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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 00625833

PROTOCOL NO.: A6061037

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo Controlled Trial of [S,S]-Reboxetine in Patients with Chronic Painful Diabetic Peripheral Neuropathy

Study Centers: 33 centers in the United States, 4 centers in Finland, 7 centers in South Africa, 6 centers in Spain, 5 centers in the Netherlands, and 6 centers in the Czech Republic.

Study Initiation and Completion Dates: 05 December 2007 to 06 November 2008
The study was terminated prematurely following an interim analysis on 08 August 2008.

Phase of Development: Phase 2b

Study Objectives:

- To evaluate the efficacy of [S,S]-reboxetine succinate ([S,S]-RBX) in subjects with diabetic peripheral neuropathy (DPN).
- To evaluate the safety and tolerability of [S,S]-RBX in subjects with DPN.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled study of [S,S]-RBX in subjects with DPN. The study comprised 4 phases: (1) 1 to 3-week screening period (depending upon prohibited medication washout), (2) 2-week single-blind placebo run-in, (3) 8-week randomized treatment period including 2-week titration, and (4) 2-week follow-up period.

Approximately 330 subjects were planned to be screened to meet the target of 230 subjects at Visit 2 (start of single-blind run-in). The study involved 8 scheduled clinic visits where efficacy and safety parameters were measured. A telephone interactive voice response pain diary system was utilized to collect subject reported outcomes of daily pain and sleep interference scores. A centralized telerandomization system was employed to manage the stratification and allocation of study treatment.

All subjects who met the entry criteria at Visit 1 entered a screening period during which a daily pain diary was maintained. Where an existing hemoglobin A1c (HbA1c) sample between 6-12 weeks prior to Visit 1 was not available, a study specific pre-screening HbA1c sample had to be taken.

Upon completion of the screening period, if the severity of pain met the required entry criteria (subjects had to have completed at least 4 daily pain diaries over the last 7 days with an average daily pain score ≥4, and a score ≥40 mm on the pain visual analogue scale [VAS]), subjects entered a 2-week single-blind placebo treatment period (Visit 2).

At Visit 3, all subjects who met the double-blind randomization criteria (subjects had to have an average daily pain score ≥4 over the last 7 days and a score ≥40 mm on the pain VAS) were then randomized (ratio 1:1) to receive either [S,S]-RBX or placebo for a period of 8 weeks. During the double-blind period, a forced dose escalation to the maximum tolerated dose (4, 6 or 8 mg/day) for each individual subject was employed. Further details regarding dose escalation are provided in the Study Treatment Section.

An internal sponsor Data Monitoring Committee (DMC) performed 1 interim analysis for efficacy based upon the change from baseline to Week 6 in weekly average pain score. The interim analysis was performed when 70 subjects in the study had completed 6 weeks of the double-blind randomized treatment period.

Subject to Institutional Review Board/Independent Ethics Committee approval/favorable opinion, this study included an additional research component involving collection of biological samples for de-identified exploratory 'omics' analysis. Subjects could have participated in this study even if they had chosen not to participate in the sample banking component.

Number of Subjects (Planned and Analyzed): It was planned to enroll 330 subjects in this study. A total of 124 subjects (62 [S,S]-RBX and 62 placebo) were treated and randomized. All treated subjects were included in the efficacy, AE, and safety analysis sets. Fifty-nine [S,S]-RBX subjects and 61 placebo subjects were included in the laboratory data analysis set.

The number of subjects recruited for this study was less than originally estimated as a planned interim analysis was carried out by the DMC. The DMC recommended to terminate this study for futility.

Diagnosis and Main Criteria for Inclusion: The study enrolled subjects, male or female of any race at least 18 years of age, with a diagnosis of type 1 or 2 diabetes mellitus (by the American Diabetic Association Clinical Practice Recommendations diagnostic criteria) for at least 1 year. Subjects had to have HbA1c levels of ≤11% at Visit 1 (with fluctuations of ≤1% in the 6 to 12 weeks prior to Visit 1); a diagnosis of painful, distal, symmetrical, sensori-motor polyneuropathy, due to diabetes, for at least 1 year; and a score ≥40 mm on the pain VAS at Visit 1.

