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GENERIC DRUG NAME / COMPOUND NUMBER: Elzasonan citrate / CP-448,187

PROTOCOL NO.: A7571001

PROTOCOL TITLE: An Eight-Week, Double-Blind, Group-Sequential Design, Placebo Controlled Trial to Evaluate the Safety and Efficacy of the Co-Administration of Sertraline and Elzasonan (CP-448,187) in Outpatients With Major Depressive Disorder

Study Centers: Twenty five (25) centers: 3 each in Chile and Estonia, 15 in the Russian Federation, and 4 in the United States (US) took part in the study and enrolled subjects.

Study Initiation and Final Completion Dates: 02 December 2005 to 19 July 2007

Phase of Development: Phase 2

Study Objectives:

Primary:

- To compare the efficacy of the administration of sertraline and elzasonan combination (SEC) to sertraline monotherapy in the acute treatment of subjects with major depressive disorder (MDD) as measured by Montgomery-Asberg Depression Rating Scale (MADRS) remission rates at Week 8.

Secondary:

- To compare the efficacy of SEC to sertraline monotherapy and sertraline monotherapy to placebo as measured by MADRS total score change from Baseline at Week 8. To compare the efficacy of SEC and sertraline monotherapy as measured by the 17-item Hamilton Depression Rating Scale (HAMD17) total score and subscale scores changes from Baseline, HAMD17 response and remission rates; Clinical Global Impression of Improvement (CGI-I) score and CGI-I response rate; Clinical Global Impression of Severity (CGI-S) score change from Baseline; and the Hamilton Anxiety Rating Scale (HAMA) total score change from Baseline at Week 8,

- To compare MADRS response rates between the administration of SEC and sertraline monotherapy at Week 8. To compare time to onset of response between the administration of SEC and sertraline monotherapy as measured by MADRS response rates,

- To characterize the population pharmacokinetics (PK) of SEC. To compare the population PK of sertraline when co-administered with elzasonan with the population PK of sertraline monotherapy,

- To evaluate the effects on sexual functioning following the administration of SEC and sertraline monotherapy as measured by the Changes in Sexual Functioning Questionnaire (CSFQ) total score and subscale scores changes from Baseline at Week 8,

- To evaluate perceived psychological health and functioning following the administration of SEC and sertraline monotherapy as measured by the Schwartz Outcomes Scale (SOS-10) brief mental health outcome measure total score change from Baseline at Week 8,

- To evaluate the safety and tolerability of the administration of SEC and sertraline monotherapy in the acute treatment of subjects with MDD.

METHODS

Study Design: This was a randomized, double-blind, parallel group, placebo-controlled study in male and female adult subjects with a diagnosis of recurrent, moderate-to-severe MDD without psychotic features. The total duration of the trial was approximately 10 weeks. The trial included a 1-week single-blind placebo lead-in, an 8-week randomized double-blind treatment period, and a 1-week follow-up visit. Subjects who met all entry criteria at the Week 0 (Baseline) visit were then enrolled into the trial (randomized) to 1 of the following double-blinded parallel treatment groups in a 2:2:1 ratio:

- Sertraline 50-200 mg plus elzasonan 3 mg co-administered once daily (QD),

- Sertraline 50-200 mg monotherapy administered QD,

- Double-dummy placebo.

Subjects were evaluated for efficacy at Weeks 1, 2, 3, 4, 6, and 8 of the double-blind treatment. The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Procedure	Screening	Treatment							Follow-Up
	Week -1	Week 0	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 9
Informed consent	X								
Medical history	X								
Physical examination	X							X	
Neurological examination	X							X	
Psychiatric interview/history	X								X
MINI	X								
Baseline symptoms/adverse event assessment	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X							X	
12-lead ECG	X[a]	X	X	X	X	X	X	X	
Thyroid panel (T3, T4, TSH)	X								
Serum β-hCG[b]	X								X
Follicle stimulating hormone[c]	X								
Urine drug screen[d]	X								
Chemistry	X	X		X		X		X	
Hematology	X	X		X		X		X	
Urinalysis (dipstick)	X	X						X	
PK samples					X[e]		X	X	
MADRS	X	X	X	X	X	X	X	X	
HAMD17	X	X	X	X	X	X	X	X	
HAMA		X	X	X	X	X	X	X	
CGI-I			X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	X	
CSFQ		X						X	
SOS-10		X						X	
PGI-D		X	X						
Dispense single-blind study medication	X								
Dispense double-blind study medication		X	X	X	X	X	X		

β-hCG = beta human chorionic gonadotropin, CGI-I = clinical global impression of improvement, CGI-S = clinical global impression of severity, CSFQ = changes in sexual functioning questionnaire, ECG = electrocardiogram, HAMA = Hamilton anxiety rating scale, HAMD17 = 17-item Hamilton depression rating scale, MADRS = Montgomery-Asberg depression rating scale, MINI = Mini International Neuropsychiatric Interview, PGI-D = patient global impression – dimensional, PK = pharmacokinetic, SOS-10 = Schwartz outcomes scale, T3 = triiodothyronine, T4 = thyroxine, TSH = thyroid stimulating hormone.

Table 1. Schedule of Activities

a. Screening ECGs were reviewed by an internist and/or cardiologist to confirm eligibility.
b. In all females of childbearing potential.
c. In all females of non-childbearing potential, unless the female of non-childbearing potential was >60 years of age or had a known history of hysterectomy and/or bilateral oophorectomy.
d. Additional urine drug testing was performed during the study at the discretion of the Investigator.
e. Blood samples for sertraline and elzasonan PK analysis were collected prior to daily dose.

Number of Subjects (Planned and Analyzed): A total 264 subjects were planned to be enrolled and 262 subjects (103 in SEC, 101 in sertraline and 58 in placebo group) were enrolled and randomized; 31 in Chile, 22 in Estonia, 179 in the Russian Federation and 30 in the US.

Diagnosis and Main Criteria for Inclusion: Adult subjects aged ≥18 years with a diagnosis of recurrent, moderate-to-severe MDD without psychotic features (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] 296.3x, with a HAMD17 score ≥22 and CGI-S score ≥4 were included in the study. MDD had to be the primary psychiatric disorder that motivated the subject to seek treatment and the current episode had to be at least 1 month in duration but no longer than 6 months in duration.

Exclusion Criteria: Subjects who, in the Investigator's judgment, would require treatment with electroconvulsive therapy, or antipsychotics, or would require a change in intensity of psychotherapy, or subjects who would require treatment with any other psychotherapeutic drugs during the course of the trial, and subjects who had ever been diagnosed with panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder, bipolar affective disorder, schizophrenia, schizoaffective disorder or other psychotic disorder, MDD with a seasonal pattern, or dissociative disorders per DSM-IV criteria were excluded from the study.

Study Treatment: Sertraline and elzasonan were provided as film-coated tablets containing 50 mg sertraline hydrochloride and 0.5 or 2 mg of elzasonan citrate, respectively. Matching placebos were provided for sertraline and for elzasonan. Subjects were randomized to 1 of the following double-blinded parallel treatment groups in a 2:2:1 ratio:

- Elzasonan 3 mg plus sertraline 50-200 mg co-administered QD,
- Sertraline 50-200 mg monotherapy administered QD,
- Double-dummy placebo.

