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GENERIC DRUG NAME / COMPOUND NUMBER: (+)-[S,S]-Reboxetine / PNU-165442G

PROTOCOL NO.: A6061025

PROTOCOL TITLE: A Double-Blind (Third Party Open), Placebo-Controlled, Parallel Group, Multiple Dose Study to Investigate the Safety, Toleration and Pharmacokinetics of [S,S]-Reboxetine in Young and Elderly Healthy Volunteers

Study Center: One (1) center in the United Kingdom took part in the study and enrolled subjects.

Study Initiation Date and Final Completion Date: 22 November 2004 to 29 March 2005

Phase of Development: Phase 1

Study Objectives:

- To investigate the safety and toleration of multiple oral doses of (+)-[S,S]-Reboxetine ((+)-[S,S]-RBX) administered once daily (QD) in an extended release formulation in young and elderly volunteers.

- To investigate the steady state pharmacokinetics (PK) of multiple oral doses of (+)-[S,S]-RBX administered QD in an extended release formulation in young and elderly volunteers.

METHODS

Study Design: This was a randomized, double-blind; third party open (ie, Sponsor unblinded), placebo-controlled, multiple dose study in 3 cohorts of healthy subjects; 2 young and 1 elderly cohort. Each cohort was planned to consist of 15 subjects, with a randomized allocation of 1 placebo to 4 active subjects in each cohort. Cohorts 1 and 2 each consisted of young healthy male and female subjects aged 18 to 45 years. Cohort 3 consisted of elderly healthy male and female subjects aged ≥65 years, with a minimum of 4 subjects aged >75 years. The treatment regimens within the young healthy volunteers were:

Cohort 1: 4 mg (+)-[S,S]-RBX or placebo on Days 1-5, followed by 8 mg (+)-[S,S]-RBX or placebo on Days 6-10.

Cohort 2: 8 mg (+)-[S,S]-RBX or placebo on Days 1-10.

The proposed treatment regimen in the elderly was:

Cohort 3: 4 mg (+)-[S,S]-RBX or placebo on Days 1-5, followed by 6 mg (+)-[S,S]-RBX or placebo on Days 6-10 followed by 8 mg (+)-[S,S]-RBX or placebo on Days 11-15.

The actual dosing regimen in the elderly could have been lower than the planned doses. Dose escalation was dependent on adequate safety and toleration of the previous dose level. The maximum dose was not to exceed 8 mg QD in any of the 3 cohorts studied.

For each subject the study consisted of a screening visit, 1 treatment period (from Day 0 until Day 10 for Cohorts 1 and 2, and from Day 0 to Day 15 for Cohort 3) and a follow-up Visit 7 to 10 days after the last dose of study drug. The study visit procedures are presented in Table 1.

Table 1. Schedule of Activities

Study Activity	Scr	Study Day																	Follow-Up
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Informed consent	X																			
Admission to unit		X																		
Medical history	X	X																		
Urine drug test	X	X																		
Pregnancy test	X[a]		X																	X
Concomitant medication	X	X																		X
Physical examination	X	X												X[b]					X[c]	X
Safety laboratory tests/urinalysis	X	X												X[b]					X[c]	X
12-Lead ECG[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	X[c]	X[c]	X[c]	X[c]	X
BP and PR (supine and standing)[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	X[c]	X[c]	X[c]	X[c]	X
Study medication[f]			X	X	X	X	X	X	X	X	X	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]		
PK blood collection[g]			X	X	X	X	X	X	X	X	X	X	X	X[c]	X[c]	X[c]	X[c]	X[c]		
Discharge from unit														X[b]					X[c]	
AE assessment	X----------X																			

AE = adverse event; BP = blood pressure; ECG = electrocardiogram; PK = pharmacokinetic; PR = pulse rate; Scr = screening.

