For the QTcF interval, patients in both treatment groups who met the QTcF PCS criteria, most of the patients had an increase in the QT interval by >60 msec, but did not exceed 500 msec. There was 1 patient in the trospium chloride group who had a QTcF interval >500 msec that had increased by >60 msec from baseline. Trospium patient 26-6300 was a 73-year-old Caucasian male with medical history that included hypertension treated with verapamil and enalapril, arrhythmia and angina (2 prior cardiac catheterizations) treated with isosorbide. This patient was found to have a QTcF interval of 535 msec on the Day 8 ECG (QTcF interval at screening was 434 msec and by Day 62 was 454 msec). For patient 26-6300, there were no clinical signs or symptoms associated with the increased QTcF interval, there was no action taken with study medication as a result of the QTcF interval increase, and the QTcF interval increase had resolved at endpoint.

There were approximately two-thirds as many patients in the trospium group who met PCS criteria for low heart rate when compared with the placebo group.

Although the numbers were small, there were more patients in the trospium chloride group who met PCS criteria for high heart rate (≥100 and increase >15 bpm) when compared with the placebo group. There was 1 patient in the trospium chloride group who met PCS criteria for high heart rate of >120 and increase >15 bpm. Narrative for this patient is provided herein:

Trospium patient 17-6782 was an 80-year old Caucasian male who was found to have a heart rate of 127 bpm on the Day 90 ECG. Atrial fibrillation was noted on the ECG at both screening (heart rate 124 bpm) and at Day 90 (heart rate 127 bpm). On Day 8 the ECG was within normal limits and heart rate was 57 bpm. Pulse recorded at all visits throughout the study ranged from 60 to 68 bpm. On Day 80, this patient reported mild flu symptoms that resolved on Day 87 with no interruption in study medication.

Reviewer's Comments

In the opinion of this reviewer, the electrocardiogram data provided is acceptable. In the analysis using Fridercia's correction, patients in trospium group did not show a higher percentage of abnormal QTc >450 msec compared with the placebo group. As demonstrated earlier, trospium was showen to be associated with a heart rate increase of 3bpm. One patient with pre-existing history of tachycardia and atrial fibrillation had a potentially clinically significant increase in heart rate..

Reviewer's Overall Safety Conclusions

•Overall, a total of 349 patients reported 1 or more treatment-emergent adverse event (TEAE). In the trospium group, 196 patients (59.6%) experienced a TEAE compared with 153 patients (46.5%) in the placebo group.

•TEAE's were most commonly reported for the gastrointestinal system with 103 patients (31.3%) in the trospium group and 55 patients (16.7%) in the placebo group experiencing such events. Dry mouth and constipation were the most frequently reported TEAEs.

TEAE's that occurred in >5.0% of patients in either treatment group were dry mouth, constipation, and headache. The TEAE's of dry mouth and constipation were significant ($p \leq 0.01$ and $p=0.02$, respectively) and were more often in the trospium group when compared with the placebo group. The number of patients who experienced headache was similar ($p=0.72$) in the trospium and placebo groups.

•TEAE's of myocardial infarction were reported in 3 trospium patients (0.9%). All 3 of these patients had multiple underlying medical conditions that were risk factors for the occurrence of a myocardial infarction. None were determined to be related to the study medication.

•TEAE's commonly associated with anticholinergic agents and as reported in this study include dry mouth, constipation, dry eyes, urinary retention and tachycardia. All these anticholinergic TEAEs were seen more often in the trospium group compared with the placebo group.

In the trospium group, the study medication was discontinued in 1 patient for each of the following anticholinergic TEAEs unless otherwise specified: dry mouth (5 patients), constipation (6 patients), urinary retention (2 patients), palpitations, and dry eyes.

•A serious adverse event (SAE) was reported for a total of 18 patients [trospium 12 patients (3.6%), placebo 6 patients (1.8%)].

There was 1 patient who experienced an adverse event leading to death. This patient developed a bowel obstruction 22 days following administration of the study medication and later experienced a myocardial infarction, which resulted in death on Day 23.

•Study medication was permanently discontinued due to TEAE's in a total of 39 patients (trospium 24 patients (7.3%), placebo 15 patients (4.6%). The most common TEAE's that led to discontinuation of study medication in the trospium group were constipation and dry mouth.

•The number of patients who met potentially clinically significant (PCS) criteria for the hematology and serum chemistry laboratory data was similar for the trospium and placebo groups. Although there were more patients in the trospium group who met PCS criteria for urinary WBC's when compared with the placebo group, the difference in the UA findings did not translate into a clinically meaningful condition.

•Overall, the number of patients who met PCS criteria for the vital signs and ECG data was also similar for both trospium and placebo groups. Although the number of patients was small, there were more patients in the trospium group who met PCS criteria for high heart rate (>100 and increase >15 bpm) when compared with the placebo group. There

was 1 patient in the trospium group who met PCS criteria for high heart rate of >120 and increase >15 bpm.

The mean change in QTcF interval from baseline in the trospium group was -0.9 msec and in the placebo group was 3.5 msec. There was 1 patient in the trospium group who had QTcF interval >500 msec that had increased by >60 msec from baseline. But this patient showed no clinical signs or symptoms associated with the increased QTcF interval which resolved at endpoint. A thorough QT study revealed no evidence that trospium prolongs the QT interval.

Reviewer's Overall Conclusions Regarding IP631-005

This was a multi-center, double-blind, placebo-controlled study of urinary frequency and urgency using trospium chloride (20-mg oral BID) versus placebo for 12 weeks with an open label extension in patients with overactive bladder. A total of 658 patients (trospium 329 patients, placebo 329 patients) were randomly assigned on a 1:1 ratio to receive either trospium 20-mg or placebo twice daily. The patient population was predominantly female (trospium 81.2%, placebo 81.8%) and Caucasian (trospium 86.3%, placebo 91.2%). The mean age for both trospium and placebo groups was 61 years. The treatment groups were well matched for demographic and baseline characteristics and are representative of the patient population commonly diagnosed with overactive bladder.

Trospium chloride demonstrated statistically significant ($p<0.0001$) improvement (i.e., decrease) for the primary efficacy variable of change in average number of daily toilet voids at Weeks 4, and 12 when compared with the placebo group.

In addition, trospium demonstrated statistically significant ($p< 0.0001$) improvement at Weeks 4, and 12 for the secondary efficacy variables of change in average urgency severity associated with toilet voids, urge frequency associated with toilet voids, volume voided per toilet void, and daily urge incontinence episodes when compared with placebo.

Specifically, trospium showed a statistically significant decrease in average urgency severity associated with toilet voids, a decrease in average urge frequency associated with toilet voids, an increase in average volume voided per toilet void, and a decrease in average number of daily urge incontinence episodes.

Sponsor emphasizes the fact that the findings of these efficacy variables are consistent with the expected pharmacodynamic effects of trospium chloride. i.e., anticholinergic relaxation of the detrusor muscle would be expected to increase maximum bladder capacity and increase volume at which the first unstable bladder contraction occurred. Thereby, providing clinical effects of decreased average daily number of toilet voids, decreased urgency severity, decreased urge frequency, increased volume voided, and decreased average daily urge incontinence episodes.

An exploratory analysis of the rate of improvement/response over time was conducted to determine onset of effect across study weeks for effect on toilet voids, urgency severity, urge frequency, volume voided, and urge incontinence episodes within 1week. The time to onset of effect across study weeks was statistically significant ($p<0.05$) for the trospium chloride group compared with the placebo group at Weeks 12, 4, and 1. The results of these analyses show that the onset of effect for trospium chloride is expected to provide clinical benefit by significantly decreasing the number of daily toilet voids, decreasing urgency severity, decreasing urge frequency, increasing the volume voided per toilet void, and decreasing the number of daily urge incontinence episodes from first week of treatment but clinically significant by week 4 and on.

TEAE's were most commonly reported for the gastrointestinal system with 103 patients (31.3%) in the trospium group and 55 patients (16.7%) in the placebo group experiencing such events. Dry mouth and constipation were the most frequently reported TEAE's.

TEAE's that occurred in >5% of patients in either treatment group were dry mouth, constipation, and headache. The TEAE's of dry mouth and constipation occurred significantly more often in the trospium group compared with the placebo group. The number TEAE's that occurred in >5.0% of patients in either treatment group were of patients who experienced headache was similar ($p=0.72$) in both trospium and placebo groups. The more frequent occurrence of dry mouth and constipation in trospium treated patients is consistent with the anticipated anticholinergic effects of trospium chloride.

TEAE's of myocardial infarction were reported in 3 trospium patients (0.9%). All three patients had multiple underlying pre-morbid conditions that were risk factors for the occurrence of a myocardial infarction.

The analysis submitted in the safety report by the sponsor concluded that the treatment-emergent cardiovascular events were relatively uncommon. A low-level incidence of cardiovascular events in patients with overactive bladder is anticipated due to the average age of this population (i.e., 61 years of age) and probably reflects the baseline incidence of cardiovascular disease in this population. The cluster analysis of cardiovascular events from both US placebo controlled studies concluded that there was no evidence of an increased incidence of cardiovascular events in patients taking trospium chloride when compared with patients taking placebo.

