | 2                       |          |        | 2     | 2 (15 %)                  |
| <i>Patients treated (n=12)</i>          |                         |          |        |       |                           |
| Dry mouth                               | 1                       |          |        | 1     | 1 (8 %)                   |
| Small voiding of urine                  | 1                       |          |        | 1     | 1 (8 %)                   |
| - Total                                 | 2                       |          |        | 2     | 2 (17 %)                  |
| <b>Young healthy subjects (n=14)</b>    | 7                       | 4        |        | 11    | 8 (57 %)                  |
| <i>Subjects treated (n=12)</i>          |                         |          |        |       |                           |
| Dry mouth                               | 4                       | 1        |        | 5     | 5 (42 %)                  |
| Bitter taste                            | 1 (1 NR)                |          |        | 1     | 1 (8 %)                   |
| Disturbed accommodation                 |                         | 1        |        | 1     | 1 (8 %)                   |
| Palpitations                            | 1                       |          |        | 1     | 1 (8 %)                   |
| Increased serum bilirubin               |                         | 1 (1 NR) |        | 1     | 1 (8 %)                   |
| - Total                                 | 6 (1 NR)                | 3 (1 NR) |        | 9     | 6 (50 %)                  |
| <i>Subjects not treated (n=2)*</i>      |                         |          |        |       |                           |
| Respiratory infection                   | 1 (1 NR)                | 1 (1 NR) |        | 2     | 2 (100 %)                 |
| - Total                                 | 1 (1 NR)                | 1 (1 NR) |        | 2     | 2 (100 %)                 |
| <b>Total (both groups)</b>              |                         |          |        |       |                           |
| - Total treated (n=24)                  | 8 (1 NR)                | 3 (1 NR) |        | 11    | 8 (33 %)                  |
| - Total enrolled (n=27)                 | 9 (2 NR)                | 4 (2 NR) |        | 13    | 10 (37 %)                 |

**Table 3. Adverse Events.**

### Other Information

- Bioavailability: 5-11%
- Primary metabolite: spiroalcohol, but mostly eliminated unchanged
- 20 mg dose in healthy volunteers: C<sub>max</sub>=\_\_\_\_\_ t<sub>max</sub>=5 hours, t<sub>1/2</sub>=12-18 hours, no induction of metabolism with multiple dose administration (20 mg BID), dose-proportional 20mg to 60 mg, no PK effect of age, gender effect in elderly

### **Study MP194/68**

**A randomized, double-blind, placebo-controlled, dose escalation study in 29 healthy men, age 20 to 45 years, to investigate the maximum tolerable oral single dose of trospium chloride. Trospium chloride was administered as a single dose in the following dose amounts: 20, 40, 80, 120, 180, 240, and 360 mg.**

### **Summary**

\*Dosing occurred 30 minutes after breakfast, so study should be interpreted with respect to relative effects of doses

\*A statistically significant change in salivary secretion was observed with the 180 mg dose and higher.

\*There was a statistically significant increase in papillary diameter (1.5 cm) for doses greater than 120 mg. This change was not dose-dependent in the range tested—the mean increase measured 12 hours after medication was similar after administration of 180 mg, 240 mg and 360 mg.

\*The mean heart rate increases from baseline at 6 hours postdose were 6 beats/min after placebo, 3 beats/min after 20 mg, 1 beat/min after 40 mg, 9 beats/min after 80 mg, 9 beats/min after 120 mg, 14 beats/min after 180 mg, 26 beats/min after 240 mg, and 17 beats/min after 360 mg of trospium.

\*Two volunteers, following treatment with 360 mg trospium, complained of an increased urge to urinate without being able to empty the bladder. The symptom lasted for 12 hours and 24 hours in the subjects.

\*Dose-dependent decrease in salivary secretion to 1/3 of baseline after doses of 180 and 360 mg corresponded with a higher number of reports of dry mouth in this dose range.

### **Methods**

\*Randomized, placebo-controlled, double-blind phase I trial to determine the maximum tolerable single dose of trospium chloride in young healthy male volunteers.

\*N=24 healthy males, 18-40 years; 6 received placebo

\*Dosing occurred 30 minutes after breakfast

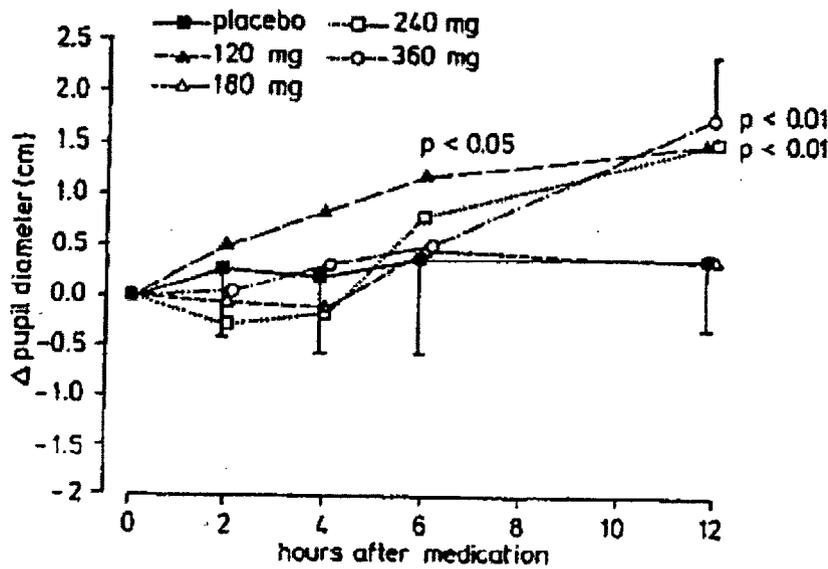
\*Single oral dose at each dose level; 1 week washout between treatments

\*Subjective tolerance, blood pressure, pulse rate, pupil diameter, and salivary flow rate were assessed as measures of the anticholinergic effect of trospium chloride.