a. Female subjects (apart from those sterilized by hysterectomy) underwent a serum pregnancy test at screening and urine test at other time points.
b. Cohorts 1 and 2 only.
c. Cohort 3 only.
d. Cohorts 1 and 2: Days 1-9: pre-dose and at 8 hours post-dose; Day 10: pre-dose and at 8, 24 and 48 hours post-dose. Cohort 3: Days 1-14: pre-dose and at 8 hours post-dose; Day 15: pre-dose and at 8, 24 and 48 hours post-dose.
e. Cohort 1: Days 1, 2, 6, 7: pre-dose and at 2, 4, 6, 8 and 12 hours post-dose; Days 3-5, 8 and 9: pre-dose and at 6 and 8 hours post-dose; Day 10: pre-dose and at 1, 2, 4, 6, 8, 12, 16, 24 and 48 hours post-dose; Cohort 2: Days 1 and 2: pre-dose and at 2, 4, 6, 8 and 12 hours post-dose; Days 3-9: pre-dose and at 6 and 8 hours post-dose; Day 10: pre-dose and at 1, 2, 4, 6, 8, 12, 16, 24 and 48 hours post-dose; Cohort 3: Days 1, 2, 6, 7, 10, 11: pre-dose and at 2, 4, 6, 8 and 12 hours post-dose; Days 3-5, 8-9, 12-14: pre-dose and at 6 and 8 hours post-dose; Day 15: pre-dose and at 1, 2, 4, 6, 8, 12, 16, 24 and 48 hours post-dose.
f. Cohorts 1 and 2: dosing on Days 1-10 inclusive. Cohort 3: dosing on Days 1-15 inclusive.
g. Cohorts 1 and 2: Days 1-9 pre-dose and Day 10 at pre-dose and at 1, 2, 4, 6, 8, 12, 16 and 24 hours post-dose. Cohort 3: Days 1-14 pre-dose and Day 15 at pre-dose and at 1, 2, 4, 6, 8, 12, 16 and 24 hours post-dose.

Number of Subjects (Planned and Analyzed): The study planned to enroll a total of 45 subjects (15 subjects in each cohort). A total of 44 subjects were screened, randomized and received study treatment (15 subjects each in Cohorts 1 and 3 and 14 subjects in Cohort 2).

Diagnosis and Main Criteria for Inclusion: The study included healthy male and/or female subjects between the ages of 18 to 45 years inclusive (Cohorts 1 and 2) and healthy male and/or female subjects aged ≥65 years (Cohort 3), with a body mass index of approximately 18 to 30 kg/m^2 and a total body weight of >50 kg (110 lbs).

Main Exclusion Criteria: Subjects with evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing); any condition possibly affecting drug absorption (eg, gastrectomy); a positive urine drug screen; history of regular alcohol consumption exceeding 14 drinks/week for females or 21 drinks/week for men; or treatment with an investigational drug within the 4 months preceding the first dose of study drug were excluded from the study.

Study Treatment: S,S-RBX Succinate was supplied as tablets containing 2 mg (+)-[S,S]-RBX as an extended release formulation for oral administration. Matched placebo tablets were also supplied for oral administration.

Each subject received either placebo or (+)-[S,S]-RBX tablets QD according to the randomization schedule following either a dose escalation step (Cohorts 1 and 3) or commencing at the maximum proposed therapeutic dose (Cohort 2). Subjects in Cohort 1 received 4 mg (+)-[S,S]-RBX or placebo on Days 1 to 5 followed by an escalated dose of 8 mg (+)-[S,S]-RBX or placebo on Days 6 to 10. Cohort 2 subjects received 8 mg (+)-[S,S]-RBX or placebo on Days 1 to 10. Cohort 3 subjects received 4 mg (+)-[S,S]-RBX or placebo on Days 1 to 5, followed by an escalated dose of 6 mg (+)-[S,S]-RBX or placebo on Days 6 to 10, followed by a further escalated dose of 8 mg (+)-[S,S]-RBX or placebo on Days 11 to 15. Study drug tablets were administered orally with 240 mL ambient temperature water and were swallowed whole and not chewed. Subjects were fasted from at least 8 hours prior to dosing until 4 hours post-dose. Water was permitted until 1 hour prior to dosing and after 2 hours post-dose.

Prior to dose escalation on either Day 6 (Cohorts 1 and 3) or Day 11 (Cohort 3), safety and toleration data were reviewed. Additionally, safety and toleration data obtained from the young subjects (Cohorts 1 and 2) were reviewed before dosing began in the elderly subjects (Cohort 3). The actual doses administered to Cohort 3 could be lower than indicated, and were selected following review of the relevant data from Cohorts 1 and 2.

Pharmacokinetic and Safety Endpoints:

Primary Endpoints: Safety and toleration of (+)-[S,S]-RBX; adverse event (AE) reporting, laboratory safety tests, 12-lead electrocardiograms (ECGs), vital signs and physical examination.

