CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-033

MEDICAL REVIEW(S)

ADDENDUM TO MEMORANDUM

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

DATE: February 20, 2008

FROM: Gwen L. Zornberg, M.D., Sc.D.
Acting Team Leader
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for Approval action for Luvox CR (fluvoxamine capsules) for treatment of Social Anxiety Disorder and Obsessive Compulsive Disorder

TO: File NDA 22-033 (fluvoxamine) 100 mg and 150 mg Capsules
Response to Approvable Letter
SN 000 (Original Letter date 28 April 2006 & PDUFA Goal date 1 March 2007)

REVIEWERS: Chemistry, Dr. David Claffey; Biopharmaceutics, Drs. Carol Noory and Ray Baweja; and Pharmacology/Toxicology, Dr. Linda Fossom.

1.0 BACKGROUND

Luvox CR® (fluvoxamine maleate) is an extended release capsule formulation of fluvoxamine (immediate release), which is an approved selective serotonin reuptake inhibitor for the treatment of OCD. Solvay submitted Luvox [redacted] Dr. Cai detailed in her NDA 22-033 review the sponsor, "Solvay Pharmaceuticals Inc, was placed under the Application Integrity Policy (AIP) by the CDER Center Director on 24 September 1997 for the following reasons: falsified stability data, falsified and missing data for drug interaction studies after approval, and other CMC information that was deemed to be falsified or missing." On 9 April 2003, AIP was lifted. An approvable action was taken for the most recent resubmission of the fluvoxamine maleate immediate-release tablet NDA submission dated 16 November 2006.

With respect to the extended release capsule formulation, Luvox CR® , this series of responses to the approvable action for the original 22-033 NDA Luvox CR® submission seeks a claim for the short-term use of fluvoxamine CR as treatment for adult patients with generalized social anxiety disorder and obsessive compulsive disorder in the range

of 100 to 300 mg/day given daily. Luvox CR was [redacted] The Luvox-CR application was re-submitted as NDA 22-033. The recommended starting dose for fluvoxamine CR in adult patients is 100 mg administered as a single dose at bedtime. It is recommended to increase the dose 50 mg every week, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. The Approvable letter issued was sent to Solvay on 27 February 2007. The main outstanding issue at that time was an impurity issue

As elaborated by Dr. David Claffey, within the fluvoxamine CR capsules are [redacted]

As it reads in the OCP review of Carol Noory dated 4 February 2008, on 20 December 2007 Solvay was notified that [redacted] On 28 December 2007, Solvay accepted the dissolution specification required in the Approvable letter dated 27 February 2007 based on the lots used in pivotal clinical pharmacology studies.

2.0 CHEMISTRY

[redacted] are manufactured by [redacted] (DMF) and Solvay has reported to the agency that it is [redacted]

The Office of Compliance found the manufacturing/testing sites to be acceptable.

Dr. David Claffey has worked since the original NDA review with Solvay and OCP to achieve resolution with high quality standards for manufacturing and drug product. Dr. Claffey describes the discrepant conclusion at issue between the CMC and OCP reviewers below in his review dated 13 February 2008.

Six-hour drug product dissolution time point issue: At the end of the previous review cycle this reviewer determined that a drug product expiry period could not be assigned due to the narrower (from [redacted] to [redacted]) drug product dissolution acceptance criterion at the 6-hour time point accepted by the Applicant on 11 DEC 2007 on the recommendation of the Office of Clinical Pharmacology. All lots met the initial acceptance criterion ([redacted] through the proposed 24-month expiry period at 25°C/60%RH and 12 months at 30°C/65%RH. However four out of the 12 pivotal stability lots were outside the revised range ([redacted]) at release. Several more of thee lots failed through the proposed expiry period under long-term stability storage

conditions and most did not remain within the modified limits through 12 months at 30°C65%RH (see chart in CMC Review #2 dated 17 December 2007).

Dr. Claffey recommends an approval action based on his review dated 13 February, 2008 of chemistry and quality issues of a resubmission by Solvay on 28 DEC 2007, based on the applicant's recent deletion of the 6-hour drug product dissolution time point as recommended by the Division Director to resolve an impasse between the CMC and OCP co-locates. Based on the at 4 hour and 8 hour time points, CMC is willing to accept the analyses in which the 6 hour time point is not included for the dissolution method and specifications that were satisfactory at the clinically relevant time intervals of 4 and 8 hours. The sponsor has provided data without the 6 hour time point, which the Chemistry reviewers stated was non-objectionable in a meeting on 19 February 2008.

As a consequence, I find no evidence of a chemistry issue with a drug expiry period of 24 months that would preclude approval of this NDA.

3.0 PHARMACOLOGY

The impurity issues were resolved satisfactorily in the opinion of Dr. Linda Fossom.