In order to standardize the dose of sertraline between treatment arms and to maximize the potential for a clinically interpretable efficacy signal, sertraline was administered as a forced titration in both the combination and monotherapy treatment arms, according to the following schedule:

- 50 mg QD beginning on Week 0,
- 100 mg QD beginning on Week 1,
- 150 mg QD beginning on Week 2.

A decision to keep a subject in the trial and/or to titrate their dose to the next allowed dose of sertraline was undertaken only if acceptable tolerability at the current dose level based on sound medical judgment had been confirmed. Dose adjustment of sertraline was done in a blinded fashion; therefore, subjects randomized to double-dummy placebo underwent dose

adjustment of the corresponding dose of sertraline placebo only. Subjects took study medication orally in the morning according to dose and treatment level as shown in Table 2.

Table 2. Number and Strength of Tablets per Dose and Treatment

Dose/Treatment	Elzasonan 0.5 mg	Elzasonan 2 mg	Sertraline 50 mg	Sertraline Placebo	Elzasonan Placebo
Elzasonan 3 mg	2	1			1
Sertraline 50 mg			1	3	
Sertraline 100 mg			2	2	
Sertraline 150 mg			3	1	
Sertraline 200 mg			4		
Elzasonan placebo					4
Sertraline placebo				4	

Efficacy and Safety Endpoints:

Primary Efficacy Endpoint:

- Remission rate at Week 8, where remission was defined as a MADRS total score of ≤11.

Secondary Efficacy Endpoints:

- Change from Baseline in MADRS total score at Week 8.
- Response rate at Week 8, where response was defined as a ≥50% decrease in MADRS total score change from Baseline.
- Time to onset of response, where onset of response was defined as the first sustained occurrence of a ≥50% decrease in MADRS total score change from Baseline. More specifically, this was defined as the number of days between the start of double-blind study treatment and the first visit at which a subject's MADRS total score became and remained at a level of 50% or more below their Baseline MADRS total score throughout the remaining duration of the trial. Subjects that did not complete the trial were considered responders if their reduction from Baseline in MADRS total was ≥50% at their last 2 visits. Subjects with a "sustained response" were a subset of the subjects classified as "responders."
- Change from Baseline in HAMD17, CGI-S, and HAMA total scores at Week 8.
- Change from Baseline in HAMD17 subscale scores at Week 8, including: depressed mood (Item 1); core (Items 1, 2, 3, 7, 8); Maier (Items 1, 2, 7, 8, 9, 10); Bech melancholia (Items 1, 2, 7, 8, 10, 13); sleep (Items 4, 5, 6,); retardation/somatization (Items 1, 7, 8, 14); and anxiety/somatization (Items 10, 11, 12, 13, 15, 17).
- Response and remission rates at Week 8, where response was defined as a ≥50% decrease in HAMD17 total score change from Baseline and remission was defined as a HAMD17 total score ≤7.

- Response rate at Week 8, where response was defined as CGI-I score ≤2.

- CSFQ total score and subscale scores changes from Baseline at Week 8. Subscores analyzed included: pleasure (Item 1); desire/frequency (Items 2 and 3); desire/interest (Items 4, 5 and 6); arousal/excitement or arousal/erection (Items 7, 8 and 9 on the CSFQ-F and -M, respectively); and orgasm/completion or orgasm/ejaculation (Items 11, 12, and 13 on the CSFQ-F and -M, respectively).

- SOS-10 total score change from Baseline at Week 8.

Secondary Safety Endpoints:

- Incidence and severity of treatment-emergent adverse events (AEs), electrocardiogram (ECG) changes, laboratory abnormalities and vital signs changes.

Safety Evaluations: AEs were obtained and recorded at all visits. Laboratory evaluations, including hepatitis screen and a urine drug screen, were performed at Screening only. Chemistry and hematology were performed at Screening and at Weeks 0, 2, 4, and 8. Urinalysis was performed at Screening and Baseline. Vital signs and single 12-lead ECG were obtained at each visit throughout the study; vital signs were also obtained at the 9-week follow-up visit. Physical and neurological examinations and weight were obtained at the Week -1 Screening Visit and at the Week 8 visit.

Statistical Methods: The population sets analyzed in the study were:

- Full analysis set (FAS): The FAS consisted of all subjects who received at least 1 dose of randomized study drug, had a Baseline and at least 1 post-baseline measurement on that efficacy variable (after taking randomized study drug), and had no major protocol violation that affected the same efficacy variable.

- Safety Analysis set: This population set consisted of all subjects who received a dose of study medication.

The primary analysis, remission rate at Week 8, where remission was defined as a MADRS total score of ≤11, was performed on the FAS for the MADRS total score endpoint and was analyzed by estimating the difference in remission rates (SEC minus sertraline) at Week 8 and providing 95% confidence intervals (CIs) and an adjusted 1-sided p-value. Change from Baseline for the MADRS total score, HAMD17 total score and subscales, CGI-I, CGI-S, HAMA, and CSFQ total score and subscores were analyzed using a repeated measures mixed model. Time to onset of response (defined as the first sustained occurrence of a ≥50% decrease in MADRS total score change from Baseline) for SEC was compared to that for sertraline. A log rank test was used to test the equality of the survivor functions between the 2 treatment groups (SEC and sertraline). Estimates of the HAMD17 Week 8 response and remission rates and CGI-I Week 8 response rates were reported by treatment group. The estimated treatment differences (SEC minus sertraline and sertraline minus placebo) in these response and remission rates and the corresponding 2-sided 95% CIs were provided. The estimated treatment difference (SEC minus sertraline) in MADRS Week 8 response rates and

the corresponding 2-sided 95% CI were provided. The secondary efficacy endpoints were also summarized using descriptive statistics. All AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 10.0 and tabulated by body system and individual body event by body system. Both treatment-emergent (all causality) and treatment-emergent/treatment-related AEs were summarized. Clinical laboratory and other safety parameters were summarized using descriptive statistics.

RESULTS

Subject Disposition and Demography: A total of 262 subjects were randomized to the study. Of the 261 subjects treated, 81 subjects discontinued from the study as shown in Table 3. Reasons for subject discontinuations are summarized in Table 4.

Table 3. Subject Disposition

Number (%) of Subjects	SEC	Sertraline	Placebo
Randomized to treatment	103	101	58
Treated	103	100	58
Completed	72 (69.9)	74 (73.3)	34 (58.6)
Discontinued	31 (30.1)	26 (25.7)	24 (41.4)
Analyzed for safety			
Adverse events	102[a] (99.0)	100 (99.0)	58 (100)
Laboratory data	98 (95.1)	94 (93.1)	55 (94.8)

SEC = sertraline and elzasonan combination.
a. One (1) subject discontinued the study.