Subjects with malignancy within the past 2 years (with the exception of basal cell carcinoma), significant hepatic impairment, clinically significant abnormal 12-lead

electrocardiogram (ECG), neurological disorders unrelated to diabetic neuropathy, a history of chronic or acute hepatitis/human immunodeficiency virus infection within the past 3 months, depression sub-scale score >10 on the Hospital and Anxiety Depression Scale (HADS), a current or recent diagnosis (past 6 months) or episode of major depressive disorder (as diagnosed by the Mini International Neuropsychiatric Interview [MINI]), at serious risk of suicide based on Beck's Scale for Suicide Ideation (BSS), history of recurrent syncope or evidence of low blood pressure (BP) (systolic <90 mmHg, diastolic <40 mmHg) or postural hypotension (a fall of 20 mmHg in systolic BP or 10 mmHg in diastolic BP on standing), history transient ischemic attack or stroke, or myocardial infarction or unstable angina within the past 3 months, were excluded from the study.

Study Treatment: [S,S]-RBX or matching placebo tablets were administered once a day, preferably in the morning. Subjects self-administered their study treatment orally. The study treatment had to be swallowed whole with water and not chewed prior to swallowing. To achieve the target randomized dose, 2 tablets per day were taken together.

Upon completion of the screening period, if the severity of pain met the required entry criteria, subjects entered a 2-week single-blind placebo treatment period. At Visit 3, all subjects who met the double-blind randomization criteria were randomized (ratio 1:1) to receive either [S,S]-RBX or placebo for a period of 8 weeks. During the double-blind period, a forced dose escalation to the maximum tolerated dose for each subject was employed (Table S1). The [S,S]-RBX escalation design is in Figure S1.

At Visit 3, subjects randomized to [S,S]-RBX began with a dose of 4 mg/day for 1 week (Days 1-7). At the end of this period, the following 2 treatment options were available at Visit 4:

1. Subjects characterized by good tolerability at 4 mg/day received a dose increase to 8 mg/day for the subsequent period of 1 week (Days 8-14).

2. Subjects characterized by poor tolerability at 4 mg were withdrawn or remained at this dose for the remainder of the study, as determined by the judgment of the investigator. There was no provision for dose reduction at this dose level.

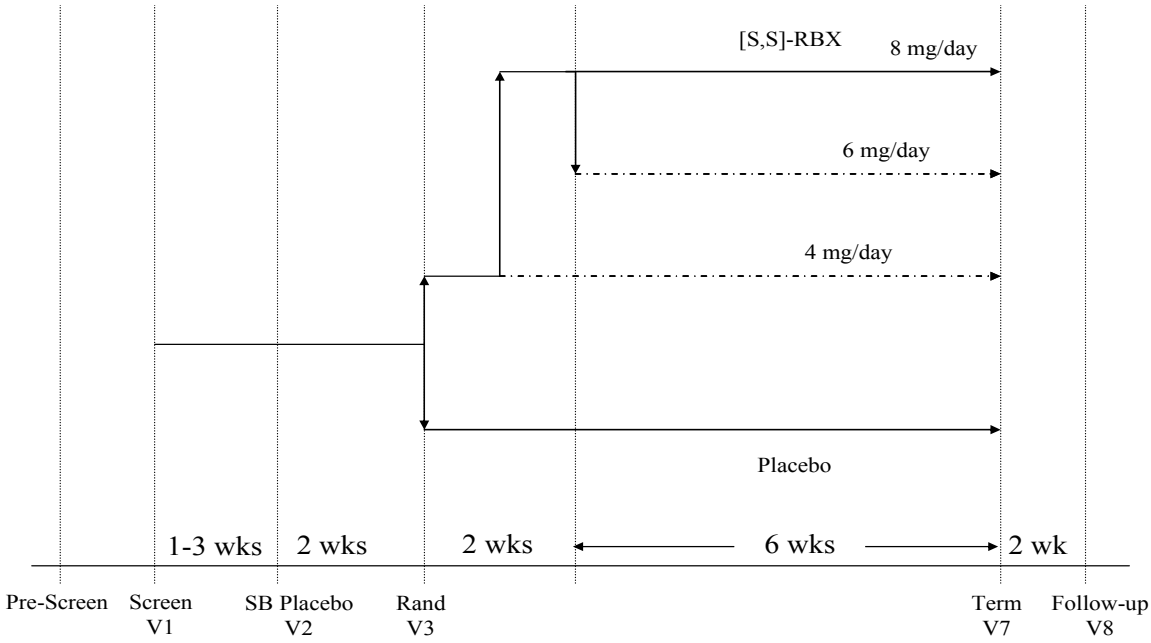
For those subjects who had their dose increased to 8 mg, following 1-week treatment at this dose level (Days 8-14), if they were unable to tolerate the dose, there was a provision for dose reduction from 8 to 6 mg/day. Following Visit 5, no further dose modification was allowed. Subjects were withdrawn if tolerability was a problem.

