5.6 Other Medically Significant Adverse Events

Blurred Vision
A total of 5 patients (all in trospium group) experienced blurred vision. In one of the five patients, the study medication was discontinued temporarily.

Tachycardia
A total of four patients (trospium 3 and placebo 1) experienced tachycardia. Out of 3 patients in trospium group, study medication was discontinued in one patient.

Palpitations
A total of 2 patients, both in trospium group, experienced palpitations. One of the events of palpitation lead to discontinuation of medication.

None of the above events were severe or serious and all resolved spontaneously without any medical intervention.

As per the sponsor, the events that either led to discontinuation of study medication or led to temporary interruption of study medication, or required dose reduction of the study medication are summarized in the table below:

Table A8. Discontinuation of Study Medication due to AEs in IPD631-003

	Number of patients (%)	
Other significant TEAE criterion	Placebo N=261	Trospium N=262
Led to discontinuation of study medication	15 (5.7)	23 (8.8)
Led to temporary interruption of study medication	8 (3.1)	16 (6.1)
Required dose reduction of study medication	0 (0.0)	1 (0.4)

5.7 Adverse Events Leading to Discontinuation of Study Medication

The sponsor reports that the study medication was permanently discontinued due to TEAE's in 38 patients (trospium 23 patients [8.8%] and placebo 15 patients [5.7%]). Most common TEAE's that led to discontinuation of the study medication occurred in gastrointestinal and urinary system, i.e., dry mouth, constipation, abdominal pain and urinary retention.

Table A9: Specific AE's Leading to Discontinuation of Study Medication In IP631-003

	Number of patients (%)	
	Placebo	Trospium
Preferred term	N=261	N=262
Total patients with at least one TEAE leading to discontinuation of study medication	**15 (5.7)**	**23 (8.8)**
Dry mouth	0 (0.0)	6 (2.3)
Constipation	1 (0.4)	4 (1.5)
Abdominal pain NOS	0 (0.0)	4 (1.5)
Urinary retention	1 (0.4)	4 (1.5)
Headache NOS	1 (0.4)	3 (1.1)
Constipation aggravated	1 (0.4)	2 (0.8)
Abdominal pain upper	3 (1.1)	1 (0.4)
Dizziness	2 (0.8)	1 (0.4)

5.8 Adverse Events Leading to Temporary Interruption of Study Medication

Sponsor reports that the study medication was temporarily interrupted due to TEAE's in 24 patients [(trospium 16 patients (6.1%) and placebo 8 patients (3.1%)] as shown in the table below. The most common TEAE's that led to temporary interruption of the study medication were non-cardiac chest pain and urinary retention.

Table A10. Specific AE's Leading to Temporary Interruption of Study Medication in IP631-003

	Number of patients (%)	
	Placebo	Trospium
Preferred term	N=261	N=262
Total patients with at lest one TEAE leading to temporary interruption of study medication	**8 (3.1)**	**16 (6.1)**
Chest pain [a]	0 (0.0)	2 (0.8)
Urinary retention	0 (0.0)	2 (0.8)
Rash NOS	2 (0.8)	0 (0.0)

5.9 Adverse Events Leading to Dose Reduction

Sponsor reports that the study medication dose was reduced due to TEAE in 1 patient on trospium, who experienced oliguria on Day 4. This led to dose reduction from 20mg twice daily to 20mg daily for 4 days. The decreased urine output resolved by Day 6.

5.10 Adverse Events by Age, Gender and Race

5.10.1 Adverse Events by Patient Age

The sponsor points out that the subgroup analysis of adverse events by age was done for the following categories: age <65 years, 65-75 years and > 75 years. There were 142/262 (54.2%) trospium patients and 148/261 (56.7%) in the placebo group under age 65 years.

It is apparent from the table below that the incidence of TEAE's was higher in the age groups 65-75 years and > 75 years when compared to patients <65 years of age in the trospium group. In the placebo group, the TEAE occurrence rates were comparable across the age categories.

For the two most common TEAE's (i.e., dry mouth and constipation) a tendency in the trospium group for an increased occurrence of these events as the patient age increased was seen.

Table A11. Incidence of Common TEAE's Reported by Age in IP631-003

System organ class/ preferred term	Number of patients (%)					
	Placebo			Trospium		
Age (in years)	<65	65 - <75	≥75	<65	65 - <75	≥75
	N=148	N=75	N=38	N=142	N=78	N=42
Total patients with at least one TEAE	**79 (53.4)**	**38 (50.7)**	**21 (55.3)**	**84 (59.2)**	**57 (73.1)**	**30 (71.4)**
Dry mouth	8 (5.4)	4 (5.3)	5 (13.2)	26 (18.3)	16 (20.5)	15 (35.7)
Constipation	4 (2.7)	6 (8.0)	0 (0.0)	11 (7.7)	9 (11.5)	5 (11.9)
Headache NOS	8 (5.4)	3 (4.0)	1 (2.6)	12 (8.5)	4 (5.1)	1 (2.4)
Abdominal pain NOS	2 (1.4)	1 (1.3)	0 (0.0)	6 (4.2)	1 (1.3)	1 (2.4)
Dyspepsia	4 (2.7)	1 (1.3)	1 (2.6)	1 (0.7)	3 (3.8)	3 (7.1)
Fatigue	2 (1.4)	1 (1.3)	0 (0.0)	4 (2.8)	2 (2.6)	1 (2.4)
Flatulence	3 (2.0)	1 (1.3)	1 (2.6)	2 (1.4)	1 (1.3)	3 (7.1)
Chest pain	1 (0.7)	0 (0.0)	0 (0.0)	4 (2.8)	2 (2.6)	0 (0.0)
Dizziness	1 (0.7)	1 (1.3)	0 (0.0)	2 (1.4)	3 (3.8)	1 (2.4)
Urinary retention	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	3 (3.8)	2 (4.8)

Reviewer's Comment

In the opinion of this reviewer, it appears that patients <65 years of age are less likely to experience dry mouth, constipation, dyspepsia and urinary retention compared to patients 65 years and older, especially those patients >75 years of age.

Therefore, it may be appropriate to lower the dose of trospium chloride to 20mg orally once daily in order to anticholinergic effects such as dry mouth, constipation, dyspepsia and urinary retention in patients (>75 years of age), in patients who are unable to tolerate 20-mg twice daily.

5.10.2 Adverse Events by Patient Gender

The most common TEAE's reported by gender for both trospium and placebo group are summarized in the table below:

Table A12. Common TEAE's Reported by Gender in IP631-003

System organ class/preferred term	Number of patients (%)			
	Placebo		Trospium	
Patient gender	Female	Male	Female	Male
	N=186	N=75	N=203	N=59
Total patients with at least 1 TEAE	**105 (56.5)**	**33 (44.0)**	**131 (64.5)**	**40 (67.8)**
Dry mouth	12 (6.5)	5 (6.7)	46 (22.7)	11 (18.6)
Constipation	7 (3.8)	3 (4.0)	20 (9.9)	5 (8.5)
Headache NOS	11 (5.9)	1 (1.3)	17 (8.4)	0 (0.0)
Abdominal pain NOS	2 (1.1)	1 (1.3)	7 (3.4)	1 (1.7)
Dyspepsia	5 (2.7)	1 (1.3)	4 (2.0)	3 (5.1)
Fatigue	3 (1.6)	0 (0.0)	5 (2.5)	2 (3.4)
Flatulence	5 (2.7)	0 (0.0)	3 (1.5)	3 (5.1)
Chest pain	0 (0.0)	1 (1.3)	4 (2.0)	2 (3.4)
Dizziness	1 (0.5)	1 (1.3)	4 (2.0)	2 (3.4)
Urinary retention	1 (0.5)	0 (0.0)	2 (1.0)	4 (6.8)

In this trial, a total of 203/262 (77.5%) trospium patients and 186/261 (71.3%) in the placebo group were female.

For the two most common TEAE's (dry mouth and constipation), the occurrence rates were comparable for females and males within the trospium group and likewise, when compared to the placebo group.

In both the trospium and the placebo groups, a higher tendency for females to experience headache is noticed in comparison to males receiving same study medication.

For TEAE of urinary retention, there was a tendency for more males to report the event in the trospium group, when compared to females receiving the same study medication.

5.10.3 Adverse Events by Patient Race

Sponsor believes that the patients who experienced TEAE's are comparable between the races within the trospium and the placebo group. In this study, 222 out of 262 (84.7%)

trospium patients and 225 of 261 (86.2%) placebo patients were Caucasian. The limited number of patients in this study who were African American, Hispanic or multiracial limits the interpretation of differences in TEAE occurrence rates between patient races. The following table summarizes the most common TEAE's by patient race:

Table A13. Common TEAE's Reported by Race in IP631-003

Preferred term	Number of patients (%)					
	Placebo			Trospium		
Patient race	Cauc N=225	Afr Am N=20	Other N=16	Cauc N=222	Afr Am N=26	Other N=14
Total patients with at least one TEAE	**121 (53.8)**	**10 (50.0)**	**7 (43.8)**	**150 (67.6)**	**15 (57.7)**	**6 (42.9)**
Dry mouth	15 (6.7)	1 (5.0)	1 (6.3)	51 (23.0)	4 (15.4)	2 (14.3)
Constipation	8 (3.6)	0 (0.0)	2 (12.5)	22 (9.9)	2 (7.7)	1 (7.1)
Headache NOS	8 (3.6)	2 (10.0)	2 (12.5)	14 (6.3)	2 (7.7)	1 (7.1)
Abdominal pain NOS	3 (1.3)	0 (0.0)	0 (0.0)	6 (2.7)	2 (7.7)	0 (0.0)
Dyspepsia	3 (1.3)	2 (10.0)	1 (6.3)	7 (3.2)	0 (0.0)	0 (0.0)
Fatigue	3 (1.3)	0 (0.0)	0 (0.0)	6 (2.7)	1 (3.8)	0 (0.0)
Flatulence	4 (1.8)	1 (5.0)	0 (0.0)	6 (2.7)	0 (0.0)	0 (0.0)
Chest pain	1 (0.4)	0 (0.0)	0 (0.0)	5 (2.3)	1 (3.8)	0 (0.0)
Dizziness	2 (0.9)	0 (0.0)	0 (0.0)	5 (2.3)	1 (3.8)	0 (0.0)
Urinary retention	1 (0.4)	0 (0.0)	0 (0.0)	5 (2.3)	1 (3.8)	0 (0.0)

Reviewer's Comment

This reviewer agrees with the fact that the commonly seen anticholinergic effects were slightly increased in ages of 65-75 and above 75 years of age in the trospium group. For race and gender, TEAE's were comparable between trospium and the placebo groups.

5.11 Deaths

As of August 2003, the date of the 120-day safety update, there was 1 patient in the trospium group that experienced an adverse event leading to death. No additional death reports were submitted in the 4-month safety update.

Patient 50-6247

An 81 year old male with significant past medical history of myocardial infarction in 1985, coronary artery bypass surgery in 1194, hypercholestrolemia and glaucoma since 1985. Patient was hospitalized on day 57 after initiation of the study medication for hemorrhagic stroke. CT scan of the head revealed left parieto-occipital intracranial hemorrhage with surrounding edema and mild mass effect. A carotid duplex scan showed a 15% occlusion of both internal carotids. The hemorrhage was attributed to pre-existing amyloid angiopathy with hypertensive hemorrhage. The study drug administration was permanently discontinued on Day 57 due to the occurrence of this event. The patient stayed stable for next 11 days and was transferred to a nursing home where he died later

on Day 125 . Cause of death as stated in the death certificate was a consequence of cerebral hemorrhage. The sponsor/investigator assessed the hemorrhagic stroke as remotely related to the study medication.

