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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Detrol® / Tolterodine

PROTOCOL NO.: A6121128

PROTOCOL TITLE: Time to Onset of Action of Tolterodine Using Force Fill Cystometry in Spinal Cord Injury Patients With Neurogenic Detrusor Overactivity

Study Center: One center in Iceland took part in the study and enrolled subjects.

Study Initiation and Final Completion Dates: 29 December 2004 to 15 April 2005

Phase of Development: Phase 4

Study Objectives:

Primary Objective:

- To compare a single oral dose of tolterodine (2 mg) with placebo on the reduction of uninhibited detrusor contractions induced by provocation testing.

Secondary Objectives:

- To evaluate the safety of tolterodine administration in subjects with spinal cord injury and pathology.

- To explore the relationships of efficacy variables with serum concentrations of tolterodine and/or its active metabolite, 5-hydroxy-methyltolterodine（DD 01).

METHODS

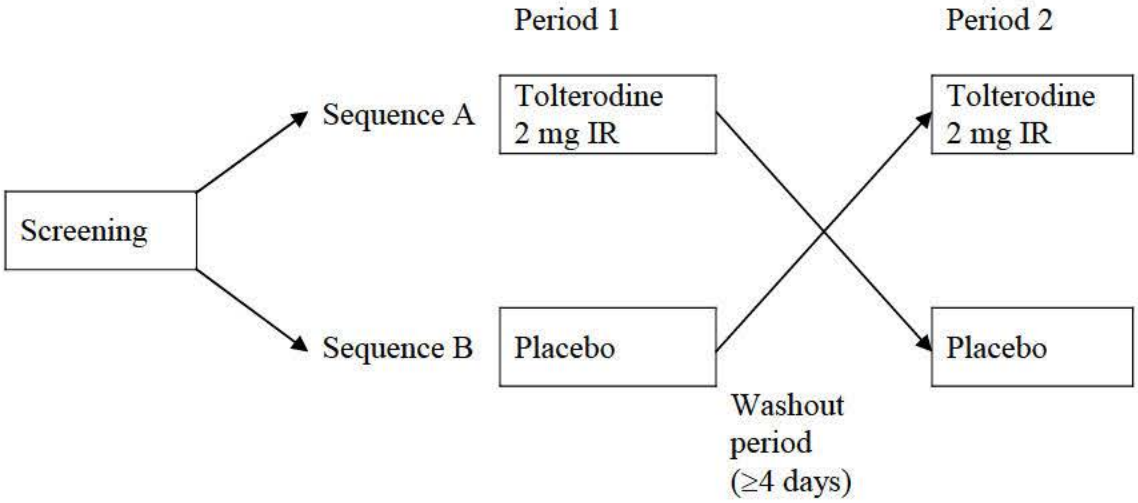
Study Design: This was a double-blind, randomized, 2-way crossover, single-dose study of tolterodine immediate release (IR) (2 mg) versus placebo in subjects with spinal cord injury or pathology. Subjects were randomly assigned to 1 of 2 sequences: A and B. Subjects in Sequence A received tolterodine in Period 1 followed by matching placebo in Period 2, whereas subjects in Sequence B received placebo in Period 1 followed by tolterodine in Period 2. Periods 1 and 2 were separated by a washout period of at least 4 days.

Subjects who met the study selection criteria underwent screening procedures, comprising a complete medical history, a physical examination and a standard 12-lead electrocardiogram (ECG). The study involved 2 or 3 outpatient visits including a screening visit and 2 treatment periods during which the investigational procedures were performed.

Prior/concomitant medications were reviewed and a beta-human chorionic gonadotropin test was conducted for females. For Period 1 baseline symptoms, adverse events (AEs), changes in the subject's medical history and vital signs were recorded. Blood pressure (BP) was monitored continuously during the procedures. Similar procedures were followed in Period 2. At the end of Period 2, a final physical examination was performed. Follow-up AE monitoring was completed by a telephone call approximately 1 week after Period 2.