Table S1. Forced [S,S]-RBX Dose Escalation Scheme

Period (Days)	1-7	8-14	15-onwards
Dose (mg/day)	4	4 or 8	4, 6 or 8

The first dose of study medication was taken on the day of Visit 2.

Figure S1. Escalation Design



[S,S]-RBX and matching placebo were provided by the sponsor. [S,S]-RBX study treatment was presented as round, light grey tablets containing either 2 or 4 mg of [S,S]-RBX in an extended release formulation. Matching placebo tablets were also supplied. The tablets were blistered in weekly packs and presented in a childproof, tamper-evident wallet.

Efficacy Evaluations: Subjects completed the following efficacy evaluations:

- Daily pain rating scale at Visits 1 to 7,
- Daily pain sleep interference rating scale at Visits 1 to 7,
- Pain VAS at Visits 1, 2, 3, and 7 (or early termination),
- Modified Brief Pain Inventory-Short Form (m-BPI-SF) at Visits 3 and 7 (or early termination),
- Patient Global Impression of Change (PGIC) at Visit 7 (or early termination),
- Neuropathic Pain Symptom Inventory (NPSI) at Visits 3 and 7 (or early termination), and
- HADS at Visits 1, 2, 3, and 7 (or early termination).

Other Evaluations:

Pharmacogenomic Sample

A pharmacogenomic sample was taken at Visit 2 and was subject to ethical review, approval and subject consent.

Mini International Neuropsychiatric Interview

The MINI was performed at the screening visit (Visit 1).

Safety Evaluations: Safety evaluations included the following:

- Adverse event (AE) assessments at Visits 3, 4, 5, 6, 7, and 8,
- Sitting and standing BP and pulse measurements at all visits,
- Height and weight measured at Visit 1, and body weight measured at Visit 7 (or early termination),
- Physical examination (including a full neurological examination) conducted at Visits 1, 3, and 7 (or early termination),
- A 12-lead ECG was recorded after the subject had been resting for 10 minutes at Visits 1, 5, and 7 (or early termination),
- BSS at Visit 1 and throughout the study, and
- Clinical laboratory assessments performed as follows:
    - Hematology samples taken at Visits 1, 2, 3, 5, and 7 (or early termination). At Visit 1 (screening) only, Hepatitis A, B and C were tested,
    - Biochemistry samples taken at Visits 1, 2, 3, 5, and 7 (or early termination),
    - HbA1c measured at Visits 1 and 7 (or early termination),
    - Fasting lipid profile measured at Visit 1, and
    - Urine pregnancy test for women of child bearing potential at Visits 1 and 2.

Statistical Methods:

Sample Size

The sample size calculation was based on the primary endpoint, the change from baseline in weekly average pain score. A conventional sample size approach was adopted. A sample size of 184 subjects was recommended. It gave an approximately 90% power to detect a

-1 point difference between treatments based on a standard deviation of 2.12 and a 2-sided significance level of 0.05. Assuming 20% of subjects who entered the placebo run-in would not be randomized, 230 subjects (115 per treatment group) were required to enter the single-blind placebo run-in phase.

Data Monitoring Committee (DMC) and Interim Analysis

The objective of the interim analysis carried out in this study was to advise the study team as to whether an invest-to-win strategy should be adopted for this project, whether this study should be stopped for futility, or whether no action should be taken. In the event that the study was not terminated for futility, then a sample size re-estimation was to be undertaken.

The DMC recommended that the study be terminated for futility as the mean observed treatment difference between [S,S]-RBX and placebo ([S,S]-RBX – placebo) was greater than -0.5.

Efficacy

Primary

The primary analysis was based on the full analysis set (FAS), which included all randomized subjects who had received at least 1 dose of double-blind study treatment, regardless of whether they had efficacy data. The primary analysis was based on the primary endpoint, change from baseline to end of treatment in weekly average pain rating score (based on the last 7 available on-treatment readings). The baseline score was calculated as the mean of the last 7 pain diary scores prior to randomization. The analysis was carried out using an analysis of covariance (ANCOVA).