TEAE's commonly associated with anticholinergic agents and reported in this study included dry mouth, constipation, urinary retention and tachycardia. These were reported more often in the trospium group compared with the placebo group.

There was 1 patient who experienced an adverse event leading to death. This patient had multiple pre-morbid clinical conditions that could have contributed to this serious adverse event i.e., death.

Study medication was permanently discontinued due to TEAE's in a total of 39 patients [trospium 24 patients (7.3%), placebo 15 patients, 4.6%]. The most common TEAEs that

led to discontinuation of study medication in the trospium chloride group were constipation and dry mouth.

The number of patients who met potentially clinically significant (PCS) criteria for the hematology and serum chemistry laboratory data was similar for the trospium chloride and placebo groups.

Overall, the number of patients who met PCS criteria for the vital signs and ECG data were similar for both trospium and placebo groups. There is some evidence of an effect of trospium on modestly increasing ECG-derived heart rates in some patients.

In conclusion, trospium chloride given as 20mg twice daily was shown to be significantly better than placebo for the primary efficacy endpoint of decreased average daily number of toilet voids and the secondary endpoints of decreased urgency severity, decreased urge frequency, increased volume voided, and decreased number of daily urge incontinence episodes. Trospium chloride was safe and generally well tolerated in this study. The data from this study supports the conclusion that trospium chloride 20 mg BID is an effective and safe treatment option in patients with overactive bladder.

Appendix C

NDA 21- 595 Trospium Chloride
Medical Officer's Review of Study MP94D2.14

Table of Contents

1.0 Study Objectives

The objective of this study was to examine the efficacy and tolerability of 20mg trospium cloride twice daily given for a period of 21 to 28 days.

2.0 Investigational Plan

2.1 Efficacy Variables

2.1.1 Primary efficacy Variables

Primary efficacy variables were assessed at visit 0 (before onset of treatment) and at visit 2 (following discontinuation of treatment). The primary efficacy variables were:

- Maximum cystometric bladder capacity (ml)
- **Volume at first unstable contraction (ml)**

Reviewer's Comment

Primary efficacy variable is acceptable

3.1.2 Secondary Efficacy

The secondary efficacy variables were assessed at visit 0 (before onset of treatment) and at visit 2 (following discontinuation of treatment). The secondary efficacy variables were:

- **Maximum detrusor pressure during first unstable detrusor contraction (cm H_2O)**
- **Volume at maximum detrusor contraction (ml)**
- **Volume of residual urine (ml)**
- **Maximum urinary flow (ml/sec)**

Reviewer's Comments

Secondary efficacy variables are acceptable

3.2 Study Design

This is a multi-center, randomized, double blind, placebo-controlled, parallel- group design for patients with overactive bladder (i.e., detrusor instability). Both males and females were included in this study. The duration of the study was 3 to 4 weeks.

There were 309 patients with overactive bladder symptoms who were enrolled in this study. Of those enrolled, 210 patients (68%) were randomized to receive the study drug (trospium) and 99 patients (32%) received placebo. 262 patients (84.8%) completed the study.

Patients with three months of urodynamic measurements prior to the start of the study were accepted into the trial. Subsequently patients were treated with trospium chloride 20-mg twice daily or placebo for 21 days to a maximum of 28 days. At the end of the study treatment (i.e., visit 2), all measurements were repeated.

Reviewer's comment
The study design and enrollment of patients is appropriate and acceptable for this supportive study.

2.3 Dosing Schedule
Patients received one tablet of trospium chloride 20-mg or placebo in the morning before breakfast and one tablet of trospium chloride or the placebo in the evening before dinner for 21 days, with a possible prolongation to 28 days if necessary. Both trospium and placebo tablets were identical with respect to size, shape, color, taste, smell and weight.

3.4 Study Population
Patients with a confirmed diagnosis of "urge syndrome" (symptoms of "detrusor instability"), who met the inclusion and exclusion criteria were included into the study.

3.4.1 Inclusion Criteria
Patients were entered in to the study only if they met the following criteria:

1. Male or female patients aged 18 and above
2. Patients with urge-syndrome (i.e., detrusor instability) verified by determining the urodynamic measurements up to three months before starting the treatment
3. Patients with no communication problems with the investigator
4. Patients who have submitted a signed informed consent to participate in the trial
5. Patients with maximum cystometric bladder capacity < 350 ml at the start of the trial
6. Patients with urological and gynaecological surgeries at least three months prior to start of the trial
7. Female patients of childbearing potential with negative pregnancy test and use of safe contraceptive methods during the study.

Reviewer's Comment
Inclusion criteria for this study are acceptable for this supportive pharmacoynamic study.

3.4.2 Exclusion Criteria
Patients were not entered in to the study or were discontinued from the study for any of the following reasons:
1. Neurogenic bladder (caused by paraplegia)
2. Closed angle glaucoma
3. Myasthenia Gravis
4. Untreated tachy-arrhythmia
5. Outflow obstruction caused by BPH with a residual volume of > 50 ml.
6. Patients with stress incontinence.

7. Acute or chronic UTI
8. Allergies or intolerance toward anticholinergics
9. Concurrent treatment with other anticholinergics, TCA's, α-blockers and β- sympathomimetics, amantidine, quinidine, disopyramid and calcium antagonists 7 days before first urodynamic measurement. (Concurrent treatment with calcium antagonists was permitted only if started 3 months prior to start of trial medication).
10. Urological or gynecological surgery within three months of enrollment
11. History of ETOH or drug abuse.
12. Patients with an obstructive micturition disorder, malignant tumor or a stone
13. Pregnancy, lactation period and women of childbearing potential without safe contraception
14. Participation in a clinical trial within the last 30 days prior to visit 1.
15. Patients with history of gastro-intestinal stenosis.

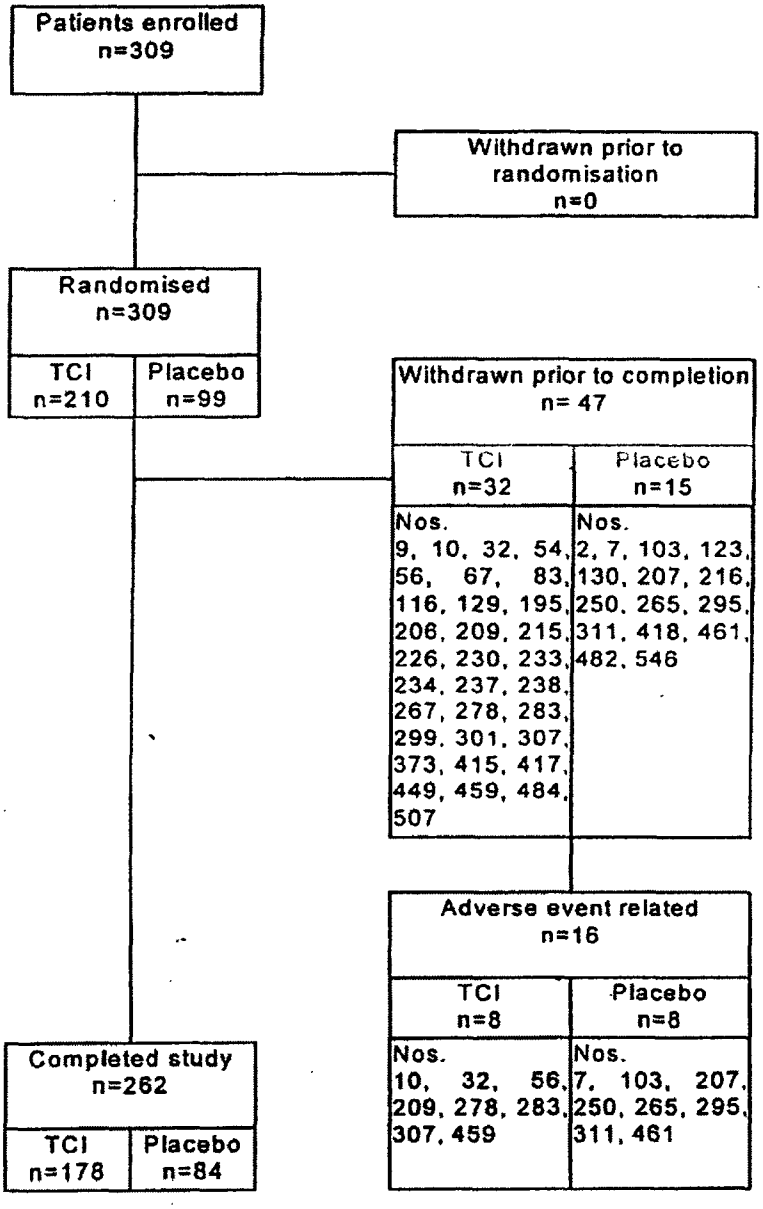
Reviewer's Comment
Exclusion criteria are adequate and acceptable for this supportive pharmacodynamic study.

3.4.3 Patient Disposition

In total 309 patients were enrolled into the study. Of the enrolled patients, 210 (68%) were treated with trospium and 99 (32%) patients received placebo. 262 patients (84.8%) completed the study (i.e., trospium 178 and placebo 84). A total of 47 patients withdrew prior to completion of the study (i.e., 32 patients in trospium group and 15 patients in placebo group.

