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**PROPRIETARY DRUG NAME®/GENERIC DRUG NAME:** [S,S]-Reboxetine succinate/esreboxetine

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** Not Applicable

**NATIONAL CLINICAL TRIAL NO.:** NCT 00141128

**PROTOCOL NO.:** A6061024

**PROTOCOL TITLE:** Measurement of Urethral Function in Women With Stress Urinary Incontinence-Evaluation of the Sensitivity of Urethral Reflectometry Compared to Urethral Pressure Profilometry, Using [S,S]-Reboxetine to Detect Pharmacological Augmentation of Urethral Pressure

**Study Center:** One study center in Denmark.

**Study Initiation and Completion Dates:** 01 December 2005 to 07 June 2006

**Phase of Development**: Phase 2

**Study Objectives:**

*Primary*

- To assess the utility of urethral reflectometry in the detection of pharmacologically induced pressure changes in the female urethra
- To compare urethral reflectometry against standard urodynamic assessment of opening and closing urethral pressure using urethral pressure profilometry (UPP) in women with stress urinary incontinence (SUI)

*Secondary*

- To assess the effect of [S,S]-reboxetine 4 mg on urethral function in women with SUI

## METHODS

**Study Design:** This was a randomized, double-blind, placebo controlled, crossover study. One to 2 weeks prior to Period 1, the subjects had a screening visit (Visit 1). At the first visit in Period 1 subjects underwent baseline UPP and reflectometry assessments (Visit 2). Subjects then received [S,S]-Reboxetine 4mg or placebo for 7 to 9 days (Period 1) followed by a washout period of ≥7 but ≤30 days before receiving the other treatment. At the start of Period 2 baseline UPP & reflectometry assessments were repeated (Visit 4). Subjects were then to 'cross-over' to receive the treatment they did not have in the first treatment period. Efficacy assessments (UPP & reflectometry) were made at the end of Periods 1 and 2 (Visits 3 and 5). Subjects had safety assessments throughout the study and a follow-up assessment 7 to 9 days after completion of Period 2.

**Number of Subjects (Planned and Analyzed):** Sufficient subjects were to be recruited to ensure that a total of 16 subjects completed the study. Eighteen subjects were randomized and included in the safety population. The full analysis set (FAS) and per-protocol analysis set (PPAS) included 17 subjects as 1 subject withdrew early (after 1 dose) and was excluded due to insufficient efficacy data.

**Diagnosis and Main Criteria for Inclusion:** Female outpatients aged 18 to 65 years with clinically significant SUI presenting with either pure SUI, or stress predominant mixed urinary incontinence (MUI). Objective evidence of SUI (without concomitant evidence of detrusor overactivity associated with urinary incontinence) was required as shown by either previous evidence of urodynamically proven SUI within 12 months of screening or during cystometry performed at the screening visit. Subjects had to have had symptoms of SUI for at least 3 months. Subjects with a history of recurrent syncope or evidence of low blood pressure (BP) (<90mmHg systolic or <40mmHg diastolic) and creatinine clearance ≤ 30 mL/minute were excluded from the study.

**Study Treatment:** There were 2 treatment periods separated by a washout period of ≥7 but ≤30 days. During each period, subjects received either [S,S]-reboxetine 4 mg tablets or matching placebo tablets for 7 to 9 days. Subjects received both treatments during the study. All study drugs could be taken without regard to food. Subjects took 1 tablet in the morning, starting the day after Visits 3 and 5, and every day at approximately the same time of day up to and including the mornings of Visits 4 and 6 (end of Periods 1 and 2, respectively).

**Efficacy Evaluations:**

*Primary efficacy:* The primary efficacy endpoint for this study was the resting opening urethral pressure as measured by reflectometry. This was measured predose and postdose in both Periods 1 and 2 (Visits 2, 3, 4 and 5). Reflectometry was performed according to the method described by Klarskov and Lose (2004).

*Secondary efficacy:* Reflectometry: The reflectometry endpoints that were measured during Visits 3, 4, 5, and 6 were squeezing opening urethral pressure, resting closing urethral pressure, opening urethral elastance (resting and squeezing), resting closing urethral elastance, and urethral hysteresis. UPP: UPP was carried out following the reflectometry

(with the bladder still approximately 50% full) and according to the recommendations of the International Continence Society (ICS). The UPP endpoints that were measured during Visits 3, 4, 5, and 6 were maximum urethral closure pressure (MUCP), maximum urethral pressure (MUP), and functional urethral length**.** Patient global impression of change (PGIC): The PGIC was completed by the subjects at the end of each treatment period, Visits 4 and 6.