Pharmacokinetic Endpoints: The PK profiles; plasma concentrations of (+)-[S,S]-RBX measured on Day 10 (young) and Day 15 (elderly) to determine the multiple dose PK of (+)-[S,S]-RBX. PK parameters evaluated were maximum observed plasma concentration (C_{max}), time to the first occurrence (T_{max}), trough observed plasma concentrations (C_{min}), area under the plasma concentration-time curve over the dosing interval (AUC_{tau}), average plasma concentration (C_{av}), peak to trough ratio (PTR) and peak to trough fluctuation (PTF). The timings for PK evaluations are presented in Table 1.

No efficacy evaluations were performed for this study.

Safety Evaluations: AEs were recorded throughout the study. Physical examinations, vital sign measurements (blood pressure [BP] and pulse rate [PR]), ECGs and clinical laboratory tests were performed at specified time points throughout the study, as indicated in Table 1.

Statistical Methods:

The analysis of PK endpoints was based on the per protocol (PP) analysis set, which included all randomized subjects who had received study drug and who had completed sufficient PK assessments through to Day 10 or Day 15 to enable steady state PK parameters to be estimated. The safety analyses were based on the safety analysis set, which consisted of all subjects who received at least 1 dose of any of the investigational treatments.

Safety data were summarized descriptively, by cohort and dose. The PK parameters AUC_{tau}, C_{max}, T_{max}, C_{min}, C_{av}, PTR and PTF were summarized by cohort. The effect of age and dose regimen on the PK parameters of (+)-[S,S]-RBX were investigated by descriptive statistics and graphs. The PK parameters AUC_{tau}, C_{max}, and C_{min} were summarized and compared for the 3 cohorts at steady state.

RESULTS

Subject Disposition and Demography: Subject disposition is presented in Table 2. A total of 44 subjects were screened and randomized to study treatment (15 subjects each in Cohorts 1 and 3 and 14 subjects in Cohort 2). All 44 subjects were included in summaries of safety data. Thirty three (33) of the 35 active subjects were included in the PK analysis. The 2 subjects that were excluded from the PK analysis had no post-baseline PK measurements.

Table 2. Evaluation Groups

Number of Subjects	Cohort 1		Cohort 2		Cohort 3	
	SS-RBX 4-8 mg	Placebo	SS-RBX 8 mg	Placebo	SS-RBX 4-6-8 mg	Placebo
Assigned to study treatment 44						
Treated	12	3	11	3	12	3
Completed	11	3	11	3	11	3
Discontinued	1	0	0	0	1	0
AEs (treatment-related)	1	0	0	0	1	0
Analyzed for pharmacokinetics	11	0	11	0	11	0
Analyzed for safety						
AEs	12	3	11	3	12	3
Laboratory data	12	3	11	3	12	3
Vital signs	12	3	11	3	12	3
Electrocardiogram	12	3	11	3	12	3

AE = adverse event; SS-RBX = (+)-[S,S]-reboxetine.

A summary of the demographic characteristics is presented in Table 3. There were 27 male and 17 female subjects who participated in the study. The number of males and females were similar in Cohorts 1 and 3 but there were 12 males and only 2 females in Cohort 2. All subjects in the study were White.

Table 3. Demographic Characteristics

Characteristic	Cohort 1		Cohort 2		Cohort 3	
	SS-RBX 4-8 mg (N=12)	Placebo (N=3)	SS-RBX 8 mg (N=11)	Placebo (N=3)	SS-RBX 4-6-8 mg (N=12)	Placebo (N=3)
Gender (n)						
Male	6	2	9	3	5	2
Female	6	1	2	0	7	1
Age (years)						
Mean	27.7	21.0	25.5	28.3	70.3	72.0
(range)	(20-45)	(19-24)	(19-45)	(19-41)	(65-78)	(67-76)
Weight (kg)						
Male	74.6	70.3	78.1	86.2	76.5	89.2
(range)	(59.2-88.0)	(61.3-79.2)	(63.3-90.6)	(79.0-98.5)	(63.2-85.0)	(86.0-92.3)
Female	66.2	59.1	66.5		64.2	58.7
(range)	(53.9-76.1)	(59.1-59.1)	(65.6-67.4)		(55.5-74.2)	(58.7-58.7)

N = total number of subjects; n = number of subjects meeting prespecified criteria;
SS-RBX = (+)-[S,S]-reboxetine.