Twelve patients (trospium 9 and placebo 3) were classified as drop outs by the investigator, but were not considered as withdrawals for statistical evaluation (ITT) as they completed the examination at visit 2. Sixteen patients (trospium 8 and placebo 8) were withdrawn due to an adverse event.

Figure C1. Patient Completion Flowchart for MP94D2.14



3.5 Treatments

Treatment regimens administered during this trial were

- Trospium chloride 20mg tablet taken orally twice daily (morning and in the evening)
- Placebo tablet orally twice daily (morning and in the evening)

4.0 Review of Efficacy in MP94D2.14

The primary purpose of this clinical trial was to demonstrate efficacy of a 3-week treatment with 20-mg trospium chloride given twice daily compared to placebo in patients with detrusor instability.

The efficacy analysis was carried out for both PP population and ITT population. There were 147 patients included in the PP population and all 309 randomized patients to ITT population.

Patients who had no evidence of unstable contractions at visit 2 and consequently no documentation for volume at first unstable contraction and volume at maximum detrusor contraction were treated as a therapeutic success in the analysis if they had a corresponding value for these variables at baseline.

Efficacy Results

Primary Efficacy: Maximum Cystometric Bladder Capacity

PP population

The treatment groups were well balanced with regard to the baseline values of maximum cystometric bladder capacity. A mean increase of 79ml was seen in trospium group after three weeks of treatment compared to 5mL increase in the placebo group. The mean treatment effect (difference between trospium and placebo) was 74ml. The 95% confidence interval for the treatment effect was 38 to 109 ml. According to the sponsor's analysis, this treatment effect was statistically significant with p=0.0001. The differences are considered to be clinically relevant.

Table C1. Maximum Cystometric Bladder Capacity in mL (PP) in MP94D2.14

	Trospium chloride (n=99)			Placebo (n=48)		
	Visit 0 (ml)	Change (ml)	Relative Change (%)	Visit 0 (ml)	Change (ml)	Relative Change (%)
Mean	206.6	+79.1	+47.8	212.4	+5.2	+11.3
SD	78.56	103.06	72.10	82.74	99.16	52.44
Median	204.0	+61.0	+32.0	200.0	-4.0	-2.2
95 % CI	+38.4; +109.0					
p value	0.0001					

CI - Confidence Interval,

ITT population

A total of 308 patient had documented baseline values of maximum cystometric bladder capacity. According to the sponsor the documentation at visit 0 and 2 for patient # 529 from the placebo group was lost. At visit 2, there were 177 patients (84.2%) and 83 (83.8%) patients with urodynamic data in trospium and placebo treatment group respectively.

Table C2: Maximum Cystometric Bladder Capacity in mL (ITT) in MP94D2.14

	Trospium chloride (n=177)			Placebo (n=83)		
	Visit 0 (ml)	Change (ml)	Relative Change (%)	Visit 0 (ml)	Change (ml)	Relative Change (%)
Mean	224.5	+70.7	+44.8	227.4	+5.4	+15.1
SD	97.26	107.69	73.83	94.43	116.83	65.35
Median	217.0	+60.0	+29.2	210.0	+10.0	+4.9
95 % CI	+36.3; +94.3					
p value	< 0.00005					

CI - Confidence Interval,

As per the sponsor the baseline values for ITT population were very similar to those in the PP-analysis. The mean increase of volume was 70.7 ml in trospium group compared to 5.4 ml in the placebo group. According to the sponsor, the difference in treatment was statistically significant with $p<0.00005$. This difference is considered to be clinically relevant.

Reviewer's Comment

This reviewer agrees that there is a clinically relevant improvement in maximum bladder capacity with trospium compared to placebo in patients in both (PP and ITT) populations. The improvement in this key primary efficacy variable is not only statistically significant (per sponsor), but also clinically relevant.

Volume at First Unstable Contraction

PP population

In both treatment groups, the volume at first unstable contraction was increased from baseline to the end of treatment. However, the increase was more pronounced in trospium group (i.e., trospium 97.7 ml and placebo 42.7-ml). According to the sponsor, the difference was statistically significant ($p=0.006$). The difference is considered to be clinically relevant.

Table C3: Volume (mL) at First Unstable Contraction (PP) in MP94D2.14

	Trospium chloride (n=98)			Placebo (n=48)		
	Visit 0 (ml)	Change (ml)	Relative Change (%)	Visit 0 (ml)	Change (ml)	Relative Change (%)
Mean	119.3	+97.7	+157.1	108.5	+42.7	+96.4
SD	79.44	123.52	247.90	72.66	89.90	232.29
Median	102.5	+82.5	+78.3	95.0	+29.0	+38.8
95 % CI	+15.4; +94.6					
p value	0.0027 (t test for unequal variances)					

CI - Confidence Interval,

ITT population

In this population the effect was similar to that of PP analysis. The effect was more pronounced in trospium group (i.e., 97.4 ml) and 41.4 ml in the placebo group. The mean difference in the effect between the two treatment groups was 56 ml, accordign to sponsor, a statistically significant change with p = 0.0001. The change was considered to be clinically relevant.

Table C4: Volume (mL) at First Unstable Contraction (ITT) in MP94D2.14

	Trospium chloride (n=173)			Placebo (n=83)		
	Visit 0 (ml)	Change (ml)	Relative Change (%)	Visit 0 (ml)	Change (ml)	Relative Change (%)
Mean	118.4	+97.4	+145.8	113.7	+41.4	+97.1
SD	77.56	124.37	229.69	78.53	88.81	216.28
Median	100.0	+75.0	+67.0	90.0	+30.0	+37.5
95 % CI	+26.0;+86.0					
p value	0.0001 (t test for unequal variances)					

CI - Confidence Interval,

Reviewer's Comment

This reviewer agrees that there was a clinically relevant increase in volume at first contraction among patients in both treatment groups. However, the increase in volume was more pronounced in the trospium group.

The sponsor also conducted a subgroup analysis for both primary variables in patients with age <65 years and >65 years. As is evident from the table below, there is a small but significant difference in change in both primary variables between the two age groups. The change is slightly more pronounced in patients >65 years of age for volume at first contration.

Table C5: Changes in Primary Variables from Baseline by Age in MP94D2.14

		Age < 65 years		Age >= 65 years	
		Trospium chloride	Placebo	Trospium chloride	Placebo
Maximum cystometric bladder capacity (ml)	n Mean SD	62 +80.0 111.22	28 +15.8 82.93	37 +77.5 89.18	20 -9.7 118.97
Treatment effect	Mean	+64.2		+87.2	
Test for interaction	p	> 0.5			
Volume at first unstable contraction (ml)	n Mean SD	62 +90.2 121.18	28 +43.9 95.32	37 +110.1 127.97	20 +41.0 84.12
Treatment effect	Mean	+46.3		+69.1	
Test for interaction	p	> 0.2			

Reviewer's Comment

It is clear from Table C5 that the improvement in both primary variables (i.e., maximum bladder capacity and volume at first contraction) was more marked in the age group 65 years and above. Therefore, in the opinion of this reviewer, this supports the contention that trospium chloride will prove to be beneficial in controlling symptoms of OAB due to detrusor instability especially in elderly (>65 years), where the condition is more commonly seen.

Secondary Efficacy Variables

Maximum Detrusor Pressure at First Unstable Contraction

PP Population

Maximum detrusor pressure of the first unstable contraction at baseline was similar in two treatment groups (i.e., trospium 46.6 cm H_2O and placebo 43.1 cm H_2O) that decreased by 1.5 cm and 4.0 cm H_2O respectively. This effect was not statistically significant (p=0.66)

Table C6: Maximum Det Pressure (mm Hg) at First Unstable Contraction (PP)

	Trospium chloride (n=71)			Placebo (n=42)		
	Visit 0 (ml)	Change (ml)	Relative Change (%)	Visit 0 (ml)	Change (ml)	Relative Change (%)
Mean	46.6	-1.5	+26.9	43.1	-4.0	-1.0
SD	37.36	32.29	107.38	38.38	22.73	50.72
Median	33.0	0.0	0.0	27.5	-4.5	-11.18
95 % CI	-8.7; +13.7					
p value	0.66 (t-test for unequal variances)					

CI - Confidence Interval,

ITT Population

There was similar change as in PP analysis. The change in detrusor pressure on trospium group was -0.9 ml and -2.4 ml in the placebo group. This change was minimal and statistically not significant (p=0.68)

Table C8: Maximum Detrusor Pressure (mm Hg) at First Unstable Contraction (PP) in MP94D2.14

	Trospium chloride (n=130)			Placebo (n=74)		
	Visit 0 (ml)	Change (ml)	Relative Change (%)	Visit 0 (ml)	Change (ml)	Relative Change (%)
Mean	36.5	-0.9	+103.6	37.8	-2.4	+1.0
SD	32.32	28.54	840.42	33.58	22.44	69.65
Median	23.5	-0.4	-1.0	25.0	-3.5	-38.10
95 % CI	-6.1; +9.1					
p value	0.68 (t-test for unequal variances)					

CI - confidence interval,

Reviewer's Comment

It apparent from the data submitted that there was not much improvement seen in detrusor pressure at first contraction with trospium in either population.