As a further sensitivity analysis, the change from baseline in weekly average pain score at Week 8 of the double-blind treatment phase was analyzed using a mixed effects repeated measures model with terms for baseline score, country, week, treatment and week by treatment interaction fitted as fixed effects and subject fitted as a random effect. The repeated measures analysis was based on the FAS. An unstructured covariance structure was used.

However, the pre-planned analysis based on the primary endpoint using an ANCOVA, but using a baseline observation carried forward approach to missing data and using the per-protocol (PP) population in order to investigate the treatment effect in a population that adhered more closely to the protocol procedures were not carried out due to the study being terminated for futility.

Secondary

Responder rates (subjects with a 30% reduction from baseline in weekly average pain score and subjects with a 50% reduction from baseline in weekly average pain score) were analyzed using logistic regression with model terms for center and treatment. The models were used to estimate the odds ratios and associated 95% confidence intervals (CIs) for the comparison of [S,S]-RBX and placebo.

Significance tests for the treatment comparisons were performed at the one-sided 0.025 significance level and 2-sided 95% CIs were presented.

The PGIC was analyzed by logistic regression, adjusting for center and treatment. The categories "Very Much Improved" and "Much Improved" were combined and compared to the remaining 5 categories combined. The model was used to estimate the odds ratio and associated 95% CI for the comparison of [S,S]-RBX and placebo.

The analysis of all secondary endpoints was based on the FAS.

Due to the study being terminated for futility, the pre-planned formal analysis using ANCOVA of the change from baseline in the weekly average sleep interference scale, the pain VAS, the total score and each dimension of the NPSI, each subscale of the HADS, and each question of the m-BPI-SF was not carried out. These endpoints were summarized only.

Safety

The safety analysis population consisted of all subjects who received at least 1 dose of double-blind study treatment. Safety data were listed and summarized by treatment using sponsor standard tabulations.

For summary purposes, AE investigator terms were converted to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 11.1). All causality and treatment-related AEs were summarized by body system, by incidence and severity, and by treatment group. In addition, summaries of serious adverse events (SAEs) and AEs that led to withdrawal were provided.

SAE presentations were derived from a separate, centralized, AE monitoring database that was continuously updated based on rapidly communicated reports from the investigators to the sponsor. The clinical study database was based on information provided from the case report forms. Consequently, occasional differences in data may exist between the centralized safety database and the clinical study database.

Summaries by visit and postdose changes from baseline (Visit 3) by visit in systolic BP, diastolic BP and pulse rate were tabulated by treatment group for Visit 3 onwards. Postural changes (standing–sitting) in BP and pulse rate were summarized by treatment group.

The total score and sub-scores of the BSS were summarized by treatment and visit.

RESULTS

Interim Analysis

The interim analysis was based on the adjusted treatment difference for the change from baseline to Week 6 using the modified PP population. Both treatment groups showed a decrease in mean pain score over the 6-week period. The treatment difference was 0.17 with standard error 0.41. As this met the criteria of being greater then -0.5, the DMC recommended the study be terminated.

The team recommended that those subjects in the double-blind phase of the study should have been withdrawn early; however, as there were no safety concerns, subjects obtaining benefit could have chosen to continue with the study as per the protocol.

Subject Disposition and Demography: A summary of the disposition of subjects and datasets analyzed is provided in Table S2. Given the results of the interim analysis (see above), a smaller than planned total of 337 subjects were screened, and 124 subjects (62 [S,S]-RBX and 62 placebo) were treated and randomized.

Ninety-seven subjects (45 [S,S]-RBX and 52 placebo) completed the study, and 27 subjects (17 [S,S]-RBX and 10 placebo) discontinued. Of those discontinuing, 19 subjects (11 [S,S]-RBX and 8 placebo) discontinued due to reasons related to study drug, and 8 subjects (6 [S,S]-RBX and 2 placebo) discontinued due to reasons not related to study drug.

All treated subjects were included in the efficacy, AE, and safety analysis sets. Fifty-nine [S,S]-RBX subjects and 61 placebo subjects were included in the laboratory data analysis set.