Pharmacokinetic Results:

Visual inspection of the mean predose (+)-[S,S]-RBX plasma concentrations indicated that steady state was achieved after QD dosing for 3 days from the start of treatment or dose escalation. Increasing the dose of (+)-[S,S]-RBX on Day 6 in Cohort 1 and Days 6 and 11 in Cohort 3 caused an increase in the mean predose plasma concentrations.

The mean and percent coefficient of variation (CV, %) for (+)-[S,S]-RBX plasma PK parameters on Day 10 (Cohorts 1 and 2) and Day 15 (Cohort 3) are presented in Table 4.

Mean C_{max} and AUC_{tau} values were highest in the elderly subjects (Cohort 3), but there was a wide overlap in the range of values observed across the 3 cohorts. Mean T_{max} was also slightly longer in the elderly subjects (Cohort 3) as compared to younger subjects (Cohorts 1 and 2).

Table 4. Mean and CV (%) for (+)-[S,S]-RBX Plasma Pharmacokinetic Parameters (On 8 mg QD Final Dose)

Parameter (Units)	(+)-[S,S]-RBX					
	Cohort 1 (4-8 mg) N=11		Cohort 2 (8 mg) N=11		Cohort 3 (4-6-8 mg) N=11	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
AUC_{tau} (ng hr/mL)	2926	36.1	2512	52.7	3398	34.4
C_{max} (ng/mL)	173.7	36.4	154.7	36.7	190.4	28.8
T_{max}[a] (hr)	5.8	24.1	5.6	31.0	6.9	19.9
C_{min} (ng/mL)	79.8	44.4	66.9	76.1	100.65	40.5
PTR	2.2	24.5	2.3	34.5	1.9	17.5
$C_{av\ ss}$ (ng/mL)	121.8	36.1	104.6	52.7	141.6	34.4
PTF	0.7	26.6	0.7	41.6	0.6	27.7

AUC_{tau} = area under the plasma concentration-time curve over the dosing interval; $C_{av\ ss}$ = average plasma concentration at steady state; C_{max} = maximum observed plasma concentration; C_{min} = trough observed plasma concentrations; CV (%) = percent coefficient of variation; N = total number of subjects; PTF = peak to trough fluctuation; PTR = peak to trough ratio; QD = once daily; (+)-[S,S]-RBX = (+)-[S,S]-reboxetine.
a. Arithmetic mean; all others were geometric means.

No efficacy evaluations were performed for this study.

Safety Results: Treatment-emergent AEs [TEAEs] (all causality and treatment-related) are summarized in Table 5.

All subjects, except 1 subject on placebo in Cohort 3, experienced at least 1 AE. The number of subjects with AEs was similar in all 3 cohorts; however, the number of AEs was higher in subjects receiving (+)-[S,S]-RBX in Cohort 1. The majority of AEs were mild and most of the AEs had resolved by the end of the study.

Table 5. Summary of TEAEs

Treatment-Emergent AEs	Cohort 1				Cohort 2				Cohort 3			
	(+)-[S,S]-RBX 4-8 mg		Placebo		(+)-[S,S]-RBX 8 mg		Placebo		(+)-[S,S]-RBX 4-6-8 mg		Placebo	
	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related	All Causality	Treatment Related
Number of subjects evaluable for AEs	12	12	3	3	11	11	3	3	12	12	3	3
Number of AEs	125	121	11	9	94	83	24	17	90	78	11	9
Subjects with AEs	12	12	3	2	11	11	3	3	12	12	2	2
Subjects with severe AEs	0	0	0	0	0	0	0	0	0	0	0	0
Subjects with SAEs	0	0	0	0	0	0	0	0	0	0	0	0
Subjects discontinued due to AEs	1	1	0	0	0	0	0	0	1	1	0	0

Includes data up to 30 days after last dose of study drug.
AEs = adverse events; SAEs = serious adverse events; (+)-[S,S]-RBX = (+)-[S,S] –Reboxetine; TEAEs = treatment-emergent adverse events.

A summary of the treatment-emergent AEs reported by ≥5 subjects in the 3 cohorts is given in Table 6.

