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PROPRIETARY DRUG NAME/INN: Detrusitol™ SR / Tolterodine ER

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00143377

PROTOCOL NO.: A6121122

PROTOCOL TITLE: A Global Phase IV, Double-Blind, Placebo-Controlled, Randomized Trial to Evaluate the Effectiveness of Detrusitol™ SR 4mg on Patient's Perception of Bladder Condition (PPBC)

Study Center(s): Sixty-six (66) centers in Canada (13 centers), Denmark (6 centers), Germany (11 centers), Italy (3 centers), The Netherlands (1 center), Norway (5 centers), Poland (4 centers), Spain (6 centers), Sweden (6 centers), Turkey (4 centers) and the United Kingdom (7 centers).

Study Initiation and Completion Dates: 09 July 2004 to 10 March 2005

Phase of Development: 4

Study Objective(s): The *primary objective* of the study was to determine the improvement in Patient Perception of Bladder Condition (PPBC) from baseline (Visit 2) to Week 12 (Visit 4) for tolterodine (Detrusitol™; Detrol™) extended release (ER) 4mg compared with placebo.

The *secondary objectives* were to:

1. Culturally and linguistically validate the overactive bladder (OAB) Screener (symptom bother score of the overactive bladder questionnaire [OAB-q]) and to determine the ability of the OAB Screener to identify subjects with urinary symptoms consistent with OAB (the results of these analyses will be reported in a separate document);

2. Determine the response (responsiveness analysis) and relationship to therapy as measured by micturition diary variables, OAB-q, and PPBC;

3. Determine the efficacy of the clinical trial intervention in improving: the OAB symptoms, as measured by the numerical change of OAB-q variable from baseline (Visit 2) to Week 12 (Visit 4); numerical and relative (%) change of micturition diary variables from baseline (Visit 2) to Week 1 (Visit 3) and Week 12 (Visit 4); and change of PPBC from baseline (Visit 2) to Week 1 (Visit 3).

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Additional objectives were to:

1. Evaluate the effect on adverse event (AE) reporting with evening dosing of tolterodine ER 4mg or placebo;

2. Correlate micturition diary variables with OAB-q and Bother Rating Scale (BRS);

3. Determine if baseline (Visit 2) and change from baseline (Visit 4) in micturition diary variables were predictors of the change in OAB-q;

4. Determine if baseline (Visit 2) and change from baseline (Visit 4) in PPBC were predictors of the change in OAB-q;

5. Determine the relationship of the severity of the chief complaint (most bothersome OAB symptom) on the BRS to the other baseline (Visit 2) assessments of OAB severity;

6. Determine the relationship of the severity of the chief complaint on the BRS to the response to therapy as measured by the change in micturition diary variables, OAB-q and PPBC after 12 weeks treatment;

7. Determine if differences in subject expectations, as measured by the subject expectation questions (BRS Questions 3 and 4) correlated with the difference in baseline and the change from baseline (Visit 2) in micturition diary variables, PPBC, BRS, and OAB-q;

8. Determine the rate of dry mouth and other reported AEs for active therapy versus placebo after 12 weeks treatment.

METHODS

Study Design: This was a multi-center, double-blind, placebo controlled, parallel group, randomized study in adult subjects with OAB. Subjects were randomized (2:1) to receive either tolterodine ER capsules 4mg or placebo capsules once daily (OD), in the evening, for 12 weeks.

Four visits to the study center were scheduled. The subjects were seen at a screen visit (Visit 1), at baseline (Visit 2), and after 1 and 12 weeks of treatment (Visits 3 and 4, respectively). Micturition diaries were completed for 3 days prior to study baseline, Week 1 and Week 12 (Visits 2, 3 and 4, respectively). Subjects were asked to complete questionnaires at all study visits.

Number of Subjects (Planned and Analyzed):

Planned: 480 evaluable subjects were required (320 subjects in the tolterodine ER group and 160 subjects in the placebo group).