Table S2. Subject Disposition and Datasets Analyzed

Number (%) of Subjects		[S,S]-reboxetine	Placebo
Screened	337		
Assigned Study Treatment	124		
Treated		62	62
Completed		45 (72.6)	52 (83.9)
Discontinued		17 (27.4)	10 (16.1)
Related to study drug		11 (17.7)	8 (12.9)
Adverse event		5 (8.1)	1 (1.6)
Lack of efficacy		1 (1.6)	1 (1.6)
Other		5 (8.1)	6 (9.7)
Not Related to study drug		6 (9.7)	2 (3.2)
Adverse event		2 (3.2)	0
Lost to follow-up		2 (3.2)	1 (1.6)
Other		1 (1.6)	1 (1.6)
Subject no longer willing to participate		1 (1.6)	0
Analyzed for Efficacy			
Full analysis set		62 (100.0)	62 (100.0)
Analyzed for Safety			
Adverse events		62 (100.0)	62 (100.0)
Laboratory data		59 (95.2)	61 (98.4)
Safety		62 (100.0)	62 (100.0)

More subjects were male (71 [57.3%], 36 [S,S]-RBX and 35 placebo) and were white (79 [63.7%], 38 [S,S]-RBX and 41 placebo). For [S,S]-RBX subjects, mean age was 60.6 years (range: 38-81 years), mean weight was 92.6 kg (range: 48.0-151.3 kg), and mean height was 169.6 cm (range: 117.8-191.0 cm). Similarly, for placebo subjects, mean age 60.1 years (range: 32-82 years), mean weight was 96.6 kg (range: 60.0-136.0 kg), and mean height was 168.3 cm (range: 146.0-188.0 cm).

All subjects had a primary diagnosis of diabetic neuropathy; [S,S]-RBX subjects had a mean duration of 5.1 years (range: 0-24.3 years), and placebo subjects had a mean duration of 5.7 years (range: 0.8-23.2 years) since first diagnosis.

Of the 124 subjects treated, 81 subjects (65.3%) had at least 1 disease/syndrome prior to the study, and 119 subjects (96.0%) had at least 1 disease/syndrome present at baseline. The most common conditions present at baseline (experienced by ≥10 subjects in both treatment groups) were hypertension (86 subjects, 69.4%), hyperlipidemia (35 subjects, 28.2%), hypercholestolemia (23 subjects, 18.5%), obesity (19 subjects, 15.3%), gastroesophageal reflux disease (18 subjects, 14.5%), osteoarthritis (15 subjects, 12.1%), type 2 diabetes mellitus (15 subjects, 12.1%), dyslipidemia (13 subjects, 10.5%), coronary artery disease (12 subjects, 9.7%), hypothyroidism (12 subjects, 9.7%), seasonal allergy (12 subjects, 9.7%), diabetic neuropathy (10 subjects, 8.1%), and erectile dysfunction (10 subjects, 8.1%).

A total of 123 subjects (99.2%) took at least 1 drug treatment prior to the start of study drug; the most common drugs (taken by ≥10 subjects in either treatment group) included

metformin (28 [S,S]-RBX and 31 placebo), acetylsalicylic acid (26 [S,S]-RBX and 28 placebo), lisinopril (11 [S,S]-RBX and 14 placebo), atorvastatin (9 [S,S]-RBX, 15 placebo), glibenclamide (8 [S,S]-RBX and 12 placebo), insulin glargine (9 [S,S]-RBX and 10 placebo), simvastatin (14 [S,S]-RBX and 5 placebo), hydrochlorothiazide (8 [S,S]-RBX and 10 placebo), and metformin hydrochloride (11 [S,S]-RBX and 6 placebo).

All subjects took at least 1 concomitant drug treatment during the study; the most common drugs (taken by ≥10 subjects in either treatment group) were the same as those subjects took prior to the start of study drug. Nine subjects (7.3%) had at least 1 non drug concomitant treatment; these included treatments under the cardiac disorder, investigation, and surgical and medical procedure categories.

Overall, both [S,S]-RBX and placebo subjects received treatment for a median duration of 56 days. Most subjects who received [S,S]-RBX (59 subjects, 95.2%) had a final dose of either 4 or 8 mg.

Efficacy Results:

Prior to the interim analysis, it was planned that 90% CIs were to be used in all analyses. Following changes to the stopping rules for the interim analysis, this was changed to 95%. However, the original width of 90% was reported for all analyses.

Primary

The primary endpoint was the change from baseline to end of treatment in weekly average pain rating score. Overall, decreases in weekly average pain score were shown in both the [S,S]-RBX and the placebo treatment groups. There was no significant difference in weekly average pain rating score between [S,S]-RBX and placebo. An ANCOVA main effect model of the change from baseline in endpoint weekly average pain score for the FAS is provided in Table S3.