\*Pupillary diameter assessed at 2,3,4,6,8 and 12 hours post-dose; covers Cmax

### **Results**

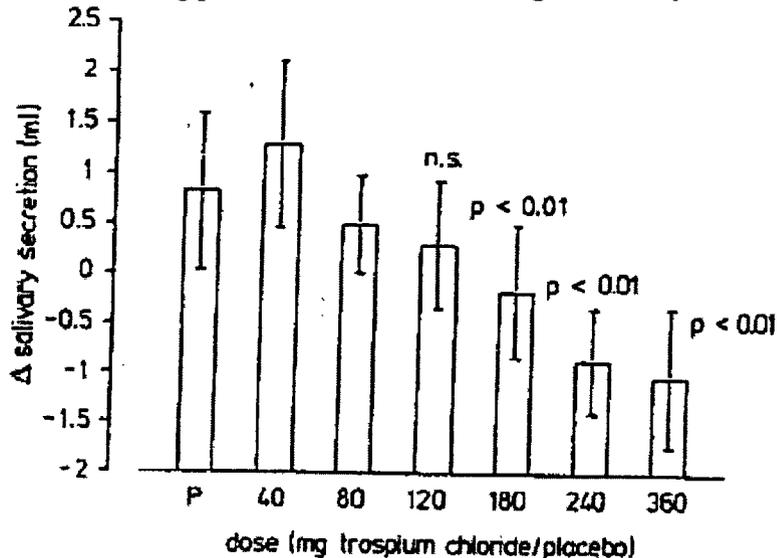
\*The following plot shows the effect of dose on change in pupil diameter



Change in Pupillary Diameter (mean +/- SD) Following Single Oral Administration of Trosipium Chloride or Placebo. Placebo: N=15; 120 mg: N=9; 180 mg: N=9; 360 mg: N=8.

\*Pupil diameter increased with time (thus, concentration) after trosipium chloride was dosed.

\*The following plot shows the effect of drug on salivary secretion.



Changes of Salivary Secretion (mean +/- SD) Following Single Oral Administration of Trosipium Chloride or Placebo (P). Placebo: N=15; 120 mg: N=9; 180 mg: N=9; 240 mg: N=9; 360 mg: N=8.

\*A statistically significant change in salivary secretion was observed with the 180 mg dose and higher.

\*The mean heart rate increases from baseline at 6 hours postdose were 6 beats/min after placebo, 3 beats/min after 20 mg, 1 beat/min after 40 mg, 9 beats/min after 80 mg, 9

beats/min after 120 mg, 14 beats/min after 180 mg, 26 beats/min after 240 mg, and 17 beats/min after 360 mg of trospium.

\*Neither the systolic nor the diastolic blood pressure was clearly affected by trospium.

\*The following table reports the incidence of adverse events for each dose.

|                              | Placebo | Trospium chloride (mg) |    |    |     |     |     |     |
|------------------------------|---------|------------------------|----|----|-----|-----|-----|-----|
|                              |         | 20                     | 40 | 80 | 120 | 180 | 240 | 360 |
| Dry mouth                    | 3       | 2                      | -  | 1  | 1   | 5   | 6   | 7   |
| Impaired nasal breathing     | -       | -                      | -  | -  | 1   | -   | -   | 1   |
| Blurred vision               | 1       | -                      | -  | -  | -   | -   | -   | -   |
| Tachycardia                  | 1       | -                      | -  | -  | -   | -   | -   | -   |
| Decreased vision             | -       | -                      | -  | -  | -   | -   | 1   | -   |
| Retention of urine/strangury | -       | -                      | -  | -  | -   | -   | -   | 2   |
| Increased salivation         | 1       | -                      | -  | -  | -   | -   | -   | -   |
| Flushing                     | -       | 1                      | -  | -  | -   | -   | -   | -   |
| Nausea/vomiting              | 2       | 1                      | -  | -  | -   | -   | -   | -   |
| Headache                     | 4       | 1                      | 1  | 3  | 1   | 3   | 4   | 3   |

**Frequency of Adverse Drug Reactions (Number of Reports).**

\*The most frequently reported adverse effects were dryness of the mouth and headache. Dryness of the mouth increased in relation to the rising dose levels and after 360 mg, it was reported by some of the volunteers as very severe and impairing their general subjective condition. Blurred vision occurred once in the placebo group and four times in the trospium group following treatment with doses of 80 or 120 mg and never at the higher levels.

\*Dose-dependent decrease in salivary secretion to 1/3 of baseline after doses of 180 and 360 mg corresponded with a higher number of reports of dry mouth in this dose range.

\*Unlike the effect on salivary secretion, the increase in papillary diameter (1.5 cm) was not dose-dependent in the range tested. The mean increase measured 12 hours after medication was similar after administration of 180 mg, 240 mg and 360 mg.

\*Two volunteers, following treatment with 360 mg trospium, complained of an increased urge to urinate without being able to empty the bladder. The symptom lasted for 12 hours and 24 hours in the subjects.

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### **Study MP194/26**

**A randomized, double-blind, placebo-controlled, dose-finding study in 25 healthy women, age 18 to 35 years, to determine the extent of the antispasmodic action of intravenously administered trospium chloride.**

#### **Summary**

- \*No discernible trend in peak detrusor pressure or maximum bladder capacity as a function of dose.
- \*Peak urinary flow rate decreased at higher trospium doses.
- \*Adverse events correlated with dose.

#### **Objective**

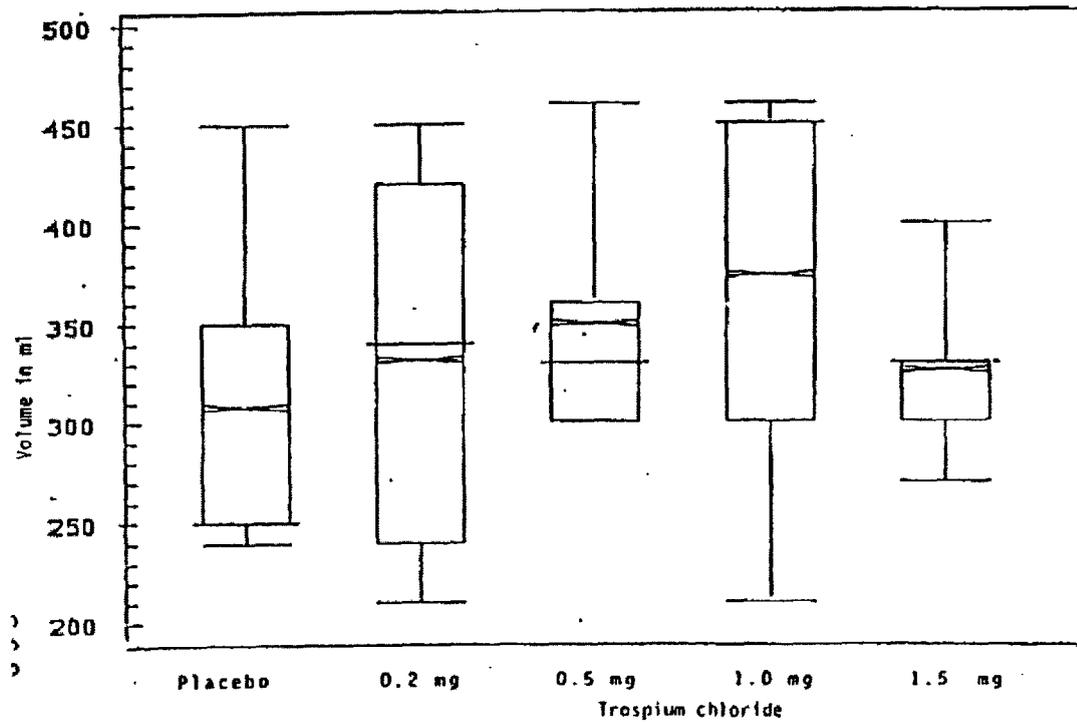
- \*Compare the relaxant actions of four dose levels of trospium chloride (0.2, 0.5, 1.0 and 1.5 mg) with each other and with a placebo and to plot a dose-effect curve.

