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PROPRIETARY DRUG NAME[®]/GENERIC DRUG NAME: Zoloft[®] / Sertraline

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00636246

PROTOCOL NO.: A0501075

PROTOCOL TITLE: Sertraline/[S,S]-Reboxetine Combination versus Sertraline and [S,S]-Reboxetine Monotherapy in Major Depressive Disorder (MDD) in a Double-Blind, Placebo-Controlled, Eight Week Study

Study Centers: Four centers in Estonia and 16 centers in Russia enrolled subjects.

Study Initiation and Completion Dates: 18 June 2004 – 09 August 2005

Phase of Development: Phase 2a

Study Objectives:

Primary Objective: To assess the efficacy of sertraline/[S,S]-reboxetine (SRC) versus placebo, sertraline monotherapy, and [S,S]-reboxetine monotherapy as measured by the mean change from baseline at the end of Week 8 in the Montgomery-Asberg Depression Rating Scale (MADRS) total score in subjects with Major Depressive Disorder (MDD)

Secondary Objectives:

1. To characterize the safety of SRC administration compared to placebo, sertraline monotherapy, and [S,S]-reboxetine monotherapy
2. To assess the efficacy of SRC compared to placebo, sertraline monotherapy, and [S,S]-reboxetine monotherapy as measured by the Hamilton Depression Rating Scale [HAMD-17], Clinical Global Impression-Severity (CGI-S), and the Clinical Global Impression-Improvement (CGI-I) total scores
3. To assess the efficacy of SRC compared to placebo, sertraline monotherapy, and [S,S]-reboxetine monotherapy in treating co-morbid anxiety or apathy-related symptoms of depression as measured by the Hamilton Anxiety Rating Scale (HAM-A) or the Apathy Evaluation Scale (AES) total scores
4. To evaluate the dose/concentration versus efficacy (MADRS) for the SRC ratios in all study arms, sertraline monotherapy, and [S,S]-reboxetine monotherapy study arms

- To characterize the influence of the short (“SS”), long (“LL”), or homozygous (“SL”) alleles of the serotonin transporter (SERT) gene promoter region in Caucasian subjects with MDD on the efficacy and safety variables

METHODS

Study Design: This was a Phase 2a, proof-of-concept, double-blind, placebo-controlled, trial in subjects who fulfilled criteria for non-psychotic MDD. The study was consisted of a single-blind, placebo lead-in, screening period of 2–7 days in duration, followed by an 8-week, double-blind, randomized, placebo- and active-controlled treatment period and a follow-up visit 7–10 days after stopping double-blind medication. The placebo lead-in screening period was designed to screen out placebo responders. The trial design had a 2 x 2 factorial structure, consisting of 4 main study arms (14 sites), supplemented with 4 satellite arms (6 sites) to help explore the question of whether there is a linear trend in increased efficacy with progressively higher doses of [S,S] Reboxetine added to sertraline monotherapy. Study sites were either assigned to the main arm or the satellite arm (sites were blinded to the assignment).

Study medication was administered once daily, in the morning (qAM) and was titrated to the full dose over the course of 5 weeks, as described in Figure 1.