Table 6. Treatment-Emergent All Causality (Treatment -Related) Adverse Events Reported in ≥5 Subjects

AE – Preferred Term	Cohort 1				Cohort 2				Cohort 3			
	(+)-[S,S]-RBX 4-8 mg		Placebo		(+)-[S,S]-RBX 8 mg		Placebo		(+)-[S,S]-RBX 4-6-8 mg		Placebo	
	All Causality, n	Treatment Related, n	All Causality, n	Treatment Related, n	All Causality, n	Treatment Related, n	All Causality, n	Treatment Related, n	All Causality, n	Treatment Related, n	All Causality, n	Treatment Related, n
Headache	7	7	1	1	8	8	1	1	2	2	0	0
Dizziness	7	7	1	1	3	3	2	1	4	4	0	0
Nausea	6	6	0	0	1	1	2	1	6	6	0	0
Constipation	4	4	0	0	4	4	1	1	4	4	1	1
Insomnia	6	6	0	0	1	1	1	1	5	5	0	0
Hot flush	5	5	1	1	2	2	0	0	3	3	0	0
Fatigue	2	2	0	0	2	2	1	1	5	5	1	1
Dizziness postural	4	4	0	0	3	3	0	0	3	3	0	0
Dermatitis contact	0	0	0	0	2	0	1	0	5	2	1	0
Feeling hot	6	6	0	0	1	1	1	1	1	1	0	0
Paraesthesia	3	3	0	0	6	5	0	0	0	0	0	0
Pharyngolaryngeal pain	4	4	1	1	2	2	2	2	0	0	0	0
Sleep disorder	0	0	0	0	6	6	0	0	2	2	1	1
Dry mouth	2	2	0	0	0	0	0	0	5	5	1	1
Dysuria	3	3	0	0	2	2	1	1	2	1	0	0
Nasopharyngitis	1	1	0	0	5	1	0	0	1	0	1	0
Back pain	2	2	0	0	2	2	1	0	2	2	0	0
Heart rate increased	4	4	0	0	2	2	0	0	0	0	0	0
Abnormal dreams	1	1	0	0	1	1	0	0	3	3	0	0
Feeling abnormal	0	0	0	0	3	3	1	0	1	1	0	0
Feeling cold	0	0	0	0	2	2	0	0	3	3	0	0

AE = adverse event; n = number of subjects; (+)-[S,S]-RBX = (+)-[S,S]-reboxetine.

Headache, dizziness, and nausea were the most frequently reported AEs (reported by 15 or more subjects). With the exception of 1 incidence of dizziness, all reports of these AEs were considered to be treatment related. Headache was more common in the young subjects (Cohorts 1 and 2) than in the elderly subjects (Cohort 3). Other frequently reported AEs occurring in ≥10 subjects across the 3 cohorts were constipation, insomnia, hot flush, fatigue, and dizziness postural. The overall incidence and severity of AEs (all causality and treatment related) appeared to be similar between cohorts and was not related to dose.

There were no deaths or serious adverse events (SAEs) in this study.

There were 2 discontinuations from the study due to AEs. Two (2) subjects, 1 young male subject in Cohort 1 and 1 elderly male subject in Cohort 3, discontinued the study due to treatment-related AEs of diarrhea and dysuria, respectively, in the (+)-(S,S)-RBX treatment groups. No temporary discontinuations or dose reductions due to AEs were reported.

Clinical Laboratory Test Results: The incidence of laboratory abnormalities (in ≥1 subject) is presented in Table 7 (without regard to baseline abnormality), Table 8 (for subjects with normal baseline values) and Table 9 (for subjects with abnormal baseline values).

Table 7. Incidence of Laboratory Abnormalities Reported in ≥1 Subjects in Any Treatment Group (Without Regard to Baseline Abnormality)

