CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-033
Drug Name:	Luvox® (Fluvoxamine CR)
Indication(s):	Obsessive Compulsive Disorder and Generalized Social Anxiety Disorder
Applicant:	Solvay Pharmaceuticals, Inc.
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Keywords: Luvox® CR, OCD, Generalized SAD, Ranked ANOVA, LOCF, MMRM

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this submission, the sponsor conducted 3 pivotal short-term Luvox® (Fluvoxamine CR) studies between April 1999 and May 2000 in the United States, Europe and South Africa. Studies 3103 and 3107 were conducted in the United States alone. The primary objectives of the studies were to evaluate the efficacy and safety of Luvox® CR compared with placebo in subjects with Generalized Social Anxiety Disorder (SAD) (Studies 3107 and 3108) and Obsessive Compulsive Disorder (OCD) (Study 3103). The primary efficacy measure was the change from baseline of LSAS total score in Studies 3107 and 3107 and the change from baseline to endpoint of Y-BOCS total score in Study 3103. No key secondary efficacy measure was pre-specified.

The analysis results support the efficacy claim of Luvox® CR in the treatment of Generalized SAD (Studies 3107 and 3108) and OCD (Study 3103) at the end of the study (Week 12). The efficacy results included those in the ANOVA and ranked ANOVA analyses with OC and LOCF data and the MMRM analyses. Together these results support the claim of Luvox® CR in the treatment of Generalized SAD and OCD at Week 12.

1.2 Brief Overview of Clinical Studies

Three pivotal studies were submitted for the evaluation of the efficacy of Luvox® CR in doses of 100 mg to 300 mg/day in the treatment of patients between ages of 18 and 70 with Generalized SAD (Studies 3107 and 3108) and OCD (Study 3103). The studies were conducted between April 1999 and May 2000 in North America, Europe and South Africa.

Studies 3107 and 3108 were multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in adult patients with Generalized SAD, with a double-blind treatment period of 12 weeks. The primary objectives of the pivotal studies were to evaluate the efficacy and safety of Luvox® CR compared with placebo in subjects with Generalized SAD. The primary efficacy measure was the change from baseline to endpoint of LSAS total score. No key secondary efficacy measure was pre-specified in protocol. In the data analyses, both studies were positive on the reduction of the primary efficacy measure in LOCF analyses. Study 3103 was also a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of Luvox® CR in patients of 18 or older with OCD. The primary efficacy measure was the change from baseline to endpoint of Y-BOCS total score. In the LOCF analyses, the study was positive on the reduction of the primary efficacy measure.

In all the efficacy studies, after the screening period (1 to 14 days), subjects were treated for 12 weeks during a double-blind phase. In the combination of Studies 3107 and 3108, a total of 579 patients were randomized in the United States, Europe, and South Africa, with 288 to the Luvox® CR group (100 to 300 mg/day) and 291 to placebo. Study 3107 was conducted in the United States alone. Of those, 541 patients were included in the ITT analysis data set, including 267 in the Luvox® CR group and 274 in the placebo group. Over three quarters of the patients were Caucasian and more than half were male. The majority of the patients were between 18 and 50 years of age.

In study 3103, a total of 253 patients were randomized across 20 centers throughout the United States, 127 to the Luvox® CR group (100 to 300 mg/day) and 126 to placebo. Of those, 237 patients were included in the ITT analysis data set, with 117 in the Luvox® CR group and 120 in the placebo group. Over three quarters of the patients were Caucasian and majority were female. The majority of the patients were between 18 and 50 years of age.

1.3 Statistical Issues and Findings

Pivotal efficacy Studies 3107, 3108 and 3103 were all 12-week, phase 3, multicenter, randomized, double blind, placebo-controlled, flexible-dose studies with the treatment group of Luvox® CR and placebo. The primary efficacy analyses on the change from baseline of the LSAS total score in Studies 3107 and 3108 (the Y-BOCS total score in Study 3103) were performed using ranked ANOVA with LOCF data.

The analysis results support the efficacy claim of Luvox® CR in the treatment of Generalized SAD (Studies 3107 and 3108) and OCD (Study 3103) at the end of the studies. The efficacy results include those in the ANOVA analyses, ranked ANOVA analyses and MMRM analyses. Together these results supported the claim of Luvox® CR in the treatment of Generalized SAD and OCD at Week 12.

2. INTRODUCTION

2.1 Overview

In this submission, three 12 week, flexible-dose studies were submitted for the evaluation of the efficacy and safety of Luvox® CR in doses of 100 to 300 mg/day in the treatment of Generalized SAD (Studies 3107 and 3108) and OCD (Study 3103) in adult outpatients (Table 2.1).