Table 4. Subject Discontinuations

Number (%) of Subjects	SEC	Sertraline	Placebo
N	103	100	58
Subject died	0	1	0
Related to study drug	10 (9.7)	8 (8.0)	4 (6.9)
Adverse event	10 (9.7)	8 (8.0)	4 (6.9)
Not related to study drug	21 (20.4)	17 (17.0)	20 (34.5)
Adverse event	3 (2.9)	3 (3.0)	1 (1.7)
Laboratory abnormality	1 (1.0)	0	1 (1.7)
Other	5 (4.9)	4 (4.0)	15 (25.9)
Subject defaulted	12 (11.7)	10 (10.0)	3 (5.2)
Total	31 (30.1)	26 (26.0)	24 (41.4)

N = total number of subjects, SEC = sertraline and elzasonan combination.

The majority of subjects were White females. The subject demography is presented in Table 5.

Table 5. Subject Demographics

		SEC (N=103)	Sertraline (N=100)	Placebo (N=58)
Gender	Male	32	18	16
	Female	71	82	42
Age (years)	Mean	42.1	42.7	43.3
	SD	12.7	12.3	13.2
	Range	-1[a] to 68	20 to 78	-1[a] to 68
Race	White	97	97	53
	Black	1	1	3
	Asian	2	1	2
	Other	3	1	0
Weight (kg)	Mean	70.7	68.4	71.2
	SD	12.8	13.9	14.5
	Range	46.3 to 103.5	47.6 to 124.7	49.7 to 111.0
Height (cm)	Mean	167.8	165.6	166.6
	SD	8.8	8.5	9.6
	Range	150.0 to 191.0	147.0 to 188.2	149.0 to 192.0

N = number of subjects per treatment group, SD = standard deviation, SEC = sertraline and elzasonan combination.
a. The birth year of 2 subjects was reported incorrectly.

Efficacy Results:

Primary Efficacy Analysis: The number of MADRS Week 8 remitters in the SEC and sertraline groups was 50 and 47 subjects in each group, respectively, with the proportion of remitters being 0.50 and 0.47, respectively. While a difference was demonstrated in remission between treatment groups (0.03, or 3%), the difference did not meet the predefined criterion of at least 10% difference in remission rates for superiority of SEC compared to sertraline. The comparison of MADRS remission rates between SEC and sertraline is presented in Table 6.

Table 6. MADRS Remission Rates at Week 8 Between SEC and Sertraline

Number of Subjects	SEC	Sertraline
N	100	99
Number of remitters	50	47
Proportion of remitters	0.50	0.47
Difference in proportion	0.03	
95% CI for difference in proportion	(-0.11, 0.16)	
p-value[a]	0.17	

N = number of subjects in the full analysis set, CI = confidence interval, MADRS = Montgomery-Asberg depression rating scale, SEC = sertraline and elzasonan combination.
a. Adjusted 1-sided p-value.

MADRS remission rate at Week 8 between SEC and sertraline each compared with placebo showed a statistically significant difference from placebo (p=0.0003 and 0.001, respectively) as shown in Table 7.

Table 7. MADRS Remission Rates at Week 8 Between Active Treatments (SEC and Sertraline) and Placebo

Number of Subjects	SEC[a]	Sertraline[b]	Placebo
N	100	99	58
Number of remitters	50	47	14
Proportion of remitters	0.50	0.47	0.24
Difference in proportion	0.26	0.23	
95% CI for difference in proportion	(0.11, 0.41)	(0.09, 0.38)	
p-value	0.0003	0.001	

One-sided p-values are calculated for comparing remitter proportions based on normal distribution assumption.
CI = confidence interval, MADRS = Montgomery-Asberg depression rating scale, N = number of subjects in the full analysis set, SEC = sertraline and elzasonan combination.
a. SEC comparison is SEC-placebo.
b. Sertraline comparison is sertraline-placebo.

Secondary Efficacy Analysis:

The change from Baseline scores for the secondary efficacy endpoints based on the MADRS, HAMD17, CGI-I and HAMA are presented in Table 8.

The difference in change from Baseline in MADRS total score at Week 8 was not statistically significant between the SEC and sertraline groups (p=0.5504), but it was statistically significant between sertraline and placebo, and between SEC and placebo (each p<0.0001).

The SEC and sertraline groups each showed statistically significant differences in the HAMD17 total score change from Baseline when compared to placebo (p<0.0001), but SEC did not demonstrate a significant difference over sertraline alone. This pattern was also seen for the depressed mood, core, Maier, Bech Melancholia, retardation/somatization, and anxiety/somatization subscales, but not the sleep subscale. The subscale of sleep only displayed a significant difference when SEC was compared to placebo treatment (p=0.0083).

For the analysis of the change from Baseline in CGI-I total score, both the SEC and sertraline treatments showed statistically significant differences from placebo (each p<0.0001), but not statistically significant differences from each other (p=0.5946).

The HAMA total score change from Baseline at Week 8 showed a statistically significant difference between SEC and placebo (p=0.0001) and between sertraline and placebo (p=0.0002), but no difference was seen between the 2 active treatment groups (p=0.3793).

The analysis of the change from Baseline in the CSFQ total score demonstrated that there was no statistically significant difference between SEC and sertraline treatments, nor was there any statistically significant difference between either of treatment and placebo indicating that neither treatment negatively affected sexual functioning. This same pattern was also seen for all of the CSFQ subscale items: pleasure, desire/frequency, desire/interest, arousal/excitement/erection, or orgasm/completion/ejaculation (Table 9 and Table 10).

Table 8. Secondary Efficacy Variables Score Change From Baseline at Week 8 Between Active Treatments (SEC and Sertraline) and Placebo