A urine sample was taken for urinalysis at Screening and prior to subject participation in treatment Periods 1 and 2. Subjects with evidence of urinary tract infection (UTI) were suspended from further participation in the study until at least 2 weeks after successful treatment, as demonstrated by subsequent negative urinalysis and resolution of clinical symptoms of UTI. An overview of the study design is provided in Figure 1 and a timetable of study procedures is provided in Table 1.

Figure 1. Overview of Study Design



IR = immediate release.

Table 1. Timetable of Study Procedures/Evaluations

Study Phase	Screening	Period 1[a]	Period 2	Follow-Up
Observation/procedure				
Informed consent	X			
Serum or urine β-hCG (all females)	X	X	X	
Medical history (including prior and concomitant medications)	X	X	X	X
Physical examination	X		X	
Administer prophylactic antibiotic		X	X	
Administer study medication (tolterodine or placebo)		X	X	
Safety assessments				
Blood pressure/heart rate	X	X[b]	X[b]	
Safety laboratory	X			
Urinalysis	X	X	X	
ECG	X			
Adverse events		X	X	X
Efficacy assessments				
Fast-fill cystometry[c]		X	X	
Force-fill (provocative) cystometry[d,e]		X	X	
Other assessments				
PK sampling[d]		X	X	

β-hCG = β-subunit of Human Chorionic Gonadotropin; ECG = electrocardiogram; PK = Pharmacokinetics.

a. Period 1 procedures could be performed after enrolment and randomization on the day of screening.
b. Measured predose and during cystometry procedures.
c. Prior to tolterodine or placebo dose.
d. Predose and at 0.5, 1 and 2 hours post tolterodine or placebo dose.
e. Triplicate measurements, taken 2 to 5 minutes apart.

Number of Subjects (Planned and Analyzed): Eight subjects were planned to be enrolled, and 8 subjects (5 males and 3 females) entered the study. All the 8 subjects completed the study and were evaluated for safety, pharmacodynamics (PD) and pharmacokinetics (PK).

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 18 to 65 years with urodynamic evidence of neurogenic detrusor overactivity (phasic or uninhibited detrusor contraction) arising as a consequence of spinal cord injury or pathology were included in the study. Subjects had to have evidence of phasic uninhibited detrusor contraction and demonstrable provoked, uninhibited, detrusor contraction following fast- and force-fill cystometry, respectively, at the beginning of Period 1 and had to be willing and able to provide written informed consent.

Pregnant or lactating women, subjects with a recent history of autonomic dysreflexia that was associated with urodynamic investigations, with a known history of hypersensitivity, allergy, severe adverse drug reaction or intolerance to anti-cholinergic drugs, including tolterodine, with UTI, marked cystocele or pelvic prolapse, interstitial cystitis, bladder stones, unexplained hematuria, with a clinically significant ECG abnormality at Screening, with a history or evidence of major hematological, renal or hepatic abnormalities were excluded.

Study Treatment: Subjects were randomized to 1 of 2 sequences of treatment administration (Sequences A and B) and were administered 2 tablets of either tolterodine IR (2 x 1 mg) or matching placebo during each period. Subjects in Sequence A received tolterodine 2 mg in Period 1 followed by matching placebo in Period 2, whereas subjects in Sequence B received placebo in Period 1 followed by tolterodine 2 mg in Period 2. Subjects swallowed the study medication whole, along with 240 ml of water at an ambient temperature.

Pharmacokinetic and Pharmacodynamic Endpoints:

Primary Endpoint:

- Area under the pressure curve (AUC) of the provoked detrusor contraction

Secondary Endpoints:

- Maximum cystometric capacity
- Bladder compliance
- Maximum pressure of provoked detrusor contraction

Pharmacokinetic/Pharmacodynamic Endpoints:

- The response-exposure relationships of the primary and secondary efficacy endpoints with tolterodine and DD 01 serum concentrations, using nonlinear mixed effects modeling

No efficacy evaluations were performed for this study.

