CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-235

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #/Serial #:	22-235
DRUG NAME:	Fluvoxamine maleate (LUVOX)
INDICATION:	Treatment of Obsessions and Compulsions in patients with OCD
APPLICANT:	Solvay Pharmaceuticals Inc.
DATE OF RECEIPT:	08/03/2007
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	Division of Biometrics I
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KEY WORDS: Maintenance, Relapse Prevention

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Results of this submission demonstrate that Fluvoxamine treatment can produce improvement in OCD symptoms after 10 weeks of treatment which is maintained for up to an additional 24 weeks of therapy. The relapse rate was statistically significantly less in the Fluvoxamine group than that observed in the placebo group. This indicates the clinical benefit of Fluvoxamine in the maintenance of response in OCD symptoms.

1.2 Brief Overview of Clinical Studies

The sponsor submitted one phase III study to support the use of Fluvoxamine in maintenance therapy for patients with OCD symptoms. Study S114.2.09 was a multi-center, randomized, double blind, parallel-group, placebo-controlled trial conducted in six investigative sites in US. The study included two phases: A total of 247 patients started the open label stabilization treatment period and 116 patients completed the stabilization period and were randomized to either Fluvoxamine or placebo in the double-blind phase.

The majority of patients were Caucasian (92.3%) with an average age of 38 years. The male-female ratio was about 1 to 1. The Fluvoxamine dose of 100 mg to 300 mg per day is the dose approved for use in OCD. The primary endpoint was proportion of subjects who relapsed during the double-blind period (Part 2) of the study. The proportion of subjects in the Fluvoxamine and placebo groups who relapsed in OCD symptoms during the 24 week double-blind period were to be compared using the Cochran-Mantel-Haenszel test, stratified by center, at the 5% significance level to test the null hypothesis that the portion of subjects who relapsed was the same for the two treatment groups.

1.3 Statistical Issues and Findings

The objective of the study was to demonstrate that long-term use of LUVOX tablets prevents relapse in OCD patients who had shown an adequate short-term response. The study consisted of a 10-week single blind LUVOX treatment phase and followed by a six-month randomized, double-blind, placebo-controlled evaluation of LUVOX.

Relapse during the double-blind phase of the study was defined as a ≥30% increase in Y-BOCS score relative to the score at Week 10 (end of single-blind) at two consecutive visits, or a refusal by the subject to continue due to a substantial increase in OCD symptoms. This reviewer confirmed the sponsor's findings that LUVOX was superior to placebo in the prevention of relapse as measured by the proportion of relapse. In the LUVOX group, 18 of 56 subjects (32%) met criteria for relapse compared to 32 of 58 placebo-treated subjects (55%). This difference in relapse rates at study endpoint was statistically significant ($p = 0.0136$ based on CMH test) and appeared to be clinically relevant. Furthermore, the time to relapse analysis also supports this finding ($p=0.017$ based on log rank test).

All efficacy analyses performed on the secondary endpoints are considered for exploratory findings only due to the following two reasons: 1) those secondary endpoints are confounded with the time to relapse measure and their results may not be interpretable. 2) There was no multiplicity adjustment pre-specified in sponsor's SAP.

2 INTRODUCTION

2.1 Overview

This review provides a statistical evaluation of Fluvoxamine in the relapse prevention in the maintenance treatment of outpatients with OCD.

Obsessive-compulsive disorder (OCD) is a chronic and disabling disorder with lifetime prevalence in the United States of 3% to 4%. It is more common than schizophrenia, panic disorder or severe cognitive impairment, and is surpassed only by major depressive disorder in occurrence. Fluvoxamine maleate (LUVOX) was initially developed as an antidepressant; Fluvoxamine has also been shown to be effective in treatment of OCD. Reports from randomized, double-blind, parallel group, placebo- and reference controlled trials of Fluvoxamine in patients with OCD have demonstrated substantial efficacy, which were of up to 10 weeks duration. Since OCD is a chronic disorder, it is likely that patients will require prolonged therapy. Follow-up studies of up to four years duration have found a recurrence of symptoms within a few weeks in patients who discontinued treatment. Therefore, this study was conducted to examine the risk of recurrence of OCD symptoms in subjects who were first adequately treated with Fluvoxamine, and then discontinued under double-blind conditions.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\Cdsesub1\nonectd\N22235\N_000\2007-08-03\crt\datasets\s114209

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The following description is based on the sponsor's clinical study report. Any discrepancy between the study report and study protocol will be discussed in the section of statistical reviewer's comments.