*Other evaluations:* Micturition Diary: At screening, the subject completed a real time paper diary for 7 days prior to randomization. Based on the information, weekly incontinence episode frequency (IEF), the stress incontinence component of the weekly IEF, the urge incontinence component of the weekly IEF, and overall micturition frequency were calculated. During each treatment period, the subject completed a real time paper diary for the 3 days prior to Visit 4 and the 3 days prior to Visit 6.

Dosing Diary: During the treatment periods, subjects completed a diary to record dosing times and any adverse events (AEs) and concomitant medication.

Cystometry: This procedure was carried out according to the ICS recommendation on good urodynamic practice.

**Pharmacokinetic Evaluations:** Four pharmacokinetic (PK) samples were collected during the study. Samples were taken at Visit 3 (predose Period 1), Visit 4 (to confirm Period 1 compliance), Visit 5 (predose Period 2) and Visit 6 (to confirm Period 2 compliance). Blood samples, 7 mL to provide 3 mL plasma, were taken prior to uroflowmetry. Plasma samples were assayed for [S,S]-reboxetine concentrations.

**Safety Evaluations:** AEs were recorded at Visits 3, 4, 5, 6, and at the follow-up visit. Laboratory assessments (urinalysis, haematology, and biochemistry) were done at screening (Visit 1), Visits 4 and 6, and at follow-up. Urinalysis was also done at Visits 3 and 5. Subjects had a full physical examination at screening, Visits 4, 5 and 6, and at follow-up. Supine and standing vital sign measurements (blood pressure [BP] and pulse rate) were recorded at screening, Visits 3, 4, 5, and 6, and at follow-up. Electrocardiograms (ECGs) were recorded at screening and at follow-up. Additionally, uroflowmetry [maximum urinary flow rate (Qmax)] and post void residual (PVR) were measured at screening (Visit 2), Visits 3, 4, 5, and 6.

**Statistical Methods:** The individual values of the primary and secondary endpoints were listed and summarized by treatment. To compare urethral reflectometry against standard urodynamic assessment of opening and closing urethral pressure, the correlation between reflectometry and UPP with regard to the measured endpoints, were investigated by treatment. To assess the effect of [S,S]-reboxetine on urethral function, the primary and secondary endpoints were analyzed using an analysis of covariance (ANCOVA) model, with terms for sequence, subject within sequence, period and treatment, baseline and the following categorical variables tested in the model: Age<45 years or 45 years ≤Age≤65 years, Body Mass Index (BMI) <28 or BMI ≥28, number of urge incontinence episodes (0 and ≥1) at baseline (as determined from the screening micturition diary), and baseline weekly IEF (<14 versus ≥14) (as determined from the screening micturition diary). The comparison of interest was [S,S]-reboxetine 4 mg once daily versus placebo. The difference between treatment

means, the standard error associated with these differences and 95% confidence intervals (CIs) for the difference were presented.

## RESULTS

**Subject Disposition and Demography:** Of the 22 subjects screened, 18 subjects (81.8%) were randomized. All 18 subjects received [S,S]-reboxetine and 17 subjects (77.3%) received placebo. One subject withdrew after 1 dose of [S,S]-reboxetine due to AEs; this subject was excluded from the PPAS. Insufficient efficacy data was available for this subject so she was also excluded from the FAS. The results based on the PPAS and FAS are, therefore, identical. All treated subjects, including the subject who withdrew, were analyzed for safety.

All subjects were white females. The majority of subjects were not of child bearing potential. Demographic characteristics are summarized in Table S1.