#### **Methods**

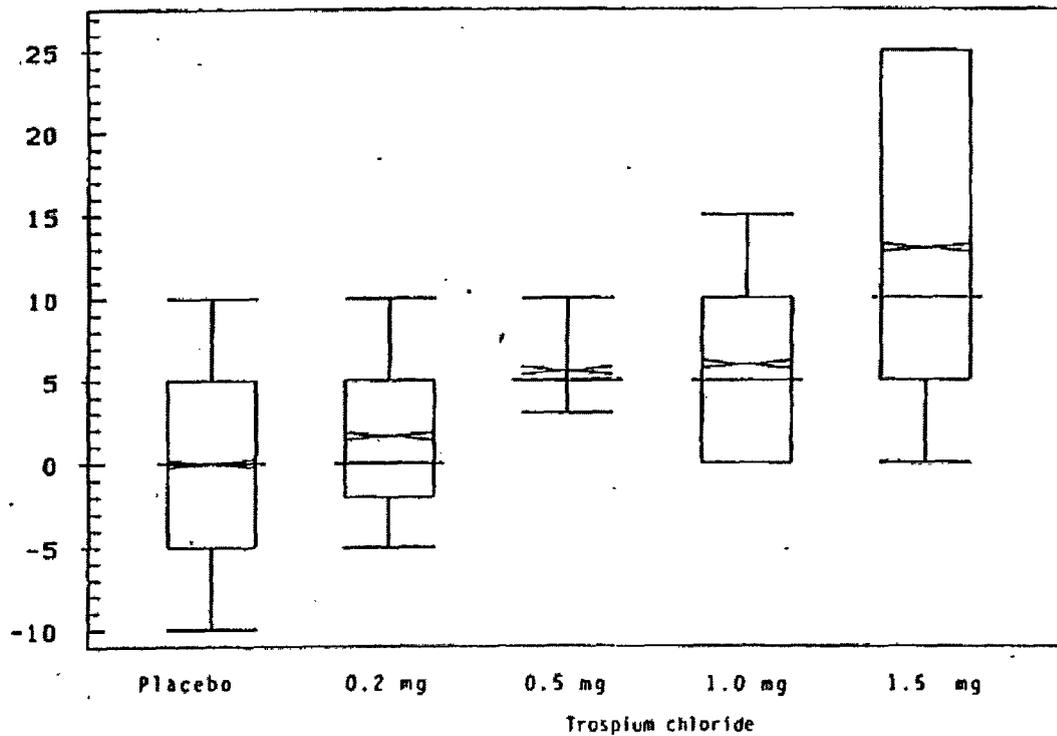
- \*Single center, randomized, double-blind, placebo-controlled, dose-finding design
- \*Single dose study in fasting state
- \*Four dose levels of trospium chloride (0.2, 0.5, 1.0, and 1.5 mg) administered.
- \*Healthy female subjects, 18-35 years of age, with no pathological changes of the urinary bladder or urinary tract
- \*N=25; 5 assigned / arm; 20 receive trospium chloride
- \*Outcomes: intravesical pressure, detrusor pressure, rate and duration of urinary outflow.
- \*Intravesical pressure determined by filling the bladder to maximum capacity with a radiopaque solution at several time points after dosing. Detrusor pressure calculated from the difference between intravesical and abdominal pressures.
- \*Urinary flow rate: continuous measurement of urine voided during normal micturition as a function of time; governed by micturition pressure and micturition resistance in the urethra. Measured 2 minutes post-dose.
- \*Adverse effects measured 3 hours post-dose.

#### **Results**

- \*No discernible trend in peak detrusor pressure or maximum bladder capacity.

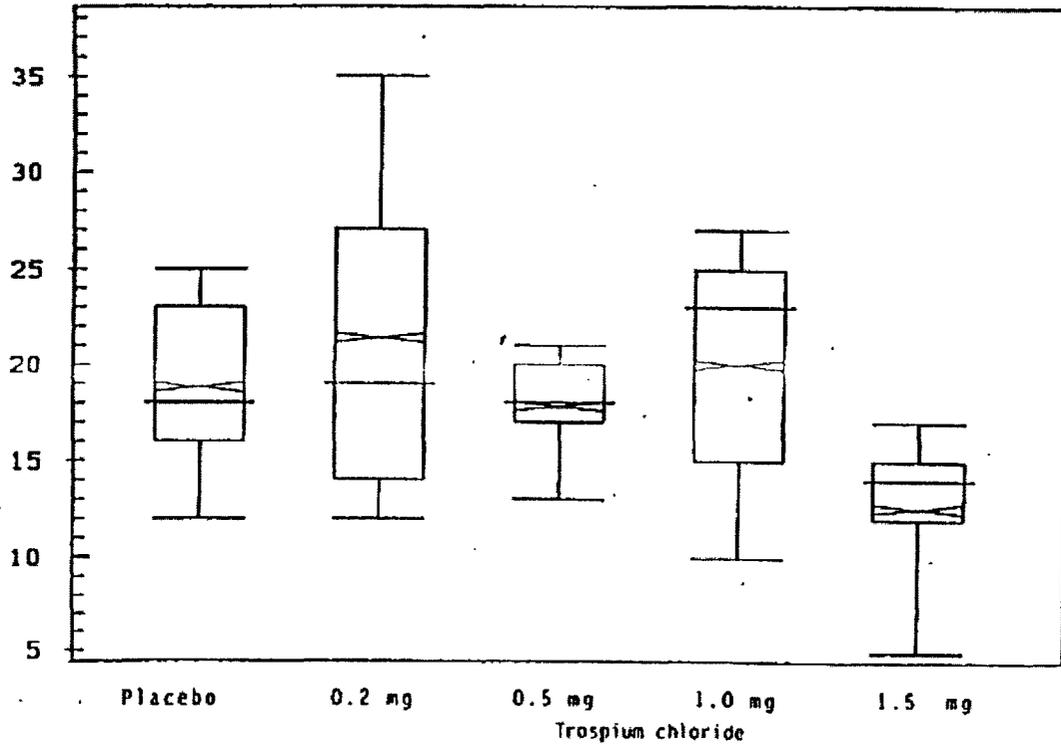


Box and whisker plot of the maximum bladder capacity after injection of the test preparation.