Volume at Maximum Detrusor Contraction

PP population

The sponsor points out that in view of an increased bladder capacity and volume at first unstable contraction, the volume at maximum detrusor contraction increased by 75.6 ml in trospium group and 16.8 ml in the placebo group. The mean difference in the treatment effect was 58.8 ml, which sponsor believes was statistically significant (p=0.0077), and clinically relevant.

Table C9: Volume (mL) at Maximum Detrusor Contraction (PP) in MP94D2.14

	Trospium chloride (n=98)			Placebo (n=48)		
	Visit 0 (ml)	Change (ml)	Relative Change (%)	Visit 0 (ml)	Change (ml)	Relative Change (%)
Mean	168.6	+75.6	+99.1	168.2	+16.8	+48.9
SD	83.35	127.57	214.31	93.14	114.71	118.9
Median	174.5	+67.0	+37.1	158.5	+8.0	+5.5
95 % CI	+15.8; +102.0					
p value	0.0077					

CI - Confidence Interval,

ITT Population

The outcome of the ITT analysis was similar to that of PP population. The maximum detrusor contraction increased by 68.5 ml in tropsium group and by 18.8 ml in the placebo. The difference between the groups was statistically significant with p = 0.0024.

Table C10: Volume (mL) at Maximum Detrusor Contraction (PP) in MP94D2.14

	Trospium chloride (n=175)			Placebo (n=83)		
	Visit 0 (ml)	Change (ml)	Relative Change (%)	Visit 0 (ml)	Change (ml)	Relative Change (%)
Mean	185.6	+68.5	+79.1	181.8	+18.8	+41.6
SD	102.18	126 43	174.09	94.45	110.32	106.01
Median	180.0	+55.0	+32.9	180.0	+15.0	+13.6
95 % CI	+17.8; +81.6					
p value	0.0024					

CI - Confidence Interval,

Reviewer's Comment

This reviewer agrees that there was a increase in volume at maximum detrusor contraction and the increase was more marked in trospium group in both (PP and ITT) populations.

Volume of Residual Urine

The mean volume of residual urine in trospium group increased in both PP and ITT populations (10.6 ml and 9.1 ml respectively). The increase in the placebo group was markedly lower (2.4 ml and 0.3 ml respectively. Although, the overall increase is low, it did not prove to be statistically significant.

Table C11. Volume of Residual Urine (mL) in MP94D2.14 (PP)

	Trospium chloride (n=98)			Placebo (n=45)		
	Visit 0 (ml)	Change (ml)	Relative Change (%) (n=33)	Visit 0 (ml)	Change (ml)	Relative Change (%) (n=8)
Mean	10.2	+10.6	+12.9	5.1	+2.4	-1.1
SD	17.96	53.31	129.51	12.99	14.05	72.51
Median	0.0	0.0	-12.5	0.0	0.0	-7.1
95 % CI	-7.8; +24.2					
p value	0.31					

CI - Confidence Interval

Table C12. Volume of Residual Urine (mL) in MP94D2.14 (ITT)

	Trospium chloride (n=175)			Placebo (n=79)		
	Visit 0 (ml)	Change (ml)	Relative Change (%) (n=63)	Visit 0 (ml)	Change (ml)	Relative Change (%) (n=22)
Mean	10.5	+9.1	+16.0	6.8	+0.3	-12.1
SD	21.60	46.76	159.26	16.05	16.16	71.01
Median	0.0	0.0	-12.5	0.0	0.0	-14.3
95 % CI	-1.9; +19.4					
p value	0.10					

CI - Confidence Interval

Reviewer's Comment

Although, the increase in residual volume is not great (10.6 ml in trospium group), other studies have clearly shown an increase in the volume voided per micturition.

Maximum Urinary Flow

Overall, the maximum urinary flow did not change in either treatment groups (PP or ITT population) as is evident from the tables below.

Table C13. Maximum urinary flow rate (mL/sec) in MPD2.14 (PP)

	Trospium chloride (n=83)			Placebo (n=36)		
	Visit 0 (ml/sec)	Change (ml/sec)	Relative Change (%)	Visit 0 (ml/sec)	Change (ml/sec)	Relative Change (%)
Mean	15.7	+1.7	+27.2	13.8	-0.6	+7.9
SD	9.65	8.52	84.81	7.91	7.67	73.43
Median	13.0	+1.5	+13.1	14.1	-2.0	-15.5
95 % CI	-1.0; +5.6					
p value	0.17					

CI - Confidence Interval,

Table C14. Maximum urinary flow rate (mL/sec) in MPD2.14 (ITT)

	Trospium chloride (n=151)			Placebo (n=66)		
	Visit 0 (ml/sec)	Change (ml/sec)	Relative Change (%)	Visit 0 (ml/sec)	Change (ml/sec)	Relative Change (%)
Mean	17.2	+0.6	+18.5	16.3	-0.4	+11.1
SD	9.88	9.02	74.62	8.70	7.76	76.19
Median	15.0	+0.1	+0.5	15.3	-1.3	-9.8
95 % CI	-1.5; +3.5					
p value	0.41					

CI - Confidence Interval,

Assessment of Efficacy by the Investigator and by the Patients

PP Population

The global efficacy assessment by the patients differed from the investigator assessment in almost all categories. The differences recorded were in favor of the active treatment group. This was more apparent in the category of marked improvement.

Table C15. Global assessments of efficacy in MP94D2.14 (PP)

	Treatment group			
	TCI n=99		Placebo n=48	
	N	%	N	%
Investigator				
cured	12	12.1	1	2.1
marked improvement	36	36.4	9	18.8
slight improvement	24	24.2	13	27.1
no improvement	26	26.3	21	43.8
worsened	1	1.0	4	8.3
Patient				
cured	11	11.1	2	4.2
marked improvement	47	47.5	9	18.8
slight improvement	19	19.2	20	41.7
no improvement	21	21.2	16	33.3
worsened	1	1.0	1	2.1

ITT Population

The global assessment for ITT population was similar to PP population for both the investigator and patient assessment.

Table C16. Global assessments of efficacy in MP94D2.14 (ITT)

	Treatment group			
	TCI n=210		Placebo n=99	
	N	%	N	%
Investigator				
[2]	28	13.3	11	11.1
cured	28	13.3	3	3.0
marked improvement	67	31.9	23	23.2
slight improvement	45	21.4	26	26.3
no improvement	39	18.6	29	29.3
worsened	3	1.4	5	5.1
Patient				
	28	13.3	10	10.1
cured	25	11.9	3	3.0
marked improvement	84	40.0	25	25.3
slight improvement	36	17.1	32	32.3
no improvement	35	16.7	27	27.3
worsened	2	1.0	2	2.0

Reviewer's Comment

This reviewer acknowledges that both the investigators and the patient's assessment of efficacy found a meaningful improvement in symptoms of OAB in this trial.

Efficacy Conclusions Regading MPD294.14

This study provides pharmacodynamic evidence of an improvement in both the primary efficacy variables (i.e., maximum cystometric bladder capacity and volume at first unstable contraction) as a result of treatment with trospium.

Maximum cystometric bladder capacity increased in both PP and ITT populations (by 79.1 ml in trospium group and 5.2 ml in placebo group) with a mean treatment effect of 73.9 ml (PP) and 65.3 ml (ITT). This treatment difference was clinically relevant.

The increase in volume at first unstable contraction was also higher in the trospium group versus placebo (PP 97.7 ml in trospium and 42.7 ml in placebo). This treatment effect improvement was also clinically relevant. The results were similar in ITT population.

The secondary variable for efficacy i.e., maximum detrusor pressure at first unstable contraction, mildly decreased in both treatment groups, but was more pronounced in trospium group than in placebo. The volume at maximum detrusor contraction also increased in the trospium group compared to the placebo group.

A subjective global assessment of efficacy was conducted by both investigators and patients. An improvement in overall perception of OAB symptoms was noticed by patients in trospium group in both PP as well as ITT population when compared to placebo.

Sponsor also conducted a sub-group analysis for patients < 65 years and > 65 years. This analysis did reveal a slightly greater improvement in ages 65 years and above with respect to primary efficacy variables.

The micturition diary data collected was scant and not appropriate for detailed review.

Reviewer's Overall Efficacy Comment for MP94D2.14
In the opinion of this reviewer, trospium chloride was demonstrated to provide a benefit in both primary efficacy variables chosen for this study.

This reviewer concludes that the evidence from this controlled study supports the effectiveness of trospium chloride (20-mg bid) for the treatment of overactive bladder.

Review of Safety in MP94D2.14
Brief Statement of safety
The adverse event profile of trospium chloride appears to be similar to that of other anti-cholinergic drugs in its class. Most affected organ system being gastrointestinal, and the frequent adverse events reported were dry mouth, nausea, constipation and diarrhea during the 21 to 28 day treatment period.

Other less frequently reported but clinically important adverse events included constipation, urinary retention and UTI.

