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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Toviaz® / Fesoterodine fumarate

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT01042236

PROTOCOL NO.: A0221064

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blind, Multi-Dose, Placebo-Controlled Crossover Study of the Efficacy of Fesoterodine in Increasing Urethral Pressure in Stress Urinary Incontinence Patients

Study Center: The study was conducted at 1 center in Denmark.

Study Initiation Date and Primary Completion or Completion Dates: 29 January 2010 to 19 July 2010. The Primary Completion Date was 01 July 2010.

Phase of Development: Phase 2

Study Objectives: *Primary:* To determine whether fesoterodine increases urethral tone relative to placebo in stress urinary incontinence (SUI) patients. *Secondary:* To evaluate the effect of fesoterodine on urethral function in SUI patients, to evaluate the safety and tolerability of fesoterodine in SUI patients, and to explore efficacy of fesoterodine on diary related endpoints. *Exploratory:* To model the exposure versus response relationship for fesoterodine.

METHODS

Study Design: This was a Phase 2, single center, randomized, double-blind, placebo-controlled, 3-period crossover study conducted in female subjects with SUI using a complete block design. Each treatment period was of approximately 7 days duration, with approximately 7 to 10 days washout between treatment periods. The study consisted of 5 outpatient visits with a telephone follow-up approximately 2 weeks following the last visit. Screening was performed at Visit 1 (within 28 days prior to Visit 2). Visit 2 (Day 1 of Period 1) was used to establish baseline measures for each endpoint, and Visits 3, 4 and 5 were scheduled on the last day of each of the 3 treatment periods. Subjects were randomized to receive the following 3 treatment regimens over the 3 treatment periods (1 treatment regimen per period):

A = Fesoterodine 4 mg once daily (OD) for 7 days

B = Fesoterodine 8 mg OD for 7 days

C = Placebo OD for 7 days

Number of Subjects (Planned and Analyzed): The study was to enroll sufficient subjects to ensure that 18 subjects were evaluable for the primary analysis population. All subjects who were randomized and received at least 1 dose of study treatment (fesoterodine 4 mg [20 subjects], fesoterodine 8 mg [22 subjects], placebo [20 subjects]) were analyzed for efficacy (Full Analysis Set; FAS) and adverse events (AEs) under the treatment received.

Diagnosis and Main Criteria for Inclusion: Female subjects aged 18 to 65 years with clinically significant SUI presenting either as pure SUI, or as stress predominant mixed urinary incontinence with history of symptoms greater than 3 months and objective evidence of SUI (without concomitant evidence of detrusor overactivity associated with urinary incontinence).

Study Treatment: The treatments administered included fesoterodine 4 mg sustain release tablet, fesoterodine 8 mg sustain release tablet and placebo tablet. Each treatment was to be administered in the morning OD for 7 days separated by a washout period of approximately 7 to 10 days. The tablets had to be taken orally with water without chewing. On Day 1 of Period 1, subjects had to take the tablet in the clinic prior to going home. On the morning of Day 1 of Periods 2 and 3, subjects were telephoned to remind them to take their study treatment for that period and also to complete their dosing diaries as appropriate.

Efficacy Evaluations: Urethral reflectometry was to be performed prior to dosing on Day 1 of Period 1, and between 4 and 8 hours following the last dose of each treatment period. The efficacy endpoints derived from reflectometry included:

Primary endpoint

- Opening urethral pressure (OUP)

This was calculated as the mean of all of the OUP measurements obtained in triplicate at each time point for each subject.

Secondary endpoint

- Closing urethral pressure
- Opening urethral elastance
- Closing urethral elastance

These were each calculated as the mean of each of their respective measurements obtained in triplicate at each time point for each subject.

The subjects had to complete a real time urinary diary for 3 days prior to randomization and in the final 3 days of each treatment period. The efficacy endpoints derived from urinary diary data included:

- Incontinence episode frequency (IEF): This was calculated as the average daily total incontinence episodes (stress or urgency) occurring during the 3 days prior to randomization and the end of each treatment period.

- Stress incontinence episode frequency (stress incontinence component of the daily IEF): This was calculated as the average daily number of stress leakage episodes that occurred during the 3 days prior to randomization and the end of each treatment period.

- Urgency urinary incontinence episode frequency (urgency incontinence component of the daily IEF): This was calculated as the average daily number of urgency leakage episodes that occurred during the 3 days prior to randomization and the end of each treatment period.

Pharmacokinetic Evaluations: Blood samples (6 mL each) to provide a minimum of 2.5 mL of plasma for analysis of 5-hydroxymethyl tolterodine (5-HMT) (active metabolite of prodrug fesoterodine) were collected into appropriately labeled tubes containing sodium heparin just prior to reflectometry and immediately following reflectometry on the final dosing day of each treatment period. Plasma samples were analyzed for 5-HMT concentrations using a validated, sensitive and specific high performance liquid chromatography tandem mass spectrometry method.