Analyzed: 612 subjects were treated and included in the safety population (408 subjects in the tolterodine ER group and 204 subjects in the placebo group).

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Diagnosis and Main Criteria for Inclusion: The population of this study included outpatients, 18 years of age or older, who were reporting: OAB symptoms for 3 or more months prior to the screening visit; a urinary frequency of at least 8 micturition episodes per 24 hours; and a minimum of 3 episodes in 3 days of urgency or urgency incontinence. The degree of bothersomeness of their most bothersome OAB symptom was "moderate", "a great deal", or "a very great deal" as per OAB BRS.

Study Treatment: Subjects were instructed to take 1 capsule of study drug, either tolterodine ER 4mg or placebo, OD in the evening prior to bed for 12 weeks. No dose adjustment was allowed. Study medication was taken with fluids; there was no restriction on intake of food.

Efficacy Evaluations:

Primary efficacy endpoint: The proportion of subjects who reported improvement (a negative difference of scores) from their treatment at Week 12 (Visit 4) (last observation carried forward [LOCF]) compared to baseline (Visit 2), as measured by the PPBC questionnaire using the intent-to-treat (ITT) population.

Safety Evaluations: Safety variables included extent of exposure; treatment-emergent AEs, treatment-emergent SAEs and deaths; and early discontinuation of treatment along with reasons for discontinuation.

Statistical Methods:

Efficacy: The analysis of the primary efficacy endpoint was performed using the 2-sided Cochran-Mantel-Haenszel (CMH) test for general association stratified by region at the 5% level of significance, comparing tolterodine ER group with placebo. Regions were defined based on similar geography, culture background and total number of enrolled subjects.

Safety: All reported AEs were summarized in standard output tables and were coded into MedDRA preferred terms. The frequency of subjects experiencing a specific AE was tabulated for each treatment group by system organ class and preferred term. Data were also summarized with respect to intensity, relation to study drug, action taken, outcome of the event, and seriousness of the event.

RESULTS

Subject Disposition and Demography: Table S1, below, shows subject disposition and subjects analyzed.

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Table S1 Subject Disposition and Subjects Analyzed

n (%)[1]	Tolterodine ER 4mg	Placebo
Randomized	410	207
Treated	408	204
Completed study	372 (91.2)	182 (89.2)
Discontinued study[2]	36 (8.8)	22 (10.8)
Lack of efficacy	3 (0.7)	9 (4.4)
Protocol deviation	10 (2.5)	5 (2.5)
Lost to follow-up	6 (1.5)	3 (1.5)
Non-fatal adverse event[3]	12 (2.9)	2 (1.0)
Other	2 (0.5)	2 (1.0)
Refusal to participate further	3 (0.7)	1 (0.5)
Death	0	0
Pregnancy	0	0
Did not meet inclusion/exclusion criteria	0	0
Study terminated by sponsor	0	0
Analyzed for Efficacy	402	201
ITT population[4,5]	402	201
ITT population at Week 1 in window	396	196
ITT population at Week 12 in window	399	198
PP population at Week 1[6]	359	183
PP population at Week 1 in window	341	173
PP population at Week 12[6]	338	165
PP population at Week 12 in window	268	132
Analyzed for Safety[7]	408	204

1. Percentage calculated using the number of treated subjects as the total population.
2. Treated subjects.
3. Adverse events leading to death within the study period are counted as death.
4. Includes subjects with at least 1 dose of study medication and post-baseline efficacy.
5. Last observation carried forward used in ITT analysis to impute values for missing Week 12 assessment from a valid Week 1 assessment.
6. Includes ITT subjects who were ≥80% dosing compliant and without prohibited concomitant medication at given visit.
7. Includes subjects with at least 1 dose of study medication.

Demographic characteristics were similar between the 2 treatment groups and are presented in Table S2, below.

