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PROPRIETARY DRUG NAME/INN: Zoloft/Sertraline

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

Sertraline is a selective serotonin reuptake inhibitor, approved in the US for the treatment of major depressive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder and social anxiety disorder in adults, and obsessive-compulsive disorder in adults and children.

PROTOCOL NO.: PROTOCOL A0501066

PROTOCOL TITLE: A Multicenter Randomized, Double-Blind, Parallel-Group Study of Sertraline Versus Venlafaxine XR in the Acute Treatment of Outpatients with Major Depressive Disorder

Study Center(s): Thirteen (13) centers (6 in Australia and 7 in Turkey)

Study Initiation and Completion Dates: 09 October 2002 to 23 September 2003

Phase of Development: Phase 4

Study Objective(s):

Primary objective:

- To assess the comparative efficacy of sertraline versus venlafaxine XR on measures of quality of life (QOL).

Secondary objectives:

- To assess the comparative safety and tolerability of sertraline and venlafaxine XR.
- To assess number and severity of discontinuation symptoms, and time to termination of taper, at the end of acute treatment with sertraline versus venlafaxine XR.
- To assess the comparative efficacy of sertraline and venlafaxine XR on measures of depressive symptomatology, including response and remission rates.

METHODS

Study Design: This was an 8-week, double-blind, double-dummy, parallel-group study of outpatients with Major Depressive Disorder (MDD) who were randomized to flexibly-titrated doses of sertraline (50-150 mg/day) or venlafaxine XR (75-225 mg/day). The treatment phase was preceded by a 1-week screening phase to determine subject eligibility. At the end of 8 weeks of double-blind treatment, subjects tapered off study medication, at a rate not exceeding 50 mg for sertraline and 75 mg for venlafaxine XR every 4 days, during a 2-week taper

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(discontinuation) phase. The maximum duration of exposure to study drug for an individual subject was 10 weeks.

Number of Subjects (planned and analyzed): A sample size of 160 subjects (80 per treatment group) was planned. In this study, 163 subjects were randomized to receive sertraline (n=79) or venlafaxine XR (n=84).

Diagnosis and Main Criteria for Inclusion: Male or female outpatients ≥ 18 years with MDD, diagnosed using the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), with Hamilton-Depression rating scale (HAM-D; 17 item) total score ≥ 18 and HAM-D item 1 (depressed mood) score ≥ 2 , were eligible for entry into this study.

Study Treatment: Following a 1-week screening period, eligible subjects received double-dummy study medication (sertraline 50 mg tablets and venlafaxine placebo or venlafaxine XR 75 mg capsules and sertraline placebo) orally for 10 weeks. Flexible titration of study drug was allowed during the 8-week study treatment period: sertraline 50-150 mg/day, venlafaxine XR 75-225 mg/day. For subjects who did not experience adequate clinical response and dose-limiting side effects, study physicians could increase the dose of drug to the maximum of 150 mg/day for sertraline and 225 mg/day for venlafaxine XR. Packaging of study medication allowed the study physician to raise the dose of drug to 100 mg/day for sertraline or 150 mg/day for venlafaxine XR as early as Week 2, and to 150 mg/day for sertraline or 225 mg/day for venlafaxine XR at Week 3. At the end of the 8-week treatment period, subjects were tapered off study medication; medications were dispensed with instructions to reduce the dose by 1 tablet (sertraline) or 1 capsule (venlafaxine XR) every 4 days during the 2-week taper (discontinuation) phase.