Safety Evaluations: Safety evaluations included AE monitoring, laboratory tests, physical examination, vital signs and electrocardiograms (ECGs). Hematology and chemistry tests were performed at screening only. Urinalysis was performed at screening, prior to dosing on Day 1 of Period 1, and following the last dose of each of the 3 treatment periods. Physical examination, vital signs (sitting blood pressure and pulse rate) and single 12-lead ECG were recorded at screening only.

Statistical Methods: *Efficacy:* The efficacy analysis sets included Per Protocol Analysis Set (PPAS) and FAS. The PPAS was the primary analysis set consisting of all randomized subjects who had completed the study and received treatment in all the 3 study periods until the end of treatment visit in the third study period and who were not serious protocol violators. The FAS was the secondary analysis set consisting of all randomized subjects who had taken at least 1 dose of study treatment.

To assess the effect of fesoterodine on urethral function, changes from baseline in the primary endpoint (OUP measured by urethral reflectometry) at the end of the treatment period was analyzed using an analysis of covariance (ANCOVA) model, with fixed effect terms for sequence, period and treatment, using baseline (prior to Period 1) as a covariate, and subject within sequence as a random effect. A treatment by period interaction term was to be included in the ANCOVA model if this was significant at 10% significance level. The primary comparison of interest was fesoterodine 8 mg multiple dose versus placebo. The

secondary comparison was fesoterodine 4 mg multiple dose versus placebo. The difference between treatment means, the standard error associated with these differences and 95% confidence intervals (CIs) for the difference were presented, and the corresponding p-value was derived from the calculation of least square means from the ANCOVA.

A secondary efficacy analysis on the primary endpoint similar to the primary efficacy analysis was performed using the FAS. This analysis was done without imputing missing values as well as using the baseline observation carried forward (BOCF) method for imputing missing values. Additional sub-group summaries (for exploratory purpose) by treatment were produced for the primary endpoint. All secondary endpoints were analyzed using the same techniques as the primary endpoint.

Pharmacokinetic: Plasma 5-HMT concentration data were listed and summarized by treatment.

Safety: The safety analysis set consisted of all subjects who were known to have received study treatment. Safety data were presented in tabular format and summarized descriptively, where appropriate, in accordance with the sponsor's reporting standards.

RESULTS

Subject Disposition and Demography: A total of 22 female subjects with SUI were randomized and treated in this 3-period crossover study. Of the 22 subjects who were treated, 18 subjects received all doses of the 3 study treatments and completed the study and 4 subjects discontinued, all during the fesoterodine 8 mg period. Three subjects discontinued due to AEs and 1 subject was withdrawn due to protocol violation (did not take fesoterodine 8 mg on the last 3 days of the final treatment period).

All subjects included in the study were white females, aged between 34 to 64 years (mean [standard deviation (SD)]): 47.9 (8.4) years.

Efficacy Results: *Primary Efficacy Endpoint*: The primary efficacy results did not show a clinically or statistically significant improvement from baseline in OUP for fesoterodine 4 mg and 8 mg compared to placebo. The difference in adjusted means for OUP between fesoterodine 8 mg and placebo was 0.61 cmH_2O (95% CI: −1.18, 2.41; p=0.4907). Similarly, the difference in adjusted means between fesoterodine 4 mg and placebo was −0.47 cmH_2O (95% CI: −2.27, 1.32; p=0.5944) (Table 1). Covariates for baseline, period and sequence were included in the model. There was evidence of a significant period effect (p=0.0155); however there was no significant treatment by period interaction (p=0.8553).

The results of the secondary efficacy analysis of OUP based on the FAS were similar to the PPAS results. Overall for the exploratory subgroup analyses, similar results were observed for the categorical covariates of each of these subgroups.

Table 1. Statistical Summary of Change From Baseline in Opening Urethral Pressure (cmH_2O) by Treatment (Per Protocol Analysis Set)

	Fesoterodine 4 mg	Fesoterodine 8 mg	Placebo
N[a]	17	17	17
Adjusted Mean[b] (SE)	−1.73 (1.26)	−0.64 (1.26)	−1.26 (1.26)
Difference Between Treatment Means (95% CI)[c]	-0.47[d] (−2.27, 1.32)	0.61[e] (−1.18, 2.41)	-
p-value[c]	0.5944	0.4907	-

SE=Standard error; CI=Confidence interval
A treatment by period interaction term was not included in the analysis as this was not significant at 10% significance level.
[a] Number of subjects whose data was used in this analysis (ie, per protocol analysis set).
[b] Least square mean, adjusted for baseline, period and sequence.
[c] Estimates based on comparison of least square means.
[d] Fesoterodine 4 mg versus placebo.
[e] Fesoterodine 8 mg versus placebo.