Sponsor completed study MP94D2.14 at multiple sites in Europe. 309 patients with overactive bladder due to detrusor instability were enrolled and received at least one dose of study medication. The population used for evaluation of safety data and the ITT population was identical in this clinical trial.

The median treatment duration was calculated as 21 to 28 days. A total of 55 patients (17.8%) had at least one adverse event (AE) during this clinical trial.
In the trospium group there were 40 patients (19%) who had adverse events (AE's) compared with 15 patients (15.2%) in the placebo group.

Three patients (1%) [2 from trospium and 1 from the placebo] experienced a serious adverse event (SAE). The SAE's in the trospium group were stroke and fecal and urinary retention. The causality of stroke was determined by the investigator as not related, but the causality of fecal and urinary retention was determined as probably related to the study drug. One SAE in the placebo group was urinary retention, which was moderate in intensity.

Data from adverse events, clinical laboratory test results, vital signs and deaths were reviewed to evaluate the safety and tolerability of trospium chloride.

Table C17. Overall Adverse Events in MP94D2.14

Number of adverse events per patient	Trospium chloride (n=210)	Placebo (n=99)	Total (n=309)
1	29 (13.8)	13 (13.1)	42 (13.6)
2	5 (2.4)	2 (2.0)	7 (2.3)
3	3 (1.4)	0 (0.0)	3 (1.0)
4	2 (1.0)	0 (0.0)	2 (0.6)
5	1 (0.5)	0 (0.0)	1 (0.3)

Table C17a. Severity and Causality of Adverse Events in MP94D2.14

Body system Disorders	Trospium chloride (n=210)					
Intensity	Mild		Moderate		Severe	
Relationship	Not related or not assessable	Related	Not related or not assessable	Related	Not related or not assessable	Related
Gastro-intestinal disorders	-	1 (0.5) No. 289	-	10 (n=9, 3.8) Nos. 32, 47, 187, 209 [2AE], 266,283, 289,356,360	1 (0.5) (No. 427)	5 (n=3, 1.4) Nos. 56 [3 AE], 284, 356
Urinary system disorders	5 (2.4) Nos. 225, 231, 413, 501, 508	-	1 (0.5) No. 145	2 (1.0) Nos. 55, 283	1 (0.5) No. 282	1 (0.5) No. 10
Centr. & periph. nervous system d.	1 (0.5) No. 69	-	-	2 (1.0) Nos. 46, 209	-	1 (0.5) No. 56
Body as whole general d.	1 (0.5) No. 541	-	-	-	-	-
Liver & biliary system disorders	3 (1.4) Nos. 537, 540, 541	-	-	-	-	-
Respiratory system disorders	1 (0.5) No. 307	1 (0.5) No. 187	1 (0.5) No. 483	-	-	1(0.5) No. 360
Metabolic & nutritional disorders	1 (0.5) (No. 213)	-	-	-	-	1 (0.5) No. 319
Skin and appendages disorders	-	-	-	-	-	1 (0.5) No. 459
Cardiovasc. disorders (gen.)	-	-	-	1 (0.5) No. 356	-	-
Musculo-skeletal system disorders	2 (1.0) Nos. 307, (427)	-	-	-	-	-
White cell and respirat. disorders	2 (1.0) Nos. 497, 543	-	-	-	-	-
Platelet, bleeding, clotting d.	1 (0.5) (No. 187)	-	-	-	-	-
Myo endo-pericardial & valve d.	-	-	-	1 (0.5) No. 289	-	-
Vision disorders	-	1 (0.5) No. 289	-	-	-	-
Resist. Mechanism disorders	-	-	1 (0.5) No. 340	-	-	-
Vascular (extracar-diac) disorders	-	-	-	-	1 (0.5) No. 278	-

Table C17b. Severity and Causality of Adverse Events in MP94D2.14 (placebo)

Body system Disorders	Placebo (n=99)					
Intensity	Mild		Moderate		Severe	
Relationship	Not related or not assessable	Related	Not related or not assessable	Related	Not related or not assessable	Related
Gastro-intestinal disorders	-	-	-	1 (1.0) No. 7	-	-
Urinary system disorders	2 (2.0) Nos. 223, 506	-	1 (1.0) No. 293	-	-	2 (2.0) Nos. 295, 311
Body as whole general d.	-	-	-	1 (1.0) No. 250	-	1 (1.0) No. 265
Liver & biliary system disorders	2 (2.0) Nos. 494, 536	-	-	-	-	-
Skin and appendages disorders	-	-	-	-	-	1 (1.0) Nos. 461

Specific Commonly Reported Adverse Events

Table C18. Specific Adverse Events by System in MP94D2.14

Adverse Events	Trospium	Placebo
Gastrointestinal	15	1
Urinary Disorders	10	3
Urinary Retention	1	3
Dizziness and Headache	4	2
Respiratory Symptoms	4	0
Exanthema &Visual Abnormality	1	2

Fifteen (15) patients in trospium group experienced adverse events, which were mostly gastrointestinal. Apart from one patient, all events were considered tropium-related. Six patients experienced dry mouth, two patients had constipation, and three had diarrhea. Other adverse events reported were nausea, epigastric pain, bloating, retching and constipation. In two patients #209 and # 56, the medication was stopped due to adverse events. There was one patient in the placebo group, who experienced vomiting but recovered and continued the study medication.

Urinary disorders, mostly mild to moderate in severity, were reported in 11 patients in trospium group. Of those eleven, urinary retention was reported in one patient in whom the study drug was stopped. Urinary infection was reported in four patients and was considered not related in three of the four. There were five patients in the trospium group and three patients in placebo group, who experienced abnormal urine (by urine stick measurement) without any accompanying clinical symptoms. In the placebo group, two out of 3 events of urinary retention were judged as drug-related by the investigator.

There were 3 patients who experienced dizziness and one had headache in the trospium group. In two out of four patients (#56 and # 209) the treatment with trospium was stopped. In placebo group, there were two patients who experienced headache that resolved.

There were 4 patients in trospium group who experienced respiratory symptoms such as dyspnea, cough and bronchitis. In two out of four, the symptoms were thought by the investigator to be related to the study medication, but in all patients the symptoms resolved without any intervention.

There was one patient in the trospium group and two in the placebo, who experienced exanthema and mild visual disturbance that resolved sponstaneously.

Withdrawals Due to Adverse Events
There were 8 patients from each treatment group who withdrew from the study as a result of adverse events (some judged to be related to study medication and some not, as determined by the investigator).

In the trospium group, the events leading to discontinuation were: urinary retention, stomach upset, nausea, diarrhea, headache, retching, dry mouth, constipation, urinary retention, exanthema and respiratory symptoms.

In the placebo group, patients were discontinued as a consequence of exanthema, headache, allergy and urinary retention.

Deaths
There were no deaths reported during the course of this trial.

Serious Adverse Events
There were no serious adverse events reported during this clinical trial.

Adverse Events Leading to Dose Reduction
There were no serious adverse events reported which resulted in medication dose reduction

Reviewer's Comment
This reviewer agrees with the assessment in this submission that there were no serious treatment emergent adverse events reported. In regard to the commonly reported adverse events (i.e., dry mouth, constipation, headache and urinary retention), these were mild in severity and commonly seen with other anticholinergic agents

Other Medically Significant Adverse Eents
There were 3 patients (trospium 2 and placebo 1) who experienced other significant (not serious) adverse events, however, these were all considered to be sequalae of pre-morbid medical conditions and none resulted in a serious event. Narratives for these follow:

Patient # 278 (trospium Chloride)
This 84-year-old male patient with past medical history significant for CHF, BPH experienced a stroke while on trospium chloride and developed mild hemiparesis. The patient was hospitalized and the study medication was discontinued. The relation to the

study medication as determined by the investigator was improbable. Patient improved and later was discharged home.

Patient # 283 (trospium chloride)
This 79-year-old male patient with diabetes mellitus, two days after being on trospium developed both fecal impaction and urinary retention. The study medication was withdrawn. The causality was determined by the investigator as probably related. The patient recovered completely.

Patient # 295 (Placebo)
This 56-year-old male patient with no significant past medical history and no concurrent medication use developed moderate urinary retention after 15 days of being on treatment with placebo. Study medication was withdrawn and patient recovered.

Reviewer's Comment
It is the opinion of this reviewer that stroke in patient #278 was most likely a result of his pre-morbid medical condition and not a result of taking trospium. However, urinary retention is a known side effect of antichloinergics. Therefore, as discussed previously, the frequency of trospium chloride may be reduced to 20mg daily in the elderly depending on tolerability.

Laboratory Evaluation
Based on the study protocol, routine laboratory tests were conducted at screening and at the end of the trial. Hematology, chemistry, and urinalysis data were reviewed for changes that occurred from baseline to on-treatment. The sponsor reports that there was no treatment related relevant change in any laboratory values seen during this trial.

Reviewer's Comment
This reviewer agrees with the sponsor that there were no patients with any abnormal laboratory values or clinically relevant physical examination changes seen during this trial.

Vital Signs and Physical Examination
No clinically relevant changes were recorded in physical examination and vital signs.