Reviewer's Comments

This reviewer agrees with the assessment stated in this submission. It is unlikely that the study medication could have caused or led to hemorrhagic stroke given that the patient had extensive pre-morbid medical conditions.

5.12 Laboratory Evaluation

Based on the study protocol, routine laboratory testing was conducted at screening and day 84 (Week 12) visits during this trial. Hematology, chemistry, and urinalysis data were reviewed for changes that occurred from baseline to on-treatment. In addition, laboratory data were analyzed using predefined criteria to identify potentially clinically significant (PCS) abnormal laboratory values.

5.12.1 Hematology PCS Values

Sponsor reports that a total of 32 patients [trospium 18 patients (7.2%) and placebo 14 patients (5.8%)] met PCS criteria for 1 or more abnormal hematology value. The most common hematology PCS abnormal values were high monocytes and a mildly low hematocrit as summarized in the table below. These two abnormal PCs values were similar between the trospium and placebo groups.

Table A14. Hematology – PCS abnormal values – in IP631-003

	Placebo		Trospium	
Total patient sample	**261**		**262**	
Hematology PCS abnormal value	**n/N (%)**	**N at BL**	**n/N (%)**	**N at BL**
Number of patients with at least one hematology PCS abnormal value	**14/240 (5.8)**	**9**	**18/249 (7.2)**	**13**
WBC low (≤2.8 x 10^3 /mm^3)	1/238 (0.4)	1	1/245 (0.4)	1
Monocytes high (≥15%)	7/237 (3.0)	5	5/245 (2.0)	3
Eosinophils high (≥10%)	0/237 (0.0)	0	4/245 (1.6)	4
Neutrophils low (≤15%)	1/237 (0.4)	1	2/245 (0.8)	2
Hematocrit low (F ≤32% or M ≤37%)	5/238 (2.1)	2	4/245 (1.6)	3
Hemoglobin low (F ≤9.5 or M ≤11.5 g/dL)	2/238 (0.8)	1	0/245 (0.0)	0
PT high (≥16 seconds)	2/230 (0.9)	0	1/239 (0.4)	1
PTT high (≥45 seconds)	2/230 (0.9)	1	3/239 (1.3)	1

5.12.2 Serum Chemistry PCS Values

Sponsor reported a total of 62 patients [trospium 28 patients (11.2%) and placebo 34 patients (14.2%)] met PCS criteria for 1 or more abnormal serum chemistry value. That

abnormal PCS value was low HDL seen in 15 trospium (6.0%) patients and 20 placebo (8.3%) patients.

Table A15. Serum Chemistry PCS abnormal values in IP631-003

	Placebo		Trospium	
Total patient sample	**261**		**262**	
Total patients with laboratory value [a]	**240**		**249**	
Chemistry PCS abnormal value	**n [b] (%)**	**N at BL**	**n [b] (%)**	**N at BL**
Number of patients with at least one chemistry PCS abnormal value	**34 (14.2)**	**22**	**28 (11.2)**	**20**
BUN high (≥30 mg/dL)	4 (1.7)	2	4 (1.6)	3
Uric acid high (F ≥8.5 or M ≥10.5 mg/dL)	1 (0.4)	1	2 (0.8)	2
Bilirubin direct (≥0.5 mg/dL)	1 (0.4)	1	0 (0.0)	0
CPK high (F ≥702 or M ≥1191 IU/L)	1 (0.4)	1	3 (1.2)	3
Glucose (random) high (>250 mg/dL)	2 (0.8)	2	4 (1.6)	2
Triglycerides high (>600 mg/dL)	2 (0.8)	1	0 (0.0)	0
HDL low (≤30 mg/dL)	20 (8.3)	11	15 (6.0)	10
LDL high (≥200 mg/dL)	3 (1.3) [c]	1	2 (0.8) [c]	1
Calcium low (<8.2 mg/dL)	1 (0.4)	1	0 (0.0)	0
Sodium low (≤126 mmol/L)	1 (0.4)	1	0 (0.0)	0
Sodium high (≥156 mmol/L)	1 (0.4)	1	0 (0.0)	0
Potassium low (≤3 mmol/L)	0 (0.0)	0	1 (0.4)	1
Bicarbonate low (≤19 mmol/L)	1 (0.4)	1	0 (0.0)	0

5.12.3 Urinalysis PCS Values

Sponsor reported a total of 88 patients [trospium 51 patients (20.6%) and placebo 37 patients (15.5%) who met PCS criteria for 1 or more abnormal urinalysis value.

The most common urinalysis PCS values were presence of crystals, epithelial cells, RBC's, and WBC's in urine. The presence of epithelial cells and WBC's were more frequent in trospium group than in placebo group. Four (4) out of 18 patients in the trospium group, who met UA WBC PCS criteria at the endpoint, had a clinical UTI that contributed to high WBC levels. Sponsor also emphasizes that none of these patients in the trospium group had urinary retention.

Although there were more patients in trospium group with high epithelial cells and WBC's in urine, these findings did not translate into clinically meaningful differences. Therefore no further investigation was conducted.

Table A16. Urinalysis – PCS abnormal values – in IP631-003

	Placebo		Trospium	
Total patient sample	**261**		**262**	
Total patients with laboratory value [a]	**238**		**248**	
Urinalysis PCS abnormal value	**N [b] (%)**	**N at BL**	**n [b] (%)**	**N at BL**
Number of patients with at least one urinalysis PCS abnormal value	**37 (15.5)**	**33**	**51 (20.6)**	**46**
Glucose (≥3+)	1 (0.4)	1	2 (0.8)	2
Ketones (≥2+)	0 (0.0)	0	1 (0.4)	1
Blood (≥3+)	1 (0.4)	1	3 (1.2)	3
Protein (≥2+)	2 (0.8)	1	0 (0.0)	0
Crystals (≥4/LPF)	5 (2.1)	5	4 (1.6)	3
Epithelial cells many (>10/HPF)	12 (5.0)	12	23 (9.3)	22
RBCs (>8/HPF)	12 (5.0)	10	10 (4.0)	8
WBCs (>10/HPF)	10 (4.2)	8	18 (7.3)	15

Reviewer's Comment

This reviewer agrees with the sponsor that the number of patients with hematology PCS abnormal values and serum chemistry PCS abnormal values is similar between trospium and placebo groups. Reviewer also agrees to the fact that a mild increase in epithelial cells and WBC's in patients other than suffering from UTI dies not translate into clinically meaningful result.

5.13 Vital Signs Data

Vital signs of blood pressure (systolic and diastolic) pulse rate and ECG were measured at screening, baseline, Day 8 (week 1), Day 28 (week 4) and Day 84 (week 12).

5.13.1 Blood Pressure

The mean and median changes from the baseline for the blood pressure variables (systolic and diastolic) were small (3 beats per minute) and similar in both trospium and placebo groups.

5.13.2 Pulse

At baseline the mean pulse in trospium group was 71.5bpm and in the placebo group was 71.7bpm. On treatment at endpoint, the mean change in pulse from baseline in the trospium group was 3.3bpm and in the placebo group was 0.2bpm. Therefore there was a very small increase in the pulse from baseline in the trospium group when compared to placebo group.

A total of 178 patients [trospium 91 patients (35%) and placebo 87 patients (34%)] met PCS criteria for 1 or more abnormal vital signs variables at endpoint. The vital signs PCS values on treatment at endpoint are summarized in the table below.

The sponsor reports that the number of patients who met PCS criteria for systolic and diastolic blood pressure were similar on treatment at endpoint between the trospium and the placebo groups. For pulse, there were approximately one-half as many patients in the trospium group who met PCS criteria for low pulse when compared to the placebo group.

Overall, the number of patients who met PCS criteria for the vital signs data was similar for both trospium and placebo groups. There was a small increase (3 to 4 bpm) in pulse from baseline for the trospium group when compared with the placebo group.

Table A17: Vital Signs- PCS abnormal values (BP and Pulse)- in IP631-003

	Placebo		Trospium	
Total patient sample	261		262	
Total patients with vital sign data [b]	256		260	
Vital sign PCS abnormal value	n [c] (%)	N at BL	n [c] (%)	N at BL
Number of patients with at least one vital sign PCS value	**87 (34.0)**	**83**	**91 (35.0)**	**89**
Systolic blood pressure:				
Low: <90 or decrease ≥20 mm Hg	29 (11.3)	27	31 (11.9)	29
High: >180 or increase ≥20 mm Hg	22 (8.6)	22	28 (10.8)	28
Diastolic blood pressure:				
Low: <50 or decrease ≥15 mm Hg	20 (7.8)	17	16 (6.2)	16
High: >105 or increase ≥15 mm Hg	13 (5.1)	12	20 (7.7)	20
Pulse:				
Low 1: <50 bpm only	4 (1.6)	3	0 (0.0)	0
Low 2: decrease ≥15 bpm only	22 (8.6)	20	10 (3.8)	10
Low 3: <50 & decrease ≥15 bpm	0 (0.0)	0	0 (0.0)	0
Total low pulse (1, 2, & 3 above):	**26 (10.2)**	**23**	**10 (3.8)**	**10**
High 1: >100 & increase ≥15 bpm	2 (0.8)	2	1 (0.4)	1
High 2: >120 & increase <15 bpm	0 (0.0)	0	0 (0.0)	0
Total high pulse (1 & 2 above):	**2 (0.8)**	**2**	**1 (0.4)**	**1**

Reviewer's Comment

The vital signs data, which is similar in both trospium and the placebo groups, is acceptable.

5.13.3 Electrocardiographic Data

12 lead ECG's were obtained at screening, Day 8 (week 1) and Day 84 (week 12) during this trial.

PR and QRS intervals

The number of patients who met ECG PCs criteria for abnormal PR and QRS were similar between trospium and the placebo groups.

QT and QTcF intervals

The number of patients who met ECG PCS criteria for abnormal QT and QTcF (using Fridercia criteria) intervals were similar between trospium and the placebo groups.

There were a total of 2 patients, 1 patient in each treatment group (trospium patient 20-6468 and placebo patient 02-6086) who had QTcF intervals >500msec that had increased by >60 msec from baseline. For both these patients there were no accompanying clinical signs associated with increased QTcF interval and in both the patients the increases resolved at endpoint.