Table 2.1: Studies Supporting the Efficacy and Safety of Luvox® CR in the Treatment of Generalized SAD and OCD

Protocol	Study Description	Study Treatment	No. of Subjects[a]
S1143107	12-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study	Placebo	140
		Luvox® CR (flexible dose 100 to 300 mg/day)	139
S1143108	12-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study	Placebo	151
		Luvox® CR (flexible dose 100 to 300 mg/day)	149
S1143103	12-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study	Placebo	126
		Luvox® CR (flexible dose 100 to 300 mg/day)	127

a: Includes all subjects who were randomized.
Source: Reviewer.

All the pivotal studies were multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose studies (100 to 300 mg/day) in adult patients with Generalized SAD (for Studies 3107 and 3108) and OCD (for Study 3103), with a double-blind treatment period of 12 weeks. The efficacy results are evaluated in this review.

These studies were conducted between April 1999 and May 2000 (July 6, 1999 to January 21, 2000 for Study 3107, September 10, 1999 to May 10, 2000 for Study 3108, and April 29, 1999 to February 24, 2000 for Study 3103) in the United States, Europe and South Africa. In the pooled pivotal Studies 3103, 3107 and 3108, a total of 832 subjects were randomized. Of those, 778 subjects were included in the ITT analysis data sets, including 384 subjects in the Luvox® CR group (100 to 300 mg/day), and 394 subjects in the placebo group. The numbers of subjects in all studies are given in Table 2.1.

2.2 Data Sources

The study reports were provided in paper form and electronic SAS transport data sets for the studies were provided in \\cdsesub1\n22033\n_000\2006-04-28\crt and \\cdsesub1\n22033\n_000\2006-07-14\crt.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The pivotal efficacy studies were all 12-week, multicentered, randomized, double-blind, placebo-controlled, flexible-dose studies. Each was designed to evaluate the efficacy and safety of Luvox® CR compared with placebo in subjects with Generalized SAD or OCD. Eligible subjects were randomly assigned to receive flexible doses of Luvox® CR (range of 100 to 300 mg/day) or placebo (Table 2.1). Patients randomized to Luvox® CR group started with 100 mg/day. The dose was to be increased in increment of 50 mg/day in intervals of at least one week during the first 5 weeks to a maximum of 300 mg/day. From Week 1 to Week 5, the dose could be decreased once by 50 mg/day in the event of intolerable adverse event. No dose adjustment was permitted during Week 6 to Week 12 of the double-blind phase.

In Studies 3107 and 3108, eligible subjects were from 18 to 70 years of age, with a predominant DSM-IV diagnosis of Generalized SAD using modified SCID-I for at least six months prior to the Screen Visit and a minimum score of 60 at Screening. In Study 3103, eligible subjects were aged 18 or above, having a DSM-IV diagnose of OCD, scored at least 21 on the Y-BOCS at the Screening and Baseline visits and score $\leq$ 16 on the 17-item HamD at the Screening visit.

In Studies 3107 and 3108, the change from baseline to the endpoint (Week 12) in the LSAS total score was the primary variable. Secondary variables included the CGI Improvement score and PGI of Improvement score at endpoint, the changes from baseline to endpoint in the SDS total score, CGI-S, MADRS total score and the ASD total score. The primary variable of Study 3103 was the change from baseline to endpoint in the Y-BOCS total score. The secondary variable included CGI Improvement score at endpoint, proportion of responders, and the change from baseline to endpoint in the CGI Severity of Illness. The tests were two sided and the overall significance level for each study was α=0.05.

3.1.1 Dispositions

The number of subjects randomly assigned to each treatment group and those included in the ITT analysis data set are shown in Table 3.1. In Study 3107, a total of 279 subjects were randomized to trial treatments, and of these, 247 subjects were included in the ITT analysis data set, including 121 subjects in the Luvox® CR treatment group and 126 subjects in placebo. All (14) subjects enrolled at Center 14 were excluded from the ITT population due to scientific misconduct and non-compliance with GCP at this site. The medical reviewer agreed to the exclusion of this center from the primary analysis. Of the 14 subjects, 6 were randomized to the Luvox® CR group and 8 were randomized to placebo. In addition, 5 patients didn't take medication and 13 patients didn't have the post-baseline efficacy measurements. These were excluded from the ITT population as well. In Study 3108, a total of 300 subjects were randomized to trial treatments, and of these, 294 subjects were included in the ITT analysis data set, including 146 subjects in the Luvox® CR group and 148 subjects in placebo. In Study 3103, a total of 253 subjects were randomized to trial treatments, and of these, 237 subjects were included in the ITT analysis data set, including 117 subjects in the Luvox® CR group and 120 in placebo. The reasons for excluding these patients from ITT population were not taking medication and lacking post-randomization efficacy measurements.