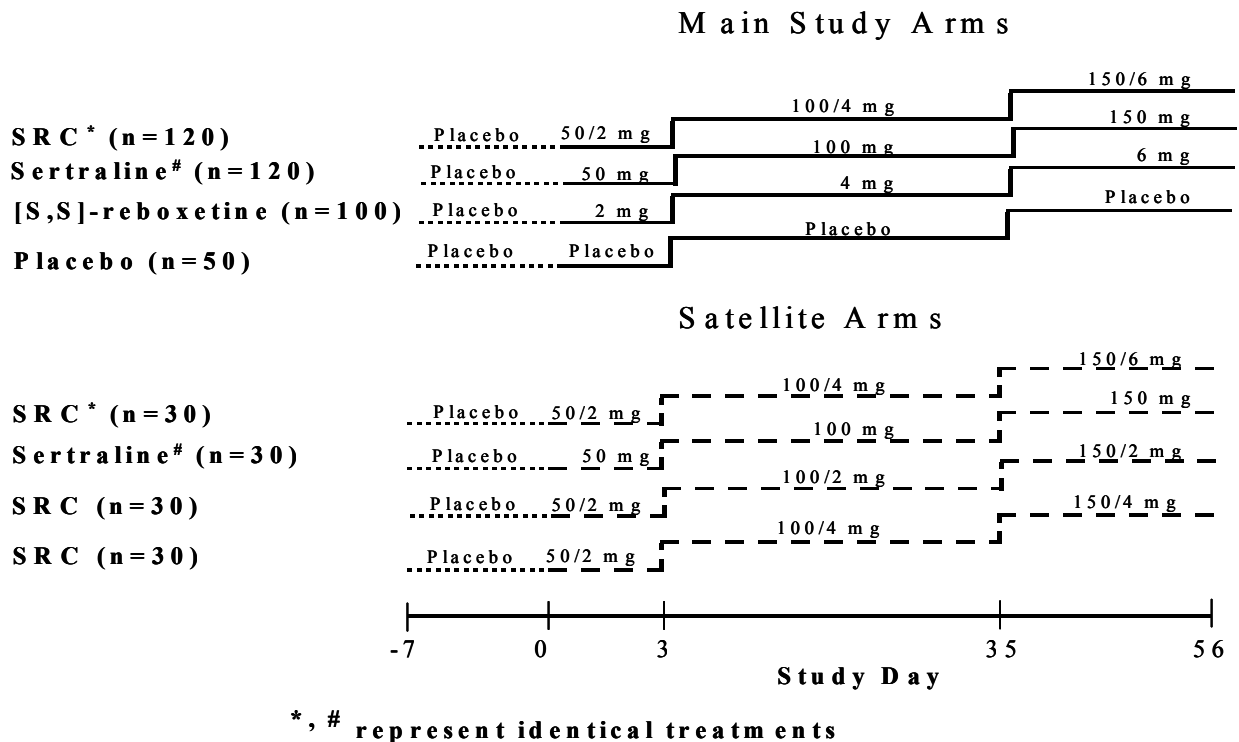


Figure 1. Study Schematic

Number of Subjects (Planned and Analyzed):

Planned: A maximum of 510 subjects were planned to be included as follows: 50 subjects in the placebo arm, 100 subjects in the 6-mg [S,S]-reboxetine monotherapy arm, 120 subjects in the 150-mg sertraline monotherapy main study arm and 30 subjects in 150-mg satellite sertraline monotherapy arm, 120 subjects in 150-mg sertraline/6 mg [S,S]-reboxetine combination main study arm and 30 subjects in satellite arm, 30 subjects in 150-mg sertraline/2-mg [S,S]-reboxetine satellite combination arm, and 30 subjects in 150-mg sertraline/4-mg [S,S]-reboxetine satellite combination arm.

Analyzed: Five hundred nineteen subjects were assessed for safety and efficacy as follows: 51 subjects in the placebo arm, 101 subjects in the 6-mg [S,S]-reboxetine monotherapy arm, 152 subjects in the 150-mg sertraline monotherapy main study arm and the satellite arm, 152 subjects in 150-mg sertraline/6 mg [S,S]-reboxetine combination main study arm and satellite arm, 31 subjects in 150-mg sertraline/2-mg [S,S]-reboxetine satellite combination arm, and 32 subjects in 150-mg sertraline/4-mg [S,S]-reboxetine satellite combination arm.

Diagnosis and Main Criteria for Inclusion: Male or female Caucasian subjects aged 18–65 years inclusive, who fulfilled criteria for nonpsychotic MDD as defined by Diagnostic And Statistical Manual Of Mental Disorders, Fourth Edition (DSM-IV), with a HAM-D score ≥ 22 at screening and ≥ 20 at baseline and a minimum CGI-S ≥ 4 at screening and at baseline, were included in the study.

Study Treatment: Sertraline was provided as 50 mg and 100 mg tablets, [S,S]-reboxetine as extended release 2 mg and 4 mg tablets, and placebo tablets. All medications were supplied as identical tablets as the study was conducted in a double-dummy fashion.

Subjects were provided with study drug at the baseline visit after all evaluations were completed. Subjects were provided with 7 \pm 2 days supply of study medication at each visit and were instructed to begin treatment on Study Day 1 (the day following the baseline visit). Dose titrations were performed at intervals described in the dosing schedule in Table S1.

Table S1. Dosing Schedule

Treatment Group	Day –7–0	Day 1–3	Day 4–35	Day 36–56
Main study arms				
Placebo	Placebo	Placebo	Placebo	Placebo
Sertraline	Placebo	50 mg	100 mg	150 mg
[S,S]-Reboxetine	Placebo	2 mg	4 mg	6 mg
Sertraline + [S,S]-Reboxetine	Placebo	50 mg + 2 mg	100 mg + 4 mg	150 mg + 6 mg
Satellite arms				
Sertraline	Placebo	50 mg	100 mg	150 mg
Sertraline + [S,S]-Reboxetine	Placebo	50 mg + 2 mg	100 mg + 4 mg	150 mg + 6 mg
Sertraline + [S,S]-Reboxetine	Placebo	50 mg + 2 mg	100 mg + 2 mg	150 mg + 2 mg
Sertraline + [S,S]-Reboxetine	Placebo	50 mg + 2 mg	100 mg + 4 mg	150 mg + 4 mg

Efficacy Evaluations: The efficacy endpoints used in this study are listed in Table S2. The rating instruments were used to measure the depressive and psychological symptoms of the subjects and any changes that occurred. The MADRS and HAM-D rating instruments were

administered by certified raters. For each rating scale used, no missing numerical scores for any item were allowed.