Box and Whisker Plot of the Extreme Detrusor Pressure After Injection of the Test Preparation.

\*Peak urinary flow rate decreased at higher trospium doses.



**Box and Whisker Plot of the Peak Urinary Flow Rate After Injection of the Test Preparation.**

\*Adverse events related to dose: 6 reports in the 0.2 mg group, 9 reports in the 0.5 mg group, 10 in the 1.0 mg group, and 13 in the 1.5 mg group.

\*80% (16 patients out of 20 patients) reported dry mouth with 2, 4, 5, and 5 subjects reporting from each of the 0.2, 0.5, 1, and 1.5 mg dose groups, respectively.

\*25% of patients (5 patients out of 20 patients) experienced retching and nausea

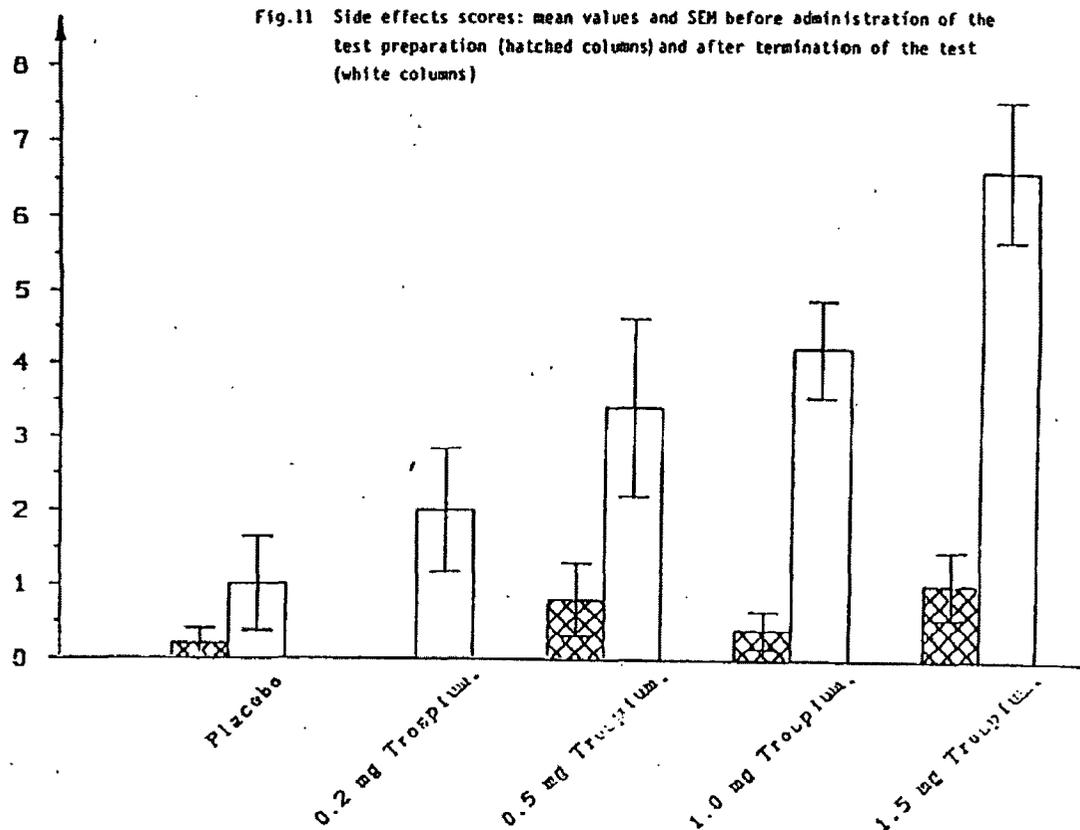
\*25% of patients (5 patients out of 20 patients) experienced palpitations

\*25% of patients (5 patients out of 20 patients) experienced dizziness

\*Mean heart rate showed a marked dose-related increase at 2, 15, 30 and 60 minutes post-infusion.

\*Side effects were considerably higher for a 1.5 mg dose compared to 1.0 mg trospium chloride.

\*Side effects differed marginally between 1.0 mg and 0.5 mg trospium chloride.



Side Effects Scores: Mean Values and SEM Before Administration of the Test Preparation (Hatched Columns) and After Termination of the Test (White Columns).

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## **Study IP631-007**

### **Pharmacokinetics of Orally Administered Trospium Chloride 40 mg in Subjects with Mild and Moderate-to-Severe Hepatic Dysfunction**

#### **Summary**

- No subject with severe hepatic dysfunction enrolled
- N=8 with mild impairment (Child-Pugh 5-6) and N=8 with moderate impairment (Child-Pugh 7-8) studied
- Confidence intervals for the ratio of geometric LS means were outside the predefined range of 80 to 125% for AUC(0-∞) and 70 to 143% for C<sub>max</sub>.
- Parameter estimates not precise
- Renal clearance increased with decreasing hepatic function
- There is a 60% increase in C<sub>max</sub> in moderate hepatic impairment.
- There is a 50% increase in renal clearance in moderate hepatic impairment (statistically significant)
- There is no information on severe hepatic impairment, but based on the trend, there may be a considerable increase in C<sub>max</sub> and CL<sub>renal</sub>.
- No significant change in t<sub>max</sub> or t<sub>1/2</sub> with hepatic impairment
- The incidence of adverse events was greater in moderate hepatic impairment (87.5%) than mild hepatic impairment (37.5%) in comparison to subjects with normal hepatic function (25.0%).
- A total of 12 out of 24 subjects (50%) experienced 18 adverse events during the study; all were mild in severity.

#### **Objective**

- Describe and compare the single 40 mg dose pharmacokinetics of trospium in subjects with impaired hepatic function and gender-, age-, and weight-matched normal healthy subjects.
- Describe and compare the safety and tolerability of a single 40 mg dose of trospium chloride in subjects with impaired hepatic function and gender-, age-, and weight-matched normal healthy subjects.

#### **Design**

- Single-center, open-label, single dose (40 mg) study in a total of N=24 subjects
- Dosing under fasted conditions; meals started 4 hours post-dose
- N=8 with mild hepatic impairment (Child-Pugh 5-6)
- N=8 with moderate hepatic impairment (Child-Pugh 7-8)
- N=8 with normal hepatic function
- Plasma and urine samples collected up to 72 hours after dosing.
  - Blood: 1,2,4,6,8,10,12,18,24,48,72 hours
  - Urine: 0-12, 12-24, 24-48, 48-72 hours
- Hepatically impaired male and female subjects; 18 and 65 years
- Gender-, age-, and weight-matched healthy subjects

#### **Methods**

- If the 90% CIs for comparing each of the two hepatic impairment groups with the control group fell within 80 to 125% for AUC(0-∞) and 70 to 143% for C<sub>max</sub>, then it was concluded that hepatic impairment did not affect the pharmacokinetics of trospium.
- Liquid chromatography. \_\_\_\_\_ methods used for the quantitative determination of trospium concentrations in heparinized plasma and in urine.
- The validated plasma method has a standard curve range of \_\_\_\_\_ using 50 μL plasma.
- The standard curve range for the validated urine method was \_\_\_\_\_ using 100 μL urine.