Table A18. ECG – PCS abnormal values – in IP631-003

	Placebo		Trospium	
Total patient sample	**261**		**262**	
Total patients with ECG data [a]	**256**		**258**	
ECG PCS abnormal interval	**n [b] (%)**	**N at BL**	**n [b] (%)**	**N at BL**
PR interval [c]				
>200 msec only	11 (4.4)	3	10 (3.9)	3
Increase ≥20 msec only	29 (11.5)	29	35 (13.6)	35
>200 and increase ≥20 msec	6 (2.4)	3	5 (1.9)	5
Total PR interval high	**46 (18.3)**	**35**	**50 (19.4)**	**43**
QRS interval				
>100 msec only	38 (14.8)	6	31 (12.0)	4
Increase ≥10 msec only	24 (9.4)	24	30 (11.6)	30
>100 and increase ≥10 msec	19 (7.4)	13	16 (6.2)	15
Total QRS interval high	**81 (31.6)**	**43**	**77 (29.8)**	**49**
QT interval				
>500 msec only	1 (0.4)	0	0 (0.0)	0
Increase ≥60 msec only	6 (2.3)	6	3 (1.2)	3
>500 and increase ≥60 msec	1 (0.4)	1	2 (0.8)	2
Total QT interval high	**8 (3.1)**	**7**	**5 (1.9)**	**5**
QTcF interval				
>500 msec only	0 (0.0)	0	1 (0.4)	1
Increase ≥60 msec only	8 (3.1)	8	3 (1.2)	3
>500 and increase ≥60 msec	1 (0.4)	1	1 (0.4)	1
Total QTcF interval high	**9 (3.5)**	**9**	**5 (1.9)**	**5**
Heart rate				
<50 bpm only	8 (3.1)	4	3 (1.2)	1
Decrease ≥15 bpm only	12 (4.7)	12	9 (3.5)	9
<50 and decrease ≥15 bpm	0 (0.0)	0	1 (0.4)	1
Total low heart rate	**20 (7.8)**	**16**	**13 (5.0)**	**11**
>100 and increase ≥15 bpm	3 (1.2)	3	6 (2.3)	6
>120 and increase <15 bpm	0 (0.0)	0	0 (0.0)	0
Total high heart rate	**3 (1.2)**	**3**	**6 (2.3)**	**6**

Heart Rate

Sponsor points out that there were approximately one-half as many patients in the trospium group who met PCS criteria for low heart rate when compared to placebo group. There were slightly more patients who met PCS criteria for high heart rate (>100 with an increase of >15bpm) in the trospium group [n=6; 2.3%] when compared to the placebo group [n=3; 1.2%]. There were no patients who met PCS criteria for high heart rate of >120 and an increase of <15bpm.

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 shown to be associated with a heart rate increase of 3bpm above the baseline when compared to placebo, which does not alone translate into a clinically meaningful change.

5.14 Reviewer's Safety Conclusions from IP631-003

* Overall, a total of 309 patients reported one or more TEAE [trospium 171 patients (65.3%) and 138 patients (52.9%) in the placebo group. TEAE's most commonly reported were from the 92 patients (35.1%) in the trospium group and 62 patients (23.8%) in the placebo group. Among the GI adverse events, dry mouth and constipation were the most frequently reported in trospium group when compared to placebo group. In addition, TEAE's of urinary retention, and non-ischemic chest pain were increased in the trospium patients when compared to the placebo group.

* In the trospium group, the study medication was discontinued in 6 patients for dry mouth, 6 patients for constipation, 4 patients for urinary retention. None of these TEAE's were deemed serious.

* A serious adverse event (SAE) was reported in 15 patients (trospium 9 patients (3.4%) and placebo 6 patients (2.3%). None of the serious events were assessed by the investigator to be related to the study medication.

* There was 1 patient from the trospium group, who experienced an adverse event leading to death after experiencing a hemorrhagic stroke. This event was assessed by the investigator as remotely related to the study medication.

* Study medication was permanently discontinued due to TEAE's in 38 patients [trospium 23 patients (8.8%) and placebo 15 patients (5.7%)]. The most common TEAE's that led to discontinuation of the study medication in trospium group was dry mouth, constipation and urinary retention.

* Subgroup analyses for age, gender and race showed a higher tendency for age categories >65 years and >75 years of age to experience a TEAE when compared with trospium patients <65 years of age. There was an increased occurrence of headache in the

female patients when compared to male patients. There also was an increased occurrence of urinary retention in the male patients when compared to female patients.

* The number of patients who met potentially clinically significant (PCS) criteria for hematology and serum chemistry laboratory data were similar for both trospium and placebo groups. Although there were no patients in the tropium group who met the PCS criteria for urinary WBC's and epithelial cells when compared to placebo group, these findings cannot be translated into clinically meanigful differences.

* Overall, the number of patients who met PCS criteria for vital signs and ECG data was similar for the trospium and placebo groups.

5.15 Reviewer's Overall Conclusions for Study IP631-003

This was a multi-center, double-blind, placebo-controlled study of trospium (20mg oral bid) versus placebo for 12 weeks in patients with overactive bladder associated with predominate urge incontinence.

A total of 523 subjects (trospium 262 patients, placebo 261 patients) were randomly assigned on a 1:1 ratio to receive either trospium 20mg or placebo twice daily. The patient population was predominantly female (trospium 77.5% and placebo 71.3%). The mean age in the trospium group was 61.7 years and in the placebo group was 61.5 years. The treatment groups were well matched for baseline and demographic variables and are representative of the patient population commonly diagnosed with overactive bladder.

Trospium demonstrated a statistically significant ($p<0.05$) improvement (i.e., decrease) for the primary efficacy variables of change in average number of toilet voids per 24 hours (at Weeks 1,4, and 12) and change in average urge incontinence episodes per 24 hours (at Weeks 4 and 12) when compared with the placebo group.

Trospium demonstrated a statistically significant ($p<0.05$) improvement (i.e., decrease) in average number of urge incontinence episodes per week at both Weeks 4 and 12 when compared with placebo.

The results from a descriptive analysis using a univariate procedure showed that 71% of the patients treated with trospium had a 50% reduction in the number of incontinence episodes per 24 hours whereas, only 54% of the placebo-treated patients had the same effect. Similarly, 21% of the trospium-treated patients had their number of incontinence episodes reduced to zero (0) per 24 hours while only 11% of the placebo-treated patients achieved this endpoint. In other words, trospium was able to eliminate incontinence episodes in twice as many patients as did placebo. The results from these analyses suggest a high likelihood for a patient treated with trospium to experience a clinically meaningful decrease and possible elimination of urinary incontinence episodes.

The findings from the primary efficacy analyses are further supported by findings from key secondary efficacy analyses of statistically significant increases in average volume voided (in ml) per toilet void and decreases in urgency severity associated with toilet voids for the trospium group when compared with the placebo group. The findings for these 4 key efficacy variables are consistent with the expected pharmaco-dynamic effects of trospium.

Anti-cholinergic 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 number of toilet voids, decreased average number of urge incontinence episodes, increased average volume voided (in ml) per toilet void, and decreased urgency severity associated with toilet voids.

The results of exploratory analyses for onset of effect for trospium is expected to provide some clinical benefit by significantly decreasing the number of toilet voids, decreasing the number of urge incontinence episodes, and decreasing the number of total micturitions per 24 hours within the first week of treatment.

TEAEs were most commonly reported for the gastrointestinal system with 92 patients (35.1%) in the trospium group and 62 patients (23.8%) in the placebo group experiencing such events. Dry mouth and constipation were the most frequently reported TEAEs and occurred significantly ($p \leq 0.01$) more often in the trospium group compared with the placebo group. The more frequent occurrence of dry mouth and constipation in trospium-treated patients is consistent with the anticipated anticholinergic effects of trospium.

Other most common TEAEs (occurred in 2.0% of patients in either treatment group and were reported in more trospium patients) were headache, abdominal pain, chest pain, and urinary retention.

TEAEs reported in this study and commonly associated with anti-cholinergic agents include dry mouth, constipation, urinary retention, residual urine volume, vision blurred, dry eyes and tachycardia. Overall, expected anticholinergic TEAEs occurred more often in the trospium group compared with the placebo group. Dry mouth and constipation were the 2 most common TEAEs reported in this study. In addition, the anti-cholinergic TEAEs of urinary retention, residual urine volume, dry eyes and tachycardia were reported in more trospium patients when compared with placebo patients.

In the trospium group, study medication was discontinued in 1 patient for each of the following anti-cholinergic TEAEs unless otherwise specified: dry mouth (6 patients), constipation (6 patients), urinary retention (4 patients) and tachycardia. None of these anti-cholinergic events were serious.

A serious adverse event (SAE) was reported for a total of 15 patients (trospium 9 patients, 3.4%; placebo 6 patients, 2.3%). None of the serious adverse events were assessed by the investigator as related to study medication.

Study medication was permanently discontinued due to TEAEs in a total of 38 patients (trospium 23 patients, 8.8%; placebo 15 patients, 5.7%). The most common TEAEs that led to discontinuation of study medication in the trospium group were dry mouth, constipation and urinary retention.

Subgroup analyses was done by patient age, gender, and race for the most common TEAEs (i.e., occurred in 2.0% of patients in either treatment group and were reported in more trospium patients than placebo patients). Findings from these analyses showed an overall tendency for a higher percentage of trospium patients in age categories of 65 to 75 years and >75 years of age to experience a TEAE when compared with trospium patients <65 years of age. There was a tendency in the trospium group for an increased occurrence of dry mouth and constipation as patient age increased. Subgroup analyses by gender showed a tendency in the trospium group for an increased occurrence of headache in the female patients when compared to male patients. In addition, there was a tendency in the trospium group for an increased occurrence of urinary retention in the male patients when compared to female patients.

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 WBCs and epithelial cells when compared with the placebo group, the differences in the UA findings did not translate into clinically meaningful differences.

Overall, the number of patients who met PCS criteria for the vital signs and ECG data were similar for the trospium and placebo groups. Although the number of patients who met PCS criteria for high heart rate of 100 with an increase of <15 bpm) were small, there appeared to be more patients in the trospium group when compared with the placebo group. There were no patients in either treatment group who met PCS criteria for high heart rate of 120 and an increase of <15 bpm. There were a total of 2 patients, 1 patient in each treatment group, who had QTcF intervals >500 msec that had increased by >60 sec from baseline. For both of these patients, 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 both of the QTcF interval increases had resolved at endpoint. A thorough QT trial did not reveal any QT-prolonging effect of trospium.

In conclusion, trospium given as 20mg twice daily has shown to be significantly better than placebo for the two co-primary efficacy endpoints of decreased average number of toilet voids/24 hours and decreased average number of urge incontinence episodes/24 hours, as well as other key endpoints including increased average volume voided/ 24 hours and decreased average urgency severity associated with toilet voids/24 hours. Trospium was safe and generally well tolerated in this study. The data from this study support the conclusion that trospium 20mg bid is an effective and generally safe treatment option in patients with overactive bladder with predominant urge incontinence.

Appendix B.

NDA 21- 595 Trospium Chloride
Medical officer's Review of Pivotal Study IP 631-005

Application Information

NDA #	**21-595**
Study	IP631-005
Submission Date	February 28, 2004
Extended PDUFA Goal Date	May 28, 2004
Review Status	Standard (10 + 3 Months Extension)

Drug Name	
Generic Name	**Trospium Chloride**
Proposed Trade Name	Sanctura

Drug Categorization

Chemical Classification	New Molecular Entity (NME)
Pharmacological Class	Anticholinergic
Proposed Indication	Treatment of Patients with Overactive Bladder
Proposed Dose Regimen	20-mg BID
Strength and Dosage Form	20-mg tablets
Route of Administration	Oral

Having completed study IP631-003 in March 2003, over 400 patients from both treatment groups of this study continued into an open-label treatment phase, in which all patients received trospium chloride 20-mg tablets twice daily for up to 9 months.

This study protocol, protocol **IP631-005** was designed to further explore the effects of trospium chloride, 20 mg tablets, twice daily, on urinary frequency, urgency and incontinence associated with OAB. This study specifically focused on the effects of trospium chloride on toilet void frequency, urinary urgency severity, urge frequency, onset of action, and daytime and nighttime toilet void frequency.

The sponsor believes that assessing urinary urgency is a key health outcome reported by patients with OAB. Reducing the degree of urgency that patients experience may have an association with clinical and quality of life benefits.

Study Objectives

The objective of this study was to determine the effect of 20mg of trospium chloride versus placebo given twice daily for urinary frequency and other related symptoms associated with overactive bladder over a period of 12 weeks with an open-label extension available to all patients who participated in the double blind period.