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Table S2 Subject Demographics – Safety Population

	Tolterodine ER 4mg N=408	Placebo N=204
Gender, n (%)		
Male	112 (27.5)	60 (29.4)
Female	296 (72.5)	144 (70.6)
Premenarchal	0	0
Premenopausal	92 (31.1)	43 (29.9)
Postmenopausal	204 (68.9)	101 (70.1)
Age (years)		
Mean (SD)	57.4 (13.03)	57.3 (13.52)
Median (range)	58 (22 to 87)	59 (22 to 86)
Race, n (%)		
White	397 (97.3)	199 (97.5)
Black	4 (1.0)	5 (2.5)
Asian	3 (0.7)	0
Other	4 (1.0)	0
Smoking status, n (%)		
Current smoker	87 (21.3)	34 (16.7)
Ex-smoker	122 (29.9)	57 (27.9)
Non-smoker	199 (48.8)	113 (55.4)

ER: extended release; SD: standard deviation.

The duration of the primary diagnosis is summarized for the safety population in Table S3. Both the mean and the median age at diagnosis of OAB and number of years since diagnosis of OAB were similar for the 2 treatment groups for the safety population. Age at primary diagnosis and duration of the diagnosis presented by chief complaint for the safety population were similar to the data seen for the total safety population.

Table S3 Duration of Primary Diagnosis - Safety Population

	Tolterodine ER 4mg N=408	Placebo N=204
N[1]	406	203
Age at diagnosis of OAB (years)		
Mean (SD)	52 (14.84)	51 (15.13)
Median (range)	53 (4 to 84)	53 (7 to 81)
Years since diagnosis of OAB		
Mean (SD)	5 (7.54)	6 (8.34)
Median (range)	3 (0 to 63)	2 (0 to 41)

1. The number of subjects who had primary diagnosis data.

ER: extended release; OAB: overactive bladder; SD: standard deviation.

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Efficacy Results:

Primary Efficacy Analysis: The baseline profile of PPBC was similar for the 2 treatment groups (Table S4). The percentage of subjects who were categorized as having an improvement in their PPBC at Week 12 (Visit 4) was slightly higher in the tolterodine ER group (64.9%) compared with the placebo group (58.1%); however the treatment difference was not statistically significant (p=0.0978).

Table S4 Change from Baseline to Week 12 in Patient Perception of Bladder Condition (Improvement, No Improvement) - Intent-to-Treat Population

n (%)	Tolterodine ER 4mg N=402		Placebo N=201
N[1]	399		198
Baseline			
Not any problems at all	0		0
Some very minor problems	3 (0.8)		0
Some minor problems	14 (3.5)		7 (3.5)
Some moderate problems	113 (28.3)		55 (27.8)
Severe problems	175 (43.9)		95 (48.0)
Many severe problems	94 (23.6)		41 (20.7)
Week 12			
Not any problems at all	15 (3.8)		3 (1.5)
Some very minor problems	76 (19.0)		29 (14.6)
Some minor problems	82 (20.6)		37 (18.7)
Some moderate problems	121 (30.3)		68 (34.3)
Severe problems	70 (17.5)		44 (22.2)
Many severe problems	35 (8.8)		17 (8.6)
Change from baseline to Week 12 (2-category analysis)			
Improvement[2]	259 (64.9)		115 (58.1)
No improvement[3]	140 (35.1)		83 (41.9)
p-value, CMH test		0.0978	

1. Number of subjects with data available at baseline (Visit 2) and at Week 12 (Visit 4).
2. Negative difference of scores.
3. Difference of scores was 0 or more.

CMH: Cochran-Mantel-Haenszel; ER: extended release.

Because the results of the primary efficacy analyses were unexpected, due to their lack of statistical significance, a post-hoc analysis was conducted to look at the primary variable by country. It was found that the Norwegian sites reported a high (9/10 [90.0%]) placebo rate for improvement in PPBC from baseline (Visit 2) to Week 12 (Visit 4); the second largest placebo response was noted in Germany (25/41 [61.0%]). Excluding the Norwegian ITT subjects, the difference in the proportion of subjects reporting an improvement between the 2 treatment groups (65.0% in the tolterodine ER group and 56.4% in the placebo group) was statistically significant (p=0.0437).