	SEC[a]	Sertraline[b]	Placebo[c]
MADRS Total Score			
LS means (SE)	-21.18 (0.88)	-21.34 (0.88)	-14.88 (1.22)
LS means of treatment difference (SE)	0.16 (1.24)	-6.45 (1.50)	-6.30 (1.50)
95% CI for LS means of treatment difference	(-2.27, 2.59)	(-9.40, -3.50)	(-9.24, -3.36)
p-value	0.5504	<0.0001	<0.0001
HAMD17			
Total score			
LS means (SE)	-17.09 (0.70)	-17.58 (0.71)	-11.99 (0.98)
LS means of treatment difference (SE)	0.48 (0.99)	-5.58 (1.21)	-5.10 (1.20)
95% CI for LS means of treatment difference	(-1.46, 2.43)	(-7.95, -3.22)	(-7.45, -2.74)
p-value	0.6873	<0.0001	<0.0001
Depressed mood (Item 1)			
LS means (SE)	-2.19 (0.10)	-2.24 (0.10)	-1.54 (0.14)
LS means of treatment difference (SE)	0.05 (0.14)	-0.70 (0.17)	-0.65 (0.17)
95% CI for LS means of treatment difference	(-0.22, 0.32)	(-1.03, -0.37)	(-0.98, -0.32)
p-value	0.6415	<0.0001	0.0001
Core (Items 1, 2, 3, 7, 8)			
LS means (SE)	-6.49 (0.29)	-6.86 (0.29)	-4.80 (0.40)
LS means of treatment difference (SE)	0.36 (0.41)	-2.06 (0.50)	-1.70 (0.49)
95% CI for LS means of treatment difference	(-0.44, 1.16)	(-3.03, -1.09)	(-2.67, -0.73)
p-value	0.8129	<0.0001	0.0003
Maier (Items 1, 2, 7, 8, 9, 10)			
LS means (SE)	-8.24 (0.35)	-8.69 (0.35)	-5.73 (0.48)
LS means of treatment difference (SE)	0.46 (0.49)	-2.97 (0.60)	-2.51 (0.60)
95% CI for LS means of treatment difference	(-0.51, 1.42)	(-4.14, -1.80)	(-3.68, -1.34)
p-value	0.8231	<0.0001	<0.0001
Bech melancholia (Items 1, 2, 7, 8, 10, 13)			
LS means (SE)	-8.58 (0.37)	-8.91 (0.37)	-6.17 (0.51)
LS means of treatment difference (SE)	0.32 (0.52)	-2.74 (0.63)	-2.41 (0.63)
95% CI for LS means of treatment difference	(-0.69, 1.34)	(-3.97, -1.51)	(-3.64, -1.19)
p-value	0.7331	<0.0001	0.0001
Sleep (Items 4, 5, 6)			
LS means (SE)	-3.05 (0.17)	-2.79 (0.17)	-2.33 (0.24)
LS means of treatment difference (SE)	-0.26 (0.24)	-0.46 (0.30)	-0.72 (0.30)
95% CI for LS means of treatment difference	(-0.74, 0.22)	(-1.05, 0.12)	(-1.30, -0.13)
p-value	0.1477	0.0613	0.0083
Retardation/somatization (Items 1, 7, 8, 14)			
LS means (SE)		-5.37 (0.27)	-3.75 (0.37)
LS means of treatment difference (SE)			-1.62 (0.46)
95% CI for LS means of treatment difference			(-2.51, -0.72)
p-value			0.0002
Anxiety/Somatization (Items 10, 11, 12, 13, 15, 17)			
LS means (SE)	-5.77 (0.25)	-5.77 (0.25)	-4.00 (0.35)
LS means of treatment difference (SE)	-0.01 (0.36)	-1.77 (0.43)	-1.78 (0.43)
95% CI for LS means of treatment difference	(-0.71, 0.69)	(-2.62, -0.92)	(-2.63, -0.93)
p-value	0.4919	<0.0001	<0.0001
CGI-I Total Score			
LS means (SE)	-2.52 (0.11)	-2.55 (0.11)	-1.73 (0.15)
LS means of treatment difference (SE)	0.04 (0.15)	-0.83 (0.18)	-0.79 (0.18)
95% CI for LS means of treatment difference	(-0.26, 0.33)	(-1.19, -0.46)	(-1.15, -0.43)
p-value	0.5946	<0.0001	<0.0001

Table 8. Secondary Efficacy Variables Score Change From Baseline at Week 8 Between Active Treatments (SEC and Sertraline) and Placebo

	SEC[a]	Sertraline[b]	Placebo[c]
HAMA Total Score			
LS means (SE)	-14.95 (0.67)	-14.66 (0.68)	-10.51 (0.94)
LS means of treatment difference (SE)	-0.29 (0.95)	-4.15 (1.16)	-4.44 (1.15)
95% CI for LS means of treatment difference	(-2.16, 1.57)	(-6.42, -1.88)	(-6.70, -2.18)
p-value	0.3793	0.0002	0.0001

CI = confidence interval, CGI-I = clinical global impression of improvement, CSFQ = Changes in Sexual Functioning Questionnaire, HAMA = Hamilton Anxiety Rating Scale, HAMD17 = 17-item Hamilton Depression Rating Scale, LS = least square, MADRS = Montgomery-Asberg depression rating scale, SE = standard error, SEC = sertraline and elzasonan combination.

a. SEC comparison is SEC-sertraline.
b. Sertraline comparison is sertraline-placebo.
c. Placebo comparison is SEC-placebo.

Table 9. Statistical Analysis of Change From Baseline in CSFQ Total Score and Subscales at Week 8 Between SEC and Sertraline and Sertraline and Placebo

CFSQ	SEC[a]	Sertraline[b]	Placebo
Total score			
LS means (SE)	6.28 (0.96)	4.38 (0.92)	4.24 (1.31)
LS means of treatment difference (SE)	1.90 (1.22)	0.14 (1.53)	
95% CI for LS means of treatment differences	(-0.52, 4.32)	(-2.89, 3.17)	
p-value	0.9387	0.5362	
Pleasure (Item 1)			
LS means (SE)	0.94 (0.12)	0.71 (0.11)	0.72 (0.16)
LS means of treatment difference (SE)	0.24 (0.15)	-0.01 (0.19)	
95% CI for LS means of treatment differences	(-0.06, 0.53)	(-0.39, 0.36)	
p-value	0.9395	0.4730	
Desire/Frequency (Items 2,3)			
LS means (SE)	1.06 (0.19)	0.83 (0.18)	0.97 (0.26)
LS means of treatment difference (SE)	0.23 (0.24)	-0.15 (0.30)	
95% CI for LS means of treatment differences	(-0.24, 0.70)	(-0.74, 0.45)	
p-value	0.8312	0.3157	
Desire/Interest (Items 4,5,6)			
LS means (SE)	1.46 (0.26)	1.10 (0.25)	0.89 (0.35)
LS means of treatment difference (SE)	0.36 (0.33)	0.22 (0.41)	
95% CI for LS means of treatment differences	(-0.29, 1.00)	(-0.59, 1.03)	
p-value	0.8607	0.7008	
Arousal/Excitement or Arousal/Erection (Items 7,8,9)			
LS means (SE)	1.36 (0.29)	1.00 (0.28)	1.12 (0.40)
LS means of treatment difference (SE)	0.36 (0.38)	-0.13 (0.47)	
95% CI for LS means of treatment differences	(-0.38, 1.11)	(-1.06, 0.81)	
p-value	0.8312	0.3949	
Orgasm/Completion or Orgasm/Ejaculation (Items 11,12,13)			
LS means (SE)	1.56 (0.31)	0.67 (0.30)	0.81 (0.42)
LS means of treatment difference (SE)	0.89 (0.39)	-0.14 (0.49)	
95% CI for LS means of treatment differences	(0.11, 1.67)	(-1.12, 0.84)	
p-value	0.9875	0.3882	

The p-values were for 1-sided tests of superiority for the treatment comparisons.
Results are obtained from an analysis of covariance model with the change from Baseline in CSFQ total score (or subscale score) at Week 8 as the dependent variable and treatment and site as the explanatory variables with baseline CSFQ total score (or baseline subscale score) as the covariate.
CI = confidence interval, CSFQ = Changes in Sexual Functioning Questionnaire, LS = least squared, SE = standard error, SEC = sertraline and elzasonan combination.
a. SEC comparison is SEC-sertraline.
b. Sertraline comparison is sertraline-placebo.