I am not aware of any pharmacology/toxicology issues at this point that would preclude an approval action for this efficacy supplement.

4.0 BIOPHARMACEUTICS

While the acceptance criteria for the 4 an d8 hour time points were non-objectionable to OCP, the 6 hour time point also submitted by Solvay, had raised complex issues resistant to resolution between the Chemistry and the OCP reviewer teams as Dr. Baweja of OCP remained resolute that the 6 hour time point required a —— acceptance criterion. However, Dr. Baweja had conveyed to the team in an internal meeting that he would have been satisfied if the 6 hour time point had not been included at all by Solvay with the 4 and 8 hour time points for the dissolution method and specifications. The sponsor has provided data without the 6 hour time point. It should be conveyed that Dr. Baweja stated to the team that the recommendations of the OCP review team for the 27 February action date on 19 February remain unchanged.

Due to the resolution by the Division Director of the differences of review opinions regarding the one 6-hour time point in the dissolution specifications that lends little clinical relevance when the 4 hour an d8 hour time points are satisfactory to all reviewers for a drug that is used to treat chronic intractable conditions, I am aware now of no further biopharmaceutics issue that would preclude approval for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Conclusions Regarding the Efficacy Data

The effect sizes were similar to those seen in other positive SAD and OCD trials. In the Approvable Letter dated 27 FEB 2007, the Division found that the sponsor provided sufficient evidence in three short-term 12-week, double-blind, placebo-controlled trials to support the claim of short-term efficacy of Luvox CR in the treatment of SAD (2 trials, 3107 and 3108, change from baseline to endpoint in Liebowitz Social Anxiety Scale Total Score) and OCD (1 trial, 3103, change from baseline to endpoint in YBOCS Total Score) the 27 February 2007 based on the clincial reviews of Dr. Cai and the Biometrics review of Dr. Fanhui Kong. No adequate double-blind, controlled long-term data in the treatment of Social Anxiety Disorder or OCD have ever been submitted to the application by Solvay. At that time there was concern that AEs were inconsistent between the tabulations and the CRFS and narratives. The sponsor provided no data pertaining to longer term efficacy and safety for SAD and OCD.

On 2 November 2007, Dr. Cai provided her review of demographic data analyses that had been provided by Solvay in a submission dated 21 June 2007 in response to the clinical requirement specified in the 27 February 2007 Approvable letter. Following and below is text excerpted from Dr. Cai's review
:

Demographic analysis of the AEs pooled from the three placebo-controlled studies:
a) Age group analysis (≤50 years of age vs. ≥51 years of age): There was no age group differences among all the common AEs listed.
b) Race group analysis: The sponsor separated subjects into two groups – White vs. non-white. The only AE appears statistically significantly more in White is somnolence (p=0.029).
c) Gender analysis: There was no common AE that appear statistically different between the two groups.

5.2 Safety Data

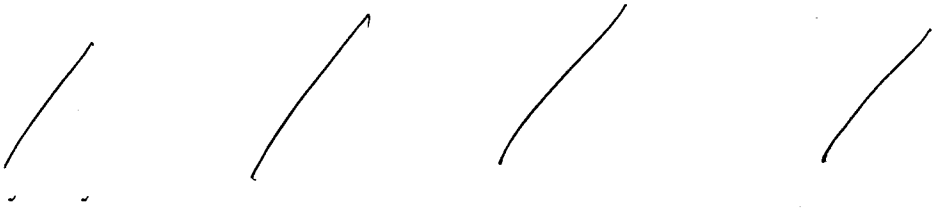
5.2.1 Clinical Data Sources for Safety Review

Inspections were conducted at 6 sites, and data form all 6 sites were deemed to be acceptable. The undersigned reviewed the consistency of the AE tabulations, narratives and CRFs regarding adverse drug reaction data by requesting all relevant AE tabulation, CRF and narrative data that had been identified by Dr. Cai. A matching of the data form the same patient from the 3 different sources was conducted by Dr. Ripi Kohli-Chhabra, a novice reviewer who was completely blinded to the issues germane to the NDA and all prior reviews or pinions at the time of her evaluation). She found the data to be largely consistent. On review of Dr. Kohli-Chhabra's matching of the patient data, I again found the quality of the AE data to be non-objectionable in keeping with the description of the data in a teleconference with Solvay that they set up expeditiously with all available on

31 October 2007 as arranged by Bill Bender, who was covering briefly as Project Manager.

5.3 Clinical Sections of Labeling

Modifications to the sponsors' proposed Luvox CR labeling that had been sent to the sponsor for review on 11 December 2007 and ?? February 2008. The sponsor responded with no objections to all of our recommendations for approved labeling. The sponsor wished to include