Table S2. Efficacy Endpoints

Rating Instrument	Efficacy Endpoint
Primary endpoint	
MADRS	Mean change from baseline to Week 8 in MADRS total score
Secondary Endpoints	
MADRS	Mean change from baseline in the total score by week (Weeks 1, 2, 3, 5, 6 and 8)
HAM-D (17 item)	Mean change from baseline in the total score by week (Weeks 1, 2, 3, 5, 6, and 8)
HAM-A (14 item)	Mean change from baseline in the total score at Week 5 and Week 8
CGI-S	Mean change from baseline in the total score by week (Weeks 1, 2, 3, 5, 6, and 8)
CGI-I	Mean score (averaged over 8 weeks)
AES	Mean change in score from baseline to Week 5 and Week 8
Other secondary endpoints	
MADRS responder	Subject who reached a 50% reduction in the total score change from baseline and maintained the reduction for the remainder of the study
MADRS remitter	Subject with a sustained total score for MADRS ≤ 11
HAMD responder	Subject who reached a 50% reduction in the total score change from baseline and maintained the reduction for the remainder of the study
HAMD remitter	Subject with a sustained total score for HAMD ≤ 7

AES=Apathy Evaluation Scale; CGI-I=Clinical Global Impression-Improvement;
 CGI-S=Clinical Global Impression-Severity; HAM-A=Hamilton Anxiety Rating Scale;
 HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale

Pharmacokinetic and Other Evaluations: Separate blood samples were collected at baseline, and at Weeks 2, 5, 6, and 8 (or at early termination from study) for pharmacokinetic (PK) analyses. Pharmacokinetic samples were collected within 15 minutes following vital signs and electrocardiogram (ECG) measurements. Samples were assayed for the determination of sertraline or [S,S]-reboxetine by a validated analytical method in compliance with the Sponsor’s standard operating procedures.

Pharmacogenetic: A non-anonymized genotyping blood sample was collected at screening and was used to determine subject’s serotonin transporter genotype.

Subjects who signed a separate informed consent to participate in the anonymized genotyping portion of the study gave a whole blood sample at screening to investigate genetic association of various markers with specific clinical endpoints of the study. All genotyping data derived from these samples was anonymous.

Safety Evaluations: Safety evaluations comprised of adverse event (AE) information, clinical laboratory values, vital signs, and ECGs. These evaluations were recorded as follows:

- AEs: At each study visit
- Clinical laboratory as follows:
 - At screening - Hepatitis screen, T3, T4, TSH, serum β -hCG pregnancy test (repeated at Week 8), FSH, and urine drug screen

- At screening, baseline, end of Weeks 2, 5, 6 and 8, at the time of follow-up, or in the event of study discontinuation - Hematology, chemistry, and urinalysis
- Tests for the abnormal analyses were repeated within 24 to 48 hours and then at intervals determined in consultation with the clinical monitor until the abnormalities resolved
- Vital signs (blood pressure, heart rate, and temperature) were measured at each visit
- ECG was performed at screening, baseline (in triplicate), end of Weeks 2, 5, 6, and 8, and at the time of follow-up

Complete physical examinations were conducted at screening and at the final study visit (end of Week 8 or at early termination). Clinically significant changes in physical examination findings (abnormalities) according to the investigator were recorded as AEs.

Statistical Methods: The primary efficacy endpoint was a mean change in MADRS total score from baseline to Week 8. Changes from baseline in the MADRS total score were assessed using a repeated measures mixed linear model.

The primary population for determination of efficacy was the All Subjects population, defined as those subjects who were randomized and received at least 1 dose of study medication, and had at least 1 efficacy evaluation post-baseline. For efficacy parameters that measured a change from baseline, a baseline value was also required for each parameter for this population.

The primary analysis assessed the efficacy of SRC 150/6 mg versus placebo, sertraline monotherapy and [S,S]-reboxetine monotherapy as measured by the mean change from baseline to end of Week 8 in the MADRS total score using the overall, week averaged analysis. The least squares means and appropriate standard errors were also used as the definitive measures to summarize treatment group means and differences between treatment group means.

The primary method for addressing multiple comparisons was the step-down approach as mentioned below:

- The *first hypothesis test* compared the 150 mg sertraline/6 mg [S,S]-reboxetine combination to placebo at $\alpha=0.05$, two-sided.
- If the first hypothesis test was rejected, then a *second hypothesis test* compared the 150 mg sertraline/6 mg [S,S]-reboxetine combination to 6 mg [S,S]-reboxetine monotherapy ($\alpha=0.05$, two-sided).
- If the second hypothesis was rejected, then the *third hypothesis test* compared 150 mg sertraline/6 mg [S,S]-reboxetine combination to 150 mg sertraline monotherapy ($\alpha=0.05$, two-sided).
- If one of the hypothesis tests in the sequence failed to reject, then further testing ended with treatment differences being concluded for tests that preceded the first failed test.

