

## TROSPIUM CHLORIDE IMPROVES OVERACTIVE BLADDER SYMPTOMS: A MULTICENTER PHASE III TRIAL

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### ABSTRACT

**Purpose:** Trospium chloride is an anticholinergic agent with predominantly peripheral nonselective antimuscarinic activity lacking central nervous system effects. It has no known drug-drug interactions, an advantage for patients taking many medications. Because these qualities may provide added benefit when treating patients with symptoms associated with overactive bladder (OAB) and urge incontinence, we studied the effectiveness of trospium in treating these conditions.

**Materials and Methods:** Patients with OAB with urge incontinence were randomized 1:1 to 20 mg trospium twice daily or placebo in this 12-week, multicenter, parallel, double-blind, placebo controlled trial. Dual primary end points were change in average number of toilet voids and change in urge incontinent episodes per 24 hours. Secondary efficacy variables were change in average of volume per void, voiding urge severity, urinations during day and night, time to onset of action and change in Incontinence Impact Questionnaire.

**Results:** A total of 523 patients were entered at 51 sites. Trospium significantly decreased average frequency of toilet voids and urge incontinent episodes compared to placebo. It significantly increased average volume per void, and decreased average urge severity and daytime frequency. All effects occurred by week 1 and all were sustained throughout the study. Nocturnal frequency decreased significantly by week 4 and Incontinence Impact Questionnaire scores improved at week 12. Trospium was well tolerated.

**Conclusions:** Trospium was found to have sustained effectiveness beginning at the end of week 1 in decreasing the number of voids, urge incontinent episodes, total daily micturitions and urge severity, and in increasing volume per void. It also improved symptoms of OAB and quality of life.

**KEY WORDS:** bladder, neurogenic; cholinergic antagonists

Overactive bladder (OAB) is characterized as a syndrome consisting of “urgency with or without urge incontinence, usually with frequency and nocturia.”<sup>1</sup> The diagnosis can only be made in the absence of an obvious pathological disorder. More than 17 million Americans have this condition.

A complex of neural mechanisms supplies the normal bladder. During filling these mechanisms cause the detrusor to relax, and outflow structures to contract and sustain continence. During urination these mechanisms cause the detrusor to contract and outflow structures to relax. These intricately managed cyclical functions are largely controlled by

adrenergic and cholinergic afferent and efferent innervation to the bladder and outflow system, and further controlled by central mechanisms in the cerebral cortex, brain stem and spinal cord. Parasympathetic cholinergic innervation stimulates muscarinic receptors within the detrusor to contract.<sup>2</sup> This process is often associated with the subjective sensation of urgency and the objective experience of urge incontinence. Current medications are effective in decreasing urinary urgency and urge incontinence but are associated with unpleasant side effects such as dry mouth and constipation. These adverse effects limit the usefulness of these drugs because patients often take less than optimal dosages to avoid the side effects or stop taking the medication altogether. More than 70% of patients do not continue therapy beyond 9 months.<sup>3</sup> There is a significant need for compounds that are as effective in relieving symptoms of OAB as those currently available but that produce fewer unpleasant side effects.

Trospium chloride, a quaternary amine, is an anticholinergic agent<sup>4</sup> with predominantly peripheral nonselective antimuscarinic activity, lacking central nervous system effects.<sup>5–7</sup> The compound antagonizes the effect of acetylcholine on cholinergic nerves, and exhibits parasympatholytic action by decreasing detrusor tone and uncontrolled detrusor contractions that can cause OAB with incontinence.<sup>8</sup>

Trospium is absorbed slowly from the gastrointestinal tract. Bioavailability has been estimated to be between 10% and 12% in man.<sup>9</sup> Maximum plasma levels are achieved 5

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hours after oral administration. Plasma half-life ranges from 12 to 18 hours.<sup>9</sup> The drug is not a substrate or inhibitor of the cytochrome P450 isoenzyme metabolic system and has no known drug-drug interactions.<sup>10</sup> It is not highly metabolized and is eliminated in the urine primarily as trospium.<sup>9,11</sup>