Safety Evaluations: Safety was assessed by AEs (throughout the 2 treatment periods up to follow-up), clinical laboratory assessments (Screening only), urinalysis (Screening, predose during Periods 1 and 2), pregnancy testing (all females at Screening, Periods 1 and 2) and the monitoring of BP and heart rate (predose and throughout cystometry procedures). A standard 12-lead ECG was taken at Screening.

Statistical Methods: The population sets used in the analysis were:

- Full Analysis Set: The full analysis set (FAS) included all randomized subjects who have completed both treatment periods, and were labelled 'Full Analysis Set'.

- Safety Analysis Set: The safety analysis set included all subjects who got atleast 1 dose of any of the study drug.

All subjects were included in the full analysis set and were analyzed for safety and PD. All subjects were analyzed for PK during the tolterodine treatment period.

The response-exposure relationships of the primary and secondary endpoints with tolterodine and DD 01 serum concentrations, using nonlinear mixed effects modeling was to be carried out and results were to be reported separately.

The analyses of the primary and secondary variables were performed on the FAS. There was no Per Protocol analysis set due to the low number of subjects (8). The primary PD endpoint (the AUC of the provoked detrusor contraction) was analyzed using an analysis of variance (ANOVA) model with terms for subject, treatment and period. An ANOVA model which additionally included sequence effect was used to test the sequence effect at the 10% significance level. If the test for sequence effect was significant at the 10% level it was to be explored graphically. The secondary PD endpoint (maximum detrusor pressure) was analyzed using the same methodology as the primary endpoint. The results from fast-fill cystometry at 0 hours were listed and summarized using descriptive statistics by treatment and/or treatment sequence and period, based on the FAS. Safety endpoints (AEs, clinical laboratory parameters, vital signs, and ECG) were summarized and/or listed.

RESULTS

Subject Disposition and Demography: All 8 (5 males and 3 females) subjects that were screened, entered the study and there were no discontinuations.

Table 2. Subject Disposition and Subjects Analyzed

	Tolterodine IR (2 mg)	Placebo
Number of subjects		
Screened 8		
Assigned to treatment: 8		
Treated	8	8
Completed	8	8
Discontinued	0	0
Analyzed for pharmacokinetics:		
Pharmacokinetics	8	0
Analyzed for safety:		
Adverse events	8	8
Laboratory data	3	4
Full analysis set	8	8
Safety population	8	8

IR = Immediate release.

All subjects were White. The age range for male subjects was 28 to 53 years; weight was between 57.0 to 95.0 kg. Female subjects were aged 30 to 49 years and weighed between 62.0 and 68.0 kg. All subjects were analyzed for safety and PD.

Pharmacokinetic and Pharmacodynamic Results:

Pharmacodynamics:

Summary statistics for the AUC of the provoked detrusor contraction and maximum detrusor pressure are presented in Table 3 and Table 4. The results of the primary and secondary evaluations showed consistent downward trends in mean AUCs and mean maximum detrusor pressures over time following a single dose of tolterodine. While a similar trend was also noted with the placebo treatment, the mean AUCs of the provoked detrusor contraction following force-fill cystometry testing and mean maximum detrusor pressures decreased more quickly following dosing with tolterodine than with placebo. The differences between treatments observed at 0.5 hours postdose approached statistical significance for the AUC of the provoked detrusor contraction and reached statistical significance for the mean maximum detrusor pressure.

During predose fast-fill cystometry, the volume and pressure of first detrusor contraction, maximum detrusor pressure during filling, maximum bladder capacity and bladder compliance were numerically lower during the tolterodine treatment period than during the placebo treatment period. The maximum detrusor pressure was the same (51 cm H_2O) during both treatment periods. Data for the remaining fast-fill cystometry variables were only available for 3 of the 8 subjects enrolled in the study. All 8 subjects had detrusor contraction(s) during filling following both treatments. All 8 subjects also experienced dysynergia following both treatments.