In addition to performing hypothesis testing, two-sided 95% CIs were constructed for the true difference between treatment group means using the least squares means and appropriate standard errors. However, the 95% Confidence Intervals (CIs) were not subject to the step-down multiple comparison procedure.

In order to confirm the results of the primary analysis, data were also analyzed using a linear model using the mean change in MADRS scores from baseline to end of Week 8 Last Observation Carried Forward (LOCF) with the following terms: Treatment, Design block (sites using main factorial treatment arms, sites using satellite treatment arms), Site nested within design block, Genotype (SS, LL, SL), Baseline MADRS (continuous covariate). The same multiple comparison approach was also employed as in the primary analysis, as well as the construction of confidence intervals.

The secondary efficacy analysis was performed using the same mixed linear model as the primary analysis. Details are as follows:

- MADRS: Changes from baseline in MADRS (continuous covariate) at each planned visit (at the end of Weeks 1, 2, 3, 5, 6, and 8) were performed. The LOCF analysis was conducted as a back-up.
- HAM-D: Changes from baseline in HAM-D (continuous covariate) at each planned visit (at the end of Weeks 1, 2, 3, 5, 6, and 8) and averaged over the 8 weeks.
- CGI-I: CGI-I (continuous covariate) averaged over the 8 weeks, and at each planned visit (at the end of Weeks 1, 2, 3, 5, 6, and 8).
- CGI-S: Changes from baseline in CGI-S (continuous covariate) averaged over the 8 weeks, and at each planned visit (at the end of Weeks 1, 2, 3, 5, 6, and 8).
- HAM-A: Changes from baseline in HAM-A (continuous covariate) averaged over the 8 weeks, and at each planned visit (at the end of Weeks 5 and 8) were performed separately using the same mixed linear model.
- AES: Changes from baseline in AES (continuous covariate) averaged over the 8 weeks, and at each planned visit (at the end of Weeks 5 and 8) was performed separately using the same mixed linear model.

The least squares means and appropriate standard errors were used as the definitive measures to summarize treatment group means and differences between treatment group means. Other descriptive statistics involving sample size, sample mean, and sample standard deviation were used to help further summarize the data. Two-sided 95% CIs were constructed for the true difference between treatment group means using the least squares means and appropriate standard errors.

The proportion of responders was analyzed using asymptotic normal theory. Pair-wise differences in the proportions were made between each of the active treatment groups and the placebo separately, using a two-sided test at $\alpha=0.05$. Two-sided 95% CIs for the true

difference in the proportions were constructed based on asymptotic normal theory with no adjustment made for making multiple comparisons. Remitter analysis was to be conducted using the same procedures.

Non-anonymized Genotyping: An exploratory modeling approach was employed to understand any possible interaction (ie, non-parallelism) between treatment and genotype at baseline. A mixed model with terms (treatment, design block [two levels], site nested within design block, genotype [three levels: LL, SS, and SL], baseline MADRS [continuous covariate], treatment X genotype, between subject error, week, treatment-by-week, and within subject error) was used to investigate this interaction.

Point estimates and corresponding 95% two-sided CIs were constructed for SRC 150/6 mg minus sertraline 150 mg; SRC 150/6 mg minus [S,S]-reboxetine 6 mg; SRC 150/6 mg minus placebo, at each of the genotype levels (LL, SL, and SS). The 95% CIs were constructed using the least squares means and the appropriate standard errors of the least squares means difference.

Safety data was summarized separately for all randomized subjects who took at least 1 dose of study medication.

RESULTS

Subject Disposition and Demography: Of the 584 subjects screened, 519 subjects were randomized, and treated with study drug ([152 subjects SRC 150/6 mg, 32 subjects SRC 150/4 mg, 31 subjects SRC 150/2 mg, 152 subjects sertraline 150 mg, 101 subjects [S,S]-reboxetine 6 mg] and 51 subjects, placebo). Of the 519 randomized subjects, 376 (72.4%) subjects in all completed the study. Subject disposition is summarized in Table S3.

Table S3. Subject Disposition (Number [%] of Subjects)

	SRC 150/6 mg N=152	SRC 150/4 mg N=32	SRC 150/2 mg N=31	Sertraline 150 mg N=152	[S,S]- Reboxetine 6 mg N=101	Placebo N=51
Number Screened=584						
Assigned to Treatment	152	32	31	152	101	51
Treated	152	32	31	152	101	51
Completed	114 (75.0)	22 (68.8)	28 (90.3)	110 (72.4)	74 (73.3)	28 (54.9)
Discontinued	38 (25.0)	10 (31.3)	3 (9.7)	42 (27.6)	27 (26.7)	23 (45.1)
Analyzed for Safety:						
Adverse Events	152 (100.0)	32 (100.0)	31 (100.0)	152 (100.0)	101 (100.0)	51 (100.0)
Laboratory Data	146 (96.1)	30 (93.8)	31(100.0)	148 (97.4)	100 (99.0)	49 (96.1)
Discontinuations by Reason:						
Adverse events						
Study Drug Related	17 (11.2)	2 (6.3)	2 (6.5)	6 (3.9)	7 (6.9)	1 (2.0)
Non Study Drug Related	2 (1.3)	1 (3.1)	0	4 (2.6)	0	0
Other ^a	6 (3.9)	0	0	12 (7.9)	12 (11.9)	12 (23.5)
Subject defaulted ^b	13 (8.6)	7 (21.9)	1 (3.2)	20 (13.2)	8 (7.9)	10 (19.6)