3.1.1 OBJECTIVES OF PROTOCOL 114.2.09

The objective of this study was to demonstrate the effectiveness of Fluvoxamine 1), in the prevention of relapse and 2), in the long-term maintenance or augmentation of improvement in subjects with OCD who had shown an adequate short-term response.

3.1.2 STUDY DESIGN

This study consisted of a two-week single-blind placebo run-in/screening phase, then a 10-week single-blind Fluvoxamine treatment phase (Part 1) followed by a six-month randomized, double-blind, placebo-controlled evaluation of Fluvoxamine in the prevention of OCD relapse (Part 2). A total of 300 subjects were planned to enter Part 1 to provide 100 subjects who would then enter Part 2.

Following the placebo screening phase, Fluvoxamine therapy was started at a dose of 50 mg daily at bedtime and increased in 50-mg increments every seven days as tolerated to achieve the optimal therapeutic response. Fluvoxamine was administered in the dose range of 100 mg to 300 mg daily after initial titration. Subjects were evaluated in the clinic at the end of Weeks 2, 4, 6, 8, and 10. The Yale-Brown Obsessive Compulsive Scale (YBOCS) was assessed on Day 1 of the Fluvoxamine single-blind phase and compared to the score after Weeks 8 and 10 of therapy to determine response and eligibility for the double-blind phase. At the end of Part 1 (Day 71), responders (defined at those subjects whose Y-BOCS scores at the end of Weeks 8 and 10 were at least 30% lower than the Single bind baseline Y-BOCS) were identified to proceed into the double-blind phase of the study (Part 2). Subjects received 24 weeks of treatment in Part 2.

After single-blind Fluvoxamine treatment, responders were identified as those subjects whose YBOCS scores were at least 30% lower at the end of Weeks 8 and 10 compared to Day 1 of Part 1. These responders were then randomized to either Fluvoxamine or placebo for an additional six months of treatment in Part 2 of the study.

3.1.3 EFFICACY MEASURES

The primary efficacy variable was the proportion of subjects who relapsed during the double-blind period (Part 2) of the study. Subjects were considered to have relapsed if the Y-BOCS score increased by at least 30% for two consecutive visits compared to the score at baseline for Part 2 or if they refused to continue due to a substantial increase in OCD symptoms. When relapse criteria were met, the subject was discontinued from the study.

The selected secondary endpoints were the time to relapse, mean changes in Y-BOCS Total score, CGI and PGI scales.

3.1.3.1 Statistical Analysis Plan

The proportion of subjects in the Fluvoxamine and placebo groups who relapsed in OCD symptoms during the 24 week double-blind period were to be compared using the Cochran-Mantel-Haenszel test, stratified by center, at the 5% significance level.

The time to relapse was to be examined by Kaplan-Meier curve analysis. ANOVA with treatment, center, and treatment by center as fixed effects was to be performed on the YBOCS total, CGI and PGI scales. Both last observation carry-forward (LOCF) and visit wise (OC) data would be examined at each efficacy assessment for exploratory purposes.
All statistical analysis was to be two-sided and would be performed on the intent-to-treat subject population at the 5% significance level. The ITT efficacy population would be defined as all subjects entering the single-blind Fluvoxamine treatment phase of the study who took at least one table of study medication, with a baseline evaluation for the double-blind phase and at least one efficacy evaluation during the double-blind phase of the study while on medication.

The study would be regarded as positive if a statistically significant outcome was found on the primary efficacy parameter at a 5% level of significance. All statistical analyses performed on the secondary parameters would be for exploratory purposes only.

3.1.3.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 247 subjects enrolled into the single-blind phase of the study and 116 subjects completed the phase (47%). The study was conducted from January 23, 1996 to November 02, 2000. Six (6) subjects had records indicating no single-blind medication was taken and no post-baseline safety assessments. Most subjects discontinued due to ineffectiveness (22.7%) and adverse event (13.8%), see Table 1.