Investigational Plan

Efficacy Variables

Primary Efficacy Variable

Change in average number of daily toilet voids

The primary efficacy analyses was based on data collected over 7 days prior to the baseline, Day 8 (week 1), Day 28 (week 4), and Day 84 (week 12) visits.

Reviewer's Comment

Primary efficacy variable is acceptable

Secondary Efficacy

Change in average volume voided per toilet void.
Change in urge severity and frequency associated with toilet voids
Change in average number of urge incontinence episodes per 24 hours.

The secondary efficacy assessments were collected over 7 days prior to the baseline, Day 8 (week 1), Day 28 (week 4), and Day 84 (week 12) visits using data recorded in patient diaries. Volume voided was collected for 2 full days prior to each visit.

Reviewer's Comments

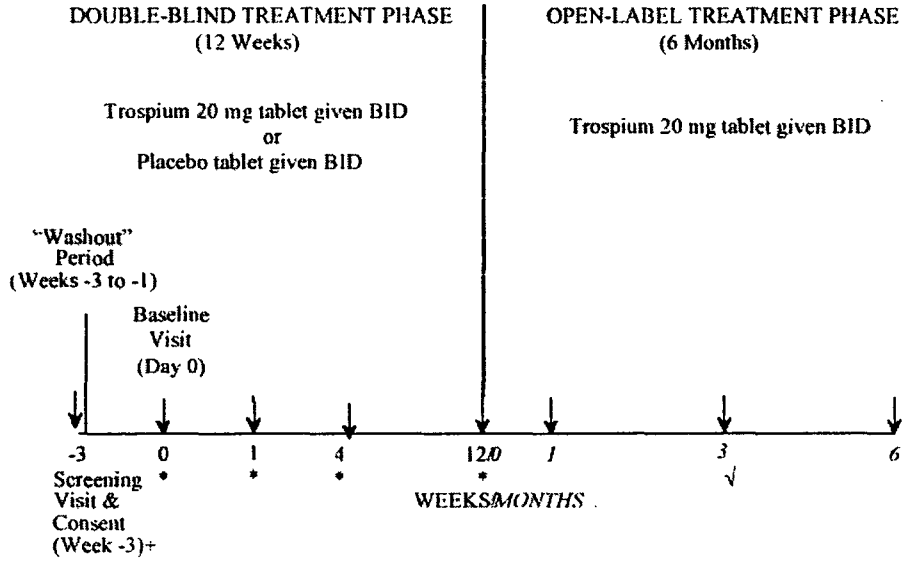
Secondary efficacy variables are acceptable

Study Design and Randomization

This is a multi-center, randomized, double blind, placebo controlled, parallel group trial conducted at sites all across the United States, in patients with overactive bladder (OAB). Patients were randomized on 1:1 basis to receive either placebo or trospium chloride 20 mg oral twice daily. The randomization was stratified by the mean baseline number of micturitions (i.e., toilet voids) per 24 hours. The data was collected via the patient daily diaries over seven days. Randomization treatment assignment was accomplished with the use of an interactive voice response system (IVRS). Using IVRS, patients randomized were required to have > 10 micturitions per day over a seven day period and > 7 urge incontinence episodes over a period of seven days. Once the randomization process was completed, the IVRS provided each site with a four-digit study medication kit number. A combination of both kit and the site numbers were chosen to be the patient's identification number.

A total of approximately 560 patients were planned to enter the study. Upon completion of the Day 84 (Week 12) visit, if desired, patients could continue into an open-label treatment phase and receive 20-mg trospium chloride twice daily for up to 6 months. Patients lost to follow-up or who withdrew from the study were not replaced.

Study Design



* 7-day patient urinary diary and 2-day daily volumes voided collections were done prior to study visits.

+ Week -1 for naïve patients, not currently taking OAB medications.

↓ Clinical Assessments
√ Interim Telephone Call (Health Status Check)

Reviewer's comment
The study design is acceptable and the randomization process is appropriate.

Dosing Schedule
Each patient was instructed to receive one tablet of study medication both in the morning and in the evening at least 1 hour before meals. The study medication was taken as a whole (i.e., not chewed) with water.

Planned Ammendments
There were 2 protocol amendments. Both amendments took effect after the enrollment period had begun. The primary purpose of Amendment-1 was to update and provide further details regarding the primary and secondary endpoints and plan for the statistical analyses of the data from IP631-005. This amendment increased the planned sample size from 500 patients to approximately 560 patients. In addition, a prospective validation of the urgency severity scale was added which required an additional assessment tool (i.e., the OAB-q) in a subset of patients.

> ***Reviewer's comment: It is still unclear whether the new Indevus Urgency Severity Scale is formally validated.***

The purpose of amendment-2 was to amend the distribution of open-label extension study medication, clarify study visit windows, and provide further details regarding safety and efficacy of endpoints, as well as statistical analysis of the data from IP631-005.

Study Population
Inclusion Criteria
Patients were entered in the study only if they met all of the following criteria:

* Male and female patients, 18 years and older
* Patients with Overactive Bladder (OAB) defined as:
* Urinary frequency of > 70 micturitions per week, as recorded in the patient diary
* Symptoms of urgency (i.e., sudden desire to micturite)
* Pure urge or mixed urinary incontinence with predominant urge incontinence.
* Patients with at least seven urge incontinence episodes per week.
* Symptoms of OAB for 6 or more months
* Able and willing to correctly and independently complete the patient urinary diaries for 7 days and complete the quality of life questionnaire
* Ability to use bathroom without assistance
* Females of childbearing potential must have had a negative pregnancy test prior to enrollment. They should not be breast-feeding, and not at an appreciable risk of becoming pregnant.

* Able to consent to participate by signing an informed consent form following an explanation of the nature and purpose of this study

Reviewer's Comment
Inclusion criteria for this study are adequate and acceptable

Exclusion Criteria
Patients were not entered into the study or were discontinued from the study for any of the following reasons:

* History of total daily volume voided greater than 3000 ml collected in patient urinary diary
* History of total average volume voided greater than 250 ml per void collected in patient urinary diary
* Patients with stress incontinence, insensate incontinence (those incapable of distinguishing discrete incontinence episodes) and overflow incontinence, as major reason for urine loss or urinary frequency as determined by the investigator
* Patients with history of neurogenic bladder
* Patients with clinically significant renal disease
* Patients with uninvestigated hematuria
* Patients with acute urinary tract infections (UTI) during washout period and a negative urinalysis at screening visit, or recurrent UTI defined as receiving treatment for symptomatic UTI more than 2 times in the past year
* Patients with clinically significant bladder neck obstruction defined as post-void residual urine greater than 100 ml
* Patients with indwelling catheter or requiring intermittent catheterization
* Patients with bladder surgeries performed within the past 6 months or those who had surgeries leading to complications such as fistula
* Females diagnosed with bladder cancer, interstitial cystitis within the past 6 months
* Males with PSA > 10 Ng/ml or diagnosed with bladder cancer, prostate cancer, chronic prostatitis, or interstitial cystitis within the past 6 months
* Patients treated within 21 days prior to randomization with any anti-cholinergic drug or other drug therapy for overactive bladder
* Patients taking diuretics or estrogen therapy that was not part of a long-term stable program.
* Patients employing bladder retraining / bladder drill programs
* Patients who were anticipated to begin or change other bladder therapies (non-medicinal) such as biofeedback or kegels, during the course of the study
* Patients with prior pelvic malignancies requiring radiation therapy or whose surgery had led to complications such as fistulas, etc
* Patients with the history of any medical condition or taking concomitant medications that would have interfered with the patient's suitability and/or effective participation in the trial

* Patients with the history of closed-angle glaucoma
* Patients with the history of myasthenia gravis
* Patients with hypersensitivity toward atropine, oxybutanin or adjuvants contained in the sugar-coated trospium chloride tablets
* Females who were pregnant or breast feeding and if capable of bearing children, were not willing to use reliable contraception
* Patients participating in another clinical trial or receiving a non-approved drug less than 30 days prior to screening

Reviewer's Comment
Exclusion criteria are adequate and acceptable

End Points
Primary Efficacy Endpoint
Change in average number of daily toilet voids

The primary efficacy analyses was based on data collected over 7 days prior to the baseline, Day 8 (week 1), Day 28 (week 4), and Day 84 (week 12) visits.

Secondary Endpoints
Change in average volume voided per toilet void.
Change in urge severity and frequency associated with toilet voids
Change in average number of urge incontinence episodes /24 hours

The secondary efficacy assessments were collected over 7 days prior to the baseline, Day 8 (week 1), Day 28 (week 4), and Day 84 (week 12) visits using data recorded in patient diaries. Volume voided was collected for 2 full days prior to each visit.

Data to monitor both primary and secondary efficacy endpoints was provided by patient recorded urinary diary. The data for toilet void frequency and number of incontinence episodes was recorded for seven full days prior to baseline, week 1, 4 and 12 visits. Data for average volume voided was collected for two full days prior to the clinic visit.

The measure used in the efficacy analysis was expressed as **change** (as computed by [Endpoint-Baseline]) and **percent change** (as computed by [Endpoint-baseline] / Baseline). The primary efficacy analysis was conducted using absolute change.

Patient Disposition
Treatments
The identity of the study medication was blinded. The study medication was provided in the form of brownish-yellow, sugar coated tablets with no markings. The tablets either contained trospium chloride 20mg or a matching placebo tablet.

Patient Assignment to the treatment Group
Each patient was assigned a screening number at the screening. Patients were randomized on 1:1 basis to receive either placebo or trospium chloride 20 mg twice daily during the study. Randomization for patients was stratified by the mean baseline number of micturitions (i.e., toilet voids and incontinence episodes per 24 hours collected via the patient diary over 7 days), using the stratified categories of 10 to 15, 16 to 20, and > 21 mean micturitions per 24 hours.

Randomized treatment assignment was accomplished with the use of an Interactive Voice Response System (IVRS). The IVRS performed the randomization using a two step process. The first step ensured that equal number of patients was assigned to each treatment group within the micturition stratification groups. The second step ensured that no site had >4 sequential assignments of the same study medication therapy. Once the randomization process was completed, the IVRS provided the study site.

Reviewer's comments
The main reason for randomizing subjects in the first place is the desirability of establishing treatment groups that are free of patient and physician selection bias.

Data suggests that the randomization worked well in this pivotal study. Trospium and placebo groups were comparable with regard to the factors that may affect patient response to the treatment.

Dosing, Labeling and Compliance
Each patient during this study was instructed by the investigator to take one tablet of study medication twice daily at least one hour before meals. The study medication was packaged in 60 count, high-density polyethylene (HDPE) bottles with child-resistant closures and shipped to each site.

Each bottle was attached with a three part tear-off label. The label contained the following information: patient number, name/address of sponsor, investigational new drug statement, study number (IP 631-005), directions for use, storage instructions, and contents of the bottle with instructions to return the bottle and any unused medication.

Patients were instructed by the investigator of the study to bring their bottles containing unused study medication with them for a compliance assessment at Day 8, Day 28, and Day 84 study visits. Compliance was assessed by unused tablet counts and details recorded in eCRF.

Integrated Review of Efficacy
The sponsor conducted the review of efficacy in three phases: **Screening, Baseline, Double-blind treatment phase and Open-Label treatment phase.**

During the **screening visit** i.e., Day (-) 21 for patients, who were currently on OAB medication and Day (-) 8 for patients, who were not currently taking OAB medication, screening assessments were made for patient's eligibility for the study.