In a head-to-head trial of 20 mg trospium chloride twice daily (bid) versus 5 mg oxybutynin bid, Halaska et al demonstrated that both drugs were equivalent in decreasing urinary voiding frequency.<sup>12</sup> Trospium demonstrated a more favorable dry mouth adverse event profile.<sup>12</sup> In another trial comparing 20 mg trospium bid to 2 mg tolterodine bid, Junemann and Al-Shukri showed that trospium was statistically more effective in decreasing urinary frequency and equivalent in decreasing urgency incontinence compared to placebo.<sup>13</sup>

The current trial was designed to expand on our knowledge of the effect of trospium chloride at 20 mg twice daily versus placebo in patients presenting with overactive bladder associated with urge incontinence. Findings from this trial address the need to identify an improved balance between efficacy and tolerability in this class of drugs.

#### MATERIAL AND METHODS

**Patients.** Eligible male and female patients were 18 years or older with OAB symptoms for at least 6 months. Subjects were required to have urinary urgency, a minimum voiding frequency of 70 voids per week with at least 7 urge incontinence episodes per week. Subjects with incontinence that was predominantly stress, insensate or overflow in nature were excluded from study as were those with neurogenic bladder disorders, significant renal disease, uninvestigated hematuria and urinary tract infection at washout or more than twice during the prior year. Also excluded from study were patients with significant bladder outlet obstruction defined as post-void residual volume greater than 100 ml. Patients concurrently using any anticholinergic drug or other drug therapy for overactive bladder within 21 days before randomization, those who had undergone bladder surgery within 6 months before randomization, or those with bladder cancer or interstitial cystitis were excluded from study, as were males with prostate specific antigen greater than 10 ng/ml. Further exclusion criteria were diuretic use, estrogen therapy and nonmedical bladder therapy that was not part of a stable, long-term program.

**Study design.** This trial was a parallel, randomized, double-blind, placebo controlled study of patients with OAB conducted at 51 sites. Patients being treated with medications for OAB at screening underwent a 2-week washout. At week 0 patients collected a 7-day baseline urinary diary that included measurements of voided volume for days 6 and 7. Those meeting eligibility criteria were randomized 1:1 to 20 mg trospium twice daily or matching placebo for 12 weeks. Seven-day diaries with format identical to that of the screening diaries were collected before each study visit at weeks 1, 4 and 12. Diaries and drug accountability were reviewed for accuracy at each visit, and adverse events were logged and assessed. Patients successfully completing the week 12 visit were eligible to enroll in a 9-month open label extension to receive 20 mg trospium bid. Results from the extension are beyond the scope of this report. Institutional review boards approved all study sites and all patients signed written informed consents. Patients lost to followup or who withdrew from the study were not replaced.

**Outcome parameters.** The dual primary efficacy variables were change in average number of toilet voids per 24 hours and change in average number of urge incontinence episodes per 24 hours. Secondary efficacy variables were time from baseline to onset of efficacy, average volume per void, average urgency (degree and frequency), and average number of diurnal and nocturnal voids. Urgency severity was measured

with the Indevus Urgency Severity Scale (IUSS), a 4-point validated scale<sup>14</sup> rating patient perception of urgency severity at each void (see Appendix). In females quality of life and symptom annoyance were assessed with the Incontinence Impact Questionnaire (IIQ)<sup>15</sup> with subscales of impacts on travel, physical activity, social relationships and emotional health. The IIQ was modified from the Veterans Bladder Function Survey for males.<sup>16</sup> The safety parameters collected during this study included adverse events, clinical laboratory tests, vital signs, and 12-lead electrocardiograms at baseline and week 12.

All primary and secondary efficacy assessments were performed using the Intent-To-Treat patient sample. Efficacy analyses were done using the Last Observation Carried Forward data set, consisting of data recorded or carried forward at each visit. Safety assessments and patient characteristics were summarized using the total patient sample.

Analysis of variance models with treatment, center and treatment by center interaction were used for all continuous data analyses. Interaction terms were dropped from efficacy analysis models when they were not significant ( $p > 0.10$ ) at week 12. Homogeneity of variance was assessed using Levene's test, and normality was examined using Q-Q plots of the residuals and the Shapiro-Wilk test ( $p \leq 0.10$ ). Rank transformations of the original data or the median test were used if the data were not normally distributed.