Table 1 Reason for Discontinuation – Single-blind Phase

	Treatment
Reason for Discontinuation	Fluvoxamine (N=247)
Completed phase	116 (46.96)
Terminated due to:	
Ineffectiveness	56 (22.67)
Adverse event	34 (13.77)
Lost to follow up	16 (6.48)
Protocol violation	13 (5.26)
Other	12 (4.86)

[Source: Sponsor's Table 5 of CSR]

One hundred sixteen subjects were randomized into the double-blind phase of the study. A total of 114 subjects were included the double-blind phase efficacy population, rather than the 113 subjects who were responders at the end of the single-blind phase. This difference in patient numbers was a result of 5 subjects who were 'nonresponders' being randomized into the double-blind phase while another 4 'responders' were not included in the double-blind phase efficacy population, see Table 2. Thus, there was a net gain of one subject in the efficacy population for the double-blind phase [113 + (5 – 4)].

Table 2 **List of excluded responders and included nonresponders**

	Subject ID	Relapse	Treatment
Non Responders Entered DB	91019	No	Fluvox
	91038	No	Fluvox
	96049	No	Fluvox
	91042	Yes	Placebo
	92043	No	Placebo
Responders Excluded From DB	93039	N/A	N/A
	94035	N/A	N/A
	94065	N/A	Fluvox
	95010	N/A	Fluvox

[Source: Reviewer's result]

A total of 33 subjects (56.9%) in the Fluvoxamine group and 25 subjects (43.1%) in the placebo group completed the phase. Far fewer Fluvoxamine-treated subjects discontinued due to relapse (12%) compared to placebo-treated subjects (41%). Few subjects in either group terminated due to adverse event, See Table 3.

Table 3 **Reasons for Discontinuation – Double-blind Phase**

	Treatment	
Reason for Discontinuation	Fluvoxamine (N=58)	Placebo (N=58)
Completed study	33 (56.90)	25 (43.10)
Terminated due to:		
Adverse event	3 (5.17)	1 (1.72)
Lost to follow up	4 (6.90)	2 (3.45)
Protocol violation	3 (5.17)	1 (1.72)
Relapse	7 (12.07)	24 (41.38)
Other	8 (13.79)	5 (8.62)

[Source: Sponsor's Table 6 of CSR]

Table 4 presents baseline demographic information for subjects who entered the single-blind phase of the study. Subjects had a mean age of 38 years, were predominately Caucasians and were evenly divided between males and females.

Table 4 Demographic Characteristics – Single-blind Phase

Parameter	Category	Statistic	Treatment
			Fluvoxamine (N=247)
Age (years)		Mean (se)	38.0 (0.75)
		Median	35.8
		Min - max	18.9 – 73.4
Age category (years)	18 – 30	n (%)	79 (31.98)
	31 – 40	n (%)	79 (31.98)
	41 – 50	n (%)	53 (21.46)
	51 – 64	n (%)	29 (11.74)
	≥ 65	n (%)	7 (2.83)
Gender	Male	n (%)	123 (49.80)
	Female	n (%)	124 (50.20)
Ethnicity	Caucasian	n (%)	228 (92.31)
	Negroid	n (%)	3 (1.21)
	Oriental	n (%)	6 (2.43)
	Other	n (%)	10 (4.05)

[Source: Sponsor's Table 7 of CSR]

Subjects in the Fluvoxamine and placebo treatment groups in the double-blind phase were comparable in age, race (primarily Caucasian) and gender distribution, see Table 5.

Table 5 Demographic Characteristics – Double-blind Phase

Parameter	Category	Statistic	Treatment	
			Fluvoxamine (N=58)	Placebo (N=58)
Age (years)		Mean (se)	39.8 (1.70)	38.0 (1.50)
		Median	36.7	35.9
		Min - max	19.6-66.9	19.1 – 65.8
Gender	Male	n (%)	26 (44.83)	30 (51.72)
	Female	n (%)	32 (55.17)	28 (48.28)
Ethnicity	Caucasian	n (%)	54 (93.10)	53 (91.38)
	Negroid	n (%)	2 (3.45)	0 (0.00)
	Oriental	n (%)	0 (0.00)	3 (5.17)
	Other	n (%)	2 (3.45)	2 (3.45)

[Source: Sponsor's Table 11 of CSR]