## Results

- Table 1 provides a summary of demographics; note that the subjects with moderate hepatic impairment were all males.

| Variable/Category |       | Group 1<br>(N = 8) | Group 2<br>(N = 8) | Group 3<br>(N = 8) | All Subjects<br>(N = 24) |
|-------------------|-------|--------------------|--------------------|--------------------|--------------------------|
| <b>Gender</b>     |       |                    |                    |                    |                          |
| Female            | N (%) | 2 (25%)            | 3 (38%)            | 0 (0%)             | 5 (21%)                  |
| Male              | N (%) | 6 (75%)            | 5 (62%)            | 8 (100%)           | 19 (79%)                 |
| <b>Race</b>       |       |                    |                    |                    |                          |
| Caucasian         | N (%) | 0 (0%)             | 5 (62%)            | 4 (50%)            | 9 (38%)                  |
| African           | N (%) | 0 (0%)             | 1 (13%)            | 0 (0%)             | 1 (4%)                   |
| Hispanic          | N (%) | 8 (100%)           | 2 (25%)            | 4 (50%)            | 14 (58%)                 |

**Table 1. Demographics and Baseline Characteristics for Each Hepatic Function Group.** Group 1 = Normal hepatic function; Group 2 = mild hepatic impairment; Group 3 = moderate hepatic impairment.

- Table 2 shows a summary of the PK parameters observed in the three subject groups.

|                             | Group [a] | N | Geometric LS Mean | Pair | Ratio (%) | 90% CI          |
|-----------------------------|-----------|---|-------------------|------|-----------|-----------------|
| C <sub>max</sub><br>(ng/mL) | 1         | 8 | 3.721             | -    | -         | -               |
|                             | 2         | 8 | 4.159             | 2/1  | 111.76    | (54.65-228.54)  |
|                             | 3         | 8 | 6.083             | 3/1  | 163.45    | (79.93-334.25)  |
| AUC(0-∞)<br>(ng*h/mL)       | 1         | 8 | 64.30             | -    | -         | -               |
|                             | 2         | 7 | 60.94             | 2/1  | 94.77     | (56.8-158.11)   |
|                             | 3         | 8 | 54.96             | 3/1  | 85.47     | (52.13-140.14)  |
| CL <sub>po</sub><br>(L/h)   | 1         | 8 | 570.8             | -    | -         | -               |
|                             | 2         | 7 | 601.9             | 2/1  | 105.45    | (63.2-175.96)   |
|                             | 3         | 8 | 667.0             | 3/1  | 116.86    | (71.26-191.65)  |
| CL <sub>R</sub><br>(L/h)    | 1         | 5 | 13.52             | -    | -         | -               |
|                             | 2         | 7 | 14.41             | 2/1  | 106.59    | (77.93-145.77)  |
|                             | 3         | 6 | 20.44             | 3/1  | 151.25    | (109.42-209.09) |

**Table 2. Comparison of Pharmacokinetic Parameters Observed.** Note that Group 1 = Normal hepatic function; Group 2 = mild hepatic impairment; Group 3 = moderate hepatic impairment.

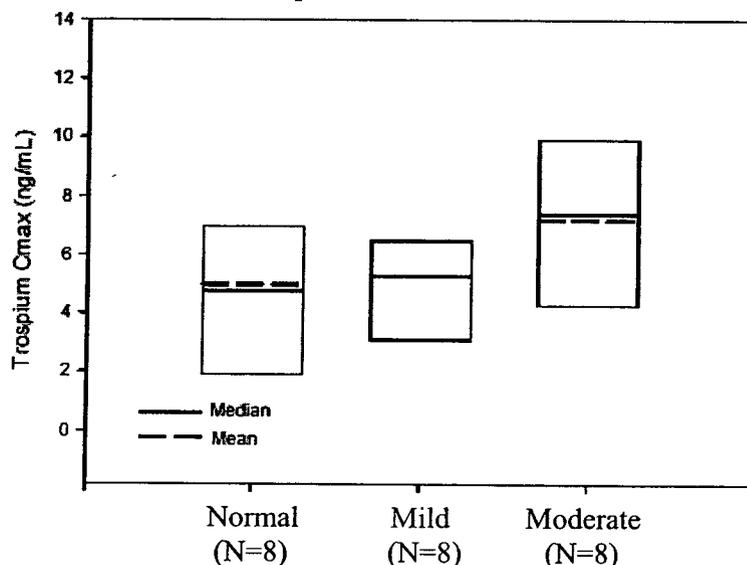
- Note in Table 2:
  - C<sub>max</sub> increases with a decrease in hepatic function
  - Renal clearance and oral clearance increase with a decrease in hepatic function
  - AUC decreases with a decrease in hepatic function
  - Confidence intervals for the ratio of geometric LS means were outside the predefined range of 80 to 125% for AUC(0-∞) and 70 to 143% for C<sub>max</sub>.
  - Parameter estimates not precise; study may not have good power to detect the difference.
  - Statistically significant increase in renal impairment in subjects with moderate hepatic impairment.

• Table 3 presents the results in Table 1 in terms of mean fold change in parameter value.

|                     | Mild Impairment<br>(Child-Pugh 5-6) | Moderate Impairment<br>(Child-Pugh 7-8) |
|---------------------|-------------------------------------|---|
| C <sub>max</sub>    | 1.1                                 | 1.6                                     |
| AUC <sub>0-∞</sub>  | 0.95                                | 0.85                                    |
| CL                  | 1.1                                 | 1.2                                     |
| CL <sub>renal</sub> | 1.1                                 | 1.5                                     |