All other fast-fill cystometry data are summarized in Table 5.

Table 3. Area Under the Pressure Curve of the Provoked Detrusor Contraction (FAS)

Time Postdose (Hour)	Area Under the Pressure Curve ($cmH_2O.s$)						Mean Difference[a] [Tolterodine-Placebo] (95%CI)	p-Value
	Tolterodine IR (2 mg)			Placebo				
	N	Mean	SD	N	Mean	SD		
0	8	3713	1702	8	3464	1342	249 (-733, 1231)	0.5576
0.5	8	1513	996	8	2213	1134	-700 (-1506, 106)	0.0777
1	8	1036	383	8	2067	2144	-1031 (-2701, 639)	0.1817
2	8	1133	718	8	1363	899	-231 (-1191, 730)	0.5786

ANOVA = analysis of variance; CI = confidence interval; FAS = full analysis set; IR = immediate release; N = number of subjects; SD = standard deviation.

a. Mean and 95% CI for difference between treatments (Tolterodine IR-Placebo) calculated from ANOVA for crossover design (with factors for subject, treatment and period).

Table 4. Maximum Pressure of the Provoked Detrusor Contraction (FAS)

Time Postdose (Hour)	Maximum Detrusor Pressure (cmH_2O)						Mean Difference[a] [Tolterodine-Placebo] (95%CI)	p-Value
	Tolterodine IR (2 mg)			Placebo				
	N	Mean	SD	N	Mean	SD		
0	8	49	22	8	48	30	2 (-13, 17)	0.7977
0.5	8	25	22	8	35	27	-10 (-19, -1)	0.0338
1	8	14	5	8	26	26	-13 (-34, 8)	0.1886
2	8	13	7	8	21	24	-8 (-28, 12)	0.3653

ANOVA = analysis of variance; CI = confidence interval; FAS = full analysis set; IR = immediate release; N = number of subjects; SD = standard deviation.

a. Mean and 95% CI for difference between treatments (Tolterodine IR-Placebo) calculated from ANOVA for crossover design (with factors for subject, treatment and period.

Table 5. Summary of Fast-Fill Cystometry Data Pre-Dose (0 Hour) (FAS)

Variable Treatment	N	Mean	SD
Volume of first detrusor contraction (ml)			
Tolterodine	8	225.3	120.6
Placebo	8	269.5	149.4
Pressure at first detrusor contraction (cmH_2O)			
Tolterodine	8	8.9	2.4
Placebo	8	10.1	6.5
Maximum detrusor pressure during filling (cmH_2O)			
Tolterodine	8	45.6	21.4
Placebo	8	49.4	25.6
Maximum bladder capacity (ml)			
Tolterodine	8	315.5	177.0
Placebo	8	375.3	160.2
Maximum detrusor pressure (cmH_2O)			
Tolterodine	8	50.6	21.1
Placebo	8	50.9	24.5
Bladder compliance (ml/cmH_2O)			
Tolterodine	8	27.4	18.5
Placebo	8	34.2	27.7
Maximum flow rate (ml/s)			
Tolterodine	2	3.0	1.4
Placebo	1	2.0	–
Average flow rate (ml/s)			
Tolterodine	2	1.5	0.7
Placebo	1	1.0	–
Maximum detrusor pressure during voiding (cmH_2O)			
Tolterodine	2	46.0	12.7
Placebo	1	45.0	–
Voided volume (ml)			
Tolterodine	2	69.0	67.9
Placebo	1	117.0	–
Post-void residual (ml)			
Tolterodine	2	177.5	74.2
Placebo	1	410.0	–

FAS = full analysis set; N = number of subjects; SD = standard deviation.