Baseline phase from Day (-) 8 to Day 0, was the time when the indicated baseline assessments were made, including assessment of week 1 of patient urinary diary data prior to the first dose of study medication.

Double-blind treatment phase included Day 1 to Day 84 (week 12). During this time, patients either received the placebo or trospium chloride 20-mg tablet twice daily (BID) in a double blind fashion. Dosing according to the sponsor was begun on Day 1 following the baseline visit (Day 0).

Open-Label treatment Phase (part II) included administration of study medication in the morning on the day following the week 12 (Day 84) visit of double blind treatment phase for those patients wishing to continue.

Efficacy Results

The primary and secondary efficacy assessments were done on the intent-to-treat (ITT) patient sample. The ITT sample included all patients who were enrolled (after randomization were given study medication) and had at least 1 post-baseline evaluation.

Efficacy analyses were done using the last observation carried forward (LOCF) data set. The LOCF data set consisted of data recorded or carried forward at each visit. If no data were recorded at analysis Weeks 4 or 12, then the data were carried forward from the most recent visit. If no data were recorded at Week 1 and there were baseline and analysis Week 4 evaluations, then Week 1 was calculated as the average of the baseline and analysis Week 4 values.

Supportive analyses were done for the primary efficacy variable using the observed cases (OC) data set. The OC data set consisted of only the actual data recorded at each visit. This data set was used to investigate if replacement of missing data in the LOCF data set may have biased the results.

Results are shown in Table B1 below.

Table B1. Sumary of efficacy results from Study IP631-005

IP631-005 Summary of results for selected efficacy endpoints – ITT population

		Mean change from baseline		
		Placebo	Trospium	P-value
Efficacy endpoint	**Week**	**N = 325**	**N = 323**	
Number of daily toilet voids[a]		**N = 325**	**N = 323**	
Baseline		13.17	12.94	0.3169
Change from baseline	1	-0.96	-1.42	0.0039
	4	-1.55	-2.34	<0.0001
	12	-1.76	-2.67	<0.0001
Urgency severity score associated with toilet voids[a]		**N = 325**	**N = 323**	
Baseline		1.75	1.79	0.4100
Change from baseline	1	-0.01	-0.09	0.0023
	4	-0.04	-0.19	<0.0001
	12	-0.02	-0.21	<0.0001
Volume voided (mL) per toilet void/24 hours[a]		**N = 320**	**N = 319**	
Baseline		154.64	154.80	0.9667
Change from baseline	1	6.05	29.23	<0.0001
	4	9.45	39.50	<0.0001
	12	9.44	35.59	<0.0001
Urge frequency associated with toilet voids[a]		**N = 325**	**N = 323**	
Baseline		11.81	11.71	0.7158
Change from baseline	1	-0.87	-1.41	0.0033
	4	-1.43	-2.48	<0.0001
	12	-1.53	-2.76	<0.0001
Number of daily urge incontinence episodes[b]		**N = 325**	**N = 323**	
Baseline		3.90	3.84	0.9849
Change from baseline	1	-0.93	-1.62	<0.0001
	4	-1.60	-2.14	<0.0001
	12	-1.73	-2.31	<0.0001

Primary Efficacy Results

Change in Average Number of Daily Toilet Voids

The results from the primary efficacy analyses for change in average number of daily toilet voids at Weeks 1, 4, and 12 compared with baseline are summarized in the table above.

Trospium chloride demonstrated a statistically significant ($p < 0.0001$) improvement (i.e., decrease) in average number of daily toilet voids at Weeks 4, and 12 when compared with placebo. The magnitude of improvement in number of toilet voids for the trospium chloride group compared with the placebo group was statistically significant beginning at Week 4 and continued to increase until week 12 of the study.

Table B2: Change in the average number of daily toilet voids in IP631-005

		Mean Change from Baseline		
		Placebo	Trospium	P-value
	Week	N = 325	N = 323	Model[a]
Baseline		13.17 (0.17)	12.94 (0.17)	0.3169
Change from baseline[b]	1	-0.96 (0.11)	-1.42 (0.11)	0.0039
	4	-1.55 (0.14)	-2.34 (0.14)	<0.0001
	12	-1.76 (0.15)	-2.67 (0.15)	<0.0001

Using the OC data, trospium chloride demonstrated a statistically significant ($p< 0.0001$) improvement (i.e., decrease) in average number of daily toilet voids at Weeks 4, and 12 when compared with placebo. Therefore, the OC data analyses provided further support for the findings from the LOCF data analyses.

As per the sponsor, the baseline toilet void data was examined for significant baseline imbalances. Toilet voids were assessed using the baseline randomization strata (i.e., 10 to 15, 16 to 20, and =21 average number of daily toilet voids), as well as categories defined using the overall study baseline quartiles. No significant baseline imbalances were observed.

Secondary Efficacy Results

The secondary efficacy variables were also collected over 7 days prior to the baseline, Week 1, Week 4, and Week 12 visits, using data recorded in patient urinary diaries. Volume voided was collected for 2 full days prior to each study visit. The key efficacy analyses focused on the change from baseline to Week 12 visits. The secondary efficacy assessments are described below.

Table B3. Change in average urgency severity associated with toilet voids/IP631-005

		Mean change from baseline		
		Placebo	Trospium	P-value
Efficacy endpoint	Week	N = 325	N = 323	
Baseline		1.75	1.79	0.4100
Change from baseline	1	-0.01	-0.09	0.0023
	4	-0.04	-0.19	<0.0001
	12	-0.02	-0.21	<0.0001

Trospium chloride demonstrated a statistically significant ($p<0.05$) improvement (i.e., decrease) in average urgency severity associated with toilet voids at Week 4, and the improvement continued to week 12 when compared with placebo.

Reviewer's comment: It remains unclear that this scale is validated. Nevertheless, these results provide some support for the primary endpoint.

Table B4. Change in Average Volume Voided per Toilet Void/IP631-005

		Mean change from baseline		
		Placebo	Trospium	P-value
Efficacy endpoint	Week	N = 325	N = 323	
Baseline		154.64	154.80	0.9667
Change from baseline	1	6.05	29.23	<0.0001
	4	9.45	38.50	<0.0001
	12	9.44	35.59	<0.0001

Trospium chloride demonstrated a statistically significant ($p< 0.0001$) improvement (i.e., increase) in average volume voided (in ml) per toilet void at Weeks 1, 4, and 12 when compared with placebo. At Week 12, the mean increase from baseline in volume voided (ml) for the trospium chloride group was 35.59 ml compared with 9.44 ml for the placebo group.

Table B5. Change in Average "Urge Frequency" Associated with Toilet Voids/IP631-005

	Weeks	Placebo	Trospium	p
Urge frequency associated with toilet voids[a]		N = 325	N = 323	
Baseline		11.81	11.71	0.7158
Change from baseline	1	-0.87	-1.41	0.0033
	4	-1.43	-2.48	<0.0001
	12	-1.53	-2.76	<0.0001

Trospium chloride demonstrated a statistically significant ($p< 0.0001$) improvement (i.e., decrease) in average daily urge frequency associated with toilet voids at Weeks 4 - 12 when compared with placebo. The finding of a statistically significant decrease in average daily urge frequency associated with toilet voids for the trospium chloride group when compared with the placebo group is consistent with the expected pharmacodynamic effects of trospium chloride. Anticholinergic relaxation of the detrusor muscle would be expected to decrease the urge frequency associated with toilet voids.

Table B6. Number of daily urge incontinence episodes in IP631-005

	Weeks	Placebo	Trospium	p
Number of daily urge incontinence episodes[b]		**N = 325**	**N = 323**	
Baseline		3.90	3.84	0.9849
Change from baseline	1	-0.93	-1.62	<0.0001
	4	-1.60	-2.14	<0.0001
	12	-1.73	-2.31	<0.0001

Trospium chloride demonstrated a statistically significant ($p<0.0001$) improvement (i.e., decrease) in average number of daily urge incontinence episodes at Weeks 1, 4, and 12 when compared with placebo.

The magnitude of improvement in percent change in urge incontinence episodes for the trospium chloride group compared with the placebo group was statistically significant beginning at Week 1 and continued to increase at Weeks 4 and 12 of the study.

Trospium chloride-treated population as a whole experienced an average **reduction of 2.31 urge incontinence episodes per 24 hours representing a 65.9% reduction in the number of incontinence episodes relative to baseline**

In an effort to express these findings in terms of the degree of response for individual patients, the incontinence data were analyzed using descriptive statistics (univariate procedure). The results of the descriptive analysis showed that 72.4% of the patients treated with trospium chloride had a 50% reduction in the number of daily incontinence episodes whereas, only 51.7% of the placebo-treated patients had the same effect. Similarly, 30% of the trospium chloride treated patients had their number of daily incontinence episodes reduced to zero (0) while only 14.2% of the placebo-treated patients achieved this endpoint. In other words, trospium chloride was able to "eliminate" incontinence episodes in twice as many patients as did placebo. The results from these analyses suggest a high likelihood for a patient treated with trospium chloride to experience a clinically meaningful decrease and possible elimination of urinary incontinence episodes.

Trospium chloride demonstrated a statistically significant ($p<0.05$) **improvement (i.e., decrease)** in average number of **diurnal urge incontinence episodes** per 24 hours at weeks 1, 4, and 12 when compared with placebo as seen in the table below.

Table B7. Change in Average Number of Diurnal Urge Incontinence Episodes in IP631-005

	Week	N	Placebo (Mean)	N	Trospium (Mean)
Baseline		319	3.18	322	3.22
Change from Baseline	1	319	-0.77	322	-1.37
	4	319	-1.30	322	-1.84
	12	319	-1.41	322	-1.95

Sponsor points out in this submission that there was no statistically significant **improvement (i.e., decrease) in average number of nocturnal urge incontinence** episodes per 24 hours at weeks 4 or 12 as seen in the table below. Sponsor points out that the patients were not required to have nocturnal urge incontinence episodes to be eligible for inclusion in this study.

Table B8: Average number of Nocturnal Urge Incontinence Episodes in IP631-005

	Week	N	Placebo (Mean)	N	Trospium (Mean)
Baseline		319	0.69	322	0.62
Change from Baseline	1	319	-0.15	322	-0.25
	4	319	-0.27	322	-0.30
	12	319	-0.29	322	-0.35

Change in average Number of Total Incontinence Episodes per 24 Hours

Trospium chloride demonstrated a statistically significant ($p<0.05$) improvement (i.e.,decrease) in average number of daily total incontinence episodes at Weeks 1, 4, and 12 when compared with placebo. This is consistent with the findings for the analysis of the average number of daily urge incontinence episodes, which showed a **statistically significant ($p<0.05$) improvement (i.e., decrease)** in favor of the trospium chloride group when compared with the placebo group.

Table B9: Average number of Total Incontinence Episodes/24 hours in IP631-005

	Week	N	Placebo (Mean)	N	Trospium (Mean)
Baseline		325	4.36	323	4.33
Change from Baseline	1	325	-1.05	323	-1.81
	4	325	-1.83	323	-2.41
	12	325	-1.94	323	-2.53

Sponsor's Efficacy Conclusions for IP631-003

Trospium chloride demonstrated statistically significant improvement for the primary efficacy variable as well as the key secondary efficacy variables when compared with placebo. Sponsor points out that the internal consistency of the secondary efficacy analyses provides further support for the results of the primary efficacy analyses.