Study Drug	Dosage Form
Sertraline HCl	50 mg white film-coated tablets
Sertraline HCl placebo	50 mg white film-coated tablets
Venlafaxine HCl	75 mg peach-colored extended release capsules
Venlafaxine HCl placebo	75 mg peach-colored extended release capsules

Efficacy Evaluations: The primary efficacy variable was change in QOL, measured using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Secondary efficacy variables were measured using the following scales:

- Hamilton-Depression Rating Scale (HAM-D) including response ($\geq 50\%$ reduction in HAM-D total score from baseline) and remission (HAM-D total score ≤ 7) rates.
- Clinical Global Impression-Severity scale (CGI-S).
- Clinical Global Impression Improvement scale (CGI-I) including response, defined as rating of 1 (very much improved) or 2 (much improved).
- Hamilton Anxiety scale (HAM-A).
- Endicott Work Productivity Scale (EWPS)
- Visual Analogue Scale for Depression (VAS-D)
- Visual Analogue Scale for overall assessment of Pain (VAS-P)

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This study included up to 10 clinic visits: screening, baseline, Weeks 1, 2, 3, 4, 6, 8, 9 and 10. Week 8, the last visit prior to taper, was pre-specified as the principal time-point for comparisons between treatment groups.

Safety Evaluations: Safety was assessed by measuring the incidence of adverse events (AEs), serious adverse events (SAEs), discontinuations, physical examination (including vital signs), and electrocardiograph (ECG) and laboratory abnormalities.

Tolerability was assessed during treatment discontinuation (2-week taper phase) using the Signs and Symptoms of Discontinuation Scale (SSDS). The SSDS was a clinician-rated checklist, assessing the intensity (0-3 scale) and putative relationship of symptom to discontinuation (1-4 scale). The SSDS also included a Global Investigator Assessment where the investigator estimated the severity of discontinuation symptoms experienced by the subject.

Statistical Methods: All statistical tests were 2-sided, with $p < 0.05$ considered significant for treatment differences and $p < 0.10$ for interaction effects.

Efficacy: All efficacy variables (both primary and secondary) were analyzed using the Intention to Treat (ITT) analysis population. The ITT analyses were undertaken using a last observation carried forward (LOCF) methodology (baseline values were not carried forward). These were repeated among Week 8 completers in post hoc analyses. Two subgroups were pre-specified: 1) the anxious-depression subgroup, defined by a baseline HAM-D anxiety-somatization score ≥ 7 ; and 2) the severe-depression subgroup, defined a baseline HAM-D total score ≥ 26 or a baseline CGI-S ≥ 5 .

Treatment differences for changes from baseline to Week 8 on the Q-LES-Q and the other continuous data (HAM-D, HAM-A, VAS-D, and EWPS) were analyzed using analysis of covariance (ANCOVA), with baseline fitted as the covariate, and treatment and study site fitted as factors; least square (LS) means, associated 95% confidence intervals (CI) and p-values were produced. An appreciable proportion of subjects had missing VAS-P scores at baseline (since the scale was added while the study was already ongoing), rendering the analysis of change from baseline using ANCOVA inappropriate. Absolute scores for the relevant continuous variables were therefore analyzed using ANOVA with treatment and study site fitted as factors in a secondary analysis. Treatment differences on the response and remission endpoints were analyzed using a Cochran-Mantel-Haenszel (CMH) test, stratified by study site. Treatment differences on ordinal data (CGI-S and CGI-I) were analyzed using the row mean scores statistic, produced by the CMH test, stratified by site, with ranks used as the scores.

Safety: Standard summaries and listings of AEs, treatment discontinuations, laboratory data, and concomitant medications were generated. AE summaries were prepared for the entire study (i.e., baseline to study end, including the 2-week taper phase). AE summaries were also prepared from baseline to Week 7 (i.e., excluding the Week 8 visit and 2-week taper phase) in post hoc analyses. This post-hoc approach excluded data collected at Week 8 and beyond, when AEs were actively solicited using the SSDS.

Changes from baseline for blood pressure (BP) and heart rate (HR) were analysed in post hoc analyses using ANCOVA with baseline fitted as the covariate, and treatment and study site fitted as factors.

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Signs and symptoms reported in the SSDS at Weeks 9 or 10 that were not present at Week 8, or had increased in severity since Week 8, were defined as discontinuation emergent. Incidence rates for these discontinuation emergent signs and symptoms were calculated for each treatment group. Furthermore, deteriorations in individual signs and symptoms, from Week 8 to worst severity recorded during taper, were summed to form a total score. This score was analyzed using ANOVA with treatment and study site fitted as factors. In addition, the intensity score associated with each SSDS item was multiplied by its relationship to discontinuation score to yield another measure of the relationship between discontinuation emergent symptoms and drug treatment.