Table 10. Exploratory Analysis of Change From Baseline in CSFQ Total Score and Subscales at Week 8 Between SEC and Placebo

CFSQ	SEC[a]	Placebo
Total score		
LS means (SE)	6.28 (0.96)	4.24 (1.31)
LS means of treatment difference (SE)	2.04 (1.54)	
95% CI for LS means of treatment differences	(-1.02, 5.09)	
p-value	0.9055	
Pleasure (Item 1)		
LS means (SE)	0.94 (0.12)	0.72 (0.16)
LS means of treatment difference (SE)	0.22 (0.19)	
95% CI for LS means of treatment differences	(-0.16, 0.60)	
p-value	0.8770	
Desire/Frequency (Items 2,3)		
LS means (SE)	1.06 (0.19)	0.97 (0.26)
LS means of treatment difference (SE)	0.09 (0.30)	
95% CI for LS means of treatment differences	(-0.51, 0.69)	
p-value	0.6110	
Desire/Interest (Items 4,5,6)		
LS means (SE)	1.46 (0.26)	0.89 (0.35)
LS means of treatment difference (SE)	0.57 (0.41)	
95% CI for LS means of treatment differences	(-0.24, 1.39)	
p-value	0.9157	
Arousal/Excitement or Arousal/Erection (Items 7,8,9)		
LS means (SE)	1.36 (0.29)	1.12 (0.40)
LS means of treatment difference (SE)	0.24 (0.47)	
95% CI for LS means of treatment differences	(-0.70, 1.17)	
p-value	0.6901	
Orgasm/Completion or Orgasm/Ejaculation (Items 11,12,13)		
LS means (SE)	1.56 (0.31)	0.81 (0.42)
LS means of treatment difference (SE)	0.75 (0.50)	
95% CI for LS means of treatment differences	(-0.23, 1.74)	
p-value	0.9338	

The p-values were for 1-sided tests of superiority for the treatment comparisons.
Results are obtained from an analysis of covariance model with the change from Baseline in CSFQ total score (or subscale score) at Week 8 as the dependent variable and treatment and site as the explanatory variables with baseline CSFQ total score (or baseline subscale score) as the covariate.
CI = confidence interval, CSFQ = Changes in Sexual Functioning Questionnaire, LS = least squared, SE = standard error, SEC = sertraline and elzasonan combination.
a. SEC comparison is SEC-placebo.

For MADRS, the proportion of responders at Week 8 was similar between the SEC and sertraline groups (0.53 and 0.54, respectively), and both were statistically significantly higher than placebo (0.33, each $p<0.01$) as shown in Table 11 and Table 12.

Table 11. Statistical Analysis of MADRS Week 8 Response Rates Between SEC and Sertraline and Sertraline and Placebo

Number of Subjects	SEC[a]	Sertraline[b]	Placebo
N	100	99	58
Number of responders	53	53	19
Proportion of responders	0.53	0.54	0.33
Difference in proportion	-0.01	0.21	
95% CI for difference in proportion	(-0.14, 0.13)	(0.05, 0.36)	
p-value[c]	0.5302	0.0045	

N is defined as the number of subjects in the full analysis set. A responder is defined as a subject with a ≥50% decrease in the MADRS total score change from Baseline at Week 8.
CI = confidence interval, MADRS = Montgomery-Asberg depression rating scale, SEC = sertraline and elzasonan combination.
a. SEC comparison is SEC-sertraline.
b. Sertraline comparison is sertraline-placebo.
c. One-sided p-values were calculated for comparing binomial proportions based on normal distribution assumption.

Table 12. Exploratory Analysis of MADRS Week 8 Response Rates Between SEC and Placebo

Number of Subjects	SEC[a]	Placebo
N	100	58
Number of responders	53	19
Proportion of responders	0.53	0.33
Difference in proportion	0.2	
95% CI for difference in proportion	(0.05, 0.36)	
p-value[b]	0.0053	

N is defined as the number of subjects in the full analysis set. A responder is defined as a subject with a ≥50% decrease in the MADRS total score change from Baseline at Week 8.
CI = confidence interval, MADRS = Montgomery-Asberg depression rating scale, SEC = sertraline and elzasonan combination.
a. SEC comparison is SEC-placebo.
b. One-sided p-values were calculated for comparing binomial proportions based on normal distribution assumption.

For the MADRS time to onset of response, conditional on response, the SEC group showed a significantly faster time to onset of response as compared with the sertraline group (p=0.0151). At Weeks 2 and 3, 14.9% and 15.7%, respectively, of the SEC group had reached a responder status, while only 3.3% and 7.0%, respectively, of the sertraline group were rated as responders (Table 13).

Table 13. Number and Percentage of Responders by Week for MADRS Total Score

Visit[a]	SEC n (%)	Sertraline n (%)
Week 1	1 (1.0)	2 (2.0)
Week 2	13 (14.9)	3 (3.3)
Week 3	14 (15.7)	6 (7.0)
Week 4	16 (18.4)	24 (28.6)
Week 5	14 (17.1)	16 (21.1)
Week 6	3 (4.7)	6 (9.2)

Percentages were computed by dividing the observed cases at each derived week.
MADRS = Montgomery-Asberg depression rating scale, n = number of responders, SEC = sertraline and elzasonan combination.

a. Week = number of observed responders (≥50% decrease in MADRS from Baseline) at each derived (windowed) week.

The proportion of responders at Week 8 was similar between the SEC and sertraline groups for the HAMD17 analysis (0.54 and 0.55, respectively), and both were significantly higher than placebo (0.34, each $p<0.01$). The results for HAMD17 response rate at Week 8 are provided in Table 14 and Table 15.

Table 14. Statistical Analysis of HAMD17 Week 8 Response Rates Between SEC and Sertraline and Sertraline and Placebo

Number of Subjects	SEC[a]	Sertraline[b]	Placebo
N	100	99	58
Number of responders	54	54	20
Proportion of responders	0.54	0.55	0.34
Difference in proportion	-0.01	0.2	
95% CI for difference in proportion	(-0.14, 0.13)	(0.04, 0.36)	
p-value[c]	0.5308	0.0061	

N is defined as the number of subjects in the full analysis set. A responder is defined as a subject with a ≥50% decrease in the HAMD17 total score change from Baseline at Week 8.
CI = confidence interval, HAMD17 = 17-item Hamilton Depression Rating Scale, SEC = sertraline and elzasonan combination.

a. SEC comparison is SEC-sertraline.
b. Sertraline comparison is sertraline-placebo.
c. One-sided p-values were calculated for comparing binomial proportions based on normal distribution assumption.

Table 15. Exploratory Analysis of HAMD17 Week 8 Response Rates Between SEC and Placebo

	SEC[a]	Placebo
N	100	58
Number of responders	54	20
Proportion of responders	0.54	0.34
Difference in proportion	0.2	-
95% CI for difference in proportion	(0.04, 0.35)	-
p-value[b]	0.0073	-

N is defined as the number of subjects in the full analysis set. A responder is defined as a subject with a ≥50% decrease in the HAMD17 total score change from Baseline at Week 8.
CI = confidence interval, HAMD17 = 17-Item Hamilton Depression Rating Scale, SEC = sertraline and elzasonan combination.
a. SEC comparison is SEC-placebo.
b. One-sided p-values were calculated for comparing binomial proportions based on normal distribution assumption.