Reviewer's Efficacy Conclusions for IP631-003

It is the opinion of this reviewer that the patients treated with trospium chloride, in this 12 week study with an open label extension up to 6 months, not only had a decrease in the number of toilet voids per 24 hours and an average reduction of 2.31 urge incontinence episodes per 24 hours representing a 65.9% reduction and a statistically significant improvement in total incontinence episodes, but also experienced a clinically meaningful improvement in their symptoms and perhaps, in their quality of life.

The magnitude of the treatment effect was consistent across different age groups, geographic locations and baseline incontinence severity.

Therefore, this reviewer concludes that the evidence from this open label extension study supports the effectiveness of trospium chloride (20 mg bid) for the treatment of overactive bladder as is evident from the changes seen in both the primary and key secondary end points.

Review of Safety for Study IP631-005

Brief Statement of Conclusions

The adverse event profile of trospium chloride appears to be similar to that of other anti-cholinergic drugs. Dry mouth, constipation and headache were the most frequently reported events during this open label extension study. Other less frequently reported but clinically important adverse events included chest pain, angina, myocardial infarction and urinary retention.

Trospium chloride is not associated with any hepatic-toxicity and there is no evidence of any syncope among the patients with overactive bladder while being treated with this medication.

Trospium chloride has demonstrated no signal for cardiac repolarization in a thorough QT study and in the pivotal trials. One patient in this study experienced an increase of 60msec in QTcF with no associated clinical symptoms.

Description of Patient Exposure

Safety assessments were summarized using the total patient sample, which included all patients who were enrolled (i.e., randomized and dispensed double-blind study

medication). There were a total of 658 patients (trospium 329 patients, placebo 329 patients) in the total patient sample.

Data from adverse events, clinical laboratory test results, vital signs, and 12-lead electrocardiograms (ECGs) were reviewed to evaluate the safety and tolerability of trospium chloride.

Treatment Emergent Adverse Events

At least one TEAE was reported in a total of 349 patients [trospium 196 (59.6%) patients, placebo 153 (46.5%) patients]. TEAE's were most commonly reported for gastrointestinal system with 103 patients (31.3%) in the trospium group and 55 patients (16.7%) in the placebo group.

All TEAE summarized by frequency

The most common trospium related TEAE's were **dry mouth, constipation** and **headache**. TEAE's that occurred frequently in placebo group were dry mouth and constipation. The **other significant TEAE's** of interest that occurred in either treatment groups were **urinary retention, chest pain**, and **angina pectoris and MI**

Table B10. Summary of overall adverse events in Study IP631-005

	Number of patients (%)		
Preferred term	Placebo N = 329	Trospium N = 329	P-value
Total patients with at least 1 TEAE	**153 (46.5)**	**196 (59.6)**	**<0.01**
Total patients with chest pain[b]	**0 (0.0)**	**3 (0.9)**	**ND**
Severity: Mild	0 (0.0)	2 (0.6)	
Moderate	0 (0.0)	1 (0.3)	
Severe	0 (0.0)	0 (0.0)	
Serious TEAE	0 (0.0)	1 (0.3)	
Led to discontinuation	0 (0.0)	0 (0.0)	
Total patients with angina pectoris	**0 (0.0)**	**2 (0.6)**	**ND**
Severity: Mild	0 (0.0)	1 (0.3)	
Moderate	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	1 (0.3)	
Serious TEAE	0 (0.0)	0 (0.0)	
Led to discontinuation	0 (0.0)	0 (0.0)	
Total patients with myocardial infarction	**0 (0.0)**	**3 (0.9)**	**ND**
Severity: Mild	0 (0.0)	0 (0.0)	
Moderate	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	3 (0.9)	
Serious TEAE	0 (0.0)	3 (0.9)	
Led to discontinuation	0 (0.0)	2 (0.6)	

Sponsor reports that TEAEs of dry mouth and constipation occurred in >5.0% of trospium patients and occurred significantly ($p<0.01$ and $p=0.02$, respectively) more often in the trospium group when compared with the placebo group. The more frequent occurrence of dry mouth and constipation in trospium treated patients is consistent with the anticipated anticholinergic effects of trospium chloride.

Dry Mouth

A total of 82 patients [trospium 65 patients (19.8%), placebo 17 patients (5.2%)] experienced TEAEs of dry mouth. Of the 65 trospium patients who experienced TEAEs of dry mouth, 5 patients experienced dry mouth that led to discontinuation of study medication. None of the events of dry mouth were either severe or serious.

Constipation

TEAEs of constipation occurred significantly ($p=0.02$) more often in the trospium group compared with the placebo group. A total of 55 patients (trospium 36 patients (10.9%), placebo 19 patients (5.8%) experienced TEAEs of constipation. Of the 36 trospium patients who experienced TEAEs of constipation, 2 patients experienced severe constipation and 6 patients discontinued study medication due to this event. In both patients with severe constipation, the study medication was discontinued. None of the events of constipation were serious.

Sponsor points out in this submission that one of the 2 patients in the trospium group who experienced severe constipation leading to study discontinuation also experienced a concurrent event of fecal impaction.

Patient 09-6876 on Day 47 experienced constipation and fecal impaction leading to discontinuation of study medication. The patient was given suppositories by the physician and the fecal impaction and constipation resolved on Day 53.

In addition, there was 1 patient (**patient 13-6313 in trospium group**) who experienced an intestinal obstruction that was severe and led to discontinuation of study medication and resulted in hospitalization. During hospitalization, this patient 13-6313 experienced a myocardial infarction that resulted in death. Details of this event are discussed under section "Deaths".

Postoperative constipation was reported in a total of 2 patients [trospium 1 patient (0.3%) placebo 1 (0.3%)]. For the trospium patient who experienced postoperative constipation status- post hemorrhoidectomy, constipation was severe enough to prolong hospitalization that led to temporary interruption of study medication.

Headache

A total of 33 patients (trospium 18 patients (5.5%), placebo 15 patients (4.6%) experienced TEAEs of headache. The difference in incidence rates between treatment groups for TEAEs of headache was not statistically significant ($p=0.72$). Of the 18

trospium patients who experienced headache, none of the events were either serious or led to discontinuation of study medication.

Other Medically Significant Adverse Events

Urinary Retention

Sponsor reported a total of 3 patients [trospium 2 (0.6%) placebo 1 (0.3%)] who experienced TEAEs of urinary retention. Of the 2 trospium patients, 1 patient experienced severe urinary retention that led to discontinuation of study medication. None of the events of urinary retention were serious. The TEAEs of urinary retention are summarized below for all 3 patients:

Table B11. Summary of TEAE's of Urinary Retention by Patient in IP631-005

Treatment group/Pt age/gender	TEAE Investigator term – Additional explanation	AE onset day	AE stop day	Action with study med	Causal relationship/ Outcome
Trospium group:					
11-6336 62/F	Urinary retention. Also had concurrent kidney pain, constipation, and dry mouth. No relevant medical history reported.	7	8	Perm stopped	Probable/ Recovered
51-6049 85/F	Urinary retention. Also had concurrent distended stomach and dry mouth. Relevant medical history included cystocele and rectocele.	1	2	Perm stopped	Probable/ Recovered
Placebo group:					
37-6136 68/F	Urinary retention. Also had concurrent bloating. No relevant medical history reported.	46	76	Perm stopped	Possible/ Recovered

Reviewer's Comment

This reviewer agrees with the assessment in this submission that in 2 out of 3 patients who experienced urinary retention, there was probably a relationship to trospium. However, both of these patients had pre-existing medical illnesses possibly contributing to urinary retention.

Chest Pain

There were a total of 3 patients [trospium 3(0.9%) placebo 0] who experienced a TEAE of chest pain. Of the 3 trospium patients, 1 patient experienced non-cardiac chest pain that was serious because the event resulted in hospitalization. None of the events of chest pain were severe and none led to discontinuation of study medication. The TEAEs of chest pain are summarized below for all 3 patients:

Table B12. Summary of TEAE's of Chest Pain by Patient in IP631-005

Treatment group/Pt age/gender	TEAE Investigator term – Additional explanation [a]	AE onset day	AE stop day	Action with study med	Causal relationship/ Outcome
Trospium group:					
Chest pain					
09-6420 62/F	Non-cardiac chest pain.[b] Also had concurrent hyperlipidemia, HTN, dyspnea, wheezing, left BBB, cardiomyopathy, and UTI. Relevant medical history included LVH, right BBB, septal infarct on screening ECG, GERD, anxiety, and obesity.	50	53	Temp inter	Remote/ Recovered
26-6122 81/F	Chest pain. Also had concurrent dry mouth, constipation, and cough. Relevant medical history included hypercholesterolemia.	56	66	None	Remote/ Recovered
37-6444 59/F	Chest pains – intermittent, non-cardiac. Relevant medical history included elevated lipids (2003), general body aches due to age, and nicotine use (1 pack/day since 1972).	1	-	None	Defin not/ Unknown

Reviewer's comment

This reviewer agrees with the assessment in this submission that none of the 3 patients on trospium who experienced non-cardiac chest pain were due to active myocardial ischemia

Angina pectoris

Sponsor reports that there were a total of 2 patients (0.6%)in the trospium group, who experienced a TEAE of angina pectoris. None of the events of angina pectoris met serious criterion and none led to discontinuation of study medication. The TEAEs of angina pectoris are summarized below for both patients:

Table B 13. Summary of TEAE's of Angina Pectoris by Patient in IP631-005

Treatment group/Pt age/gender	TEAE Investigator term – Additional explanation [a]	AE onset day	AE stop day	Action with study med	Causal relationship/ Outcome
Trospium group:					
Angina pectoris					
37-6617 46/F	Chest pains – cardiac, increased frequency. Relevant medical history included MI (2000), intermittent chest pains (2002), myocardial ischemia noted on screening ECG, acid reflux (1999), hyperlipidemia (2003), CPK elevation at screening (266 U/L), obesity, and nicotine use (1½ pack/day for 30 yrs).	81	-	None	Def not/ Still present
42-6421 47/F	Angina. Also had shortness of breath, fatigue, subsequent Non-Q MI, and was diagnosed with 3 vessel CAD. Treated with quadruple CABG. Relevant medical history included HTN, hypercholesterolemia (2003), DM type 2 (1997), obesity, and nicotine use (7 cigarettes/day since 1983).	3	101	Temp inter	Remote/ Recovered

Reviewer's comment

This reviewer agrees with the assessment of the investigator that none of the 2 patients on trospium who experienced anginal pain, were related to the study medication. It is evident that both patients had past medical history of CAD and multiple risk factors related to CAD. Patient 42-642 experienced a non Q-wave MI on Day 84 and was treated with CABG and later recovered.

Myocardial Infarction

There were a total of 3 patients (0.9%) in the trospium group, who experienced a TEAE of myocardial infarction. The TEAEs of myocardial infarction are summarized below:

Table B13. Summary of TEAE's of MI by Patient in IP631-005

Treatment group/Pt age/gender	TEAE Investigator term – Additional explanation [a]	AE onset day	AE stop day	Action with study med	Causal relationship/ Outcome
Trospium group:					
Myocardial infarction					
13-6313 73/M	Myocardial infarction.[c] Also had concurrent intestinal obstruction (Day 22). Relevant medical history included CHF (1994), ongoing edema, HTN (1995), ruptured intestines (1997), colostomy reversal (1997 & 1998), and obesity.	23	-	None (Perm stopped on Day 22 due to bowel obstruction)	Possible/ Death
33-6022 65/F	Myocardial infarction.[b] Treated with coronary angioplasty and stent placement. Relevant medical history included MI (1998), leaking heart valve (1998), and hyperlipidemia (2002).	37	47	Perm stop	Remote/ Recovered
42-6421 47/F	Non-Q MI.[b] Also had concurrent angina, shortness of breath, fatigue, and was diagnosed with 3 vessel CAD. Treated with quadruple CABG. Relevant medical history included HTN, hypercholesterolemia (2003), DM type 2 (1997), obesity, and nicotine use (7 cigarettes/day since 1983).	84	92	Perm stop	Remote/ Recovered

Sponsor reports that all 3 of these patients had multiple underlying medical conditions that were risk factors for the occurrence of a MI. All 3 events of MI met serious criteria and 2 of the events led to discontinuation of study medication. Patient 13-6313 experienced an intestinal obstruction on Day 22 that led to hospitalization and a subsequent MI on Day 23 that resulted in death.