Signs and symptoms reported in the SSDS that were described by the clinician as at least probably related to treatment discontinuation were treated as discontinuation related. The worst severity reported for any discontinuation related sign or symptom was identified for each subject and summarized. Treatment groups were compared on this outcome using the CMH test for ordinal data stratified by site. A CMH test for ordinal data stratified by site was used to compare treatment groups on the most severe rating obtained on the Investigator Assessment of Discontinuation Symptoms score over the taper period.

The median time to termination of taper was estimated using the Kaplan-Meier method. A log-rank test was performed to test for treatment differences, and the ratio of the treatment groups' termination of taper rate (i.e., the hazard ratio) was estimated using a Cox proportional hazards model.

RESULTS

Subject Disposition and Demography:

	Sertraline	Venlafaxine XR
Screened: 210		
Randomized	79	84
Treated	79	84
Completed	66 (83.5%)	59 (70.2%)
Discontinued	13 (16.5%)	25 (29.8%)
Analyzed for Efficacy		
ITT Population	79 (100%)	84 (100%)
PP Population	74 (93.7%)	66 (78.6%)
Analyzed for Safety	79 (100%)	84 (100%)*
Subgroup Analyses		
Anxious-Depression	54 (68.4%)	66 (78.6%)
Severe-Depression	38 (48.1%)	46 (54.8%)

* Only 83 (98.8%) subjects had follow-up AE information (one patient was lost to follow-up).

There were no clinically important differences in baseline characteristics between treatment groups; baseline characteristics assessed included age, gender, time since first MD episode, and number of MDD episodes. Approximately half of the subjects in each group had experienced no previous episode of MDD (sertraline, 46.8%; venlafaxine XR, 47.6%). Family history of affective disorder was reported for 53.2% of sertraline and 40.5% of venlafaxine XR subjects.

A total of 38 (23.3%) subjects discontinued prematurely from this study. A higher proportion of subjects discontinued from venlafaxine XR treatment (n=25, 29.8%) compared with sertraline (n=13, 16.5%) in post hoc analysis (p=0.06). Notably, 13 (15.5%) of the venlafaxine XR

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discontinuations occurred during the first calendar week of the study, while there were only 3 (3.8%) discontinuations from the sertraline group during the same time interval (p=0.016, post hoc analysis). Discontinuations are summarized in the following table:

Reasons for Discontinuation

	Sertraline N=79 n (%)	Venlafaxine XR N=84 n (%)
Discontinuations‡	13 (16.5)	25 (29.8)
Related to Study Drug	3 (3.8)	5 (6.0)
Adverse Event	3 (3.8)	5 (6.0)
Not related to Study Drug	10 (12.7)	20 (23.8)
Adverse Event	0	2 (2.4)
Other*	4 (5.1)	5 (6.0)
Subject defaulted**	6 (7.6)	13 (15.5)

*Other included: protocol violation; other (e.g., relocation).

**Subject defaulted included: lost to follow-up; no longer willing to participate.

‡One subject discontinued due to AE, however, the discontinuation was not attributable to a specific AE.

Efficacy Results: There was no statistically significant difference observed between sertraline and venlafaxine XR for change from baseline to endpoint on the primary efficacy measure, Q-LES-Q, for both the ITT and PP analyses. However, clinically meaningful improvements from baseline scores were achieved with both treatments. Results for the ITT analysis population are shown in the following table:

Primary Efficacy Measure: Q-LES-Q – ITT Population

	Sertraline	Venlafaxine XR	Difference in LS means‡	95% CI	p-value
ITT analysis population	N=79	N=84			
Baseline (SD)	55.3 (9.4)	52.7 (11.2)			
Week 8 (SD)	73.4 (12.7)	71.7 (13.9)			
Change* - Week 8 (SE)	19.9 (1.8)	19.5 (1.8)	0.4	-4.2 to 5.0	0.86
Change* - Week 8/LOCF (SE)	16.8 (1.8)	17.5 (1.8)	-0.7	-5.1 to 3.7	0.74

LS, least square mean. ‡Sertraline minus venlafaxine XR: a negative difference indicates a result favoring sertraline. CI, confidence interval. SD, standard deviation. *LS mean change. SE, standard error of the mean. LOCF, last observation carried forward.