3.1.3.3 Sponsor's Efficacy Results

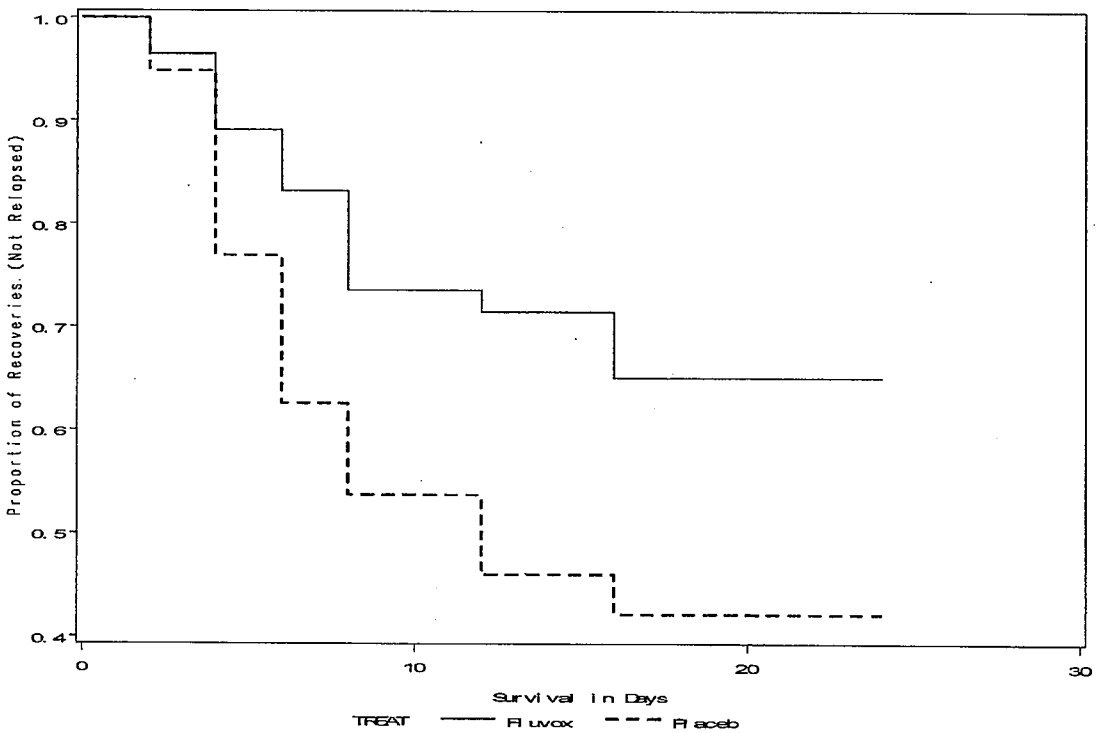
The proportions of subjects in the Fluvoxamine and placebo groups who relapsed in OCD symptoms during the 24 week double-blind period were to be compared using the CMH test, stratified by center, at the 5% significance level. The difference in relapse rates was statistically significant at study endpoint ($p = 0.0136$). In the Fluvoxamine group, 18 of 56 subjects (32%) met criteria for relapse compared to 32 of 58 placebo-treated subjects (55%).

3.1.3.4 Statistical Reviewer's Results and Comments

1. The reviewer followed the SAP and concluded that the difference in relapse rates was statistically significant with p = 0.0136. However, this primary analysis result was based on a total of 114 patients, but the study actually randomized 116 subjects into the double blind phase. However, we found out that 5 'non-responders' from single-blind phase were randomized into the double-blind phase without any reasonable justifications, but the reviewer does not believe that they can be considered as part of ITT population. Furthermore, all three Fluvox subjects' relapse results are in favor of Fluvox. Hence, the reviewer re-analyzed the primary analysis for the rest of 109 subjects. The difference in relapse rates was statistically significant at study endpoint (p = 0.0285). In the Fluvoxamine group, 18 of 53 subjects (33.96%) met criteria for relapse compared to 31 of 56 placebo-treated subjects (55.36%).

2. The Kaplan-Meier curve analysis indicated evidence of a statistically significant difference (p=0.017 based on log rank test) in time to relapse between Fluvoxamine and placebo. Fluvoxamine demonstrated a lower relapse rate than that of placebo during the 24 weeks double blind study, see Figure 1. The results of time to relapse support the findings of the primary analysis.