Table 3.1: Number of Subjects Randomly Assigned by Group in Each Study

Study Number	Luvox® CR (N=415) n (%)	Placebo (N=417) n (%)
S1143107		
All Randomized	139	140
Intent-to-Treat	121 (87%)	126 (90%)
S1143108		
All Randomized	149	151
Intent-to-Treat	146 (98%)	148 (98%)
S1143103		
All Randomized	127	126
Intent-to-Treat	117 (92%)	120 (95%)

Source: Panel 3.8.1.1 and Panel 3.8.2.1 of sponsor's Efficacy Findings.

3.1.2 Demographic Characteristics

The patient baseline demographic characteristics appear in Tables 3.2 to 3.4 for these three studies. There seemed to be no significant differences among treatment groups in the demographic characteristics. The majority of the patients were Caucasian. In Study 3107 the majority were male while in Study 3103 the majority were female. The mean age was around 38 in all three studies.

Table 3.2 Baseline Demographic Characteristics for Study 3107--ITT Population

	Statistics	Treatment Group		
		Luvox® CR (N=121)	Placebo (N=126)	Comparison P-value
Age (years)	N	121	126	0.96
	Mean (S.E.)	37.6 (1.1)	38.0 (1.0)	
	Median	37	37	
	Min., Max.	18, 67	18, 68	
Age Category				0.97
18-30	n (%)	41 (34)	33 (26)	
31-40	n (%)	28 (23)	45 (36)	
41-50	n (%)	32 (26)	29 (23)	
51-64	n (%)	19 (16)	16 (13)	
≥ 65	n (%)	1 (<1)	3 (2)	
Gender				
Male	n (%)	74 (61)	87 (69)	0.19
Female	n (%)	47 (39)	39 (31)	
Ethnicity				0.51
Caucasian	n (%)	100 (83)	100 (79)	
Black	n (%)	7 (6)	11 (9)	
Asian	n (%)	4 (3)	3 (2)	
Other	n (%)	3 (2)	4 (3)	
American Indian /Alaskan Native	n (%)	0	1 (<1)	
Hispanic	n (%)	7 (6)	7 (6)	

Source: Panel 3.8.1.2 on 3.0:v2:p167 of sponsor's Clinical Study Report.

Table 3.3 Baseline Demographic Characteristics for Study 3108--ITT Population

	Statistics	Treatment Group		
		Luvox® CR (N=146)	Placebo (N=148)	Comparison P-value
Age (years)	N	146	148	0.30
	Mean (S.E.)	38.6 (0.9)	37.2 (0.9)	
	Median	39	35	
	Min., Max.	18, 63	18, 69	
Age Category				0.21
18-30	n (%)	39 (27)	51 (34)	
31-40	n (%)	42 (29)	45 (30)	
41-50	n (%)	43 (29)	33 (22)	
51-64	n (%)	22 (15)	16 (11)	
≥ 65	n (%)	0	3 (2)	
Gender				
Male	n (%)	68 (47)	74 (50)	0.59
Female	n (%)	78 (53)	74 (50)	
Ethnicity				0.15
Caucasian	n (%)	130 (89)	138 (93)	
Black	n (%)	7 (5)	2 (1)	
Asian	n (%)	4 (3)	3 (2)	
Other	n (%)	4 (3)	4 (3)	
American Indian /Alaskan Native	n (%)	0	0	
Hispanic	n (%)	1 (<1)	1 (<1)	

Source: Panel 3.8.1.2 on 3.0:v2:p167 of sponsor's Clinical Study Report.