On the secondary efficacy measure, the HAM-D, clinically meaningful improvements from baseline scores were observed with both sertraline and venlafaxine XR treatment. However, change from baseline results for the total population, as well as for the anxious-depression and severe-depression subgroups, were not significantly different between treatments. High response ($\geq 50\%$ reduction in HAM-D total score from baseline) and remission (HAM-D total score ≤ 7) rates were observed with both treatments in the total population and subgroups, although differences between treatments were not significant on this measure. Results for the ITT analysis at Week 8/LOCF are tabulated below:

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HAM-D Response and Remission – ITT Analysis Population, Anxious-Depression and Severe-Depression Subgroups

	Sertraline	Venlafaxine XR	p-value
<u>ITT</u>	<u>N=79</u>	<u>N=84</u>	
% Response – Week 8/LOCF	70.9 (of 79)	70.9 (of 79)	0.95
% Remission – Week 8/LOCF	59.5 (of 79)	54.4 (of 79)	0.47
<u>Anxious-Depression</u>	<u>N=54</u>	<u>N=66</u>	
% Response – Week 8/LOCF	79.6 (of 54)	68.9 (of 61)	0.26
% Remission – Week 8/LOCF	63.0 (of 54)	54.1 (of 61)	0.44
<u>Severe-Depression</u>	<u>N=38</u>	<u>N=46</u>	
% Response – Week 8/LOCF	71.1 (of 38)	71.4 (of 42)	0.82
% Remission – Week 8/LOCF	63.2 (of 38)	52.4 (of 42)	0.27

LOCF, last observation carried forward.

In both the sertraline and venlafaxine XR treatment groups, clinically meaningful improvements from baseline scores were observed on all other secondary efficacy measures tested including anxiety, pain, work productivity, and global measures of clinical severity and improvement. Efficacy results determined for the ITT analysis population were supported by the PP analysis, as the results were similar for both analysis populations on all efficacy measures tested. ITT analyses for these secondary efficacy measures are shown in the following table:

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CGI-S, CGI-I, HAM-A, VAS-D, VAS-P and EWPS – ITT Analysis Population

	Sertraline N=79	Venlafaxine XR N=84	Difference in LS means†	95% CI	p-value
<u>CGI-S</u>					
Baseline (SD)	4.5 (0.8)	4.6 (0.8)			
Week 8 (SD)	1.6 (0.8)	2.0 (0.9)			0.08
Week 8/LOCF (SD)	2.0 (1.1)	2.2 (1.3)			0.45
<u>CGI-I</u>					
Week 8 (SD)	1.6 (0.7)	1.8 (1.0)			0.39
Week 8/LOCF	2.0 (1.2)	2.1 (1.4)			0.92
% Response - Week 8	88.7 (of 62)	83.1 (of 59)			0.63
% Response - Week 8/LOCF	73.4 (of 79)	69.1 (of 81)			0.41
<u>HAM-A</u>					
Baseline (SD)	21.6 (7.2)	22.4 (7.6)			
Week 8 (SD)	5.6 (5.3)	7.2 (6.1)			
Change* - Week 8 (SE)	-16.0 (0.8)	-14.7 (0.8)	-1.3†	-3.3 to 0.7	0.19
Change* - Week 8/LOCF (SE)	-14.1 (1.0)	-12.9 (1.0)	-1.2†	-3.7 to 1.2	0.32
<u>VAS-D</u>					
Baseline (SD)	63.0 (20.5)	67.8 (19.9)			
Week 8 (SD)	18.8 (18.8)	22.6 (22.2)			
Change* - Week 8 (SE)	-48.5 (3.0)	-46.6 (3.0)	-1.9†	-9.5 to 5.6	0.62
Change* - Week 8/LOCF (SE)	-45.1 (3.1)	-42.0 (3.0)	-3.0†	-11 to 4.5	0.43
<u>VAS-P</u>					
Baseline (SD)	39.0 (29.4)	29.4 (23.8)			
LS Mean Week 8 (SE)	14.2 (4.0)	10.4 (4.1)	3.8‡	-7.5 to 15.1	0.50
LS Mean Week 8/LOCF (SE)	14.6 (3.6)	11.3 (3.47)	3.3‡	-6.3 to 12.9	0.49
<u>EWPS</u>					
Baseline (SD)	40.1 (15.9)	41.2 (20.3)			
Week 8 (SD)	16.7 (14.7)	21.7 (16.2)			
Change* - Week 8 (SE)	-22.9 (2.9)	-18.4 (3.1)	-4.6†	-13 to 3.6	0.27
Change* - Week 8/LOCF (SE)	-22.0 (2.9)	-17.9 (3.1)	-4.2†	-12 to 3.9	0.31