Table S3. ANCOVA Main Effect Model of the Change from Baseline in Endpoint Weekly-Average Pain Score (FAS)

Treatment	Baseline Unadjusted Mean (SE)	End of Treatment		Contrast of [S,S]-reboxetine vs Placebo[b]		
		Unadjusted Mean (SE)	Adjusted Mean (SE)[a]	Difference (SE)	90% CI	p-value
[S,S]-reboxetine (N=62)	6.02 (0.163)	-0.91 (0.199)	-0.90 (0.192)	0.03 (0.273)	(-0.42, 0.49)	0.5483
Placebo (N=62)	6.36 (0.149)	-0.92 (0.183)	-0.93 (0.192)			

ANCOVA = Analysis of covariance; FAS = Full analysis set; N = the number of subjects in the indicated population; SE = Standard error; CI = Confidence interval
[a] Least squares mean adjusted for baseline average score.
[b] Estimates based on comparison of least square means.

Summary statistics of the change from baseline in endpoint weekly average pain score for the FAS are provided in Table S4.

Table S4. Summary Statistics of the Change from Baseline in Endpoint Weekly-Average Pain Score (FAS)

Treatment	Baseline			End of Treatment			Change from Baseline		
	Mean (SE)	(SD)	Min-Max	Mean (SE)	(SD)	Min-Max	Mean (SE)	(SD)	Min-Max
[S,S]-reboxetine (N=62)	6.02 (0.163)	(1.282)	3.7-8.1	5.11 (0.270)	(2.122)	0.0-9.0	-0.91 (0.199)	(1.566)	-5.9-1.9
Placebo (N=62)	6.36 (0.149)	(1.173)	3.1-9.3	5.44 (0.238)	(1.878)	0.1-8.6	-0.92 (0.183)	(1.440)	-5.3-1.3
All Treatments (N=124)	6.19 (0.111)	(1.235)	3.1-9.3	5.27 (0.180)	(2.002)	0.0-9.0	-0.92 (0.135)	(1.498)	-5.9-1.9

FAS = Full analysis set; N = the number of subjects in the indicated population; SE = Standard error; SD = Standard deviation; Min = Minimum; Max = Maximum

Secondary

The results for these secondary efficacy endpoints, which were analyzed, were similar to those obtained for the primary endpoint. The responder rate and PGIC showed that there was no difference between [S,S]-RBX and placebo.

Safety Results:

Adverse Events

There were no deaths during the course of this study.

A total of 41 [S,S]-RBX subjects (66.1%) and 36 placebo subjects (58.1%) experienced at least 1 AE during the study; 27 [S,S]-RBX subjects (43.5%) and 14 placebo subjects (22.6%) had at least 1 treatment-related AE per the investigator.

Most AEs were classed as gastrointestinal disorders (21 subjects), nervous system disorders (17 subjects), or infections and infestations (14 subjects).

A summary of the frequently occurring (≥2 subjects in either treatment group) all-causality treatment-emergent AEs by MedDRA preferred term is provided in Table S5. The majority of all AEs were mild or moderate in intensity; 8 subjects (3 [S,S]-RBX and 5 placebo) experienced severe AEs, and 2 of those subjects (1 [S,S]-RBX and 1 placebo) had severe SAEs.

Table S5. Frequently Occurring (≥2 Subjects in Either Treatment Group) All-Causality Treatment-Emergent Adverse Events

AEs by MedDRA Preferred Term[a]	[S,S]-reboxetine Number (%) of Subjects	Placebo Number (%) of Subjects
Constipation	10 (16.1)	1 (1.6)
Insomnia	6 (9.7)	1 (1.6)
Dry mouth	5 (8.1)	0
Dizziness	4 (6.5)	1 (1.6)
Headache	4 (6.5)	3 (4.8)
Nausea	4 (6.5)	2 (3.2)
Urinary retention	4 (6.5)	0
Dysuria	3 (4.8)	0
Hypoglycemia	3 (4.8)	2 (3.2)
Benign prostatic hyperplasia	2 (3.2)	0
Blood glucose increased	2 (3.2)	0
Dyspepsia	2 (3.2)	0
Erectile dysfunction	2 (3.2)	0
Fatigue	2 (3.2)	0
Hyperhidrosis	2 (3.2)	0
Tachycardia	2 (3.2)	1 (1.6)
Nasopharyngitis	1 (1.6)	2 (3.2)
Carpal tunnel syndrome	0	2 (3.2)
Hypertension	0	2 (3.2)
Neuropathy peripheral	0	2 (3.2)
Pruritus	0	2 (3.2)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities
[a]Sorted by descending frequency of AEs for [S,S]-reboxetine