### Table S1 Demographic Characteristics

| | **[S,S]-Reboxetine → Placebo** | **Placebo→ [S,S]-Reboxetine** |
|---|---|---|
| Number of Subjects | 8 | 10 |
| **Age (years)** | | |
| Mean (SD) | 54.6 (6.7) | 47.8 (10.9) |
| Range | 45-64 | 32-61 |
| **Weight (kg)** | | |
| Mean (SD) | 76.5 (11.9) | 75.3 (7.7) |
| Range | 63.0-101.0 | 65.0-87.0 |
| **Height (cm)** | | |
| Mean (SD) | 165.8 (6.1) | 167.3 (5.8) |
| Range | 160.0-178.0 | 160.0-176.0 |
| **Duration since first diagnosis of SUI (years)** | | |
| Mean (Range) | 7.3 (1.2–20.3) | 4.2 (0.0–10.3) |

SD = standard deviation, SUI = stress urinary incontinence

### Efficacy Results

*Primary endpoints: Resting Opening Urethral Pressure:* The analysis of the primary endpoint showed that the difference in adjusted means was 13.66 $cmH_2O$, with an associated 95% CI of (9.31, 18.01) and the corresponding p-value was <0.0001. This indicated that there was a statistically significant difference between [S,S]-reboxetine and placebo in the PPAS. The results based on the FAS were identical to the PPAS results.

*Additional Analyses and Summaries of the Primary Endpoint:* The analysis of the change from baseline gave identical results to those of absolute measurements. The analysis of the primary endpoint at baseline by period indicated that this method was reproducible over time. The descriptive summaries for the primary endpoint by age group, BMI, and baseline weekly IEF indicated that there were no major differences in the results for these subgroups. However, the summary by the number of urge incontinence episodes at baseline indicated that the primary endpoint was generally higher for subjects with at least 1 urge episode at baseline compared to those with none. This covariate was also included in the ANCOVA

model, as it was found to be significant. There was a positive correlation between reflectometry and UPP.

*Secondary Endpoints:* Reflectometry: Treatment with [S,S]-reboxetine resulted in a statistically significant increase in squeezing opening urethral pressure, resting closing urethral pressure, opening urethral elastance (resting and squeezing), resting closing urethral elastance, and urethral hysteresis compared to placebo. The statistical results are summarized in Table S2.

**Table S2 Summary of Statistical Analysis of Reflectometry Parameters**

| Reflectometry Parameters | Units | Adjusted Mean[a] | | Difference Between Treatment Means (95%CI)[b] | p-Value |
|---|---|---|---|---|---|
| | | [S,S]-Reboxetine | Placebo | | |
| Squeezing Opening Urethral Pressure | $cmH_2O$ | 66.58 | 55.17 | 11.43 (5.95, 16.91) | 0.0005 |
| Resting Closing Urethral Pressure | $cmH_2O$ | 47.00 | 34.54 | 12.46 (7.48, 17.45) | 0.0001 |
| Resting Opening Urethral Elastance | $cmH_2O/mm^2$ | 2.39 | 2.05 | 0.34 (0.06, 0.62) | 0.0202 |
| Squeezing Opening Urethral Elastance | $cmH_2O/mm^2$ | 2.83 | 2.24 | 0.59 (0.27, 0.91) | 0.0013 |
| Resting Closing Urethral Elastance | $cmH_2O/mm^2$ | 2.24 | 1.82 | 0.42 (0.21, 0.62) | 0.0007 |
| Urethral Hysteresis | $cmH_2O$ | 12.63 | 9.84 | 2.80 (0.83, 4.77) | 0.0087 |

[a]Least square mean, adjusted for corresponding baseline parameter
[b]Estimates based on least square means; CI = Confidence Interval

UPP: *MUCP:* The analysis showed that the difference in adjusted means was 8.37, with an associated 95% CI of (-0.39, 17.12) and the corresponding p-value was 0.0596. This indicated that there was no statistically significant difference between [S,S]-reboxetine and placebo.

*MUP:* The analysis showed that the difference in adjusted means was 9.87, with an associated 95% CI of (0.63, 19.10) and the corresponding p-value was 0.0380, which indicated that there was a statistically significant difference between [S,S]-reboxetine and placebo. MUP was greater for [S,S]-reboxetine than placebo.

Functional urethral length: For the PPAS, the functional urethral length (cm) was similar following treatment with [S,S]-reboxetine (absolute arithmetic mean: 2.69) and placebo (absolute arithmetic mean: 2.69).

PGIC: The analysis showed that the difference in adjusted means was -1.11, with an associated 95% CI of (-1.68, -0.53) and the corresponding p-value was 0.0009. This indicated that there was a statistically significant difference between [S,S]-reboxetine and placebo with a greater improvement following treatment with [S,S]-reboxetine compared to placebo.

*Other Endpoints:* Micturition Diary: For the PPAS, the weekly IEF by treatment, the stress incontinence component of the weekly IEF by treatment, the urge incontinence component of the weekly IEF by treatment, and the overall micturition frequency by treatment were lower following treatment with [S,S]-reboxetine compared to placebo.