Tolerability
Overall, the tolerability in trospium group was judged by both the investigator and the patients between good and very good (83.8% and 82.8%). It was similarly well-tolerated in the placebo group (82.8% and 83.8%). A global assessment of tolerability showed no statistical significant difference between the two treatment groups.

Sponsor's Safety Conclusions Regarding MP94D2.14
All 309 patients randomized took study medication at least once and were included in the safety analysis. 55 patients [40 (17.8%) tropium and 15 patients (15.2%) in the placebo group] had at least one adverse event. Most frequent adverse events in the trospium group

were gastrointestinal (dry mouth) and urinary retention. In the placebo group, the most common adverse events experienced were exanthema, allergy and urinary abnormalities. The frequency of adverse events was similar in both treatment groups and is commonly seen with anticholinergic class of drugs i.e., dry mouth and urinary retention.

The two significant adverse events that were seen with trospium were stroke and fecal/urinary retention. In the patient who experienced stroke, the causality was believed related to pre-morbid medical condition and advanced age and not trospium. However, urinary retention in another patient was attributed by the investigator as a related to trospium. The single significant adverse event in the placebo group, i.e., urinary retention, was thought to be drug related under blinded condition. No patients experienced any serious events.

No clinically relevant or meaningful changes were demonstrated in laboratory parameters or physical examination of patients at the end of the trial.

The safety and tolerability was assessed as good or very good in majority of patients by both investigators and the patients.

Reviewers Comment
In the opinion of this reviewer, for this supportive study, it is appropriate to conclude that safety evaluation of trospium chloride did not reveal any risks other than those adverse events that are commonly seen with anticholinergic drugs.

Sponsor's Overall Conclusion Regarding Study MP94D2.14
This is a multi-center, randomized, double blind, placebo-controlled, parallel- group study of trospium chloride 20-mg oral given twice daily and placebo for 3-4 weeks in patients with overactive bladder due to detrusor instability. In this trial, the main focus was to evaluate the pharmmacodynamic efficacy of trospium chloride in patients with "urge syndrome".

Patients with motor urge-syndrome (detrusor instability) have an unstable bladder, which is shown to contract spontaneously or on provocation, during the filling phase of the bladder while the patient is attempting to inhibit micturition.

In this study, patients with an instability of the detrusor, the so-called "motor urge syndrome" were included. Diagnosis was confirmed by an urodynamic measurement. The primary efficacy variables chosen in this study were appropriate for the objectives. The study showed a trospium-related improvement in the two primary efficacy variables, maximum bladder capacity and volume at first contraction. The difference in results between the trospium and placebo group was clinically relevant.

Adverse events (AE) occurred at similar frequencies in both study groups. They were mild in intensity and similar to those seen with other anticholinergics. There were no serious adverse events reported in this trial. There was no relevant influence of trospium

on the laboratory values or the physical findings both at the start and at the end of the study.

The global assessment of safety by investigators and patients reflected good tolerability.\

Reviewe's conclusion regarding MP94D2.14

It is the impression of this reviewer that trospium chloride 20-mg administered twice daily orally demonstrated activity in improving relevant urodynamic parameters in an appropriate patient population in this trial. The study showed an improvement in both primary variables (i.e., maximum bladder capacity and volume at first contraction), and in other secondary endpoints such as an increase in volume at maximum detrusor contraction. The product was reasonably well-tolerated in this trial.

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/s/

Suresh Kaul
5/28/04 11:24:50 AM
MEDICAL OFFICER

Mark S. Hirsch
5/28/04 11:27:43 AM
MEDICAL OFFICER
I concur.

NDA 21,595
Trospium chloride
Indevus Pharmaceuticals, Inc
Primary Goal Date: Feb 29th, 2004
Prepared for 45-day Filing meeting on June 12th, 2003

Medical Officer's NDA Filling Review
June 12th, 2003

I. Summary:
Objective:
The review is conducted to fulfill a regulatory requirement of reviewing a NDA to determine its suitability for filing under 21 CFR 314.101. This document will also serve as the basis for communicating to sponsor the potential review issues identified during this initial filing review period as required by CDER manual of policies and procedure (MaPP 6010.x)

Conclusion:
After the preliminary review of the clinical section of NDA submission (#21,595), this reviewer has not identified any deficiencies that would constitute the basis for a Refuse-to-File action as described in the FDA guidance 21 CFR 314.101(d) (3).
It is the impression of this reviewer that the application submitted is sufficiently complete to permit a substantive clinical review.

II. NDA Filing Review:
Drug Product:
Trospium chloride is a quaternary ammonium derivative of tropine with anticholinergic properties and peripheral muscarinic like activity, proposed for the treatment of symptoms of overactive bladder (OAB), a condition characterized by symptoms of urinary frequency, urgency and urge incontinence.

Trospium is slowly absorbed following an oral dose with maximum plasma concentrations occurring approximately 5 hours post dose. The mean absolute bioavailability is approximately 10%. Administration with high fat meal results in reduced absorption, with AUC and Cmax values 70%-80% lower than those obtained when trospium was administered while fasting. Metabolism is mediated by CYP450 and CYP 3A4, and the major route of elimination is renal excretion.

Trospium was initially authorized for marketing as a spasmolytic agent in 1966 in Germany. It is also authorized in many European countries for specific therapeutic indications including urinary frequency, nocturia, and urge incontinence.

An IND (#61,381) application for trospium was submitted in December 2000 to conduct clinical trials in the US. The Pre-NDA meeting was held in December 2002. This NDA submission comprises data from 32 clinical trials (12 clinical pharmacology studies, 12 controlled clinical studies, and 8 uncontrolled clinical studies)

Other drugs that have been approved for this indication in the US are oxybutynin (Ditropan) and tolterodine (Detrol)

Method of RTF Review:
The review is based on the three criteria proposed in FDA guidance for the filling review, which represents FDA's interpretation of 21 CFR 314.101 (d)(3):

- Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in an incomplete manner
- Failure to include evidence of effectiveness compatible with the statue and Regulations
- Omission of critical data, information or analyses needed to evaluate effectiveness and safety or failure to provide adequate directions for use.

Filing Review Results:

1. **Does the NDA omit a section required under CFR 314.50, or was the section of the NDA presented in such a manner as to render it incomplete for the clinical review?**
   Answer: No. The NDA contains the critical sections in a sufficient detail as demonstrated in Table 1. Certification is provided for all the investigators involved in the study # IP 631-003. That is the pivotal study required by the division to support the proposed indication.

Table .1. Checklist for the critical sections of NDA for a sufficient clinical review:

Required Sections (21 CFR 314.50)	**Location (Table of Contents)**
The proposed text of the labeling (c)(2)(I)	2
A summary of the data (c)(2)(viii)	3
The technical sections and integrated summaries (d)	8.12.2
Controlled clinical studies (d)(5)(ii)	8.12
Integrated summary of efficacy (d)(5)(ii)	8.7
Integrated summary of safety (d) (5) (vi)	8.8
Integrated summary of the benefits and risks (d)(5) (viii)	8.10
Required case report forms and tabulations (f)	1 and 12
Financial certification or disclosure statement (k)	19

2. **Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:**
   a. **lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant study endpoints**
   b. **presentation or what appears to be only a single adequate and well controlled trial without adequate explanation**
   c. **Use of a study design clearly inappropriate**

   Answer: **No**. As per the requirement of the division, the sponsor has provided data from one large multi-center, randomized double blind, placebo controlled, parallel group study conducted in the US to support the proposed indication and dosage (20 mg). In addition, the sponsor has also provided data from 11other controlled clinical studies with different duration conducted outside the US to support this indication. The studies appear to be adequate and well controlled.

   The primary endpoints used in this study include:
   1. Change in the average number of toilet voids per 24 hours.
   2. Change in the average number of urge incontinence episodes in 24 hours.

   The primary efficacy data is based on the diary reports collected over 7-day period.

3. **Does the NDA omit critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:**
   a. **total patient exposure at relevant doses that is clearly inadequate to evaluate safety**
   b. **clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets:**
   c. **absence of a comprehensive analysis of safety data**
   d. **absence of an analysis of data supporting the proposed dose and dose interval**

   Answer: **No**. The patients enrolled in this clinical study met the following criteria for overactive bladder (OAB).
   1. Urinary frequency of >10 micturitions per day.
   2. Symptoms of urgency
   3. Pure urge or mixed urinary incontinence with predominant urge incontinence.

   This is consistent with the division's standard for the selection of the target population. In the pivotal study, the majority of subjects are female (75%) with mean age of 62 years which is consistent with the disease distribution in the general population.

   In this study the percentage of non-white population is similar to that in general population.

The NDA contains 2772 subjects, who are exposed to study medication, and among those 208 are exposed to the drug for a year or longer in a controlled study. The NDA contains a well designed analysis of data supporting the proposed dose of 20 mg BID and it appears that the sponsor has achieved a statistical significance for the primary endpoints in this pivotal study to support the proposed dose of 20 mg BID.

IP631-003 Change in average number of toilet voids per 24 hours
Analysis of variance – ITT:LOCF

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

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

IP631-003 Change in average number of urge incontinence episodes per 24 hours
Averages with p-values from rank ANOVA – ITT:LOCF

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

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

The summary of clinical safety data appears to be well presented in the integrated safety summary (ISS).