#### RESULTS

A total of 523 patients, 389 (74.4%) female and 134 (25.6%) male, were enrolled at 51 investigational sites in the United States, 262 on trospium chloride and 261 on placebo. Baseline characteristics were comparable for the 2 treatment groups (table 1). Overall by the end of week 1 patients on trospium averaged significantly fewer toilet voids ( $p \leq 0.05$ ) and urge incontinence episodes ( $p \leq 0.001$ ) compared to placebo, and sustained this improvement throughout the study. At study end trospium treated patients experienced a significant average decrease from baseline of more than 2 incontinent episodes (60%) per 24 hours compared to 1.3 episodes (44.2%) for placebo ( $p \leq 0.0001$ ). Of the patients treated with trospium 71% had a 50% decrease in the number of incontinence episodes per 24 hours compared with 54% of those on placebo. Similarly 21% of trospium treated patients vs 11% of placebo treated patients became completely dry (table 2).

Average volume voided increased significantly compared to placebo at weeks 1, 4 and 12 ( $p \leq 0.0001$ ). Similarly, IUSS was decreased significantly by trospium ( $p \leq 0.01$  weeks 1 and 4, and  $p \leq 0.0001$  week 12, table 2) and the average number of voids with any urgency at all decreased significantly by trospium ( $p \leq 0.0001$  weeks 4 and 12) compared to placebo. Trospium treated patients had a statistically significant decrease in average number of diurnal voids at weeks 1 ( $p \leq 0.05$ ), 4 ( $p \leq 0.0001$ ) and 12 ( $p \leq 0.0001$ ) and nocturnal voids at weeks 4 ( $p \leq 0.001$ ) and 12 ( $p \leq 0.05$ ). IIQ total scores significantly improved for all females treated with trospium by week 12 compared to placebo. This improvement was not

TABLE 1. Baseline patient characteristics

	No. Placebo (%)	No. Trospium (%)
Gender:		
Female	186 (71.3)	203 (77.5)
Male	75 (28.7)	59 (22.5)
Mean age $\pm$ SE	61.5 $\pm$ 0.8	63 $\pm$ 0.8
Race:		
White	225 (86.2)	222 (84.7)
Black	20 (7.7)	26 (9.9)
Hispanic	13 (5.0)	10 (3.8)
Other	3 (1.1)	4 (1.6)
Prior OAB medications	142 (54.4)	135 (51.5)

TABLE 2. Summary of results for key diary data efficacy end points

	Wk	Placebo	Trospium
No. pts		256	256
No. voids/24 hrs			
Baseline		12.9	12.7
Change from baseline:			
1		-0.81	-1.18 (p ≤ 0.05)
4		-1.07	-2.20 (p ≤ 0.0001)
12		-1.29	-2.37 (p ≤ 0.0001)
No. urge incontinence episodes/24 hrs*			
Baseline		4.3	3.9
% Change from baseline			
1		-27.5	-40.1 (p ≤ 0.001)
4		-40.9	-58.5 (p ≤ 0.0001)
12		-44.2	-59.0 (p ≤ 0.0001)
Av vol voided (ml)/void/24 hrs			
Baseline		156.6	155.1
Change from baseline:			
1		6.6	19.9 (p ≤ 0.0001)
4		8.5	30.0 (p ≤ 0.0001)
12		7.7	32.1 (p ≤ 0.0001)
No. urgency voids/24 hrs			
Baseline		11.72	11.29
Change from baseline:			
1		-0.71	-1.13
4		-1.00	-2.10 (p ≤ 0.0001)
12		-1.08	-2.30 (p ≤ 0.0001)
Urgency severity score/void			
Baseline		1.8	1.8
Change from baseline:			
1		-0.01	-0.11 (p ≤ 0.01)
4		-0.06	-0.18 (p ≤ 0.01)
12		-0.04	-0.22 (p ≤ 0.001)
No. diurnal voids/24 hrs			
Baseline		10.9	10.6
Change from baseline:			
1		-0.68	-1.00 (p ≤ 0.05)
4		-0.89	-1.77 (p ≤ 0.0001)
12		-0.98	-1.90 (p ≤ 0.0001)
No. nocturnal voids/24 hrs			
Baseline		2.0	2.1
Change from baseline:			
1		-0.15	-0.18
4		-0.17	-0.43 (p ≤ 0.001)
12		-0.29	-0.47 (p ≤ 0.05)

\* Difference assessed by rank ANOVA while all others assessed by ANOVA.

the case for males (table 3). IIQ subscales are summarized in table 4.