Secondary Efficacy Endpoints: Fesoterodine 4 mg and 8 mg treatments did not demonstrate clinically relevant or statistically significant differences over placebo in the change from baseline in closing urethral pressure (as measured by reflectometry) at the end of the 7-day treatment period. For the PPAS, the difference in adjusted mean change from baseline for closing urethral pressure between fesoterodine 8 mg and placebo was 0.02 cmH_2O (95% CI: −1.91, 1.94; p=0.9870). The difference in adjusted means between fesoterodine 4 mg and placebo was −0.78 cmH_2O (95% CI: −2.71, 1.15; p=0.4167).

The analysis of both opening and closing urethral elastance (cmH_2O/mm^2) as measured by reflectometry indicated that there was no statistically significant difference in the change from baseline in opening or closing urethral elastance between fesoterodine (8 mg and 4 mg) and placebo.

Descriptive analysis of the IEF and stress incontinence component of IEF showed a reduction from baseline in the frequency of incontinence episodes and stress incontinence component of IEF, respectively, per 24 hours for all 3 treatments, but no meaningful difference between either of the fesoterodine doses and placebo was observed. The mean changes from baseline in the frequency of incontinence episodes following fesoterodine 4 mg, fesoterodine 8 mg and placebo treatments were −0.81, −0.54 and −0.70, respectively, for the PPAS. The mean changes from baseline in the frequency of stress incontinence episodes for fesoterodine 4 mg, fesoterodine 8 mg and placebo treatments were −0.75, −0.46 and −0.62, respectively, for the PPAS. Descriptive analysis of the urgency incontinence component of the IEF showed similar reduction from baseline in the frequency of urgency incontinence episodes per 24 hours for all 3 treatments. For the PPAS, the mean changes from baseline in the frequency of urgency incontinence episodes following fesoterodine 4 mg, fesoterodine 8 mg and placebo treatments were −0.06, −0.08 and −0.08, respectively.

Pharmacokinetic Results: Pre- and post-reflectometry mean plasma 5-HMT concentrations following fesoterodine 4 mg OD multiple doses were 2.3 and 2.2 ng/mL, respectively, and following fesoterodine 8 mg OD multiple doses were 4.9 and 5.0 ng/mL, respectively.

Safety Results: There were no deaths, treatment-related serious AEs (SAEs), dose reductions or temporary discontinuations due to AEs in this study. The incidence of AEs following fesoterodine 4 mg and placebo treatments was similar while it was higher following fesoterodine 8 mg treatment Table 2.

Table 2. Summary of All Causality (Treatment-Related) Treatment-Emergent AEs[a]

	Fesoterodine 4 mg N=20	Fesoterodine 8 mg N=22	Placebo N=20
Number of AEs	13 (11)	27 (25)	16 (13)
Subjects with AEs	8 (7)	17 (16)	8 (7)
Subjects with serious AEs	0	1 (0)	0
Subjects with severe AEs	0	1 (0)	0
Subjects discontinued due to AEs	0	2 (1)	0

AE=Adverse event
N=Number of subjects evaluable for AEs
Treatment-related in parentheses.
[a] Due to incorrect start and stop dates of a treatment-related AE (insomnia) entered in the study database for a subject who discontinued due to the AE, the AE appeared to have occurred in the post treatment phase and was reported to be a non treatment-emergent AE. Likewise the AE was not included in the 'Number of AEs', 'Subjects with AEs' and 'Subjects Discontinued due to AEs' count of treatment-emergent AEs. Based on the correct AE start date, the AE occurred 3 days after receiving the last dose of fesoterodine 8 mg (ie, washout period after Period 1) and should therefore have been reported as a treatment-emergent AE under fesoterodine 8 mg.

Table 3 summarizes the incidence of treatment-emergent all causality (treatment-related in parenthesis) AEs. Dry mouth and headache were the most frequently reported AE with all events considered treatment related. The incidence of dry mouth was more following fesoterodine 8 mg doses (12 subjects) than fesoterodine 4 mg (3 subjects) doses or placebo (2 subjects). The majority (46/56 AEs; 82%) of AEs were mild in intensity and all reported AEs had resolved by the end of the study except mild vitreous disorder associated with disease under study that was reported during placebo treatment in Period 1 and was still present at the end of study. The only severe AE reported during the study was the non treatment-related SAE of hypotension.