Table 3.4 Baseline Demographic Characteristics for Study 3103--ITT Population

	Statistics	Treatment Group		
		Luvox® CR (N=117)	Placebo (N=120)	Comparison P-value
Age (years)	N	117	120	0.66
	Mean (S.E.)	37.8 (1.1)	37.2 (1.0)	
	Median	36	36	
	Min., Max.	19, 70	18, 69	
Age Category				0.66
18-30	n (%)	37 (32)	39 (32)	
31-40	n (%)	37 (32)	38 (32)	
41-50	n (%)	24 (21)	27 (23)	
51-64	n (%)	15 (13)	14 (12)	
≥ 65	n (%)	4 (3)	2 (2)	
Gender				
Male	n (%)	47 (40)	40 (33)	0.27
Female	n (%)	70 (60)	80 (67)	
Ethnicity				0.18
Caucasian	n (%)	99 (85)	94 (78)	
Black	n (%)	5 (4)	7 (6)	
Asian	n (%)	3 (3)	3 (3)	
Other	n (%)	4 (3)	3 (3)	
American Indian /Alaskan Native	n (%)	1 (<1)	2 (2)	
Hispanic	n (%)	5 (4)	11 (9)	

Source: Panel 3.8.2.2 on 3.0:v2:p191 of sponsor's Clinical Study Report.

3.1.3 Patient Discontinuation

In Study 3107, 279 subjects were randomized and 160 (57%) completed the 12-week double-blind phase, as shown in Table 3.5. The most common reason for early withdrawal was Adverse Experience: 1% in the placebo group and 26% in the Luvox® CR group, respectively. This is very unbalanced. The second common reason for early withdrawal was Withdraw Consent: 13% in placebo group and 12% in Luvox® CR group.

In Study 3108, 300 subjects were randomized and 199 (66%) completed the 12-week double-blind phase, as shown in Table 3.5. The most common reason for early withdrawal was Adverse Experience: 5% in the placebo group and 26% in the Luvox® CR group, respectively. This is very unbalanced. In the placebo group, 9% patients dropped out early due to Lack of Efficacy while no one dropped out due to that reason in the Luvox® CR group, which is also very unbalanced.

In Study 3103, 253 subjects were randomized and 179 (71%) completed the 12-week double-blind phase, as shown in Table 3.5. The most common reason for early withdrawal was Adverse Experience: 6% in the placebo group and 19% in the Luvox® CR group, respectively.

Table 3.5 Number (%) of Subjects Who Discontinued Treatment During the Double-Blind Period by Primary Reason for Withdrawal

	Luvox® CR	Placebo	Overall
Study 3107	(N=139)	(N=140)	(N=279)
Total withdrawal	66 (47)	53 (38)	119 (43)
Reason for Withdrawal			
Lack of efficacy	1 (<1)	11 (8)	12 (4)
Adverse experience	36 (26)	2 (1)	38 (14)
Lost to follow-up	2 (1)	9 (6)	11 (4)
Protocol violation	5 (4)	5 (4)	10 (4)
Withdrew consent	17 (12)	18 (13)	35 (13)
Other	5 (4)	8 (6)	13 (5)
Study 3108	(N=149)	(N=151)	(N=300)
Total withdrawal	57 (38)	44 (29)	101 (34)
Reason for withdrawal			
Lack of efficacy	0	14 (9)	14 (5)
Adverse experience	38 (26)	8 (5)	46 (15)
Lost to follow-up	4 (3)	5 (3)	9 (3)
Protocol violation	7 (5)	9 (6)	16 (5)
Withdrew consent	5 (3)	4 (3)	9 (3)
Other	3 (2)	4 (3)	7 (2)
Study 3103	(N=127)	(N=126)	(N=253)
Total withdrawal	43 (34)	31 (25)	74 (29)
Reason for withdrawal			
Lack of efficacy	2 (2)	4 (3)	6 (2)
Adverse experience	24 (19)	8 (6)	32 (13)
Lost to follow-up	7 (6)	8 (6)	15 (6)
Protocol violation	2 (2)	2 (2)	4 (2)
Other	8 (6)	9 (7)	17 (7)

Source: Panel 6.1 in Section 8.16 of the Clinical Study Report for each study.

In the analyses, we noted that (1) Twelve subjects in the ITT population of Study 3107 did not have the post randomization observations for the primary endpoint of the total LSAS score so only 235 patients were included in the efficacy analysis. Among them, 11 were in the treatment group and 1 was in the placebo group. (2) Twenty subjects in the ITT population of Study 3108 did not have the post randomization observations for the primary endpoint of the total LSAS score so only 274 patients were included in the efficacy analysis. These patients were all from the treatment group and none from placebo group. (3) Five subjects in the ITT population of Study 3103 did not have the post randomization observations for the primary endpoint of the total Y-BOCS score so only 232 patients were included in the efficacy analysis. Among them, 4 were in the treatment group and 1 was in the placebo group.