Because of this single disparity an additional analysis was conducted to evaluate whether trospium effectiveness was altered by gender. The analysis models included treatment, gender and treatment by gender interaction effects for this specific analysis. Trospium was found to be significantly different from placebo with regard to change in number of voids per 24 hours, percent change in urge incontinence episodes per 24 hours, change in volume voided per void, change in urgency voids per 24 hours, change in urgency severity per void, and changes in diurnal and nocturnal voids per 24 hours. The interaction terms were not significant which indicates that there was no difference in the effectiveness of trospium with respect to gender.

Dry mouth occurred in 21.8% compared to 6.5% of patients treated trospium vs placebo, and constipation in 9.5% com-

pared to 3.8% of those given trospium vs placebo. Dry mouth and constipation occurred early, and tended to resolve with continuing treatment. All adverse events occurring in more than 3% of patients are listed in table 5. The overall discontinuation rate was identical between treatment groups (16.4%). Adverse events leading to discontinuation occurred in 8.8% for trospium vs 5.7% for placebo. Other adverse events usually associated with anticholinergic agents such as abnormal vision, somnolence and lethargy were comparable between treatment groups (p < 0.5%). There were no clinically significant differences in vital signs, electrocardiograms or laboratory variables.

## DISCUSSION

Trospium demonstrated statistically significant improvement for the 2 primary efficacy variables as well as all of the OAB secondary efficacy variables compared to placebo. The results from these analyses suggest that a patient treated with trospium is highly likely to experience a clinically meaningful decrease in symptoms attributable to OAB and urge urinary incontinence. Treated patients noted less frequency day and night, less urgency, less urgency incontinence, longer intervals between voiding and larger volumes voided compared to placebo. Of these patients 21% experienced complete continence, a figure twice as great as those not treated with this drug. These results are consistent with those reported earlier.<sup>9, 12, 13, 17-19</sup>

Although urgency is the key symptom of OAB, previous assessments have been limited to changes in the frequency of urge episodes and not to the severity of urgency per se. They also have not quantitated the impact of urge severity on patient quality of life. The validated urgency severity scale, IUSS,<sup>14</sup> in this study allowed for the first time an assessment of urgency severity as well as frequency. By study conclusion we learned that trospium significantly decreased average urge severity at each void. This finding paralleled an improved patient perceived quality of life (IIQ). The decrease in urge severity and improved quality of life paralleled the decreases in frequency and incontinence episodes. Furthermore, the decrease in urinations associated with any urgency at all was reduced significantly with 2.3 fewer urge associated voids per 24 hours.

Trospium demonstrated a quick onset of action. Most symptoms of OAB improved significantly by the end of week 1. This rapid onset may enable the patient and physician to determine whether alternative approaches should be considered early in the course of therapy rather than continuing with a treatment that will not help. Analyses are continuing to identify an outcome variable for assessment within a week after therapy begins to predict whether the patient would likely become a responder, which would decrease the need for weeks of exposure to an ineffective treatment. The increase in volume per void is consistent with other studies<sup>9, 12</sup> and is an expected pharmacodynamic effect of trospium caused by anticholinergic relaxation of the detrusor muscle.

In women trospium improved total IIQ (quality of life)

TABLE 3. Summary of results at week 12 for the Incontinence Impact Questionnaire

	Placebo		Trospium	
	No.	LSM (SE)	No.	LSM (SE)
All pts:				
Baseline	236	195.4 (5.6)	236	183.5 (5.6)
Change from baseline	236	-36.0 (5.6)	235	-54.0 (5.6, p ≤ 0.05)
Female pts:				
Baseline	169	201.9 (6.6)	184	191.2 (6.3)
Change from baseline	169	-35.7 (6.9)	183	-59.1 (6.6, p ≤ 0.05)
Male pts:				
Baseline	67	182.1 (10.8)	52	162.3 (12.2)
Change from baseline	67	-35.4 (9.3)	52	-32.9 (10.5)

Negative change score indicated improvement (ie decreased IIQ total score) from baseline.