Parameter	Criteria	Units	Cohort 1 SS-RBX				Cohort 2 SS-RBX				Cohort 3 SS-RBX			
			4-8 mg		Placebo		8 mg		Placebo		4-6-8 mg		Placebo	
			N	n	N	n	N	n	N	n	N	n	N	n
Number of subjects evaluable for laboratory abnormalities			12		3		11		3		12		3	
Number (%) with laboratory abnormalities			7		2		5		1		6		2	
Lymphocytes (Abs)	<0.8 x LLN	$10^3/mm^3$	12	0	3	0	11	0	3	0	12	3	3	1
	>1.2 x ULN		12	0	3	0	11	0	3	0	12	1	3	0
Total Neutrophils (Abs)	>1.2 x ULN	$10^3/mm^3$	12	0	3	0	11	0	3	0	12	1	3	0
Eosinophils (Abs)	>1.2 x ULN	$10^3/mm^3$	12	2	3	0	11	4	3	0	12	0	3	0
Monocytes (Abs)	>1.2 x ULN	$10^3/mm^3$	12	1	3	0	11	0	3	0	12	2	3	0
Potassium	<0.9 x LLN	mEq/L	12	1	3	0	11	0	3	0	12	0	3	0
Glucose (fasting)	>1.5 x ULN	mg/dL	-	-	-	-	-	-	-	-	1	0	-	-
	<0.6 x LLN		-	-	-	-	-	-	-	-	1	0	-	-
Urine Glucose (Qual)	>=1		12	0	3	1	11	0	3	0	12	1	3	0
Urine Protein (Qual)	>=1		12	0	3	0	11	1	3	0	12	1	3	0
Urine Blood/Hgb (Qual)	>=1		12	2	3	0	11	0	3	1	12	3	3	1
Urine RBC	>=6	/hpf	4	0	1	0	3	0	1	1	5	1	1	0
Urine WBC	>=6	/hpf	4	2	1	1	3	0	1	0	5	1	1	0

Abs = absolute; Hgb = hemoglobin; LLN = lower limit of normal; N = total number of subjects with at least 1 observation of the given laboratory test while on study treatment or during lag time; n = number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or during lag time; Qual = qualitative; RBC = red blood cells; SS-RBX = (+)-(S,S)-reboxetine; ULN = upper limit of normal; WBC = white blood cells.

Table 8. Incidence of Laboratory Abnormalities Reported in ≥1 Subjects in Any Treatment Group (Normal Baseline)

Parameter	Criteria	Units	Cohort 1 SS-RBX				Cohort 2 SS-RBX				Cohort 3 SS-RBX			
			4-8 mg		Placebo		8 mg		Placebo		4-6-8 mg		Placebo	
			N	n	N	n	N	n	N	n	N	n	N	n
Number of subjects evaluable for laboratory abnormalities			12		3		11		3		12		3	
Number (%) with laboratory abnormalities			6		2		1		1		4		1	
Lymphocytes (Abs)	<0.8 x LLN	$10^3/mm^3$	12	0	2	0	10	0	2	0	9	1	3	1
Eosinophils (Abs)	>1.2 x ULN	$10^3/mm^3$	11	2	3	0	8	1	3	0	12	0	3	0
Monocytes (Abs)	>1.2 x ULN	$10^3/mm^3$	12	1	3	0	11	0	3	0	11	2	3	0
Potassium	<0.9 x LLN	mEq/L	11	1	3	0	9	0	3	0	9	0	2	0
Urine Glucose (Qual)	>=1		12	0	3	1	11	0	3	0	12	1	3	0
Urine Protein (Qual)	>=1		12	0	3	0	10	0	3	0	12	1	3	0
Urine Blood/Hgb (Qual)	>=1		7	0	3	0	11	0	3	1	9	1	2	0
Urine RBC	>=6	/hpf	4	0	1	0	3	0	1	1	5	1	1	0
Urine WBC	>=6	/hpf	4	2	1	1	3	0	1	0	5	1	1	0

Abs = absolute; Hgb = hemoglobin; LLN = lower limit of normal; N = total number of subjects with normal or missing baseline with at least 1 observation of the given laboratory test while on study treatment or during lag time; n = number of subjects with normal or missing baseline with a laboratory abnormality meeting specified criteria while on study treatment or during lag time; Qual = qualitative; RBC = red blood cells; SS-RBX = (+)-(S,S)-reboxetine; ULN = upper limit of normal; WBC = white blood cells.

Table 9. Incidence of Laboratory Abnormalities Reported in ≥1 Subjects in Any Treatment Group (Abnormal Baseline)

Parameter	Primary Criteria	Secondary Criteria	Units	Cohort 1 SS-RBX				Cohort 2 SS-RBX				Cohort 3 SS-RBX			
				4-8 mg		Placebo		8 mg		Placebo		4-6-8 mg		Placebo	
				N	n	N	n	N	n	N	n	N	n	N	n
Number of subjects evaluable for laboratory abnormalities				10		1		10		2		12		3	
Number (%) with laboratory abnormalities				2		0		3		0		2		1	
Eosinophils (Abs)	>1.2 x ULN	>1.2 x baseline	$10^3/mm^3$	1	0	-	-	3	2	-	-	-	-	-	-
Urine Protein (Qual)	>=1	>=1		-	-	-	-	1	1	-	-	-	-	-	-
Urine Blood/Hgb (Qual)	>=1	>=1		5	2	-	-	-	-	-	-	3	2	1	1