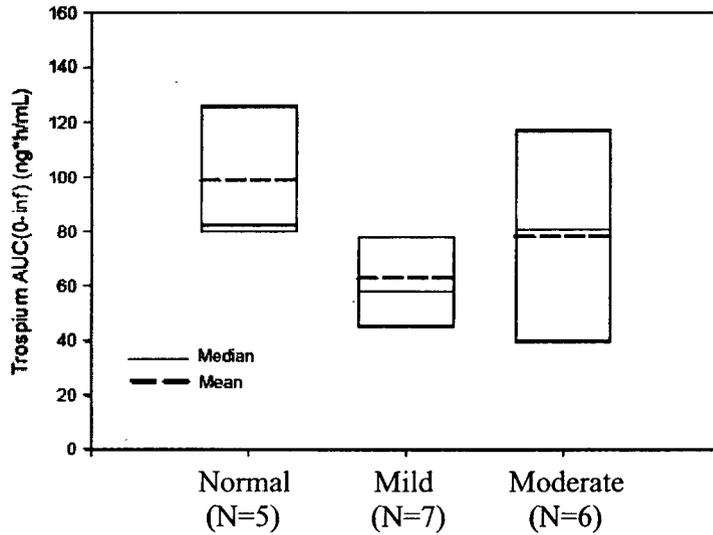
**Table 3. Ratio of Parameter Value Relative to Value Observed in Subjects With Normal Hepatic Function.**

- Note in Table 3:
  - C<sub>max</sub> and CL<sub>renal</sub> are changed the most in subjects with moderate hepatic impairment.
  - There is a 60% increase in C<sub>max</sub> in moderate hepatic impairment.
  - There is a 50% increase in renal clearance in moderate hepatic impairment
  - There is no information on severe hepatic impairment, but based on the trend, there may be a considerable increase in C<sub>max</sub> and CL<sub>renal</sub>.
- Figure 3 shows the change in C<sub>max</sub> graphically. It shows that there is an increase in C<sub>max</sub> with moderate impairment.



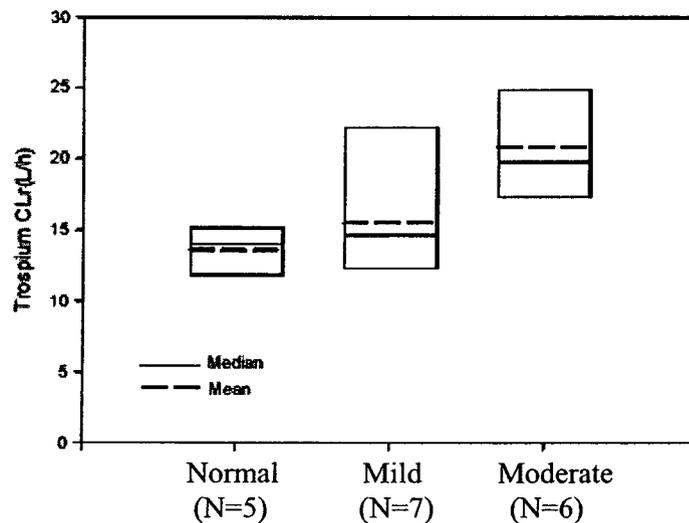
**Figure 3. Boxplot of Cmax of Trospium Chloride According to Hepatic Function.** The bottom of the box represents the 25th percentile and the top of the box represents the 75th percentile.

• Figure 4 shows the change in AUC graphically. It shows that there is greater variability in moderate impairment than in normal and mild impairment.



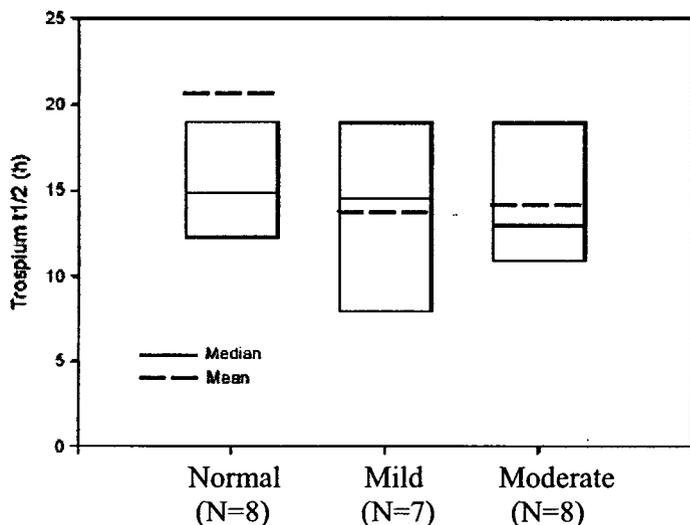
**Figure 4. Boxplot of AUC of Trospium Chloride According to Hepatic Function.** The bottom of the box represents the 25th percentile and the top of the box represents the 75th percentile.

• Figure 5 shows the change in renal clearance graphically. It shows that there is trend of increasing CLrenal with hepatic impairment.



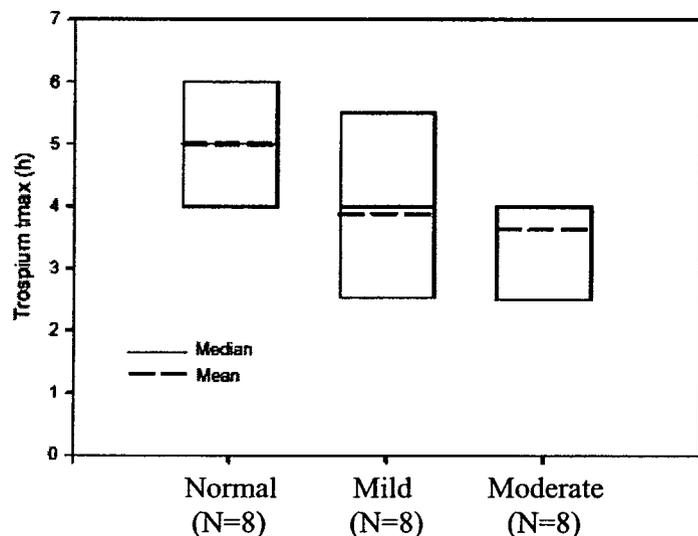
**Figure 5. Boxplot of Renal Clearance of Trospium Chloride According to Hepatic Function.** The bottom of the box represents the 25th percentile and the top of the box represents the 75th percentile.

- Figure 6 shows the change in half life graphically. It shows that there is no change in half life. Note that the mean is influenced by an outlying value.



**Figure 6. Boxplot of  $t_{1/2}$  of Trospium Chloride According to Hepatic Function.** The bottom of the box represents the 25th percentile and the top of the box represents the 75th percentile.