3.1.4 Baseline Disease Characteristics

Across the individual studies, the baseline psychiatric diagnosis and history were similar between the treatment and placebo group. At baseline, the mean LSAS total scores (Studies 3107 and 3108) and the Y-BOCS total score (Study 3103) were similar the treatment and placebo group.

3.1.5 Statistical Issues

The primary efficacy analysis was performed on the change from baseline of the LSAS total score for Studies 3107 and 3108 (Y-BOCS total score for Study 3103) at the end of the double blind phase (Week 12) in the ITT population, defined as all the subjects who were randomized, received at least 1 dose of study medication, and had a least 1 post-baseline efficacy assessment. The outcome variables were administrated at Baseline, Weeks 2, 4, 6, 8, 10 and 12. The primary comparison was conducted between Luvox® CR group and placebo.

According to the protocol, statistical significance was tested at an overall significance level of 0.05 (2-sided) in each study. LOCF was to be used as the primary analysis for the missing observations of the dropout patients. The analysis of variance (ANOVA) with treatment and pooled center as factors was used to test treatment effect. If positive treatment effect was found, homogeneity of treatment effect over centers was to be tested at α=0.15. In general, normality and homogeneity of the variance are required for the ANOVA model to be valid. However, given large sample size, such requirement is not critical due to the large sample theory. Such assumptions were proposed to be tested in protocol using the Shapiro-Wilk test and the Levene test although no alternative statistical methods were proposed if such assumptions were violated. In the Study Reports however, the sponsor suggested that if the normality assumption on any primary endpoint was rejected at the p-value of 0.001 with the Shapiro-Wilk test, then the ranked ANOVA model for the change from baseline of the primary endpoint would be applied. At the same time, if the large heterogeneity of variance was found with the Levene test, the exact F test was to be used. But no criterion for the "large heterogeneity" was given.

Centers were pooled before unblindness in order to conduct analyses with adjustment for centers and to test for interactions involving centers. However, the sponsor did not give the principle under which these centers were pooled except describing which centers were pooled. In Study 3107, Centers 1, 14, 16, 22, 23, 24 and 29 were pooled. Due to scientific misconduct at Center 14, data from this center was excluded from the ITT population for the primary efficacy analyses. The medical reviewer agreed to the exclusion of this center from the primary efficacy analysis. Such analyses with Center 14 combined with all other centers were presented in Appendix 12.2.6 of the Study Report. Results were consistent whether this center is excluded or not. Study 3108 was conducted in 42 centers in six countries (France, Germany, UK, Ireland, South Africa and Netherlands). These centers were combined into 22 centers. Panel 5.4 of the

Study Report gave the combinations. In study 3103, Centers 4, 6, 11, 13, 15 and 18 were pooled; Centers 7 and 9 were pooled; and Centers 8 and 17 were pooled.

Given the analysis data sets in Studies 3107, 3108 and 3103, the normality assumption for the change from baseline of the primary endpoints was all significant with p-values below 0.001 using the Shapiro-Wilk test. Therefore, the treatment effect was tested using the ranked ANOVA on the change from baseline of primary endpoints (LSAS total score for Studies 3107 and 3108 and Y-BOCS total score for Study 3103.). The homoscedasticity was assessed through the plot of residuals against the predicted values from ANOVA model on the change from baseline of the primary efficacy measure. No heteroscedasticity was found from the plots.

Table 3.6: Statistical Comparisons between Treatment and Placebo for Primary Efficacy Variable LSAS Total Score in Studies 3107, 3108 and Total Y-BOCS score in Study 3103–LOCF ITT Population for Week 12

	Luvox® CR	**Placebo**
Study 3107	(N=139)	(N=140)
N (ITT population)	121	126
N (ITT for LSAS Total Score)	110	125
Baseline Mean (Raw)	90.0	89.3
LS Mean change from baseline (SE)[a]	-26.6 (2.23)	-13.2 (2.16)
Median	-19.5	-10
LS Mean treat effect and 95% CI[a]	-13.4 (-19.4, -7.5)	
P-value[b]	<0.0001	
Study 3108	(N=149)	(N=151)
N (ITT population)	146	148
N (ITT for LSAS Total Score)	126	148
Baseline Mean	95.9	93.9
LS Mean change from baseline (SE)[a]	-34.6 (2.96)	-26.2 (2.83)
Median	-33	-23.5
LS Mean treat effect and 95% CI[a]	-8.4 (-15.5, -1.2)	
P-value[b]	0.023	
Study 3103	(N=117)	(N=120)
N (ITT population)	117	120
N (ITT for Y-BOCS Total Score)	113	119
Baseline Mean	26.6	26.3
LS Mean change from baseline (SE)[a]	-8.7 (0.71)	-5.9 (0.70)
Median	-7	-4
LS Mean treat effect and 95% CI[a]	-2.8 (-4.7, -0.9)	
P-value[b]	0.001	

a: Estimate is made from ANOVA model with treatment and analysis center as factors.
b: Test for no difference between treatments from ranked ANOVA model with treatment and analysis center as factors.
Note: Negative change in score indicates improvement.