^a Includes noncompliance, lack of efficacy, protocol violations and safety risks

^b Withdrew consent or was lost to follow up

N=Number of subjects; SRC=Sertraline-[S,S]-Reboxetine Combination

Subjects were predominantly female (387 subjects) and the mean age of subjects in the treatment arms ranged from 38–42.5 years. The mean duration of symptoms (recurrent major depression) ranged from 7–9 years. Demographic characteristics and history of primary diagnosis is summarized in Table S4.

Table S4. Demographic Characteristics and History of Primary Diagnosis

Number of subjects	Sertraline-[S,S]-Reboxetine			Sertraline	[S,S]-Reboxetine	Placebo
	150/6 mg N=152	150/4 mg N=32	150/2 mg N=31	150 mg N=152	6 mg N=101	N=51
Sex						
Male	46	10	4	40	20	12
Female	106	22	27	112	81	39
Age (years)						
Mean (SD)	40.9(11.9)	38.0(12.6)	39.4(11.2)	41.6(12.6)	42.5(11.5)	41.5(11.9)
Range	18-64	18-61	21-56	18-65	19-65	18-64
Weight (kg)						
Mean (SD)	69.4(13.3)	71.2(12.8)	65.2(9.5)	68.6(13.5)	68.0(13.2)	69.4(14.6)
Range	43-107	47-103	42-84	42.8-107	45-102.8	43-112
Height (cm)						
Mean (SD)	168.5(8.0)	169.4(8.3)	166.4(5.1)	167.6(8.2)	166.7(7.7)	168.5(8.3)
Range	150-191.8	156-188	153-178	148.5-192	152-188	153-192
Primary Diagnosis <i>ICDCODE Preferred term</i>						
SMD ^a No. of subjects	48	9	10	32	23	12
Number of years since first diagnosis						
Mean	0	0	1	0	0	0
Range	0-1.5	0.2-1.3	0.1-5.1	0.1-0.4	0.1-3.3	0.1-1.6
RMD ^b No. of subjects	104	23	21	120	78	39
Number of years since first diagnosis						
Mean	7	8	9	9	7	8
Range ^c	0.3-30.9	0.4-35	0.3-33.9	0.3-46.5	0.5-42.3	0.5-34.1

^a SMD=Single Major Depression, unspecified

^b RMD=Recurrent Major Depression, unspecified

^c 4 subjects, 2 each in the SRC 150/6 and the sertraline monotherapy group could not specify how long since first diagnosis

N=Number of subjects; SD=Standard Deviation

Efficacy Results: The study has met its primary objective, which was to assess the efficacy of sertraline/[S,S]-reboxetine versus placebo, sertraline monotherapy, and [S,S]-reboxetine monotherapy as measured by the mean change from baseline at the end of Week 8 in the MADRS total score in subjects with MDD. SRC 150/6 mg was statistically superior to placebo (two-sided test: $p < 0.01$) and to [S,S]-reboxetine monotherapy (two-sided test: $p = 0.0497$). It was not statistically superior to sertraline 150 mg monotherapy (two-sided test: $p = 0.5854$). There was no statistically significant linear trend of increased efficacy on average as measured by changes from baseline in MADRS total score overall and at Week 8 with increasing doses of [S,S]-reboxetine added to sertraline 150 mg a day. SRC 150/6 mg demonstrated at the maximum dose of 150/6 mg/day, a statistically significant and clinically meaningful reduction in depression symptoms over placebo and [S,S]-reboxetine 6 mg a day, as measured by MADRS total score by Week 8. The changes from baseline for MADRS and HAMD-17 are presented in Table S5.