Permanent discontinuations due to AEs are summarized in Table S6. In total, 8 subjects (7 [S,S]-RBX and 1 placebo) permanently discontinued the study due to all-causality treatment-emergent AEs. Of the 8 subjects, 6 subjects (5 [S,S]-RBX and 1 placebo) had a treatment-related AE leading to study discontinuation. No subject permanently discontinued due to an SAE.

A total of 7 subjects (5 [S,S]-RBX and 2 placebo) had their dose reduced or were temporarily discontinued due to all-causality treatment-emergent AEs. Of the 7 subjects, 5 subjects (4 [S,S]-RBX and 1 placebo) had a treatment-related AE leading to study discontinuation. No subject had their dose reduced or were temporarily discontinued due to an SAE.

Table S6. Permanent Discontinuations Due to Adverse Events

Sex/Age	Treatment	Event[a]	Severity	Relationship to Study Drug	Outcome
Female/80	[S,S]-reboxetine	Diastolic hypotenstion	Mild	Unrelated (other – possible autonomic neuropathy	Still Present
Female/54	[S,S]-reboxetine	Abdominal pain	Mild	Related	Resolved
Male/51	[S,S]-reboxetine	Ejaculation disorder	Moderate	Related	Resolved
Male/62	[S,S]-reboxetine	Urinary retention	Moderate	Related	Resolved
Male/64	[S,S]-reboxetine	Urinary retention	Mild	Related	Still Present
Male/77	[S,S]-reboxetine	Urinary retention	Mild	Related	Resolved
Male/57	[S,S]-reboxetine	Nausea	Moderate	Unrelated (other illness – virus)	Resolved
Male/62	Placebo	Abdominal distension	Moderate	Related	Still Present

[a] Medical Dictionary of Regulatory Activities Version 11.1 preferred term.

A total of 5 subjects (3 [S,S]-RBX and 2 placebo) experienced SAEs during the study; of these SAEs, 2 [S,S]-RBX subjects experienced an SAE that was considered related to the study drug. None of the SAEs led to permanent or temporary discontinuation.

Brief details for all 5 subjects are as follows:

- A 75-year-old male experienced 3 SAEs during the study. On Day 3, the subject experienced diabetes insipidus, which the investigator considered to be moderate in severity (ie, interfered to some extent with the subject's usual function), and pulmonary embolism, which the investigator considered to be mild in severity (ie, did not interfere with the subject's usual function), while receiving [S,S]-RBX 4 mg. The study drug was stopped temporarily, the subject was given treatment for both SAEs, and the SAEs were considered resolved on Day 10 and Day 3, respectively. The investigator determined that the SAE of diabetes insipidus was unrelated to study drug and was attributed to other (idiopathic), and the SAE of pulmonary embolism was related to study drug; the blind for the subject was broken due to the treatment-related AE of pulmonary embolism. On Day 34, the subject experienced a post-treatment SAE of moderate dehydration; no action was taken, and the SAE was considered resolved on Day 38. The investigator determined that the SAE was unrelated to study drug and was attributed to another illness (central diabetes insipidus).

- A 54-year-old female experienced urinary incontinence, which the investigator considered to be severe in severity (ie, interfered significantly with the subject's usual function), on Day 64 of the study while receiving [S,S]-RBX 4 mg; the subject was hospitalized, and the SAE was considered resolved on Day 78. The investigator determined that the SAE was related to study drug.

- A 58-year-old male experienced hypoglycemia, which the investigator considered to be severe in severity (ie, interfered significantly with the subject's usual function), on Day 2

while receiving [S,S]-RBX 4 mg; the subject was given treatment, and the SAE was considered resolved on Day 3. The investigator determined that the SAE was unrelated to study drug and was attributed to a concomitant treatment drug as the subject's insulin dosage was too high thus resulting in hypoglycemia.

- A 71-year-old male experienced hypoglycemia, which the investigator considered to be severe in severity (ie, interfered significantly with the subject's usual function), on Day 24 of the study while receiving placebo; the subject was hospitalized for control, and the SAE was considered resolved on the same day, Day 24. The investigator determined that the SAE was unrelated to study drug and was attributed to a concomitant treatment.