Pharmacokinetics: Mean serum concentrations of tolterodine at 0.5, 1.0 and 2.0 hours postdose were 0.93 ng/mL (standard deviation [SD] 1.60), 1.79 ng/mL (SD 2.77) and 1.40 ng/mL (SD 1.46), respectively. Mean serum concentrations of DD 01 were 0.31 ng/mL (SD 0.20), 1.31 ng/mL (SD 0.74) and 1.44 ng/mL (SD 0.64) at 0.5, 1.0 and 2.0 hours postdose, respectively. Summary statistics of concentration of tolterodine and DD 01 are presented by treatment in Table 6.

Table 6. Mean Serum Concentrations of Tolterodine and DD 01 (ng/mL) at 0, 0.5, 1, and 2 Hours Postdose

Drug Name		Time Postdose			
		0 Hour	0.5 Hour	1.0 Hour	2.0 Hours
Tolterodine	N BLQ	8	3	1	0
	N	0	5	7	8
	Mean (SD)	–	0.93 (1.60)	1.79 (2.77)	1.40 (1.46)
	Range	–	0.11 – 3.78	0.21 – 7.93	0.24 – 4.74
DD 01	N BLQ	8	2	1	0
	N	0	6	7	8
	Mean (SD)	–	0.31 (0.20)	1.31 (0.74)	1.44 (0.64)
	Range	–	0.14 – 0.67	0.41 – 2.17	0.72 – 2.70

BLQ = below limit of quantification (<0.1ng/ml); N = number of subjects; SD = standard deviation.

No efficacy evaluations were performed for this study.

Safety Results:

Two subjects reported treatment-emergent AEs during the study. One subject reported mild diarrhea following single oral dosing with tolterodine, which was attributed to gastroenteritis of unknown origin and 1 subject reported mild bladder pain following single oral dosing with placebo, which was attributed to study drug. Both events resolved after 2 and 1 days, respectively (Table 8).

A summary of all AEs is presented in Table 7.

Table 7. Summary of Treatment-Emergent Adverse Events (Safety Population)

Number of Subjects – All Causality (Treatment-Related)	Tolterodine IR 2 mg	Placebo
Subjects evaluable for AEs	8	8
Number of AEs	1	1 (1)
Subjects with AEs	1	1 (1)
Subjects with serious AEs	0	0
Subjects with severe AEs	0	0
Subjects discontinued due to AEs	0	0
Subjects with dose reduced or temporary discontinuations due to AEs	0	0

AE = adverse events, IR = immediate release.

Table 8. Treatment-Emergent Adverse Events by Subject

Treatment	Adverse Event (COSTART Term)	Study Start Day[a]/Study Stop Day[a]	Period Start Day[b]/Period Stop Day[b]	Severity/ Outcome	Action/ Causality
Tolterodine 2 mg	Diarrhoea	4/6	4/6	Mild/ Resolved	None/ Other – gastroenteritis of unknown origin
Placebo	Bladder pain	1/2	1/2	Mild/ Resolved	None/ Study drug

COSTART = The Coding Symbols for a Thesaurus of Adverse Reaction Terms.
a. Day relative to start of study treatment.
b. Day relative to first day of each treatment period. First day of each treatment period = Day 1.

There were no serious AEs, discontinuations or AEs of severe intensity, and deaths occurred during this study. There were no notable differences between the sequence groups in ECG parameters (mean heart rate, PR interval, QRS width and QT interval) or vital signs (BP and heart rate).

CONCLUSIONS:

- In subjects with spinal cord injury or pathology, consistent downward trends in mean AUCs and mean maximum detrusor pressures were observed over time following a single dose of 2 mg tolterodine.

- A single dose of 2 mg tolterodine appeared to have an effect on detrusor activity as early as 0.5 hour postdose. Compared with placebo, the differences between treatments observed at 0.5 hour postdose approached statistical significance for the mean AUC of the provoked detrusor contraction and reached statistical significance for the maximum mean detrusor pressure.

- The single dose of tolterodine 2 mg IR administered in this study was well-tolerated.