Detailed **narratives** are as follows:

Pt # 33-6022
65 year old female with history of MI, 1998, cardiac valvulopathy, and hyperlipidemia developed an inferior myocardial infarction approximately 1 month after starting double-blind treatment. She was treated with coronary angioplasty and stent placement and was discharged from hospital on a cardiac rehab program. Study drug was discontinued. The event was classified as serious and remotely related to study therapy.

Pt # 13-6313
73 year old male with history of asthma, COPD, CHF, ongoing edema, hypertension, and obesity, coronary disease, s/p stent placement, bowel obstruction, ruptured intestines, colostomy reversal, extensive abdominal adhesions and scarring, developed acute bowel obstruction approximately three weeks after starting double-blind treatment. On admission to the hospital, bowel obstruction and renal insufficiency were noted (BUN 64 mg/dL, creatinine 4.6 mg/dL) along with electrolyte abnormalities. Post-admission, the patient developed an acute myocardial infarction followed by cardiac arrest and death. The event was classified as serious and possibly related to study therapy.

Pt # 42-6421
47 year old female with h/o type II diabetes, hypercholesterolemia, hypertension, nicotine use and obesity was hospitalized with angina and myocardial infarction approximately 11 weeks after starting study drug. Angina pectoris was also reported as an adverse event. Study drug was discontinued. She was treated with a quadruple coronary artery bypass and was discharged on cardiac rehab. The event was classified as serious and remotely related to study therapy.

Reviewer's Comment
This reviewer agrees with the investigator that there were pre-existing cardiac risk factors in all three patients who experienced a myocardial infarction. However, patient 13-6313 who died secondary to a MI while being hospitalized, had significantly relevant medical and surgical risk factors that could have contributed to his death (i.e., pre-existing post-surgical abdominal adhesions and short bowel syndrome).

Therefore, in the opinion of this reviewer trospium chloride should be used with caution in patients with a history of bowel obstruction as evident from case 13-6313 where the bowel obstruction possibly contributed to a cascade of other ultimately fatal events.

Age indeterminate MI and silent MI
There were 2 patients in the trospium group who were found to have age indeterminate myocardial infarction as evident from ECG and 2 patients, one in trospium group and other in the placebo group, who had silent MI also detected from ECG. All four of these patients were clinically asymptomatic, non-serious and none led to discontinuation of study medication.

Table B14. ECG abnormalities Reported As AEs in IP631-005

Preferred term	Number of patients (%) Placebo N = 329	Trospium N = 329
Total patients with at least 1 TEAE	**153 (46.5)**	**196 (59.6)**
Total patients with at least 1 TEAE of ECG abnormality	**12 (3.6)**	**15 (4.6)**
Electrocardiogram abnormal NOS	0 (0.0)	4 (1.2)
Electrocardiogram ST-T change NOS	2 (0.6)	3 (0.9)
Bundle branch block right	2 (0.6)	2 (0.6)
Electrocardiogram QRS complex abnormal	0 (0.0)	2 (0.6)
Myocardial ischemia[a]	0 (0.0)	2 (0.6)
Atrioventricular block NOS	0 (0.0)	1 (0.3)
Bundle branch block left	0 (0.0)	1 (0.3)
Electrocardiogram Q wave abnormal	0 (0.0)	1 (0.3)
Electrocardiogram poor R wave progression	2 (0.6)	1 (0.3)
Electrocardiogram ST segment abnormal	1 (0.3)	1 (0.3)
Atrioventricular block first degree	4 (1.2)	0 (0.0)
Electrocardiogram ST segment depression	1 (0.3)	0 (0.0)
Electrocardiogram T wave abnormal	1 (0.3)	0 (0.0)

There were a total of 27 patients [trospium 15 (4.6%) placebo 12 (3.6%) who experienced a TEAE of ECG abnormality. The number of patients with a TEAE of ECG abnormality were comparable between the trospium chloride and placebo groups. None of the TEAEs of ECG abnormality were associated with clinical signs or symptoms, none of these events met serious criteria, and none of these events resulted in discontinuation of study medication.

Overall Adverse Events Possibly Related to Study Medication

There were a total of 178 patients [trospium 111 patients (33.7%), placebo 67 patients (20.4%)] who experienced 1 or more TEAEs that were assessed by the investigator as possibly related to study medication.

Possibly-related TEAEs were most commonly reported for the gastrointestinal system with 92 patients (28%) in the trospium group and 39 patients (11.9%) in the placebo group experiencing such events. The possibly related TEAEs that occurred in >5% of patients and were reported in more trospium patients than placebo patients were dry mouth and constipation. The events of dry mouth and constipation were also the most common TEAEs reported overall in the study and are consistent with the anticipated anticholinergic effects of trospium chloride.

Serious Adverse Events (Serous TEAEs)

Serious TEAEs were reported in a total of 18 patients [trospium 12 patients (3.6%), placebo 6 patients (1.8%)]. The number of patients with serious TEAEs is presented in the table below.

Table B15: Patients with Serious Adverse Event in IP631-005

Criterion for serious TEAE	Number of patients (%) Placebo N = 329	Trospium N = 329
Total patients with at least 1 TEAE	**153 (46.5)**	**196 (59.6)**
Total patients with at least 1 serious TEAE [a]	**6 (1.8)**	**12 (3.6)**
Death	0 (0.0)	1 (0.3)
Hospitalization required or prolonged	6 (1.8)	12 (3.6)

Table B16: Specific Serious Adverse Events (by prefered system)

Preferred term	Number of patients (%) Placebo N = 329	Trospium N = 329
Total patients with at least 1 TEAE	**153 (46.5)**	**196 (59.6)**
Total patients with at least 1 serious TEAE	**6 (1.8)**	**12 (3.6)**
Myocardial infarction	0 (0.0)	3 (0.9)
Chest pain [a]	0 (0.0)	1 (0.3)
Intestinal obstruction NOS	0 (0.0)	1 (0.3)
Lobar pneumonia NOS	0 (0.0)	1 (0.3)
Lumbar spinal stenosis	0 (0.0)	1 (0.3)
Meningioma benign	0 (0.0)	1 (0.3)
Pneumonia NOS	0 (0.0)	1 (0.3)
Postoperative constipation	0 (0.0)	1 (0.3)
Psychotic disorder NOS	0 (0.0)	1 (0.3)
Pyelonephritis NOS	0 (0.0)	1 (0.3)
Supraventricular tachycardia	0 (0.0)	1 (0.3)
Arthritis NOS aggravated	1 (0.3)	0 (0.0)
Bile duct stone	1 (0.3)	0 (0.0)
Cardiac failure congestive	1 (0.3)	0 (0.0)
Dehydration	1 (0.3)	0 (0.0)
Osteoarthritis NOS	1 (0.3)	0 (0.0)
Transient ischemic attack	1 (0.3)	0 (0.0)

The majority of serious TEAEs in both treatment groups met the serious criterion of requiring or prolonging hospitalization. One patient in the trospium chloride group (patient 13-6313) experienced intestinal obstruction that led to hospitalization and myocardial infarction that resulted in death.

Deaths

There was 1 patient in the trospium group that experienced an adverse event leading to death. A narrative for this patient is described below.

•Trospium **patient 13-6313** was a 73-year-old Caucasian male with significant past medical history of congestive heart failure (1994), hypertension (1995), ruptured intestines (1997), colostomy reversal (1997 and 1998), and obesity. On Day 22, the patient developed severe nausea and vomiting, abdominal pain, and became weak, dehydrated, and was unable to get out of bed. On Day 23, he was admitted to the hospital and diagnosed with a bowel obstruction. ECG showed normal sinus rhythm, PVC's and right bundle branch block. Laboratory test evaluation revealed renal insufficiency. Chest x-ray was normal. The patient was treated with meperidine, hydroxyzine, metoclopramide, dicyclomine, and famotidine. He also received topical nitroglycerin paste and verapamil. Cardiac and surgical consults were obtained. During the evening of Day 23, the patient developed shortness of breath and decreased blood pressure. He was diagnosed with a myocardial infarction. On Day 24, the patient experienced cardiac arrest and subsequently died.

Study drug administration was permanently stopped on Day 22 (July 2003). The investigator assessed the intestinal obstruction and the myocardial infarction as possibly related to study medication.

Reviewer's Comment
It is the clinical opinion of this reviewer that there were significant pre-existing medical/surgical conditions, (i.e., previous surgery for ruptured intestines resulting in post-op adhesions), that could have contributed to an intestinal obstruction rather than the study medication itself. However, it is possible that trospium chloride could have contributed to the cascade of events resulting in a MI and later to death.

Therefore, trospium, an anticholinergic drug should be used with caution in patients with past medical history of an illeas/intestinal obstruction especially in elderly population.

Table B17. Discontinuation of Study Medication Due to Adverse Events in IP631-005

	Number of patients (%)	
Other significant TEAE criterion	Placebo N = 329	Trospium N = 329
Led to discontinuation of study medication	15 (4.6)	24 (7.3)
Led to temporary interruption of study medication	12 (3.6)	13 (4.0)
Required dose reduction of study medication	2 (0.6)	1 (0.3)

Study medication was permanently discontinued due to TEAEs 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 occurred in the gastrointestinal system. i.e., dry mouth and constipation.

Study medication was also discontinued in 5 trospium patients who experienced acute renal failure, syncope, CVA, t-wave depression and uncontrolled diabetes. None of these patients had any serious medical squaelae nor were any of these events determined to be related to the study medication by study investigators.

Study medication was temporarily interrupted due to TEAEs in a total of 25 patients (trospium 13 patients, 4.0%; placebo 12 patients, 3.6%).

Study medication was also interrupted in 6 other patients for chest pain, strangulated hernia, UTI, Afib, Squamous cell CA of tongue and severe dehydration.

Adverse Events Leading to Dose Reduction

Study medication dose was reduced due to a TEAE in a total of 3 patients (trospium 1 patient, 0.3%; placebo 2 patients, 0.6%. In the trospium group, patient 39-6487 experienced dry mouth on Day 1 that led to dose reduction of the study medication (20 mg tablet once daily for 4 days). The dry mouth was assessed as possibly related to study medication and was still present as of the last study visit.

In the placebo group, the events of abdominal pain, diarrhea and decrease in the urine flow led to dose reduction of study medication.

Clinical Laboratory Evaluation

Based on the study protocol, routine laboratory testing was conducted at screening and at week 12 visits during the double-blind treatment phase. Hematology, chemistry, and urinalysis data were reviewed for changes that occurred from baseline; endpoint and change from baseline were reviewed. In addition, laboratory data were analyzed using predefined criteria to identify potentially clinically significant (PCS) abnormal laboratory values.