Table S5. Change from Baseline for MADRS and HAMD-17

	N	p ^a value vs. SRC 150/6	LS Mean (SE)	SRC Diff*	95% CI**
MADRS change from baseline for the primary analysis (Overall: Weeks 1–8)					
Placebo	50	<0.001	-10.3 (0.95)	-4.79	-6.68, -2.9
[S,S]-Reboxetine 6 mg	101	0.0497	-13.6 (0.74)	-1.47	-2.93, 0
Sertraline 150 mg	152	0.5854	-14.7 (0.57)	-0.36	-1.65, 0.93
SRC 150/2 mg	31	ND	-16.2 (1.1)	ND	ND
SRC 150/4 mg	31	ND	-14.7 (1.13)	ND	ND
SRC 150/6 mg	151	NA	-15.1 (0.59)	NA	NA
MADRS change from baseline for key secondary analysis (at Week 8)					
Placebo	30	<0.001	-19.4 (1.21)	-5.47	-7.97, -2.97
[S,S]-Reboxetine	74	0.0497	-23.0 (0.87)	-1.88	-3.75, 0
Sertraline	112	0.2842	-23.9 (0.68)	-0.91	-2.56, 0.75
SRC 150/2 mg	28	ND	-26.4 (1.33)	ND	ND
SRC 150/4 mg	22	ND	-25.1 (1.42)	ND	ND
SRC 150/6 mg	114	NA	-24.8 (0.7)	NA	NA
HAMD-17 changes from baseline (Overall: Weeks 1–8)					
Placebo	50	<0.001	-8.78(0.75)	-3.29	-4.77, -1.8
[S,S]-Reboxetine	101	0.2082	-11.33(0.58)	-0.74	-1.89, 0.41
Sertraline	152	0.8756	-12.15(0.45)	-0.08	-0.93, 1.1
SRC 150/2 mg	31	ND	-13.44(0.87)	ND	ND
SRC 150/4 mg	31	ND	-11.87(0.89)	ND	ND
SRC 150/6 mg	151	NA	-12.07(0.46)	NA	NA

^a2-sided test

*Difference between LS Means of the labeled treatment and SRC 150/6 mg

**95% confidence intervals for the true difference in the means of labeled treatment and SRC 150/6 mg

N=Number of Subjects

HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale;

NA=Not Applicable; ND=Not Determined; SRC=Sertraline-[S,S]-Reboxetine Combination

In Table S 6 MADRS responder rates for the SRC combinations (SRC 150/6 mg and SRC 150/2 mg) and sertraline 150 mg monotherapy were each superior to placebo (2-sided test: p= 0.0017, 0.0001, and 0.0498, respectively); SRC 150/4 mg and [S,S]-reboxetine 6 mg were not superior to placebo (2-sided test: p values = 0.052 and 0.1481, respectively).

HAM-D responder rates for the SRC combinations (SRC 150/6 mg, SRC 150/4 mg and SRC 150/2 mg) and sertraline 150 mg monotherapy were each superior to placebo (2-sided test: p= 0.0013, 0.0333, <0.001, and 0.0137, respectively). Statistical significance of [S,S]-reboxetine 6 mg versus placebo was considered not significant (2-sided test: p=0.0550). See Table S6 for details on MADRS and HAM-D responder analysis.

Table S6. Responder Analysis for MADRS and HAM-D

Treatment Group	N	Number of Responders	Percentage of Responders	Difference from placebo		
				Percent Responders	95% CI *	p ^a -value*vs. placebo
MADRS						
SRC 150/6 mg	151	113	74.83	24.83	0.09, 0.4	0.0017
SRC 150/4 mg	31	22	70.97	20.97	0, 0.42	0.052
SRC 150/2 mg	31	27	87.1	37.1	0.19, 0.55	0.0001
Sertraline 150 mg	152	100	65.79	15.79	0, 0.32	0.0498
[S, S]-Reboxetine 6 mg	101	63	62.38	12.38	-0.04,0.29	0.1481
Placebo	50	25	50.0			
HAM-D						
SRC 150/6 mg	151	111	73.51	25.51	0.10, 0.41	0.0013
SRC 150/4 mg	31	22	70.97	22.97	0.02, 0.44	0.0333
SRC 150/2 mg	31	27	87.1	39.1	0.21, 0.57	0.0000
Sertraline 150 mg	152	103	67.76	19.76	0.04, 0.35	0.0137
[S, S]-Reboxetine 6 mg	101	65	64.36	16.36	0.00,0.33	0.0550
Placebo	50	24	48.0			

^a2-sided test

*Confidence intervals and p values are not adjusted for multiple comparisons

N=Number of Subjects

HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale

SRC=Sertraline-[S,S]-Reboxetine Combination

No results were obtained for HAM-A, CGI-S, CGI-I, AES, MADRS remitter or HAM-D remitter.

Pharmacokinetic and Other Results: Analyses of blood samples and of the PK data were reported in a separate PK report.

Pharmacogenetic Results: This study incorporated the collection of genotyping information mainly to explore if there is a relationship between the SERT genotype and response to treatment. In Table S7, the changes from baseline in MADRS total score using the repeated measures linear mixed model, for the placebo group is presented. From the data in this study, there appears to be no supportive relationship for this hypothesis.