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Safety Results: An overview of treatment-emergent AEs is presented in Table S5.

Table S5 Overview of Treatment-Emergent Adverse Events

n (%)	Tolterodine ER 4mg N=408	Placebo N=204
Subjects who had ≥1 AE	194 (47.5)	77 (37.7)
Subjects with AEs by maximum severity[1]		
Mild	116 (28.4)	47 (23.0)
Moderate	67 (16.4)	22 (10.8)
Severe	11 (2.7)	8 (3.9)
Subjects with treatment related AEs	131 (32.1)	47 (23.0)
Subjects permanently discontinued due to an AE	14 (3.4)	10 (4.9)
Subjects temporarily discontinued due to an AE[2]	9 (2.2)	7 (3.4)
Subjects who had □1 SAE	6 (1.5)	5 (2.5)
Subjects with treatment related SAEs	0	0
Subjects who died	0	0

1. If an adverse event is reported with multiple severities, the most severe is counted.
2. No dose reductions were permitted in this study; all subjects whose dose was reduced due to an AE (9 [2.2%] in the tolterodine ER group and 7 [3.4%] in the placebo group) were temporarily discontinued.

AE: adverse event; ER: extended release; SAE: serious adverse event.

A higher proportion of subjects in the tolterodine ER group (194 subjects [47.5%]) reported a treatment-emergent AE compared with the placebo group (77 subjects [37.7%]); these AEs were considered treatment related in 131 subjects (32.1%) in the tolterodine ER group and 47 subjects (23.0%) in the placebo group.

The most frequently reported all causality AEs, occurring in more than 1% of subjects in either treatment group, are summarized by frequency in Table S6, below.

Table S6 Treatment-Emergent All Causality Adverse Events that Occurred in > 1% of Subjects by Frequency - Safety Population

Preferred Term:	Tolterodine ER 4mg (N=408) n (%)	Placebo (N=204) n (%)
Dry mouth	89 (21.8)	21 (10.3)
Headache	21 (5.1)	9 (4.4)
Fatigue	11 (2.7)	4 (2.0)
Constipation	11 (2.7)	3 (1.5)
Nasopharyngitis	9 (2.2)	5 (2.5)
Back pain	8 (2.0)	2 (1.0)
Diarrhea	7 (1.7)	4 (2.0)
Dyspepsia	7 (1.7)	0
Drug ineffective	6 (1.5)	8 (3.9)
Abdominal pain	6 (1.5)	2 (1.0)
Dry eye	6 (1.5)	2 (1.0)
Dizziness	5 (1.2)	5 (2.5)
Nausea	4 (1.0)	4 (2.0)
Bronchitis	2 (0.5)	3 (1.5)
Insomnia	1 (0.2)	3 (1.5)

ER: extended release.

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Apart from dry mouth, which was reported by a notably higher percentage of subjects in the tolterodine ER group (21.8%) compared with the placebo group (10.3%), the profile of treatment-emergent AEs reported during the study was similar for the 2 treatment groups.

Treatment related AEs reported in more than 1% of subjects in the tolterodine ER group were dry mouth (21.6%), constipation (2.5%), headache (2.5%), fatigue (2.0%), dry eye (1.5%), drug ineffective (1.5%) and dyspepsia (1.2%), and in the placebo group were dry mouth (10.3%), drug ineffective (3.9%), dizziness (2.0%), headache (2.0%), and insomnia (1.5%). Apart from dry mouth, the profile of treatment related AEs reported during the study was similar for the 2 treatment groups.