Figure 1 Time to Relapsed – All Randomized Double Blind Patients-Kaplan-Meier Curve



[Source: Reviewer's Analysis]

3. Sponsor submitted a number of analyses of secondary efficacy variables, such as Change from baseline (week 10) in Y-BOCS total score, CGI and PGI scales. However, many patients discontinued when a relapse occurred, so the analysis results of these secondary endpoints depend on patients' relapse status and time to relapse. Therefore, those secondary analysis results are confounded with the time to relapse measure and they may not be interpretable. Furthermore, the sponsor's statistical analytical plan did not specify a plan on how to adjust the multiplicity issues among those endpoints. Hence, all statistical analyses performed on the secondary endpoints will be considered for exploratory purposes only.

4. After single-blind Fluvoxamine treatment, responders were identified as those subjects whose YBOCS scores were at least 30% lower at the end of Weeks 8 and 10 compared to Day 1 of Part 1. Furthermore, sponsor submitted a response letter dated 2 October 2007 to the Agency's Filing Communication, which stated that the mean (SE) of time in continuous responder status are 3.7 (0.27) weeks for Fluvoxamine and 4.0 (2.8) for placebo. On the other hand, agency typically recommended that stabilization period to be at least 12 weeks. However, this study was first initiated in January 1996, which was approximately four years prior to Agency's recommendations on the length of stabilization period. Therefore, the decision on whether the length of stabilization period was sufficient in this study will be a matter of medical review.

3.2 Evaluation of Safety

Please read Dr. Dubitsky's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age and Race group

Table 6 shows the reviewer's subgroup analysis result for gender, race and age. The number of patients by gender and age group are very comparable and the frequency of relapses stratified by gender and age group appeared consistent with the primary result. The vast majority of the patients were classified as Caucasians (> 92%), which also produced a numerical consistent favorable result towards Fluvox. We can ignore the inconsistent result of Others race due to the low enrollment.

Table 6 Reviewer's Subgroup Analysis for Gender, Age, and Race

Subgroup	Fluvox	Placebo
Male		
No. Subjects	25	30
No. of relapses	8	14
Relapses Rate	32%	46.7%
Female		
No. Subjects	31	28
No. of relapses	10	18
Relapses Rate	32.26%	64.29%
Age < 38		
No. Subjects	29	34
No. of relapses	11	22
Relapses Rate	37.9%	64.7%
Age >= 38		
No. Subjects	27	24
No. of relapses	7	10
Relapses Rate	25.9%	41.7%
Race = Caucasians		
No. Subjects	52	53
No. of relapses	16	30
Relapses Rate	30.8%	56.6%
Race = Others		
No. Subjects	4	5
No. of relapses	2	2
Relapses Rate	50.0%	40.0%

[Source: Reviewer's result]

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The objective of the study was to demonstrate that long-term use of LUVOX tablets prevent relapse in OCD patients who had shown an adequate short-term response. The study consisted of a 10-week single blind LUVOX treatment phase and followed by a six-month randomized, double-blind, placebo-controlled evaluation of LUVOX.

Relapse during the double-blind phase of the study was defined as a ≥30% increase in Y-BOCS score relative to the score at Week 10 (end of single-blind) at two consecutive visits, or a refusal by the subject to continue due to a substantial increase in OCD symptoms. This reviewer confirmed the sponsor's findings that LUVOX was superior to placebo in the prevention of relapse as measured by the proportion of relapse. In the LUVOX group, 18 of 56 subjects (32%) met criteria for relapse compared to 32 of 58 placebo-treated subjects (55%). This difference in relapse rates at study endpoint was statistically significant ($p = 0.0136$ based on CMH test) and

appeared to be clinically relevant. Furthermore, the time to relapse analysis also supports this finding (p=0.017 based on log rank test).

All efficacy analyses performed on the secondary endpoints are considered for exploratory findings only due to the following two reasons: 1) those secondary endpoints are confounded with the time to relapse measure and their results may not be interpretable. 2) There was no multiplicity adjustment pre-specified in sponsor's SAP.

5.2 Conclusions and Recommendations

Results of this submission demonstrate that Fluvoxamine treatment can produce improvement in OCD symptoms after 10 weeks of treatment which is maintained for up to an additional 24 weeks of therapy. The relapse rate was statistically significantly less in the Fluvoxamine group than that observed in the placebo group. This indicates the clinical benefit of Fluvoxamine in the maintenance of response in OCD symptoms.

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