LS, least square mean. †Sertraline minus venlafaxine XR: a negative difference indicates a result favoring sertraline. ‡A positive difference indicates a result favoring sertraline. CI, confidence interval. SD, standard deviation. *LS mean change. SE, standard error of the mean. LOCF, last observation carried forward.

Safety Results:

Discontinuations: Discontinuation rates were higher for venlafaxine XR-treated subjects compared with sertraline-treated subjects during the study (29.8% vs. 16.5%; p=0.06 post hoc analysis). Furthermore, a significantly higher proportion of subjects in the venlafaxine XR treatment group prematurely discontinued during the first calendar week of the study compared with sertraline (15.5% vs. 3.8%; p=0.016 post hoc analysis).

Adverse Events: The incidence of AEs was comparable between treatments with the majority of AEs reported as mild to moderate in severity. The incidence of AEs reported throughout the entire study period, including AEs recorded on the SDSS during taper, was high in both treatment groups. The incidence of AEs was not as high when AEs reported during taper (Week

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8 and beyond) were removed. Incidences ($\geq 50\%$ in either treatment group during the entire study) of AEs are summarized in the following table:

Adverse Events: $\geq 50\%$ Incidence– Safety Population

Event	Baseline to Study End*	
	Sertraline N=79 n (%)	Venlafaxine XR N=84 n (%)
Anxiety	42 (53.2)	37 (44.0)
Asthenia	43 (54.4)	40 (47.6)
Dizziness	38 (48.1)	43 (51.2)
Headache	53 (67.1)	48 (57.1)
Insomnia	46 (58.2)	42 (50.0)
Nausea	45 (57.0)	50 (59.5)

*Includes acute treatment period (baseline to Week 8) and the taper period (Week 8 and beyond).

In total, 8 subjects discontinued from this study due to treatment related AEs: 3 (3.8%) sertraline subjects and 5 (6.0%) venlafaxine XR subjects. **Serious Adverse Events:** There was a total of 4 subjects with SAEs reported during this study (1 sertraline-treated subject and 3 venlafaxine XR-treated subjects). None of the SAEs recorded were considered related to study treatment. Two venlafaxine XR-treated subjects with SAEs (both took intentional overdoses of a number of medications) were permanently discontinued within a few weeks of starting the study. One sertraline-treated subject recovered from their SAE (acute anxiety) and remained in the study, and 1 venlafaxine XR-treated subject had an SAE that occurred post therapy (accidental injury and exacerbation of depression).