Hematology PCS Values

Sponsor reports that a total of 13 patients (trospium 5 patients (1.6%) placebo 8 patients, 2.6%) met PCS criteria for 1 or more abnormal hematology value. The most common hematology PCS abnormal value was low hematocrit [trospium 5 patients (1.6%) placebo 3 patients (1.0%)].

The hematology PCS abnormal values at endpoint are summarized in the table below:

Table B18. Hematology – PCS abnormal values- in IP631-005

Total patient sample	Placebo N=329		Trospium N=329	
Hematology PCS abnormal value	**n/N (%)**	**N at BL**	**n/N (%)**	**N at BL**
Number of patients with at least 1 hematology PCS abnormal value	**8/312 (2.6)**	**0**	**5/313 (1.6)**	**5**
Hematocrit low (F ≤32% or M ≤37%)	3/312 (1.0)	0	5/313 (1.6)	4
RBC low (F ≤3.0 x 10^3/mm^3 or M ≤3.5 x $10^3$$mm^3$)	0/311 (0.0)	0	1/313 (0.3)	1
Hemoglobin low (F ≤9.5 g/dL or M ≤11.5 g/dL)	0/311 (0.0)	0	1/313 (0.3)	0
Eosinophils high (≥10%)	2/306 (0.7)	0	0/308 (0.0)	0
Monocytes high (≥15%)	2/306 (0.7)	0	0/308 (0.0)	0
Platelet count high (>700 x 10^3/mm^3)	1/309 (0.3)	0	0/310 (0.0)	0

Overall, the number of patients with hematology PCS abnormal values was similar between the trospium chloride and placebo groups.

Serum Chemistry PCS Values

Sponsor reports a total of 73 patients [trospium 34 patients (10.9%) and placebo 39 patients (12.4%)] met PCS criteria for 1 or more abnormal serum chemistry value. The most common serum chemistry PCS abnormal values were low bicarbonate (trospium 12 patients (3.8%) placebo 14 patients (4.5%) and high BUN [trospium 9 (2.9%) patients, placebo 10 (3.2%) patients].

Table B19. Serum Chemistry - PCS abnormal values – in IP631-005

Total patient sample	Placebo N=329		Trospium N=329	
Total patients with laboratory value[a]	315		313	
Chemistry PCS abnormal value	n[b] (%)	N at BL	n[b] (%)	N at BL
Number of patients with at least 1 chemistry PCS abnormal value	**39 (12.4)**	**25**	**34 (10.9)**	**27**
Bicarbonate low (≤19 mmol/L)	14 (4.5)	12	12 (3.8)	11
BUN high (≥30 mg/dL)	10 (3.2)	5	9 (2.9)	6
Glucose high (>250 mg/dL)	1 (0.3)	0	3 (1.0)	3
HDL low (≤30 mg/dL)	6 (1.9)	3	3 (1.0)	2
LDL high (≥200 mg/dL) [c]	2 (0.7)	1	3 (1.0)	2
Potassium high (≥6 mmol/L)	2 (0.6)	1	2 (0.6)	2
Bilirubin direct high (≥0.5 mg/dL)	0 (0.0)	0	1 (0.3)	0
Chloride low (≤90 mmol/L)	0 (0.0)	0	1 (0.3)	1
Glucose low (<40 mg/dL)	1 (0.3)	1	1 (0.3)	1
Uric acid high (F ≥8.5 or M ≥10.5 mg/dL)	1 (0.3)	0	1 (0.3)	1
CPK high (F ≥702 or M ≥1191 IU/L)	2 (0.6)	1	0 (0.0)	0
Creatinine high (≥2 mg/dL)	2 (0.6)	1	0 (0.0)	0
Triglycerides high (>600 mg/dL)	4 (1.3)	2	0 (0.0)	0

Overall, the number of patients with serum chemistry PCS abnormal values was similar between the trospium chloride and placebo groups.

Urinalysis PCS Values

Sponsor reports a total of 112 patients [trospium 60 patients (19.3%) and placebo 52 patients (16.8%) who met PCS criteria for 1 or more abnormal urinalysis value. The urinalysis PCS values at endpoint are summarized in the table below:

Table B20. Urinalysis – PCS abnormal values at endpoint – in IP631-005

Total patient sample	Placebo N = 329		Trospium N = 329	
Total patients with laboratory value[a]	310		311	
Urinalysis PCS abnormal value	n[b] (%)	N at BL	n[b] (%)	N at BL
Number of patients with at least 1 urinalysis PCS abnormal value	52 (16.8)	46	60 (19.3)	49
WBC/HPF high (>10/HPF)	14 (4.6)	10	34 (11.0)	25
RBC/HPF high (>8/HPF)	12 (3.9)	11	15 (4.8)	12
Bacteria/HPF high (≥moderate)	12 (3.9)	12	11 (3.6)	10
Squamous epith cells/HPF high (≥many)	12 (3.9)	12	11 (3.5)	10
Calcium oxalate crystals high (≥moderate)	12 (3.9)	11	7 (2.3)	7
Amorphous sediment/HPF high (≥many)	6 (2.0)	5	6 (1.9)	6
Blood high (≥3+)	4 (1.3)	4	4 (1.3)	4
Uric acid crystals/HPF high (≥moderate)	3 (1.0)	3	2 (0.6)	1
Glucose high (≥3+)	1 (0.3)	0	1 (0.3)	1

The most common UA PCS abnormal values were WBCs (trospium 34 patients (11%) placebo 14 patients (4.6%) and RBCs (trospium 15 patients (4.8%) placebo 12 patients (3.9%) in the urine.

None of the patients in either treatment group who met UA PCS criteria had TEAEs reported for urinary retention.

Reviewer's Comment:

This reviewer agrees with the sponsor that the number of patients with hematology PCS abnormal values and serum chemistry PCS abnormal values is similar between trospium and placebo groups. Reviewer also agrees that an increase in WBC's in urine during the trial did not translate into a clinically meaningful condition such as clinical UTI in asymptomatic patients.

Vital Signs- PCS abnormal values (BP and Pulse)

A total of 159 patients [trospium 89 (27.1%), placebo 70 (21.4%)], met PCS criteria for 1 or more abnormal high vital signs variables and a total of 185 patients [trospium 83 (25.2%), placebo 102 (31.2%) met PCS criteria for 1 or more abnormal low vital signs variables. The vital signs PCS values for any high or any low value are summarized in the table below:

Table B21. Vital Signs Data –PCS Changes – in IP631-005

Total patient sample	Placebo N = 329		Trospium N = 329	
Total patients with vital signs data[a]	N = 327		N = 329	
Vital signs PCS abnormal value	n[b] (%)	N at BL	n[b] (%)	N at BL
Number of patients with at least 1 vital sign PCS value				
Low	102 (31.2)	102	83 (25.2)	82
High	70 (21.4)	69	89 (27.1)	88
Systolic blood pressure:				
Low: <90 or decrease ≥20 mm Hg	54 (16.5)	54	53 (16.1)	52
High: >180 or increase ≥20 mm Hg	53 (16.2)	53	59 (17.9)	58
Diastolic blood pressure:				
Low: <50 or decrease ≥15 mm Hg	50 (15.3)	50	27 (8.2)	26
High: >105 or increase ≥15 mm Hg	28 (8.6)	27	39 (11.9)	39
Pulse:				
Low 1: <50 bpm only	2 (0.6)	1	1 (0.3)	1
Low 2: decrease ≥15 bpm only	28 (8.6)	28	23 (7.0)	23
Low 3: <50 & decrease ≥15 bpm	0 (0.0)	0	0 (0.0)	0
Total low pulse (1, 2, & 3 above):	30 (9.2)	29	24 (7.3)	24
High 1: >100 & increase ≥15 bpm	4 (1.2)	4	4 (1.2)	4
High 2: >120 & increase <15 bpm	0 (0.0)	0	0 (0.0)	0
Total high pulse (1 & 2 above):	4 (1.2)	4	4 (1.2)	4

The sponsor reports that the number of patients who met high and low PCS criteria for systolic blood pressure was similar between the trospium and placebo groups. For diastolic blood pressure, there were more patients in the trospium chloride group who met high PCS criteria and there were more patients in the placebo group who met low PCS criteria. For pulse, the number of patients who met high and low PCS criteria were similar between the trospium and placebo groups.

Overall, the number of patients who met PCS criteria for the vital signs data was similar for the trospium chloride and placebo groups. For diastolic blood pressure, there were more patients in the trospium chloride group who met the high PCS criteria and in the placebo group there were more patients who met the low PCS criteria. There was a mean increase of 2.9 bpm in pulse rate from baseline for the trospium group compared with 0.8 bpm from baseline for the placebo group.

Reviewer's Comment

This reviewer agrees that the vital signs data is similar in both trospium and the placebo groups.

Electrocardiographic Data

Table B22. ECG Changes - Potentially Clinically Significant values – in IP631-005

Total patient sample	Placebo N = 329		Trospium N = 329	
Total patients with ECG data[a]	N = 325		N = 326	
ECG PCS abnormal interval	n[b] (%)	N at BL	n[b] (%)	N at BL
PR interval[c]				
>200 msec only	14 (4.3)	2	14 (4.3)	2
Increase ≥20 msec only	33 (10.2)	33	40 (12.3)	40
>200 and increase ≥20 msec	12 (3.7)	11	5 (1.5)	3
Total PR interval high	**59 (18.2)**	**46**	**59 (18.1)**	**45**
QRS interval				
>100 msec only	29 (8.9)	5	34 (10.4)	6
Increase ≥10 msec only	38 (11.7)	38	42 (12.9)	42
>100 and increase ≥10 msec	19 (5.8)	15	11 (3.4)	7
Total QRS interval high	**86 (26.5)**	**58**	**87 (26.7)**	**55**
QT interval				
>500 msec only	1 (0.3)	0	1 (0.3)	1
Increase ≥60 msec only	15 (4.6)	15	7 (2.1)	7
>500 and increase ≥60 msec	0 (0.0)	0	0 (0.0)	0
Total QT interval high	**16 (4.9)**	**15**	**8 (2.5)**	**8**
QTcF interval				
>500 msec only	1 (0.3)	1	0 (0.0)	0
Increase ≥60 msec only	8 (2.5)	8	7 (2.1)	7
>500 and increase ≥60 msec	0 (0.0)	0	1 (0.3)	1
Total QTcF interval high	**9 (2.8)**	**9**	**8 (2.5)**	**8**
Heart rate				
<50 bpm only	4 (1.2)	2	3 (0.9)	2
Decrease ≥15 bpm only	13 (4.0)	13	9 (2.8)	9
<50 and decrease ≥15 bpm	0 (0.0)	0	0 (0.0)	0
Total low heart rate	**17 (5.2)**	**15**	**12 (3.7)**	**11**
>100 and increase ≥15 bpm	1 (0.3)	1	6 (1.8)	6
>120 and increase <15 bpm	0 (0.0)	0	1 (0.3)	1
Total high heart rate	**1 (0.3)**	**1**	**7 (2.1)**	**7**

PR and QRS intervals

The number of patients who met ECG PCS criteria for abnormal PR and QRS intervals were similar between the trospium chloride and placebo groups.

QT and QTcF intervals

There were twice as many patients in the placebo group who had a QT interval increase of >60 msec when compared with the trospium chloride group. When the QT interval was corrected for heart rate using the Fridericia formula (QTcF), the number of patients who met ECG PCS criteria for abnormal QTcF intervals were similar between the trospium chloride and placebo groups.