Abs = absolute; Hgb = hemoglobin; N = total number of subjects with abnormal baseline with at least 1 observation of the given laboratory test while on study treatment or during lag time; n = number of subjects with abnormal baseline with a laboratory abnormality meeting specified criteria while on study treatment or during lag time; Qual = qualitative; SS-RBX = (+)-(S,S)-reboxetine; ULN = upper limit of normal.

Physical Examination: One (1) subject had mild lower abdominal tenderness on physical examination during the study. This change in physical examination findings from screening was considered to be clinically significant. The subject discontinued on Day 3 due to diarrhea.

Vital Signs: Mean changes from Baseline for the vital signs on Day 10 (Cohorts 1 and 2) and Day 15 (Cohort 3) are presented in Table 10. The mean change from Baseline data for supine and standing BP suggests an overall decrease in standing systolic BP in all 3 cohorts following administration of both (+)-[S,S]-RBX or placebo with the maximum decrease being observed in the Cohort 3 (+)-[S,S]-RBX group. Supine systolic BP increased in all subjects in Cohort 1 and decreased in most subjects in Cohort 3. There were no apparent treatment related effects on supine or standing diastolic BP.

The vital signs data suggests an increase in mean supine and standing PR in all the 3 cohorts following administration of (+)-[S,S]-RBX but the effect appears to be more pronounced in young subjects (Cohorts 1 and 2) as compared to the elderly subjects (Cohort 3). The effect on mean standing PR appears to be greater than the effect on mean supine PR, with the largest mean increase being observed in Cohort 1.

Table 10. Mean Changes From Baseline in Vital Signs

Parameters	Cohort 1 (Day 10)		Cohort 2 (Day 10)		Cohort 3 (Day 15)	
	SS-RBX N=11	Placebo N=3	SS-RBX N=11	Placebo N=3	SS-RBX N=11	Placebo N=3
Supine diastolic BP (mmHg)	7.6	-0.9	5.8	-0.3	-3.2	-6.6
Standing diastolic BP (mmHg)	2.2	-1	-3.9	1.2	-4.3	-1.6
Supine systolic BP (mmHg)	8.3	0.6	4.5	-2.8	-9.8	-3.7
Standing systolic BP (mmHg)	-2.6	-3.7	-9.2	-7	-18.3	-1.9
Supine PR (bpm)	17.3	-1.1	14.7	-2.5	11.6	3.1
Standing PR (bpm)	32.1	3	25.2	-0.6	13.7	6.9

BP = blood pressure; N = number of subjects; PR = pulse rate; SS-RBX = (+)-(S,S)-reboxetine.

ECG: Mean changes from Baseline for the ECG data suggested a small increase in heart rate for subjects treated with (+)-(S,S)-RBX. The other ECG parameters appeared to be unaffected by treatment. There were no subjects with absolute QT interval correct for heart rate (QTc) value ≥500 msec. There were no subjects with a QTc change >30 msec. No clinically significant changes in the ECG recordings were observed.

CONCLUSIONS: Mean C_{max} and AUC values were highest in the elderly subject but there was a wide overlap in the range of values observed across the 3 cohorts. Mean T_{max} was also slightly longer in the elderly subjects as compared to younger subjects.

In all 3 cohorts, an increase in mean supine and standing PR was observed following administration of (+)-[S,S]-RBX. No treatment-related effects were observed for systolic or diastolic BP.

There were no deaths, SAEs or severe AEs following administration of QD doses of (+)-[S,S]-RBX up to 8 mg in young and elderly healthy subjects. There were

2 discontinuations from the study due to treatment-related AEs in the (+)-[S,S]-RBX treatment groups. Headache, dizziness, and nausea were the most frequently reported AEs. The majority of AEs reported were mild in severity. Dose escalation appeared to have no effect on toleration as the overall incidence and severity of AEs appeared to be similar between cohorts. There appeared to be no differences in toleration of (+)-(S,S)-RBX between the young and elderly subjects at QD doses up to 8 mg.