Vital Signs: Significant differences between both treatments in their effect on systolic and diastolic BP were found in post hoc analysis of BP data. Sertraline was generally associated with a modest reduction in BP, while venlafaxine XR was associated with a more pronounced increase in BP. Differences between treatments were statistically significant at Week 8/LOCF for supine systolic (LS mean difference -3.7, 95% CI -7.3 to -0.2, $p=0.037$) and supine diastolic BP (LS mean difference -4.4, 95% CI -7.5 to -1.4, $p=0.004$).

There were also significant differences between treatments in their effect on HR; venlafaxine XR increased supine and standing HR significantly more than sertraline treatment. Change in supine HR was 0.9 ± 1.1 in the sertraline treatment group and 4.3 ± 1.1 in the venlafaxine XR treatment group (LS mean difference -3.3, 95%CI, -5.9 to -0.7, $p=0.013$). Change in standing HR was 0.4 ± 1.2 and 4.1 ± 1.1 (LS mean difference -3.7, 95%CI, -6.6 to -0.9, $p=0.01$) in subjects treated with sertraline and venlafaxine XR, respectively (Week 8/LOCF, post hoc analysis).

SSDS: The discontinuation emergent symptom profile appeared relatively comparable between sertraline and venlafaxine XR in the pre-specified analyses for SSDS, and the severity of SSDS symptoms reported was, for the most part, mild or moderate with only a small proportion of SSDS symptoms reported as severe. However, there were 4 symptoms on the SSDS that had a frequency that was 10% greater in the venlafaxine XR group when compared with the sertraline group (dizziness, fatigue, vertigo and vivid dreams); post hoc analysis results, shown in the following table, revealed significant differences between treatments on these 4 symptoms. There

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were no significant differences between sertraline and venlafaxine XR on the investigator assessment of discontinuation symptoms during the taper period.

Incidence (>10%) of Discontinuation Emergent SSDS Symptoms – Safety Population

SSDS Symptoms	Sertraline N=79		Venlafaxine XR N=84		p-value*
	Any**	Severe	Any**	Severe	
Dizziness, %	33.3	1.4	43.8	10.9	0.22
Fatigue, %	22.2	2.8	32.8	0.0	0.18
Vertigo, %	5.6	0.0	17.2	6.3	0.052
Vivid dreams, %	26.4	2.8	42.2	4.7	0.069

*p-values were calculated during post hoc analyses. **mild, moderate or severe.

Time to Termination of Taper: There was no significant difference between treatments for time to termination of taper; median time was 4 days for both treatment groups (p=0.911).

CONCLUSION(S)

Efficacy Conclusions: In this sample population of outpatients with MDD, subjects in both the sertraline and venlafaxine XR treatment groups experienced substantial improvements in QOL over the 8-week treatment period; however, there were no significant differences observed between treatments. Sertraline and venlafaxine XR were both found to be effective treatments for reduction of depressive symptomatology in MDD, as substantial and clinically meaningful changes from baseline to endpoint were observed on all efficacy measures tested during the 8-week acute treatment period of this study.

This study was adequately powered to reliably detect a clinically meaningful difference of 5.8 points between sertraline and venlafaxine XR on the Q-LES-Q at Week 8/LOCF. The estimated difference between treatments was -0.7 (favoring sertraline) and the 95% CI for the estimated treatment differences on this endpoint ranged from -5.1 to 3.7 (ITT analysis population). This result indicates that it is implausible that a clinically important difference of at least 5.8 points on Q-LES-Q exists between the treatments as administered per this protocol.

The results suggest that sertraline was comparable to venlafaxine XR in terms of antidepressant efficacy during the 8-week acute treatment period of this study. No significant differences were observed between treatments for the total study population, the anxious-depression subgroup, or the severe depression subgroup on any of the efficacy measures tested.

Safety Conclusions: The incidence of AEs was high in both the sertraline and venlafaxine XR treatment groups; however, the majority of AEs were reported as mild to moderate in severity and sertraline and venlafaxine XR were generally found to be safe and well tolerated during this study. There were some safety advantages with sertraline treatment over venlafaxine XR in terms of lower discontinuation rates and changes in BP and HR.

Based on a report completed on : 23 September 2004