HAMD17 remission rates for the FAS at Week 8 demonstrated similar results: the SEC and sertraline groups each showed statistically significant differences in the remission rates for FAS when compared to placebo ($p<0.001$), but SEC did not demonstrate a difference over sertraline alone, as shown in Table 16 and Table 17.

Table 16. Statistical Analysis of HAMD17 Week 8 Remission Rates Between SEC and Sertraline and Sertraline and Placebo

Number of Subjects	SEC[a]	Sertraline[b]	Placebo
N	100	99	58
Number of remitters	45	39	10
Proportion of remitters	0.45	0.39	0.17
Difference in proportion	0.06	0.22	
95% CI for difference in proportion	(-0.08, 0.19)	(0.08, 0.36)	
p-value[c]	0.2113	0.0008	

N is defined as the number of subjects in the full analysis set. A remitter is defined as a subject with a HAMD17 total score ≤7 at Week 8.
CI = confidence interval, HAMD17 = 17-item Hamilton Depression Rating Scale, SEC = sertraline and elzasonan combination.
a. SEC comparison is SEC-sertraline.
b. Sertraline comparison is sertraline-placebo.
c. One-sided p-values were calculated for comparing binomial proportions based on normal distribution assumption.

Table 17. Exploratory Analysis of HAMD17 Week 8 Remission Rates Between SEC and Placebo

	SEC[a]	Placebo
N	100	58
Number of remitters	45	10
Proportion of remitters	0.45	0.17
Difference in proportion	0.28	-
95% CI for difference in proportion	(0.14,0.42)	-
p-value[b]	0	-

N is defined as the number of subjects in the full analysis set. A remitter is defined as a subject with a HAMD17 total score ≤7 at Week 8.
CI = confidence interval, HAMD17 = 17-Item Hamilton Depression Rating Scale, SEC = sertraline and elzasonan combination.
a. SEC comparison is SEC-placebo.
b. One-sided p-values were calculated for comparing binomial proportions based on normal distribution assumption.

The proportion of responders at Week 8 was similar between the SEC and sertraline groups for the CGI-I analysis (0.55 and 0.60, respectively), and both were statistically significantly higher than placebo (0.36, each $p<0.01$), as shown in Table 18 and Table 19.

Table 18. Statistical Analysis of CGI-I Week 8 Response Rates Between SEC and Sertraline and Sertraline and Placebo

	SEC[a]	Sertraline[b]	Placebo
N	100	99	58
Number of responders	55	59	21
Proportion of responders	0.55	0.6	0.36
Difference in proportion	-0.05	0.23	-
95% CI for difference in proportion	(-0.18, 0.09)	(0.08, 0.39)	-
p-value[c]	0.7441	0.0017	-

N is defined as the number of subjects in the full analysis set. A responder is defined as a subject with a CGI-I score ≤2 at Week 8.
CI = confidence interval, CGI-I = Clinical Global Impression of Improvement, SEC = sertraline and elzasonan combination.
a. SEC comparison is SEC-sertraline.
b. Sertraline comparison is sertraline-placebo.
c. One-sided p-values were calculated for comparing binomial proportions based on normal distribution assumption.

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Table 19. Exploratory Analysis of CGI-I Week 8 Response Rates Between SEC and Placebo

	SEC[a]	Placebo
N	100	58
Number of responders	55	21
Proportion of responders	0.55	0.36
Difference in proportion	0.19	-
95% CI for difference in proportion	(0.03,0.35)	-
p-value[b]	0.0097	-

N is defined as the number of subjects in the full analysis set. A responder is defined as a subject with a CGI-I score ≤2 at Week 8.
CI = confidence interval, CGI-I = Clinical Global Impression of Improvement, SEC = sertraline and elzasonan combination.
a. SEC comparison is SEC-placebo.
b. One-sided p-values were calculated for comparing binomial proportions based on normal distribution assumption.

Similar to the CGI-I results (Table 8), the CGI-S total score change from Baseline at Week 8 did not demonstrate a statistically significant difference between SEC and sertraline groups (p=0.2065), while statistical significance was observed for both treatments compared to placebo (each p<0.0001), as shown in Table 20 and Table 21.

Table 20. Statistical Analysis of Change From Baseline in CGI-S Total Score at Week 8 Between SEC and Sertraline and Sertraline and Placebo

	SEC[a]	Sertraline[b]	Placebo
LS means (SE)	-2.36 (0.11)	-2.24 (0.11)	-1.46 (0.16)
LS means of treatment difference (SE)	-0.13 (0.16)	-0.78 (0.19)	
95% CI for LS means of treatment differences	(-0.43,0.18)	(-1.15,-0.41)	
p-value	0.2065	0.0000	

The p-values are for 1-sided tests of superiority for the treatment comparisons.
Results were obtained from a mixed effect repeated measures model with the change from Baseline in CGI-S total score at Weeks 1, 2, 3, 4, 6, 8 as the dependent variable and with treatment, week, treatment and week interaction, baseline CGI-S total score and site as fixed effects and subject as random effect.
CI = confidence interval, CGI-S = clinical global impression of severity, LS mean = least squared means, SE = standard error.
a. SEC comparison is SEC-sertraline.
b. Sertraline comparison is sertraline-placebo.

Table 21. Exploratory Analysis of Change From Baseline in CGI-S Total Score at Week 8 Between SEC and Placebo

	SEC[a]	Placebo
LS means (SE)	-2.36 (0.11)	-1.46 (0.16)
LS means of treatment difference (SE)	-0.91 (0.19)	
95% CI for LS means of treatment differences	(-1.28, -0.53)	
p-value[b]	0.0000	

Results are obtained from a mixed effect repeated measures analysis of variance model with the change from Baseline in CGI-S total score at Weeks 1,2,3,4,6,8 as the dependent variable, with treatment, week, baseline CGI-S total score and site as fixed effects and subject as random effect.
CGI-S = Clinical Global Impression of Severity, CI = confidence interval, LS = least squared, SE = standard error, SEC = sertraline and elzasonan combination.
a. SEC comparison is SEC-placebo.
b. The p-values are for 1-sided tests of superiority for the treatment comparisons.

SOS-10 Total and Subscale Scores:

Perceived psychological health and functioning was measured by the SOS-10. At Week 8, the SOS-10 scores increased to a similar extent for the SEC and sertraline groups (mean values 40.8 and 38.0, respectively), while the placebo group score increased to a lesser amount (mean value 33.1). The descriptive statistics for the Baseline and change from Baseline at Week 8 in the SOS-10 total score are displayed by treatment in Table 22.