Comment: The preliminary safety data does not appear to suggest that the study drug is associated with QT prolongation or liver toxicity. However this reviewer has concern over slightly higher percentage of patients reporting urinary retention and chest pain in the trospium group. Importance of this finding cannot be determined at this time.

Table 3. All TEAS reported in >2.0% of patients in either treatment or Placebo

Body System	Placebo (N=261)	Trospium (N=262) 20 mg BID
Total Patients with at least one TEAE	138(52.9)	171 (65.3)
Dry mouth	17(6.5)	57(21.8)
Constipation	10(3.8)	25(9.5)
Abdominal Pain	3 (1.1)	8 (3.1)
Diarrhea	14(5.4)	8 (3.1)
Dyspepsia	6 (2.3)	7 (2.7)
Flatulence	5 (1.9)	6 (2.3)
Nausea	7 (2.7)	5 (1.9)
Fatigue	3 (1.1)	7 (2.7)
Chest Pain	1 (0.4)	6 (2.3)
Pyrexia	8 (3.1)	1 (0.4)
Urinary Tract Infection	7 (2.7)	6 (2.3)
Urinary Retention	1 (0.4)	6 (2.3)
Headache	12(4.6)	17(6.5)
Dizziness	2 (0.8)	6 (2.3)
Skin Rash	10(3.8)	1 (0.4)

III. Final Comments:

1. Trade name consultation with ODS
2. The difference in one of the two co-primary endpoints appears to be small among the two treatment groups. Statistical reviewer needs to look at the p-value calculated by the sponsor.
3. There is concern over slightly higher percentage of subjects in trospium group, who developed urinary retention and chest pain.
4. Division needs to know the number of subjects exposed to the medication for six months or longer.
5. Proposed sites for DSI auditing: Site 20, 43, and 49

Reviewed By:

_____

Suresh Kaul, MD

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

/s/

Suresh Kaul
5/25/04 01:58:59 PM
MEDICAL OFFICER

Mark S. Hirsch
5/25/04 06:56:54 PM
MEDICAL OFFICER
I concur. This filing memo was prepared within the first 45 days of NDA submission in preparation for the filing meeting.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-595

Sponsor: Indevus Pharmaceuticals

Submission: Consult request (19 February 2004) from the Division of Reproductive and Urologic Drug Products asks the Division of Cardio-Renal Drug Products to comment upon the effects of trospium on QT and on T-wave morphology. Review materials included a revised study report for the "thorough" QT study and the electronic annotated ECGs from this study.

Review date: 26 April 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Concurrence: Douglas C. Throckmorton, M.D., Division Director, HFD-110

Trospium chloride is an anticholinergic-antimuscarinic agent under NDA review for use in the treatment of overactive urinary bladder.

Trospium is slowly absorbed and only about 10% bioavailable. Bioavailability is reduced by a high-fat meal. The half-life is 12-18 hours, increased by renal impairment, and decreased by hepatic impairment. The main metabolic pathway is ester hydrolysis; P450 enzymes are not involved.

Trospium is said to inhibit hERG with an IC50 of 22 μM, but, in a positive- (haloperidol) controlled rabbit heart model, trospium did not induce ventricular arrhythmias. In prior studies with no positive control, single doses up to 200 mg were described as showing "no significant effect on QTcF".

Review of Study IP631-010 was based on "Corrected Report. A Single Site Single-Blind Randomized Placebo and Positive Controlled, Parallel Designed Study of the Electrocardiographic Effects of Oral Trospium Chloride (20 mg bid Steady State and Supratherapeutic Levels) in Healthy Men and Women Volunteers: a Definitive or Thorough QT Trial" (submission of 11 March 2004).

Subjects were 170 normal male and female volunteers randomized to placebo, moxifloxacin 400 mg qd for 5 days, or trospium 20 mg bid for 5 days (the proposed clinical dose) or 60 mg bid for 2 days followed by 80 mg bid for 2 days followed by 100 mg bid for one day.

Continuous 12-lead Holter recordings were made on the day prior to first dose, on the first day of dosing, and on day 5. PK sampling was done on days 1, 3, and at 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours after the first dose on day 5.

Of 170 subjects enrolled, all had at least one on-treatment ECG, and 163 completed the study. One subject's day 5 ECG was "lost" and he was excluded from the primary analysis. Enrollment was planned higher in the high-dose group to compensate for an expected higher rate of withdrawal that did not materialize, so this group had somewhat greater power (n=47 at day 5) than did the other arms (n=38-40).

The principal results are shown below.

Table 1. Effects on heart rate and QT

Change from baseline and placebo	Day 1			Day 5		
	Tros L N=40	Tros H N=49	Moxi N=40	Tros L N=38	Tros H N=47	Moxi N=40
HR	1	12	1	9	18	1
QTcF	-1	-6	5	-3	-7	5
QTcI	-1	-5	5	-2	-6	5

One-sided outlier analyses detect the effect of moxifloxacin, but not the effects of trospium.

This study used a multiple-dose regimen of moxifloxacin. This is not recommended, for several reasons. It is probably less safe than single doses, and it is, if anything, apt to be easier to detect by its effects on QT than would be single doses. A better design would have called for placebo during the first 4 days followed by a single dose of moxifloxacin on day 5. This is a relatively minor issue, however; the study design was adequate for its intended purpose.

Numerous subjects were reported to have treatment-emergent T-wave inversions on placebo (n=5), moxifloxacin (n=4), low dose trospium (n=8), and high dose trospium (n=13). The distribution of such reports by time from dose is shown in Table 2.

Table 2. Distribution of times of reported T-wave inversions

	Day	Hour									
		1	2	3	4	5	6	8	10	12	24
All	0	1	6	3	1	3	8	4	1	6	2
Pcbo	1	0	2	1	0	0	2	0	4	0	1
	5	0	2	1	0	0	2	0	1	2	2
Moxi	1	0	3	2	1	1	2	2	4	1	2
	5	2	2	1	2	1	2	1	1	2	3
20	1	2	3	1	2	1	3	2	2	1	2
mg	5	3	6	4	4	5	4	3	6	6	2
60+	1	3	6	5	2	2	7	6	4	3	1
mg	5	4	8	5	4	5	9	4	5	8	4

Thus, T-wave inversions were reported more frequently on trospium than on placebo or moxifloxacin, and more commonly on day 5 than on day 1 of trospium, but there is very little to suggest a time course following a dose, perhaps because of trospium's slow absorption and long half-life.

Subjects experiencing T-wave inversions tended to be more tachycardic than other subjects of the same group, as shown in Table 3.

Table 3. Heart rate data

	Mean for all ECGs	ECGs with T-wave inversions
Placebo	74	93
Moxifloxacin	73	85
Trospium low	77	91
Trospium high	83	100

An example of the T-wave changes is shown in Figure 1.

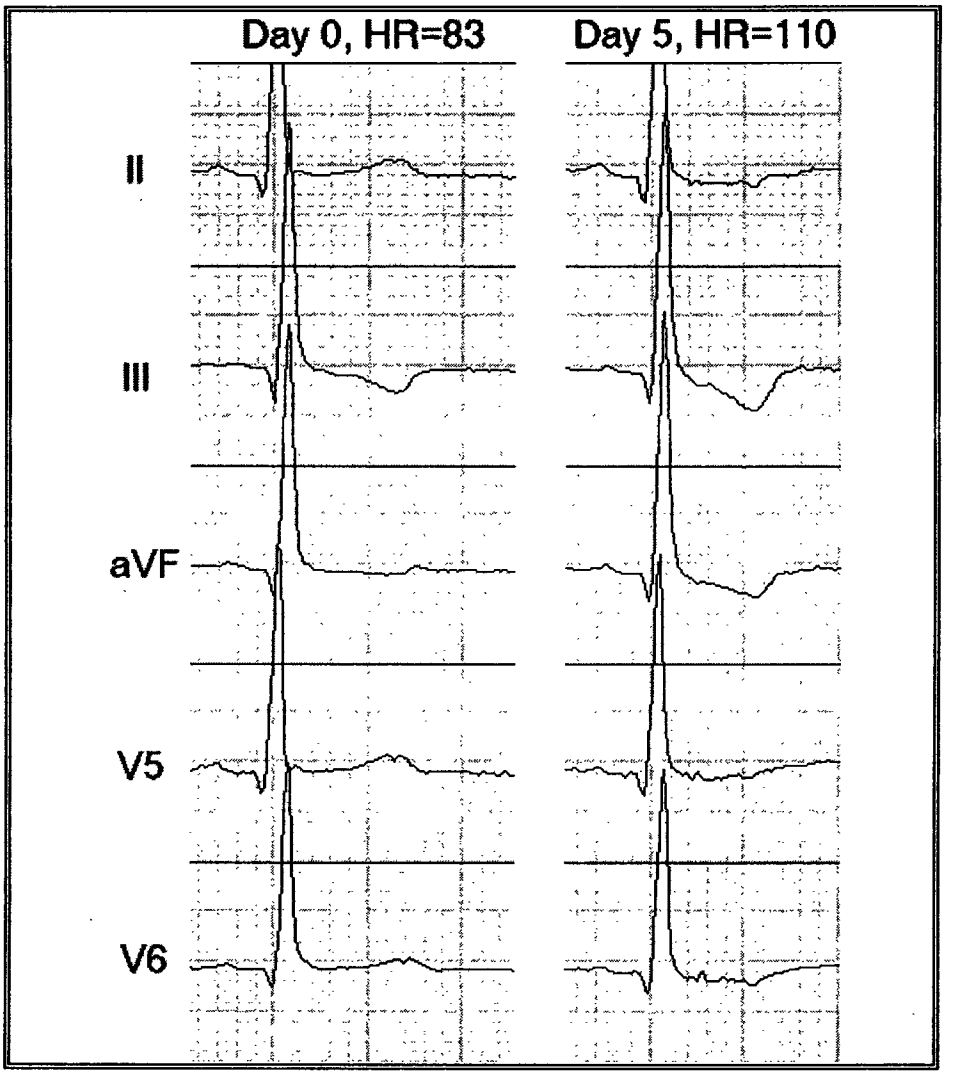

Figure 1. Sample T-wave inversion

These data are from subject 1103 (high-dose trospium).