Table S7. Sensitivity Analysis for Assessing Treatment-by-Genotype Interaction for Primary Statistical Analysis (Changes from Baseline in MADRS-Overall, Weeks 1-8), Non-Anonymized Samples

Geno- type	Change From Baseline					
	SRC 150/6 mg vs. Sertraline 150 mg		SRC 150/6 mg vs. [S,S]-Reboxetine 6 mg		SRC 150/6 mg vs. placebo	
	Difference (SE)	95% CI	Difference (SE)	95% CI	Difference (SE)	95% CI
L/L	-1.39 (1.07)	(-3.5, 0.72)	-0.4 (1.13)	(-2.63, 1.81)	-4 (1.43)	(-6.81, -1.19)
S/L	0.82 (1.02)	(-1.19, 2.83)	-2.11 (1.18)	(-4.44, 0.21)	-4.66 (1.53)	(-7.68, -1.65)
S/S	-2.23 (1.69)	(-5.55, 1.09)	-1.7 (1.85)	(-5.33, 1.94)	-6.58 (2.65)	(-11.79, -1.37)
UNK	-0.93 (3.05)	(-6.92, 5.06)	-7.15 (3.86)	(-14.73, 0.43)	-8.91 (4.13)	(-17.03, -0.79)

L/L=long/long; S/L=short/long; S/S=short/short; SRC=Sertraline-[S,S]-Reboxetine Combination
 UNK=Unknown

Anonymized genotyping samples were not analyzed.

Safety Results: One death was reported for this study. A 42 year old male died 27 days after stopping study drug (SRC 150/4 mg) on Day 14. The subject was unwilling to participate in the study any further and died on Day 41 due to coronary insufficiency. According to the investigator the death was not related to study drug.

Five other SAEs were reported for this study. Two SAEs (spontaneous abortion and suicidal attempt) occurred during the screening phase, prior to randomization and start of treatment. The remaining 3 SAEs were depression worsening, panic disorder, and exacerbation of depression; all 3 cases were judged as non-treatment related by the investigator and the sponsor.

More subjects (11.2%) discontinued study medication as a result of treatment-related AEs in SRC 150/6 mg treatment group than in other treatment groups (6.3% SRC 150/4 mg, 6.5% SRC 150/2 mg, 3.9% [S,S]-reboxetine 6 mg, and 6.9%, sertraline) or in the placebo group (2.0%). No subject discontinued study medication temporarily or was given a reduced dose during the study.

Six subjects discontinued due to AEs where the causality of the AE was listed as “disease under study” and these AEs were not related to study drug (2 subjects in the SRC 150/6 mg group, 1 subject in the SRC 150/4 mg and 2 subjects in the sertraline monotherapy group). One other subject in the sertraline 150 mg monotherapy group reported mild treatment-related nausea on Day 1 after receiving 50 mg sertraline, and later discontinued study medication (150 mg sertraline) on Day 32 due to non-drug-related tonsillitis. The AEs that led to discontinuations were insomnia (3 events), non-cardiac chest pain, tachycardia, lassitude, diarrhea, and headache.

In all treatment groups at least 50% of subjects who took active drug experienced at least 1 AE (all-causality) during the 8-week treatment period: 67.1% (SRC 150/6 mg), 65.6% (SRC

150/4 mg), 58.1% (SRC 150/2 mg), 54.6% (sertraline 150 mg), and 57.4% ([S,S]-reboxetine 6 mg). The incidence of AEs (all-causality) was lower (33.3%) in subjects who received placebo treatment. Treatment-related AEs infrequently resulted in subject discontinuations: 11.2% (SRC 150/6 mg), 6.3% (SRC 150/4 mg), 6.5% (SRC 150/2 mg), 3.9% (sertraline 150 mg), 6.9% ([S,S]-reboxetine 6 mg), and 2.0% (placebo). Most subjects considered the AEs to be mild or moderate in intensity. The incidence of subjects with treatment-related AEs rated severe was low: 10.5% (SRC 150/6 mg), 15.6% (SRC 150/4 mg), 6.5% (SRC 150/2 mg), 6.6% (sertraline 150 mg), 4.0% ([S,S]-reboxetine 6 mg), and 2.0% (placebo).

An overview of treatment-emergent AEs is provided in Table S8.

Table S8. Overview of Treatment-emergent Adverse Events (Number [%] of Subjects)

	Sertraline- 150/6 mg N=152	[S,S]-Reboxetine 150/4 mg N=32	[S,S]-Reboxetine 150/2 mg N=31	Sertraline 150 mg N=152	[S,S]-Reboxetine 6 mg N=101	Placebo N=51
AEs						
All-causality	102 (67.1)	21 (65.6)	18 (58.1)	83 (54.6)	58 (57.4)	17 (33.3)
Treatment-related	95 (62.5)	18 (56.3)	16 (51.6)	69 (45.4)	48 (47.5)	12 (23.5)
Treatment discontinuations due to AEs						
All-causality	19 (12.5)	3 (9.4)	2 (6.5)	9 (5.9)	7 (6.9)	1 (2.0)
Treatment-related	17 (11.2)	2 (6.3)	2 (6.5)	6 (3.9)	7 (6.9)	1 (2.0)
Deaths						
All-causality	0	1	0	0	0	0
Non-fatal SAEs						
All-causality	0	0	0	1 (0.7)	0	1 (2.0)
Treatment-related	0	0	0	0	0	1 (2.0)