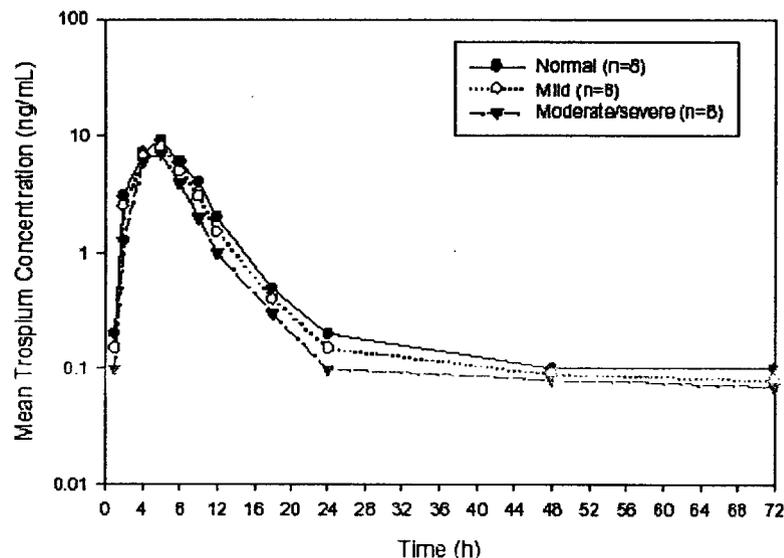
- Figure 7 shows the change  $t_{max}$  graphically. It shows that there is a decrease in  $t_{max}$  with hepatic function.



**Figure 7. Boxplot of  $t_{max}$  of Trospium Chloride According to Hepatic Function.** The bottom of the box represents the 25th percentile and the top of the box represents the 75th percentile.

- Median  $t_{max}$  was 5 hours for healthy subjects and 4 hours for hepatically impaired subjects.
- Mean elimination half-life ( $t_{1/2}$ ) was 28% and 24% lower in subjects with mild and moderate hepatic impairment compared to healthy subjects, respectively.

- Figure 8 shows the mean concentration time profile for subjects grouped by hepatic function.



**Figure 8. Semi-log Plot of Mean Trospium Concentrations over Time by Hepatic Function.** Note that although there is a group listed as "Moderate/Severe", all subjects in this group had moderate hepatic impairment. (No subject studied had severe hepatic impairment.)

- The incidence of adverse events was greater in Group 3 (87.5%) than Group 2 (37.5%) in comparison to Group 1 (25.0%).
- A total of 12 out of 24 subjects (50%) experienced 18 adverse events during the study; all were mild in severity.
- The number of subjects reporting adverse events during the treatment period was highest in the gastrointestinal disorders (6 of 24 subjects [25.0%]) and nervous system disorders (6 of 24 subjects [25.0%]) system organ classes.
- Table 4 presents information on adverse responses.

| Preferred Term | Number (%) of Subjects |                 |                 |
|----------------|------------------------|-----------------|-----------------|
|                | Group 1 (N = 8)        | Group 2 (N = 8) | Group 3 (N = 8) |
| Dry Mouth      | 0 (0.0%)               | 1 (12.5%)       | 3 (37.5%)       |
| Dyspepsia      | 0 (0.0%)               | 0 (0.0%)        | 2 (25.0%)       |
| Headache       | 1 (12.5%)              | 0 (0.0%)        | 4 (50.0%)       |
| Dysuria        | 0 (0.0%)               | 1 (12.5%)       | 1 (12.5%)       |

**Table 4. All TEAEs by Body System and Preferred Term for Each Hepatic Function Group Reported in >1 Subject.**

- There were no trends or clinically meaningful changes observed in mean or median laboratory values from baseline to end of study for any of the hepatic function groups.

#### Notes

- The major metabolite is the inactive hydrolysis product, azoniaspironortropanol.
- Approximately 50% to 80% of the drug is protein-bound at therapeutic concentrations.

- Given the low systemic bioavailability and lack of interaction with drug-metabolizing enzymes, metabolic drug interactions are not expected.
- The dose correction factor for the trospium chloride salt (molecular weight = 427.96 g/mol) is determined from the ratio of molecular weights (

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## Study IP631-006

### A Mass Balance and Metabolism Study of <sup>14</sup>C-Trospium Chloride in Healthy Male Subjects

## SUMMARY

\*Due to the lack of quantifiable drug-related radioactivity concentrations in the majority of the blood and plasma samples, the following analysis were not performed and data listings were not prepared:

- (a)
- (b)
- (c)
- (d)

\*After study completion it was determined that the extraction of drug-related radioactivity in the serial fecal homogenates was incomplete. To account for the total fecal drug-related radioactivity, the fecal matter that had been disposed in waste containers was extracted under a modified method

\*91 % of drug recovery within 72 hours; excretion essentially complete within 168 hours

\*63% recovery in feces over 288 hours

\*Cumulative percent of radioactivity in urine over 288 hours = 6%. 40% of this was metabolic products.

## PURPOSE

\*To determine the mass balance of radioactivity following a single oral dose of <sup>14</sup>C-trospium chloride (100  $\mu$ Ci/20 mg) in healthy male subjects in the fasted state.

\*To characterize the pharmacokinetics and radioactivity following a single oral dose of <sup>14</sup>C-trospium chloride.

\*To profile metabolites following a single oral dose of <sup>14</sup>C-trospium chloride (100  $\mu$ Ci/20 mg) in healthy male subjects.

\*To characterize the distribution of radioactivity in blood, red blood cells, and plasma following a single oral dose of <sup>14</sup>C-trospium chloride (100  $\mu$ Ci/20 mg) in healthy male subjects.

\*Expand on a previous study showing that drug is excreted mainly in the urine and 80% is unmetabolized.

## METHODS

### Products

\*Study drug was administered as liquid form containing 100  $\mu$ Ci/20 mg of trospium chloride per unit dose.

### Study Design

\*Single-center, single dose study in N=6 healthy males, 36-45 years

\*In-clinic period of 9-14 days

\*Single p.o. dose of <sup>14</sup>C-trospium chloride (100 micro-Ci / 20 mg) in the morning in the fasted state

\*Sampling for 168 hours post-dose

\*Radioactivity determined in blood, plasma, urine, and feces

\*Subjects in an upright position until 4 hours post-dose

\*Whole blood and plasma samples collected for radioactivity concentration determination at 0,2,4,8,12, and 24 hours post-dose to calculate distribution in blood cells.

### Assays

\*Plasma and urine concentrations determined by LC/MS/MS. The assay range for plasma and urine was \_\_\_\_\_, respectively. The following table summarizes the method precision and accuracy.

| Samples  | Accuracy <sup>a</sup> | Precision <sup>b</sup> |
|--|-----------------------|------------------------|
| <b>Plasma:</b>   |                       |                        |
| QC samples – Range of means over all concentration limits            | 2.0 to 3.2%           | 4.7 to 11.3%           |
| Calibration standards – Range of means over all concentration limits | -4.8 to 4.0%          | 0.9 to 6.7%            |
| <b>Urine:</b>  |                       |                        |
| QC samples – Range of means over all concentration limits            | 1.4 to 4.4%           | 2.9 to 7.3%            |
| Calibration standards – Range of means over all concentration limits | -5.2 to 6.4%          | 1.3 to 7.3%            |

<sup>a</sup> Accuracy expressed as % bias, relative to theoretical concentration

<sup>b</sup> Precision expressed as % coefficient of variation

\*The following table is a summary of precision and accuracy during method validation.