- A 50-year-old male experienced coronary heart disease, which the investigator considered to be moderate in severity (ie, interfered to some extent with the subject's usual function), on Day 7 of the study while receiving placebo; the subject was given treatment, and the SAE was considered resolved on Day 10. The investigator determined that the SAE was unrelated to study drug and was attributed to another illness (diabetes mellitus, obesity).

Incidence of Clinical Laboratory Test Abnormalities

For subjects with laboratory test values within the normal limits at baseline (59 [S,S]-RBX and 61 placebo), 11 [S,S]-RBX (19%) and 8 placebo subjects (13%) had at least 1 laboratory test abnormality that met the specified criteria (ie, according to the sponsor's data standards) while on study treatment or during the lag period. No [S,S]-RBX subjects and 5 placebo subjects (10%) had at least 1 abnormal laboratory test value at baseline. No subject discontinued due to an abnormal laboratory test.

Laboratory tests that were deemed clinically significant by the investigator were reported as AEs and included the following: increased blood creatinine (experienced by 1 placebo subject [1.6%]), increased blood glucose (experienced by 2 [S,S]-RBX subjects [3.2%]), decreased blood potassium (experienced by 1 placebo subject [1.6%]), and increased blood potassium (experienced by 1 placebo subject [1.6%]). None of the clinically significant laboratory tests reported as AEs were considered treatment-related by the investigator.

Beck's Scale of Suicidal Ideation

Overall, there was no detection of suicide ideation as measured by the BSS.

Vital Signs

Overall, mean and median changes from baseline to endpoint in systolic and diastolic BP were small and generally unremarkable. There was a mean increase of 8.4 bpm in pulse rate in the [S,S]-RBX-treated subjects compared with a mean decrease of 1.6 bpm in placebo-treated subjects.

Vital sign measurements that were deemed clinically significant by the investigator were reported as AEs and included the following: sinus tachycardia (experienced by 1 [S,S]-RBX subject [1.6%]), tachycardia (experienced by 2 [S,S]-RBX subjects [3.2%] and 1 placebo

subject [1.6%]), diastolic hypotension (experienced by 1 [S,S]-RBX subject [1.6%]), syncope (experienced by 1 [S,S]-RBX subject [1.6%], and increased heart rate (experienced by 1 [S,S]-RBX subject [1.6%]). The tachycardia AEs reported for both [S,S]-RBX subjects and the AE increased heart rate reported for 1 [S,S]-RBX subject were all considered treatment-related as determined by the investigator. There were no cases of increased BP/hypertension reported as AEs.

Physical Examination

There were no clinically relevant physical examination changes from screening.

Weight

Mean weight decreased slightly from baseline to Week 8/termination for [S,S]-RBX subjects (decrease of 1.1 kg) and increased slightly for placebo subjects (increase of 0.6 kg). Weight gain was reported as a treatment-related AE for 1 placebo subject. There were no cases of weight loss reported as an AE.

12-Lead Electrocardiogram

Overall, there were few clinically significant changes in ECG findings from baseline. At Week 2, 2 [S,S]-RBX subjects (3.2%) had clinically significant changes from baseline as judged by the investigator, but these findings did not preclude continuation in the study. At Week 8, 1 [S,S]-RBX subject (1.6%) had a clinically significant change from baseline (atrial fibrillation). No placebo subjects had clinically significant changes in ECG findings from baseline.

CONCLUSIONS:

- It was planned to enroll 330 subjects in this study; however, given the efficacy results at the planned interim analysis, the study was terminated prematurely on 08 August 2008 on the basis of futility. A total of 124 subjects were treated and randomized; all were included in the efficacy, AE, and safety analysis sets, and 120 subjects were included in the laboratory data analysis set.

- Overall, there was no difference in weekly average pain rating score between [S,S]-RBX and placebo treatment.

- Results for the secondary efficacy endpoints, which were analyzed, generally confirmed those obtained for the primary endpoint.

- [S,S]-RBX was well tolerated, and there were no new or unexpected safety findings or treatment-emergent AEs experienced during this study. The majority of AEs experienced by [S,S]-RBX subjects, ie, constipation and dry mouth, were similar to those previously reported in other [S,S]-RBX studies. Additionally, the increase in pulse rate in the [S,S]-RBX-treated subjects was similar to the increase seen in previous [S,S]-RBX studies.