A similar pattern of T-wave changes is seen among subjects in all treatment groups. Some subjects had T-wave inversions at baseline. The interpretation of Dr. Karen Hicks, cardiologist in the Division, is that these changes probably represent ischemia unmasked by tachycardia.

Thus, while the effect is probably not a direct effect of the drug, the tachycardia it induces presents additional stress visible in susceptible individuals. Whether this drug is any more risky than other approved agents for this indication, whether such risk is offset by benefits of treatment, and whether the risk can be mitigated by monitoring or patient selection all bear consideration.

There is no known clinical significance to a small reduction in QTc like the one shown in this study.

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/s/

Norman Stockbridge
4/26/04 12:42:13 PM
MEDICAL OFFICER

Doug Throckmorton
4/27/04 10:36:22 AM
MEDICAL OFFICER

Division of Cardio-Renal Drug Products (HFD-110)
Medical Officer Review of Protocol Submitted Under IND

TABLE OF CONTENT

GENERAL INFORMATION

NDA#: 21595
Drug name: Trospium Chloride
Date received: 1/06/04
Sponsor: Indevus
Type of document: Consult from the division of DRUDP
Date Reviewed: 1/22/04
Dosage and Route of Administration: 20 to [redacted] mg in 20 mg tablets
Proposed Indication: Overactive bladder
Reviewer: Salma L. Lemtouni, M.D., M.P.H.

DRUDP QUESTIONS/REQUESTS

Review of Study IP631-001_Main

Title of Study: "A placebo-Controlled Trial of Trospium Chloride on QTc interval in Healthy, Normal Subjects Following Steady-State and Single Oral Dosing"

Objective

The primary objective is to assess the effect of Trospium chloride in a single dose and at steady state compared to placebo on cardiac repolarization as measured by the duration of the QTc interval on the standard 12-lead ECG.

The secondary objective was to assess the safety of Trospium Chloride in a single dose and at steady state levels using the incidence of AEs and the number of subjects with clinically significant laboratory abnormalities.

Study Design

The study was a multicenter, parallel group, randomized, double blind placebo-controlled study in healthy volunteers. The study had two components: Part I tested the effect of 20 mg and 40 mg bid given for 6 days compared to placebo; and Part II tested the effect of 20 mg and 200 mg given in single administrations compared to placebo. A total of 45 subjects were randomized to one of three groups (A, B and C), completed Part I of the study, had a one-week washout period and entered Part II of the study in the same grouping. Stratification was done by gender so each group would have nine females and six males each.

Part I or Steady State phase:

Groups A, B and C were to receive 20 mg, 40 mg and placebo bid for six days. Serial ECG assessments were obtained at baseline and the parameters were averaged to define baseline

values. Subjects were instructed to take their medication one hour before meals and to adopt a low fat diet. ECG assessments were done and plasma samples were taken on days 3 and 6 one hour before study drug administration, and were repeated at hours 3, 5, 7, 9, and 12 post morning dose administration. Vital signs were measured and AEs were assessed periodically. Following a one-week wash-out phase, subjects were to begin Part II.

Part II or Single Dose Phase:

Subjects returned to the outpatient research unit on the morning of Day 13. A pre-dose ECG and a plasma sample were obtained. Subjects remained in the same group they were randomly assigned to in Part I, and groups A, B and C received single doses of 20 mg, 200 mg Trospium and placebo. Serial ECGs and plasma samples were obtained at hours 3, 5, 7, 9, and 12 post-dose. Similarly vitals sign measurements and AEs event assessment were done periodically.

Study population

Subjects were healthy volunteers 18 to 45 years of age who weighed 50 to 90 kg and women of low childbearing potential.

Dosage/Administration/Follow-up:

During the steady state phase group A took one 20 mg Trospium chloride tablet and one placebo tablet twice daily, group B took two 20 mg tablets twice daily and group C took 2 placebo tablets twice daily for six days. In the single dose phase, group A took one 20 mg tablet and nine placebo tablets, group B took ten 20 mg tablets and group C took ten placebo tablets.

Efficacy Evaluation

None performed.

Safety Evaluation

Safety was primarily assessed by studying the 12-lead ECG parameters in correlation with plasma levels of Trospium chloride. Other data including recorded AEs, vital signs and clinical laboratory results were used.

QT Analysis Results (Using Tables provided by Dr. Leslie Kenna)

Baseline Results:

Subjects randomized to group (receiving the therapeutic dose) had the lowest baseline mean QTcF (384.4). They were followed by subjects in group C (placebo) with a baseline mean of 386.3, and those in group B (receiving the supratherapeutic dose) with baseline mean QTcF of 393.9.

None of the subjects showed a QTcF interval greater than 450 msec.

Single Dose Results

The mean change from baseline in QTcF was negative for both the placebo and supratherapeutic dose groups (-4.4 and -9.6 respectively) and positive (1.2) for the therapeutic group.

None of the subjects showed an increase greater than 60 msec or a QTcF interval greater than 450 msec.

An increase in QTcF interval was observed in 4 (27%) subjects out of 15 receiving the therapeutic dose, 2 (13.3%) subjects receiving placebo and 1 (6.7%) subject receiving the supratherapeutic dose.

Steady State Dose Results

Again here the change from baseline in mean QTcF was in the negative direction for the placebo and the supratherapeutic dose groups (-1.5 and -7.1 respectively) and in the positive direction for the therapeutic dose group (2.5).

An increase in QTcF interval was seen in 2 (13.3%) subjects out of 15 receiving the therapeutic dose vs. 1 (6.7%) subject in the supratherapeutic dose and 1 (6.7%) subject in the placebo dose groups.

None of the subjects in the 20 mg steady state phase showed an increase greater than 60 msec, but one subject had his/her QTcF > 450 msec.

Discussion of Results

Argument in favor of a QT effect

--The groups are not comparable and the numbers were too small for randomization to render them comparable. As a result, we might have ended up with a group with more responders (group exposed to the therapeutic dose) than the other two groups. The results were duplicated when the same subjects were exposed in Part I.

Arguments against the presence of a QT effect

--The variability of the results within the therapeutic dose group: Twice as many subjects (4 vs. 2) had a QTcF prolongation between 30 and 60 msec on the single dose regimen than on the steady state regimen.

--The lack of consistency in the results: Four subjects in the therapeutic dose vs. only one subject in the supratherapeutic dose had an increase between 30 and 60 msec while on the single dose regimen. Twice as many subjects (2) in the therapeutic dose developed a prolongation of QTcF between 30 and 60 msec compared to the supratherapeutic dose (1) while on the steady state regimen.

--The change in the placebo group was similar if not worse than that observed in the supratherapeutic dose group.

--Regression to the mean: The group on the therapeutic dose which had more and positive (mean) changes in QTcF had the smallest mean value at baseline compared to the other two groups which had fewer, smaller and negative (mean) changes. These two groups had higher values at baseline, especially the one on supratherapeutic dose regimen who showed the greatest change toward the mean.

--Regularly a dose response effect strengthens the association between an exposure and an effect. In this case this would have applied if it were in a positive direction, that is if the frequency and/or intensity of the adverse effect went in the same direction as the dose. Not taking into account the effect on placebo, the dose response effect seen here suggests that Trospium chloride reduces the risk of QTcF prolongation which does not make sense.

CONCLUSION

There are many issues that come in the way of interpreting the results of this study. First no positive control group was used, second the numbers are too small for randomization to blunt differences as can be seen from baseline QTcF values, and for a small effect to be detected with accuracy and in a significant way.

Given what we have, there is not enough evidence to either confirm or refute an effect of Trospium chloride on cardiac repolarization.

The variability of the above findings suggests one or any combination of three possible phenomena:
--Regression to the mean;
--The groups were not very comparable with a concentration of responders in the group that received the therapeutic dose;
--Chance findings;

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/s/

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1/26/04 10:56:37 AM
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Doug Throckmorton
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NDA 21-595
Sanctura

Safety Review

Review of 4-Month Safety Update included in Medical Officer's Integrated Summary of Safety