Table 22. Descriptive Statistics for Baseline and Change From Baseline in SOS-10 Total Score at Week 8

Visit	Statistic	SEC	Sertraline	Placebo
Baseline	N	83	81	51
	Mean (SD)	19.3 (9.99)	17.7 (9.18)	19.5 (9.50)
	Min-max	3-44	1-41	5-42
	Mean change from Baseline (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
	Min-max change from Baseline	0-0	0-0	0-0
Week 8	N	62	64	30
	Baseline mean[a] (SD)	19.4 (10.01)	17.8 (9.10)	19.6 (10.31)
	Baseline min-max	3-41	1-41	5-42
	Mean (SD)	40.8 (12.83)	38.0 (13.06)	33.1 (8.85)
	Min-max	6-58	8-60	9-49
	Mean change from Baseline (SD)	21.4 (14.16)	20.3 (13.55)	13.5 (9.52)
	Min-max change from Baseline	(-8) -50	(-6) -50	(-2) -34

Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation, SOS-10 = Schwartz Outcome Scale.
a. Baseline mean denotes the average of baseline SOS-10 scores of subjects who were still in the study at Week 8.

Safety Results:

The number of subjects reporting AEs was 56 (54.4%) in the SEC group, 66 (66.0%) in the sertraline group, and 26 (44.8%) in the placebo group. The number of AEs reported was 168 in the SEC group, 172 in the sertraline group, and 66 in the placebo group. In general, the incidence and severity of AEs was lowest in the placebo group and highest in the

sertraline group. All-causality and treatment-related AEs were most often observed in the system organ class of gastrointestinal disorders, nervous system disorders, psychiatric disorders, and skin and subcutaneous tissue disorders. Table 23 summarizes the AEs observed in ≥2 subjects in any treatment group for all-causality AEs.

Table 23. Treatment-Emergent Adverse Events Occurring in ≥2 Subjects in Any Treatment Group - All Causality

System Organ Class Preferred Term	SEC (N=103) n (%)	Sertraline (N=100) n (%)	Placebo (N=58) n (%)
Cardiac disorders			
Palpitations	2 (1.9)	2 (2.0)	0
Tachycardia	3 (2.9)	3 (3.0)	0
Ear and labyrinth disorders			
Vertigo	1 (1.0)	2 (2.0)	0
Eye disorders			
Vision blurred	0	2 (2.0)	0
Gastrointestinal disorders			
Abdominal distention	2 (1.9)	0	0
Abdominal pain upper	1 (1.0)	2 (2.0)	1 (1.7)
Diarrhoea	8 (7.8)	5 (5.0)	3 (5.2)
Dry mouth	2 (1.9)	9 (9.0)	2 (3.4)
Dyspepsia	2 (1.9)	0	1 (1.7)
Gastritis	0	3 (3.0)	0
Nausea	16 (15.5)	17 (17.0)	4 (6.9)
Vomiting	1 (1.0)	2 (2.0)	1 (1.7)
General disorders and administration site conditions			
Asthenia	3 (2.9)	3 (3.0)	0
Fatigue	0	2 (2.0)	0
Feeling cold	2 (1.9)	0	0
Irritability	2 (1.9)	2 (2.0)	0
Pain	0	0	2 (3.4)
Infections and infestations			
Acute tonsillitis	2 (1.9)	0	0
Gastroenteritis	0	2 (2.0)	1 (1.7)
Influenza	3 (2.9)	3 (3.0)	2 (3.4)
Pharyngitis	0	0	2 (3.4)
Respiratory tract infection	1 (1.0)	2 (2.0)	0
Injury, poisoning and procedural complications			
Contusion	2 (1.9)	1 (1.0)	0
Investigations			
Blood bilirubin increased	0	0	2 (3.4)
Metabolism and nutrition disorders			
Decreased appetite	4 (3.9)	4 (4.0)	0
Musculoskeletal and connective tissue disorders			
Arthralgia	2 (1.9)	0	1 (1.7)
Muscular weakness	2 (1.9)	0	0
Nervous system disorders			
Dizziness	6 (5.8)	7 (7.0)	3 (5.2)
Head discomfort	3 (2.9)	0	2 (3.4)
Headache	13 (12.6)	10 (10.0)	11 (19.0)
Somnolence	2 (1.9)	2 (2.0)	1 (1.7)
Tremor	6 (5.8)	5 (5.0)	0
Psychiatric disorders			
Anxiety	6 (5.8)	10 (10.0)	3 (5.2)
Depression	3 (2.9)	6 (6.0)	2 (3.4)
Insomnia	9 (8.7)	15 (15.0)	4 (6.9)

Table 23. Treatment-Emergent Adverse Events Occurring in ≥2 Subjects in Any Treatment Group - All Causality

System Organ Class Preferred Term	SEC (N=103) n (%)	Sertraline (N=100) n (%)	Placebo (N=58) n (%)
Neurosis	2 (1.9)	1 (1.0)	0
Orgasm abnormal	0	2 (2.0)	0
Sleep disorder	2 (1.9)	1 (1.0)	0
Somatoform disorder	2 (1.9)	0	0
Reproductive system and breast disorders			
Ejaculation failure	0	2 (2.0)	0
Skin and subcutaneous disorders			
Hyperhidrosis	15 (14.6)	6 (6.0)	2 (3.4)
Vascular disorders			
Hot flush	2 (1.9)	1 (1.0)	0

Non-serious AEs and SAEs are not separated out.
Includes data up to 22 days after last dose of study drug.
MEdDRA (v10.0) coding dictionary applied.
AE = adverse event, MEdDRA = Medical Dictionary for Regulatory Activities, N = number of subjects per treatment group, n = number of subjects with AEs, SAE = serious adverse event, SEC = sertraline and elzasonan combination, v = version.

Treatment-related AEs occurring in ≥2 subjects in any treatment group are presented in Table 24.

Table 24. Treatment-Emergent Adverse Events Occurring in ≥2 Subjects in Any Treatment Group – Treatment-Related

System Organ Class Preferred Term	SEC (N=103) n (%)	Sertraline (N=100) n (%)	Placebo (N=58) n (%)
Cardiac disorders			
Palpitations	2 (1.9)	2 (2.0)	0
Tachycardia	3 (2.9)	2 (2.0)	0
Ear and labyrinth disorders			
Vertigo	1 (1.0)	2 (2.0)	0
Gastrointestinal disorders			
Abdominal distention	2 (1.9)	0	0
Abdominal pain upper	1 (1.0)	2 (2.0)	1 (1.7)
Diarrhoea	8 (7.8)	4 (4.0)	2 (3.4)
Dry mouth	2 (1.9)	9 (9.0)	1 (1.7)
Dyspepsia	2 (1.9)	0	1 (1.7)
Nausea	15 (4.6)	17 (17.0)	4 (6.9)
Vomiting	0	2 (2.0)	1 (1.7)
General disorders and administration site conditions			
Asthenia	3 (2.9)	3 (3.0)	0
Fatigue	0	2 (2.0)	0
Feeling cold	2 (1.9)	0	0
Irritability	2 (1.9)	2 (2.0)	0
Metabolism and nutrition disorders			
Decreased appetite	4 (3.9)	4 (4.0)	0
Musculoskeletal and connective tissue disorders			
Muscular weakness	2 (1.9)	0	0
Nervous system disorders			
Dizziness	6 (5.8)	7 (7.0)	3 (5.2)
Head discomfort	3 (2.9)	0	2 (3.4)
Headache	11 (10.7)	7 (7.0)	10 (17.2)
Somnolence	2 (1.9)	2 (2.0)	1 (1.7)
Tremor	5 (4.9)	5 (5.0)	0
Psychiatric disorders			
Anxiety	6 (5.8)	9 (9.0)	2 (3.4)
Depression	0	6 (6.0)	1 (1.7)
Insomnia	9 (8.7)	13 (13.0)	4 (6.9)
Neurosis	2 (1.9)	1 (1.0)	0
Orgasm abnormal	0	2 (2.0)	0
Sleep disorder	2 (1.9)	1 (1.0)	0
Somatoform disorder	2 (1.9)	0	0
Reproductive system and breast disorders			
Ejaculation failure	0	2 (2.0)	0
Skin and subcutaneous disorders			
Hyperhidrosis	15 (14.6)	6 (6.0)	2 (3.4)
Vascular disorders			
Hot flush	2 (1.9)	1 (1.0)	0