**Pharmacokinetic Results:** Plasma PK concentrations are not presented in this report.

**Safety Results:** There were no deaths or serious adverse events (SAEs) reported during the study. There were no temporary discontinuations or dose reductions due to AEs and no discontinuations due to abnormal laboratory test results. One subject permanently discontinued from the study due to treatment-related AEs (dizziness, dry mouth, insomnia, altered mood, palpitations and paraesthesia) after the first day of treatment with [S,S]-reboxetine. There was a higher incidence of all causality AEs during treatment with [S,S]-reboxetine (18 subjects ) compared to placebo (7 subjects). The AE profile observed during the study was as expected for a norepinephrine reuptake inhibitor (NRI). All the AEs were mild in severity. Table S3 summarizes individual events reported by at least 2 subjects in any treatment group.

**Table S3 Summary of Treatment Emergent All Causality AEs – AEs Reported by ≥ 2 Subjects per Treatment Group**

| Number of Subjects With | [S,S]-Reboxetine (N=18) | Placebo (n=17) |
|---|---|---|
| AEs | 18 (18) | 7 (4) |
| Number of AEs | 85 (80) | 13 (9 |
| Dry Mouth | 10 (10) | 2 (2) |
| Insomnia | 9 (9) | 1 (1) |
| Chills | 8 (8) | 0 (0) |
| Constipation | 5 (4) | 1 (0) |
| Decreased Appetite | 5 (5) | 0 (0) |
| Hot Flush | 4 (4) | 0 (0) |
| Nausea | 3 (3) | 1 (1) |
| Dizziness | 3 (3) | 1 (1) |
| Paraesthesia | 3 (3) | 0 (0) |
| Mood Altered | 3 (3) | 0 (0) |
| Hyperhidrosis | 3 (3) | 0 (0) |
| Fatigue | 2 (2) | 0 (0) |
| Sensation of Heaviness | 2 (2) | 0 (0) |
| Piloerection | 2(2) | 0 (0) |

The numbers shown in parentheses are for treatment-related AEs

There were no clinically significant laboratory test abnormalities, physical changes, or ECG changes. The number of subjects with an abnormal laboratory test result was similar in each treatment group; 5 subjects in the [S,S] - reboxetine treatment group, and 4 subjects in the placebo treatment group. Urine blood was the most frequently reported laboratory test abnormality. The median changes from baseline to last observation did not vary significantly between the 2 treatment groups for vital signs. The mean change from baseline in Qmax was greater for [S,S]-reboxetine (-3.76 mL/sec) than for placebo (0.34 mL/sec). The mean change from baseline in PVR was greater for [S,S]-reboxetine (3.71 mL) than for placebo (0.41 mL).

**CONCLUSIONS:** A statistically significant difference between [S,S]-reboxetine and placebo was observed for the primary endpoint of resting opening urethral pressure as measured by reflectometry.

There was a statistically significant difference between [S,S]-reboxetine and placebo in squeezing opening urethral pressure, resting closing urethral pressure, resting opening urethral elastance, squeezing opening urethral elastance, resting closing urethral elastance, and urethral hysteresis as measured by reflectometry. There was no statistically significant difference between [S,S]-reboxetine and placebo in MUCP as measured by UPP. However, there was a statistically significant difference between [S,S]-reboxetine and placebo in MUP as measured by UPP. There was no difference in functional urethral length (cm) following treatment with [S,S]-reboxetine and placebo. There was a statistically significant difference in PGIC between [S,S]-reboxetine and placebo, and a greater improvement in PGIC for [S,S]-reboxetine compared to placebo.

There were no deaths or SAEs reported during the study. There was 1 permanent discontinuation from the study due to treatment-related AEs during treatment with [S,S]-reboxetine. There were no temporary discontinuations or dose reductions due to AEs and no discontinuations due to abnormal laboratory test results. There was a higher incidence of all causality AEs on [S,S]-reboxetine (18 subjects ) compared to placebo (7 subjects). The most frequently reported all causality AEs for subjects administered [S,S]-reboxetine were dry mouth, insomnia, and chills. All the AEs were mild in severity. The AE profile observed during the study was as expected for an NRI. None of the laboratory test abnormalities, abnormal physical examination findings, vital signs and ECG changes from screening was considered to be clinically significant.