Table 3. Incidence of All Causality (Treatment-Related) Treatment-Emergent AEs[a]

Number of Subjects with AE (MedDRA v13.0 Preferred Term)	Fesoterodine 4 mg N=20	Fesoterodine 8 mg N=22	Placebo N=20
Dry Mouth	3 (3)	12 (12)	2 (2)
Headache	4 (4)	5 (5)	2 (2)
Diarrhea	2 (2)	2 (2)	0
Constipation	0	2 (2)	1 (1)
Nausea	0	0	3 (3)
Abdominal Distension	0	1 (1)	1 (1)
Dysmenorrhea	1 (0)	1 (0)	0
Insomnia[a]	0	1 (1)	0
Cystitis	0	1 (1)	0
Dysuria	1 (1)	0	0
Malaise	1 (1)	0	0
Dry Eye	0	1 (1)	0
Oropharyngeal Pain	0	1 (1)	0
Hypotension[b]	0	1 (0)	0
Abdominal Pain Upper	1 (0)	0	0
Abdominal Pain	0	0	1 (1)
Pyrexia	0	0	1 (1)
Influenza	0	0	1 (1)
Vulvovaginal Discomfort	0	0	1 (1)
Vomiting	0	0	1 (0)
Musculoskeletal Stiffness	0	0	1 (0)
Vitreous Disorder	0	0	1 (0)

AE=Adverse event; MedDRA=Medical Dictionary for Regulatory Activities
N=Number of subjects evaluable for AEs
Subjects with treatment-related AEs are presented in parentheses.
[a] Due to incorrect start and stop dates of a treatment-related AE (insomnia) entered in the study database, the AE appeared to have occurred in the post treatment phase and was reported to be non treatment-emergent AE. Based on the correct AE start date, the AE occurred 3 days after receiving the last dose of fesoterodine 8 mg and has therefore been included as a treatment-emergent AE in this table.
[b] Reported as serious AE.

Three subjects discontinued due to AEs (Table 4).

Table 4. Discontinuations Due to Adverse Events

Subject	Adverse Event	Treatment at Onset of AE	AE Start/ Stop Day[a]	Time Postdose (Hrs)	Severity / Outcome	Relationship to Treatment
Female, 47 years	Insomnia	Fesoterodine 8 mg	10/ 15	>72	Mild / Resolved	Related
Female, 51 years	Dry Mouth	Fesoterodine 8 mg	2/ 4	23	Moderate / Resolved	Related
Female, 36 years	Hypotension	Fesoterodine 8 mg	1/ 6	2	Moderate / Resolved	Not Related (Disease Under Study)

AE=Adverse Event
[a] Day relative to first day of each treatment period. First day of each treatment period=Day 1.

One subject had a non treatment-related severe SAE of hypotension on Day 6 of Period 3. On Day 1 of Period 3, the subject had an AE of moderate hypotension 2 hours after receiving the first dose of fesoterodine 8 mg. The treatment was discontinued and the hypotension resolved on Day 6. The hypotension was attributed to disease under study. On Day 6 (approximately 120 hours postdose) of Period 3, the subject further developed severe hypotension for which she was hospitalized. The hypotension was not considered to be related to treatment and resolved on Day 7.

None of the laboratory urinary parameter abnormalities were considered to be clinically significant or reported as AEs.

CONCLUSIONS:

- Fesoterodine was not efficacious in increasing urethral tone or improving urethral function relative to placebo as measured by reflectometry in this study population of subjects with SUI. For the primary efficacy endpoint, OUP, fesoterodine 4 mg and 8 mg administered as OD multiple doses did not demonstrate clinically relevant or statistically significant improvements over placebo after 7 days of treatment. Similarly, no significant improvements in other endpoints derived from reflectometry were observed for both fesoterodine 4 mg and 8 mg doses compared to placebo.

- No meaningful improvement in stress incontinence episode frequency and other diary related endpoints was observed following fesoterodine treatment compared to placebo during the study.

- Fesoterodine administered at doses of 4 mg and 8 mg OD was safe and generally well-tolerated in this study population of white female subjects with SUI. The incidence of AEs was similar for fesoterodine 4 mg and placebo treatments while it was higher for the fesoterodine 8 mg treatment due to a higher incidence of dry mouth following the 8 mg doses. There were no deaths or treatment-related SAEs reported during this study. Two permanent discontinuations due to 1 treatment-related AE each were reported with fesoterodine 8 mg treatment. Overall, the safety profile was consistent with that observed in previous fesoterodine overactive bladder studies with a higher rate of AEs at the 8 mg dose compared to the 4 mg dose.

- Since no efficacy response was observed, the exploratory objective to model the exposure versus response relationship for fesoterodine was not addressed.