Non-serious AEs and SAE are not separated out.
Includes data up to 22 days after the last dose of study drug.
MEdDRA (v10.0) coding dictionary applied.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects per treatment group, n = number of subjects with adverse events, SAE = serious adverse event, SEC = sertraline and elzasonan combination, v = version.

Treatment-emergent serious adverse events (SAEs) were reported for 6 subjects: 2 (1.9%) in the SEC group, 3 (3.0%) in the sertraline group, and 1 (1.7%) in the placebo group. Of these, 1 event in the sertraline group was considered to be treatment related. There was also 1 post-treatment SAE in the sertraline group. A summary of SAEs is presented in Table 25.

Table 25. Serious Adverse Events

Serial Number	Randomized to Treatment Group	Preferred Term	Day of Onset Relative to Study Drug Start	Therapy Stop Day	Causality per Investigator
1	SEC	Depression	51	37	Unrelated
2	SEC	Major depression	46	52	Unrelated
3	Sertraline	Acute psychosis	34	14	Unrelated
4	Sertraline	Depression, anxiety	7	39	Related
5	Sertraline	Fall	28	26	Unrelated
6	Sertraline	Depression	80[a]	56	Unrelated
7	Placebo	Renal colic	59	57	Unrelated

SEC = sertraline and elzasonan combination.
a. Post-treatment serious adverse event.

A total of 33 subjects were discontinued from the study due to AEs: 14 (13.6%) in the SEC group, 13 (13.0%) in the sertraline group, and 6 (10.3%) in the placebo group. Of these, 11 events in the SEC group, 9 in the sertraline group, and 4 in the placebo group were considered treatment-related. One event (in the SEC group) was an SAE: the subject experienced depression on Study Day 52, which was considered severe. It was resolved on Study Day 83. The majority of events were considered moderate in severity and related to study drug. Table 26 presents the AEs that led to permanent discontinuation from the study.

Table 26. Discontinuations due to Adverse Events

System Organ Class	MedDRA Preferred Term	SEC	Sertraline	Placebo
Total number of subjects who discontinued due to AEs		14	11	6
Gastrointestinal disorders	Diarrhea	2	0	0
	Nausea	4	2	0
	Exacerbation of chronic superficial gastritis	0	1	0
Respiratory, thoracic, and mediastinal disorders	Shortness of breath	1	0	0
Eye disorders	Vision distortion	1	0	0
General disorders and administration site conditions	Sickness	1	0	0
	Asthenia	0	1	0
Nervous system disorders	Dizziness	1	0	1
	Sedation	1	0	0
	Over-sedation	0	1	0
	Feeling of internal tremble	1	0	0
	Headache	1	0	0
Psychiatric disorders	Anxiety	3	2	2
	Increase of anxiety	2	0	0
	Insomnia	3	3	1
	Panic attack	1	0	0
	Depression	1	0	0
	Worsening of depression	0	3	1
	Exacerbation of depressive disorder	0	0	1
Skin and subcutaneous tissue disorders	Toxicodermia	1	0	0
	Allergic dermatitis	1	0	0
Renal and urinary disorders	Retention urine	0	1	0
	Renal colic	0	1	0
Metabolism and nutrition disorders	Decreased appetite	0	1	0
Investigations	HCV AB positive	1	0	0
	High bilirubin value	0	0	1
	High level of bilirubin	0	0	1

AB = antibody, AE = adverse event, HCV = hepatitis C virus, MedDRA = Medical Dictionary for Regulatory Activities, SEC = sertraline and elzasonan combination.

There was 1 death during the study, which was not considered to be related to treatment. A female subject in the sertraline group had an SAE of fall that resulted in death (causality was considered the disease under study).

The most common abnormal laboratory tests (regardless of Baseline) were elevated potassium >1.1 x upper limits of normal (5% of subjects from the SEC group, and no subjects from the sertraline or placebo groups), reduced bicarbonate <0.9x lower limits of normal (8% of the SEC group, 11% of the sertraline group, and 5% of the placebo group), and reduced total neutrophils <0.8x lower limits of normal (2% of the SEC, 5% of the sertraline, and 2% of the placebo group). Urinalysis results showed elevated urine

blood/hemoglobin in 14 of 25 subjects in the SEC group, 20 of 29 in the sertraline group, and 10 of 17 in the placebo group. The treatment groups were similar at Baseline for mean supine systolic and diastolic blood pressure and pulse. The mean changes from Baseline through end of study for these variables were minimal for all treatment groups. The changes from Baseline in ECG data were small, and were similar between treatment groups.

CONCLUSION:

- SEC did not demonstrate a significant difference compared to sertraline alone in MADRS remission rate.

- Time to onset of response, as measured by MADRS, was statistically significantly more rapid in the SEC group compared to the sertraline group.

- For MADRS total score change from Baseline and response rates; HAMD17 total score change from Baseline and all subscale scores except for the sleep subscale, and response and remission rates; CGI-I, CGI-S, and HAMA scores change from Baseline, and the proportion of CGI-I responders; a statistically significant difference was seen between each of the SEC and sertraline groups relative to placebo, but not when comparing the SEC group to the sertraline group.

- The CSFQ total and subscale scores showed no difference between any treatment groups. The SOS-10 total and subscale scores showed similar increases in the SEC and sertraline groups, while the placebo group increased to a lesser extent.

- SEC therapy was well-tolerated by the population. No serious safety concerns were identified. In the sertraline group, there was 1 fatal outcome, and it was considered not related to study drug. During the active portion of the study, 6 subjects experienced treatment-emergent SAEs, 1 of which (in the sertraline group) was considered related to study drug.

- AEs were experienced by 54.4% of subjects in the SEC group, 66.0% of subjects in the sertraline group, and 44.8% of subjects in the placebo group; 22 AEs were considered severe, and 31 subjects discontinued the study due to AEs.

- Most AEs were considered mild and unrelated to treatment.