| Matrix      | Samples                  | Accuracy <sup>a</sup> | Precision <sup>b</sup> |
|-------------|--------------------------|-----------------------|------------------------|
| Plasma      | Radioactivity Validation | 0.6 to 3.8%           | 0.81 to 5.74%          |
| Urine       | Radioactivity Validation | -3.1 to 0.2%          | 0.69 to 2.60%          |
| Whole blood | Radioactivity Validation | -6.2 to 8.8%          | 0.11 to 5.36%          |
| Feces       | Radioactivity Validation | -4.4 to 6.8%          | 1.25 to 5.85%          |

<sup>a</sup> Accuracy expressed as % relative error

<sup>b</sup> Precision expressed as % coefficient of variation

\*The following table summarizes the limits of quantitation for each test substance.

| Matrix      | Based on Counted DPM Values | Converted into Weight Equivalents of the Trospium Chloride Salt | Expressed as Weight Equivalents of the Trospium Free Base |
|-------------|-----------------------------|---|---|
| Feces       | 90 dpm/g                    | 8.1 ng/g  | Not applicable  |
| Urine       | 54 dpm/mL                   | 4.8 ng/mL   | Not applicable  |
| Plasma      |                             |   |   |
| Whole Blood |                             |   |   |

Note: The LOQ in this table is listed as \_\_\_\_\_

The conversion to free base was not applicable for urine and feces, since all calculations and comparisons were based on the percent of <sup>14</sup>C-radioactivity recovered. For plasma and whole blood, <sup>14</sup>C-radioactivity comparisons were performed on weight/volume and adjustments to the weight equivalent of the trospium free based were to match the unchanged trospium data were required.

### Data Analysis

\*Noncompartmental analysis of C<sub>max</sub>, t<sub>max</sub>, AUC, A<sub>e</sub>

### BACKGROUND

\*Orally administered trospium chloride is slowly absorbed; t<sub>max</sub> = 5-6 hours.

\*Oral bioavailability = 9.6 +/- 4.5% in man; intraindividual var in F = 20% at steady state

\*Oral bioavailability is reduced by high-fat food intake

\*Dose linearity over a 20-60 mg dose range

\*No evidence of age or gender differences in intestinal absorption or elimination

\*Half life = 12-18 hours

\*The major metabolite is the inactive hydrolysis product azoniaspironortropanol.

\*Approximately 50% to 80% of the drug is protein-bound at therapeutic concentrations.

\*Bioavailability higher in the fasted than fed state.

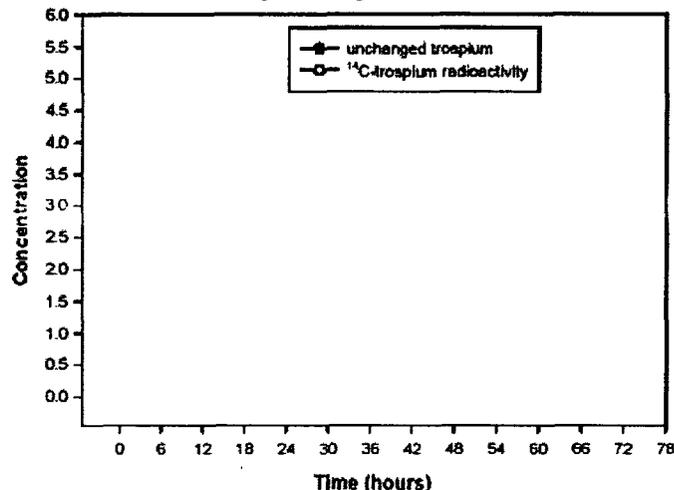
### RESULTS

\*Trospium was quantifiable in plasma up to 48 hours; given that the terminal half life is estimated as approximately 20 hours, perhaps the assay was not of sufficient sensitivity?

\*T<sub>max</sub> observed at 6 hours post-dose

\*There is little variability in T<sub>max</sub>; perhaps a reflection of sampling times?

\*Blood and plasma radioactivity PK parameters could be determined in zero (0) and one (1), respectively, of the 6 subjects because concentrations were too low. The following plot shows the plasma trospium and radioactivity concentration in the one subject. Note that the assay is unable to pick up radioactivity at concentrations below 1 ng/mL trospium.



\*Blood radioactivity, pharmacokinetic parameters, blood to plasma ratios, and <sup>14</sup>C-radioactivity distribution into erythrocytes could not be calculated due to lack of quantifiable <sup>14</sup>C drug-related radioactivity in most plasma and whole blood samples.

\*Table 1 reports the pharmacokinetic parameters of trospium chloride in plasma. Note that a considerable % of the AUC is extrapolated to time infinity (21-48%). This is reflected in a wide variability in AUC and CL<sub>po</sub>.

| Pharmacokinetic Parameters            | Arithmetic Mean (CV %)<br>Trospium (n = 6) | Trospium<br>(Subject 01-003) | Radioactivity<br>(Subject 01-003) |
|---------------------------------------|--|------------------------------|-----------------------------------|
| C <sub>max</sub> (ng/mL) <sup>a</sup> | 1.14 (55.3)                                |                              |                                   |
| AUC(0-last) (ng·h/mL) <sup>a</sup>    | 16.06 (68.5)                               | 29.87                        | 35.87 <sup>c</sup>                |
| AUC(0-∞) (ng·h/mL) <sup>a</sup>       | 27.38 (46.0)                               | 39.44                        | --                                |
| AUC(0-10) (ng·h/mL) <sup>a</sup>      | Not applicable                             | 11.64 <sup>c</sup>           | 35.87                             |
| CL <sub>po</sub> (L/h)                | 875.8 (67.4)                               | 465                          | --                                |
| λ <sub>z</sub> (1/h)                  | 0.038 (36.0)                               | 0.030                        | --                                |
| t <sub>1/2</sub> (h)                  | 19.7 (24.9)                                | 23.0                         | --                                |
| t <sub>max</sub> (h)                  | 6.0 (6.00 to 6.08) <sup>b</sup>            | 6.0                          | 8.0                               |

a For radioactivity pharmacokinetic parameters, ng is replaced by the equivalent radioactivity unit of ng·Eq.

b Median value (range).

c Quantifiable data up to 10 hours [the matching trospium AUC(0-10) was used for the calculation of AUC trospium/<sup>14</sup>C plasma radioactivity ratio.]

Table 1. Plasma Trospium Chloride Pharmacokinetics.

\*The major route of radioactivity elimination was the feces.

\*During the extraction process of the individual fecal samples, incomplete recovery of drug material occurred. For this reason, the exact percent of drug-related radioactivity in individual fecal samples is unknown.

\*Excretion of drug-related radioactivity was essentially complete within