TABLE 4. Summary of results at week 12 from Incontinence Impact Questionnaire subscales

	Placebo		Tropium	
	No.	LSM (SE)	No.	LSM (SE)
Travel subscale baseline	237	55.6 (1.7)	237	52.4 (1.7)
Change from baseline	237	-9.9 (1.7)	237	-14.9 (1.7, $p \leq 0.05$ )
Social relationships baseline	237	40.3 (1.5)	238	37.8 (1.5)
Change from baseline	237	-6.3 (1.4)	238	-10.8 (1.4, $p \leq 0.05$ )
Emotional health baseline	237	49.6 (1.6)	237	47.1 (1.6)
Change from baseline	237	-9.2 (1.5)	236	-14.1 (1.5, $p \leq 0.05$ )
Physical activity baseline	236	50.2 (1.6)	239	46.1 (1.6)
Change from baseline	236	-11.0 (1.7)	239	-13.5 (1.7)

Negative change score indicated improvement (ie decreased IIQ total score) from baseline.

TABLE 5. Incidence of all treatment emergent adverse events reported in 3.0% or more of patients treated with tropium

	No. Placebo (%)	No. Tropium (%)
Dry mouth	17 (6.5)	57 (21.8)
Constipation	10 (3.8)	25 (9.5)
Headache not otherwise specified	12 (4.6)	17 (6.5)
Abdominal pain not otherwise specified	3 (1.1)	8 (3.1)
Diarrhea not otherwise specified	14 (5.4)	8 (3.1)

scores and all subscale scores except for physical activity. It had a positive effect on the IIQ subscales of emotional health, social relationships and travel. Improvement was seen in such specific items as sleep, feelings of anxiety, feelings of frustration and embarrassment, the way patients dressed, fear of odor and travel to unfamiliar places. The improvement in sleep may be associated with the decrease in nocturnal void frequency observed in this study. Similarly, the improvement in emotional health may be a surrogate for the decrease in urgency (severity) and improvement in sleep. The increase in patient control over the condition may have contributed to decreased anxiety and frustration, which could also have been reflected in increased comfort with travel. Tropium did not affect the physical activity subscale, which reflects the impact of incontinence on patient perception of overall physical health, shopping activities and ability to perform household chores.

In men IIQ scores did not improve. The modified IIQ scale used for male patients in this study was not validated and perhaps it should not have been used. Further work will be needed to clarify this point. In all other respects further analyses of data indicate that there were no other measured differences with respect to gender when tropium is compared to placebo.

Tropium was well tolerated as evidenced by the small difference in the discontinuation rate for adverse events between treatment groups. Central nervous system adverse events usually associated with anticholinergic agents were not seen with tropium, most likely due to the quaternary amine structure that inhibits the ability to cross the blood-brain barrier. Previous studies measuring quantitative electroencephalogram changes<sup>5</sup> and sleep parameters<sup>20</sup> are consistent with the lack of central nervous effects of tropium. The most common adverse events associated with tropium, dry mouth and constipation, are typically associated with the oral antimuscarinic class of drugs.

The results from this investigation and previous studies of tropium with its features of rapid clinical activity, lack of central nervous system impact and lack of potential drug-drug interactions suggest that tropium will provide the clinician with an additional useful therapeutic tool for treating patients with OAB.

#### APPENDIX: INDEVUS URGENCY SEVERITY SCALE (IUSS)<sup>15</sup>

“Degree of Urgency” is meant to describe your urge to urinate. Sometimes you may feel a very strong urge to urinate,

and at other times, you may feel a milder urge prior to the onset of a “Toilet Void.” Rate this feeling by circling 0, 1, 2, or 3 defined as:

0: NONE—no urgency

1: MILD—awareness of urgency, but easily tolerated and you can continue with your usual activity or tasks

2: MODERATE—enough urgency discomfort that it interferes with or shortens your usual activity or tasks

3: SEVERE—extreme urgency discomfort that abruptly stops all activity or tasks

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