Source: Reviewer.

Table 3.7: Statistical Comparisons between Treatment and Placebo for Primary Efficacy Variable LSAS Total Score in Study 3107 – LOCF ITT Population for Weeks 2-10

Study 3107	Luvox® CR	Placebo
	(N=139)	(N=140)
N (ITT population)	121	126
N (ITT for LSAS Total Score)	110	125
Baseline Mean (Raw)	90.0	89.3
Week 2		
N (ITT for LSAS Total Score)	108	124
LS Mean change from baseline (SE) [a]	-8.4 (1.25)	-6.7 (1.22)
LS Mean treat effect and 95% CI [a]	-1.7 (-5.0, 1.6)	
P-value [b]	0.14	
Week 4		
N (ITT for LSAS Total Score)	110	125
LS Mean change from baseline (SE) [a]	-14.0 (1.41)	-9.5 (1.37)
LS Mean treat effect and 95% CI [a]	-4.5 (-8.2, -0.7)	
P-value [b]	0.037	
Week 6		
N (ITT for LSAS Total Score)	110	125
LS Mean change from baseline (SE) [a]	-20.4 (1.79)	-11.8 (-1.74)
LS Mean treat effect and 95% CI [a]	-8.6 (-13.3, -3.8)	
P-value [b]	0.0003	
Week 8		
N (ITT for LSAS Total Score)	110	125
LS Mean change from baseline (SE) [a]	-24.3 (1.96)	-12.0 (1.90)
LS Mean treat effect and 95% CI [a]	-12.2 (-17.4, -7.0)	
P-value [b]	<0.0001	
Week 10		
N (ITT for LSAS Total Score)	110	125
LS Mean change from baseline (SE) [a]	-25.9 (2.15)	-13.5 (2.08)
LS Mean treat effect and 95% CI [a]	-12.4 (-18.1, -6.7)	
P-value [b]	<0.0001	

a: Estimate is made from ANOVA model with treatment and analysis center as factors.
b: Test for no difference between treatments from ranked ANOVA model with treatment and analysis center as factors. Not adjusted for multiplicity.
Note: Negative change in score indicates improvement.

Source: Reviewer.

Table 3.8: Statistical Comparisons between Treatment and Placebo for Primary Efficacy Variable LSAS Total Score in Study 3108 – LOCF ITT Population for Weeks 2-10

Study 3108	Luvox® CR	Placebo
	(N=149)	(N=151)
N (ITT population)	146	148
N (ITT for LSAS Total Score)	126	148
Baseline Mean (Raw)	95.9	93.9
Week 2		
N (ITT for LSAS Total Score)	126	148
LS Mean change from baseline (SE) [a]	-8.8 (1.58)	-7.6 (1.51)
LS Mean treat effect and 95% CI [a]	-1.2 (-5.0, 2.58)	
P-value [b]	0.57	
Week 4		
N (ITT for LSAS Total Score)	126	148
LS Mean change from baseline (SE) [a]	-17.2 (1.99)	-12.4 (1.90)
LS Mean treat effect and 95% CI [a]	-4.8 (-9.6, -0.02)	
P-value [b]	0.024	
Week 6		
N (ITT for LSAS Total Score)	126	148
LS Mean change from baseline (SE) [a]	-22.9 (2.42)	-17.7 (2.31)
LS Mean treat effect and 95% CI [a]	-5.2 (-11.0, 0.6)	
P-value [b]	0.07	
Week 8		
N (ITT for LSAS Total Score)	126	148
LS Mean change from baseline (SE) [a]	-28.8 (2.77)	-20.2 (2.65)
LS Mean treat effect and 95% CI [a]	-8.6 (-15.3, -2.0)	
P-value [b]	0.008	
Week 10		
N (ITT for LSAS Total Score)	126	148
LS Mean change from baseline (SE) [a]	-30.6 (2.83)	-23.9 (2.71)
LS Mean treat effect and 95% CI [a]	-6.7 (-13.5, 0.08) [a]	
P-value [b]	0.02 [b]	

a: Estimate is made from ANOVA model with treatment and analysis center as factors.
b: Test for no difference between treatments from ranked ANOVA model with treatment and analysis center as factors. Not adjusted for multiplicity.
Note: Negative change in score indicates improvement.