Most subjects in both treatment groups reported AEs as mild or moderate: a greater proportion of subjects in the tolterodine ER, compared with the placebo treatment group, reported mild AEs (28.4% versus 23.0%) or moderate AEs (16.4% versus 10.8%); fewer subjects in the tolterodine ER group, compared with the placebo group, reported AEs as severe (2.7% versus 3.9%). Similarly, most subjects in both treatment groups reported treatment related AEs as mild or moderate: a greater proportion of subjects in the tolterodine ER, compared with the placebo treatment group, reported mild AEs (22.5% versus 16.2%) or moderate AEs (8.3% versus 4.9%); fewer subjects in the tolterodine ER group, compared with the placebo group, reported AEs as severe (1.2% versus 2.0%).

Adverse events leading to permanent discontinuation from the study are summarized in Table S7, below.

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Table S7 Adverse Events Leading to Permanent Discontinuation – Safety Population

Preferred Term:	Tolterodine ER 4mg (N=408) n (%)	Placebo (N=204) n (%)
Subjects permanently discontinued due to AEs*	14 (3.4)	10 (4.9)
Drug ineffective	3 (0.7)	7 (3.4)
Dry mouth	2 (0.5)	0
Headache	2 (0.5)	0
Abdominal pain	1 (0.2)	0
Constipation	1 (0.2)	1 (0.5)
Depression	1 (0.2)	0
Dizziness	1 (0.2)	1 (0.5)
Dry eye	1 (0.2)	0
Dyspepsia	1 (0.2)	0
Erythema	1 (0.2)	0
Fatigue	1 (0.2)	0
Nausea	1 (0.2)	0
Parathesia	1 (0.2)	0
Pyelonephritis	1 (0.2)	0
Visual disturbance	1 (0.2)	0
Arrhythmia	0	1 (0.5)
Hypertension	0	1 (0.5)
Insomnia	0	1 (0.5)
Vertigo	0	1 (0.5)

ER: extended release
*Although a subject could discontinue due to multiple AEs, the subject was only counted once in the overall total.

Additionally, 9 subjects (2.2%) and 7 subjects (3.4%) discontinued temporarily due to an AE in the tolterodine ER and placebo treatment groups, respectively.

A total of 6 subjects (1.5%) and 5 subjects (2.5%) in the tolterodine ER and placebo treatment groups, respectively, experienced at least 1 SAE; these are summarized in Table S8.

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Table S8 Serious Adverse Events – Safety Population

Subject Sex/Age	Event Term	Event Onset Day	Action Taken
Tolterodine ER 4mg Treatment Group			
Female/43	Recurrent acute pain of right lunate bone due to arthrosis	Day 28	No action taken
Female/71	Recurrence of lentigo maligna	Day -11	No action taken
Female/62	Acute spondylodiscitis	Day 79	No action taken
	Bilateral adrenal tumor	Day 85	No action taken
Female/56	Lumbar pain	Day 4	No action taken
Female/54	Acute pyelonephritis	Day 9	Multiple challenge/rechallenge/ interruption
Female/64	Acute bronchospasm	Day 63	No action taken
Placebo Treatment Group			
Female/60	Transient cerebral ischemia	Day 25	No action taken
Female/73	Malignant mesenchymal tissue with suspicion of stromacell sarcoma	Day 86	Post-therapy – drug previously discontinued
Male/69	Cardiac arrhythmic disorder	Day 71	Permanently discontinued
Female/72	Mid-aortic syndrome	Day 49	Multiple challenge/rechallenge/ interruption
Male/72	Cellulitis	Day 16	Multiple challenge/rechallenge/ interruption

ER: extended release.

None of the SAEs in either treatment group were considered related to treatment.

There were no deaths among subjects who participated in this study.

CONCLUSION(S): More subjects reported an improvement PPBC at Week 12 (Visit 4) in the tolterodine ER group compared with the placebo group, although the treatment difference was not statistically significant. In addition, tolterodine ER was shown to have a comparable safety profile to placebo in the clinical trial setting, except for the known AE of dry mouth.

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