N=Number of Subjects

AE=Adverse Events; SAE=Serious Adverse Events

The most frequently occurring treatment-emergent, treatment-related AEs with an incidence of $\geq 10\%$ were dry mouth (23.0%), hyperhydrosis (16.4%), and insomnia (14.5%) in SRC 150/6 mg treatment group, dry mouth (25.0%) and hyperhydrosis (25.0%) in the SRC 150/4 mg treatment, constipation (12.9%) and nausea (16.1%) in the SRC 150/2 mg treatment, nausea (22.4%) in the sertraline 150 mg treatment group, dry mouth (18.8%) and nausea (11.9%) in the [S,S]-reboxetine 6 mg treatment group; there were no AEs with an incidence of $>10\%$ for the placebo group. The most frequent AEs (all causalities) are presented in Table S9.

Table S9. Most Frequent (≥ 5% of Subjects) Adverse Events– All Causalities (Number [%] of Subjects)

MedDRA Preferred Term	Sertraline- [S,S]-Reboxetine			Sertraline	[S,S]-Reboxetine	Placebo
	150/6 mg N=152	150/4 mg N=32	150/2 mg N=31	150 mg N=152	6 mg N=101	
Dry mouth	35 (23.0)	8 (25.0)	3 (9.7)	14 (9.2)	19 (18.8)	4 (7.8)
Insomnia	28 (18.4)	2 (6.3)	0	11 (7.2)	9 (8.9)	2 (3.9)
Hyperhydrosis	26 (17.1)	8 (25.0)	3 (9.7)	12 (7.9)	10 (9.9)	3 (5.9)
Nausea	25 (16.4)	3 (9.4)	6 (19.4)	34 (22.4)	14 (13.9)	2 (3.9)
Headache	18 (11.8)	4 (12.5)	0	16 (10.5)	9 (8.9)	2 (3.9)
Tachycardia	10 (6.6)	1 (3.1)	2 (6.5)	1(0.7)	5 (5.0)	0
Anorexia	10 (6.6)	0	0	1 (0.7)	4 (4.0)	0
Dizziness	9 (5.9)	2 (6.3)	3 (9.7)	11 (7.2)	3 (3.0)	2 (3.9)
Anxiety	9 (5.9)	0	0	8 (5.3)	8 (7.9)	2 (3.9)
Tremor	9 (5.9)	3 (9.4)	0	2 (1.3)	5 (5.0)	0
Palpitations	8 (5.3)	1 (3.1)	1 (3.2)	1 (0.7)	7 (6.9)	1 (2.0)

N=Number of Subjects

There were no findings of note in hematology or serum chemistry analytes. Median changes in laboratory test values from baseline to last observation were small and few subjects met criteria for clinically significant values. No subjects discontinued treatment due to laboratory AEs.

There were no notable changes in median blood pressure or heart rate values, or mean ECG measurements. One female subject who had received SRC 150/4 mg, had a QTcF value of 502 msec on Day 15; the subject discontinued study medication on Day 28 due to an AE (tachycardia) and the last recorded QTcF value was 495 msec (Day 37). One female subject who received (SRC 150/6 mg) had a value of 529 msec on Day 15 and 457 msec on Day 63. Another female subject who received placebo, had QTcF values 506 msec at baseline and 510 msec at Day 64. Another female subject who received sertraline 150 mg reported abnormal QTcF readings, 1870 msec on Day 0 and 1894 msec on Day 35 but normal values otherwise, 396 msec (Day 14) and 432 msec (Day 63).

Conclusions: This 9-week, proof-of-concept study compared the safety and efficacy of the sertraline 150 mg/[S,S]-reboxetine 6 mg combination (SRC) to sertraline 150 mg and [S,S]-reboxetine 6 mg monotherapies and to placebo. The SRC 150/6 mg was statistically superior to placebo and [S,S]-reboxetine 6 mg monotherapy but was not superior to sertraline 150 mg monotherapy in reducing depressive symptoms as assessed by changes in the MADRS total scores. MADRS responder rates for SRC (150/6 mg and 150/2 mg) were each statistically superior to placebo; SRC 150/4 mg was not superior to placebo. HAM-D responder rates for SRC (150/6 mg, 150/4 mg, and 150/2 mg) were each statistically superior to placebo. Overall, all treatments were safe and well tolerated and there were few treatment-related discontinuations due to AEs. Adverse events that may affect tolerability of sertraline/reboxetine combinations were dry mouth and hyperhydrosis. There were no data suggestive of a new safety concern. Based on the results of this study a decision was made not to further pursue the SRC development program.