Source: Reviewer.

Table 3.9: Statistical Comparisons between Treatment and Placebo for Primary Efficacy Variable Total Y-BOCS Score in Study 3103 – LOCF ITT Population for Weeks 2-10

Study 3103	Luvox® CR	Placebo
	(N=117)	(N=120)
N (ITT population)	117	120
N (ITT for Y-BOCS Total Score)	113	119
Baseline Mean (Raw)	26.6	26.3
Week 2		
N (ITT for Y-BOCS Total Score)	112	118
LS Mean change from baseline (SE) [a]	-4.0 (0.46)	-2.3 (0.45)
LS Mean treat effect and 95% CI [a]	-1.7 (-2.9, -0.4)	
P-value [b]	0.024	
Week 4		
N (ITT for Y-BOCS Total Score)	113	119
LS Mean change from baseline (SE) [a]	-5.5 (0.50)	-3.9 (0.50)
LS Mean treat effect and 95% CI [a]	-1.6 (-3.0, -0.3)	
P-value [b]	0.017	
Week 6		
N (ITT for Y-BOCS Total Score)	113	119
LS Mean change from baseline (SE) [a]	-7.5 (0.61)	-5.2 (0.60)
LS Mean treat effect and 95% CI [a]	-2.3 (-3.9, -0.6)	
P-value [b]	0.0024	
Week 8		
N (ITT for Y-BOCS Total Score)	113	119
LS Mean change from baseline (SE) [a]	-8.0 (0.66)	-5.3 (0.65)
LS Mean treat effect and 95% CI [a]	-2.7 (-4.5, -0.9)	
P-value [b]	0.0003	
Week 10		
N (ITT for Y-BOCS Total Score)	113	119
LS Mean change from baseline (SE) [a]	-8.2 (0.70)	-5.9 (0.69)
LS Mean treat effect and 95% CI [a]	-2.3 (-4.2, -0.4)	
P-value [b]	0.004	

a: Estimate is made from ANOVA model with treatment and analysis center as factors.
b: Test for no difference between treatments from ranked ANOVA model with treatment and analysis center as factors. Not adjusted for multiplicity.
Note: Negative change in score indicates improvement.

Source: Reviewer.

3.1.6 Statistical Results

Using the data sets provided by the sponsor, the reviewer confirmed their efficacy results, yet with slight differences. The efficacy results for the primary endpoints at the Endpoint and those at each week for all the studies are presented in Tables 3.6 to 3.9. No key secondary endpoints were pre-specified in the protocol so the efficacy results regarding the secondary endpoints are not reported here. In these tables, the LS means and their confidence intervals are given by the ANOVA procedure with the raw change from baseline of the primary endpoint while the p-values are given by the ranked ANOVA. Both the ANOVA and the ranked ANOVA procedures give similar p-values for the treatment efficacy.

From Tables 3.6 to 3.9, we see that Studies 3107 and 3103 give quite consistent significance results from Week 6 to the end of study, while Study 3108 gives inconsistent significance results. However, even in Studies 3107 and 3103, the p-values are only nominal and not adjusted for multiplicity caused by multiple observations, so one must be very cautious in making any inferences regarding the consistence of the significance results for treatment efficacy.

On the other hand, the high percentages of patient dropout as indicated in Table 3.5 raise concerns on the reliability and interpretability of the efficacy results. In general, LOCF procedure is reliable only when the mean of the outcome measure is stable over the whole study period. This is not the case as shown in Table 3.6. As sensitivity analyses, OC and MMRM are applied for the primary efficacy measure by the reviewer. OC gives the efficacy result for the patients who stayed in the study to the endpoint of double-blind period. But this is not an ITT analysis. MMRM gives reliable efficacy results if the patient dropouts were non-informative, with dropouts only depending on the observed outcome values, not on the unobserved values. Although this assumption cannot be directly verified, positive results in the MMRM analysis support the effectiveness claim of the treatment.

In all three studies, the OC and MMRM analyses gave statistically significant efficacy results for the primary endpoints for the Luvox® CR group versus placebo. P-values in MMRM analyses were below 0.0001 for all the three studies. These results supported the effectiveness of Luvox® CR in the treatment of generalized SAD (Studies 3107 and 3108) and OCD (Study 3103) in adult outpatients with their corresponding primary endpoints.

In conclusion, the protocol specified primary analyses using LOCF procedure in flexible dose Studies 3107, 3108 and 3103 gave positive efficacy results supporting the claim of the effectiveness of Luvox® CR in the treatment of generalized SAD (Studies 3107 and 3108) and OCD (Study 3103) in adult outpatients. These results were supported by the OC and MMRM analyses. Together these results supported the effectiveness of Luvox® CR in the treatment of Generalized SAD and OCD.

3.2 Evaluation of Safety

See medical review for detail.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The treatment effects in all the treatment by sex groups are depicted in Table 4.1.The effect of sex on the treatment effect on primary endpoint was explored by testing the significance of the treatment effect at a nominal level of 0.05 after the adjustment of sex alone, and sex by treatment interaction on the change from baseline of the primary efficacy variable in each study. Sex and its interaction with treatment group were not statistically significant in Study 3107. In Study 3108 however, sex is quite significant in the ANOVA analysis (p=0.01), so is the interaction between sex and treatment (0.05). This indicates a possible difference in treatment effect between male and female patients. But sex in the model does not change the significance level of the treatment. This indicates that sex could account for a part of the overall treatment effect. Table 4.1 shows that male patients have a larger treatment effect than female patients. In Study 3103, sex is not statistically significant in the ANOVA analysis. But the interaction of sex and treatment is (p=0.065). This indicates that sex does not account for treatment effect, but there is a possible difference in treatment effect between male and female patients. Table 4.1 indicates that Luvox® CR improves on the primary endpoint within female patients, not in male patients.

Table 4.1 Treatment Effect by Sex on the effect size in Studies 3107, 3108 and 3103 (LOCF Analysis)

Study	Luvox® CR	Placebo
Study 3107		
Male	N=66	N=86
Mean Change From Baseline	-27.2	-13.0
Female	N=44	N=38
Mean Change From Baseline	-25.9	-10.7
Study 3108		
Male	N=60	N=74
Mean Change From Baseline	-41.2	-26.7
Female	N=66	N=74
Mean Change From Baseline	-31.4	-27.9
Study 3103		
Male	N=46	N=40
Mean Change From Baseline	-7.3	-7.2
Female	N=67	N=79
Mean Change From Baseline	-9.2	-4.7

Source: FDA analysis.

To consider the treatment effect in different ethnic groups, we note that there were about 80% white in all the studies. As for the treatment effect in age groups, we note that the vast majority of the patients were middle aged. More than 85% of the patients were between 18 and 50, and more than 98% were between the age of 18 and 65.

4.2 Other Special/Subgroup Populations

Not available.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Studies 3107, 3108 and 3103 were all 12-week, phase 3, multicenter, randomized, double blind, placebo-controlled, flexible-dose studies with treatment arms of Luvox® CR group and placebo for the treatment of Generalized SAD (Studies 3107 and 3108) and OCD (Study 3103) in adult outpatients. The primary efficacy analyses on the change from baseline of the LSAS total score in Studies 3107 and 3108 (Y-BOCS total score in Study 3103) were performed using the ranked ANOVA with LOCF data. No key secondary endpoint was pre-specified in protocol.

The statistical analysis results support the efficacy claim of Luvox® CR in the treatment of Generalized SAD (Studies 3107 and 3108) and OCD (Study 3103) at the end of the study (Week 12). The efficacy results included those in the ANOVA and ranked ANOVA analyses with OC and LOCF data and the MMRM analyses. Together these results support the claim of Luvox® CR in the treatment of Generalized SAD and OCD at Week 12.

5.2 Conclusions and Recommendations

In this submission, the sponsor conducted 3 pivotal short-term Luvox® (Fluvoxamine CR) studies between April 1999 and May 2000 in the United States, Europe and South Africa. The primary objectives of the studies were to evaluate the efficacy and safety of Luvox® CR compared with placebo in subjects with Generalized SAD (Studies 3107 and 3108) and OCD (Study 3103). The primary efficacy measure was the change from baseline of the LSAS total score (Studies 3107 and 3108) and the change from baseline of the Y-BOCS total score (Study 3103). No key secondary measure was pre-specified in protocol.

The analysis results support the efficacy claim of Luvox® CR in the treatment of Generalized SAD (Studies 3107 and 3108) and OCD (Study 3103) at the end of the study (Week 12). The efficacy results included those in the ANOVA and ranked ANOVA analyses with OC and LOCF data and the MMRM analyses. Together these results support the claim of Luvox® CR in the treatment of Generalized SAD and OCD at Week 12.

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