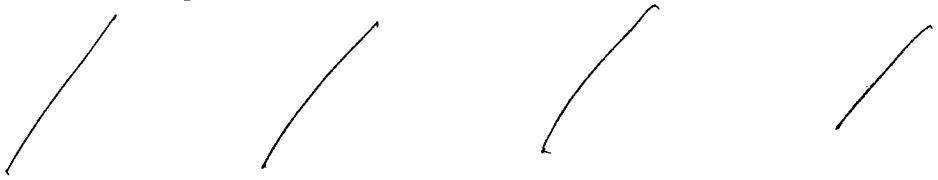
Consequently, Dr. Cai concluded in her review dated 2 November 2007: "Based on the above review, from clinical point of view I recommend the division taking an approval action for this NDA."

6.0 CONCLUSIONS AND RECOMMENDATIONS

I recommend that an approval action be taken based on resolution of the final issue chemistry/quality discrepancy precluding approval that has been resolved by the revision of the 6-hour drug product dissolution specification on the recommendation of the Division Director. Based on Dr. Laughren's conclusion stated in the 27 February 2007 review drawn in part on Dr. Cai's and Dubitsky's clinical and Dr. Kong's statistical reviews coupled with confirmation of the reasonable consistency of the data on more meticulous examination of the adverse event data by Dr. Kohli-Chhabra blinded to knowledge of the NDA and further information supplied by Solvay at my request for a focused evaluation, I believe that Solvay has submitted sufficient clinical data to support that Luvox CR is effective and acceptably safe in the treatment of patients diagnosed with generalized social anxiety disorder and obsessive compulsive disorder.

The chemistry issues have been adequately addressed and the discrepancies with OCP have been resolved to the point that there appears to be little clinical relevance arising from differing viewpoints to preclude an approval action.

In terms of labeling,



The fluvoxamine CR product will carry a *MedGuide*.

Post Marketing Commitments

Pediatric studies

We have requested that Solvay commit to conducting studies that assess the safety and effectiveness of fluvoxamine maleate as a treatment for generalized social anxiety disorder in adolescent patients ages 12 to 17 years. We request that the sponsor commit to submission of the results of the studies no later than 3 years after the date of the issuance of the approval letter of this NDA.

Long Term Efficacy Studies

With respect to postmarketing commitments, in the approvable letter sent 27 FEB 2007, we emphasized also that since OCD and Social Anxiety Disorder are chronic illnesses, that Solvay must commit to conduct research to assess the longer-term effectiveness and safety of fluvoxamine CR in Social Anxiety Disorder and OCD. This was reiterated in the CDTL memo dated on review of Solvay's response to the approvable letter dated 27 FEB 2007.

cc: Original NDA 22-033
HFD-130
HFD-130/GZornberg/MMathis/TLaughren /RGrewal/SHardeman

DOC:Luvox CR_GeneralizedSADandOCD_Zornberg_AE_Memo.doc

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/s/

Gwen Zornberg
2/20/2008 09:59:34 AM
MEDICAL OFFICER

CDTL recommendation of Approval given agreement on Labeling and Postmarketing commitments of Pediatric studies (PWR) and at least one adequate long-term efficacy and safety trial for both SAD and OCD given no further OCP or CMC issues to preclude AP.

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

DATE: December 23, 2007

FROM: Gwen L. Zornberg, M.D., Sc.D.
Acting Team Leader
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approvable action for Luvox CR (fluvoxamine capsules) for Generalized Social Anxiety Disorder and Obsessive Compulsive Disorder

TO: File NDA 22-033 (fluvoxamine) Capsules
Response to Approvable Letter
SN 000

REVIEWERS: Chemistry, Dr. David Claffey; Biopharmaceutics, Dr. Ray Baweja; Clinical, Drs. June Cai, Kavneet Kohli-Chhabra, and Gwen Zornberg; and Pharmacology Toxicology, Dr. Linda Fossom.

1.0 BACKGROUND

Luvox CR (fluvoxamine extended release) is an extended release formulation of fluvoxamine (immediate release), which is an approved selective serotonin reuptake inhibitor for the treatment of OCD. This response to the approvable action for the original NDA submission seeks a claim for the short-term use of Luvox CR as treatment for patients with generalized social anxiety disorder and obsessive compulsive disorder in the range of 100 to 300 mg/day given daily. Luvox CR was initially submitted in NDA 21-309 on 1December 2001, but was subsequently withdrawn due to manufacturing difficulties. This represents the response to the Approvable letter sent February 27, 2007.

2.0 CHEMISTRY

Dr. David Claffey recommends an approval action based on review of quality issues. He has confirmed in an email dated 11 December 2007 at 9:35 am that "he outstanding issues with new drug substance manufacturing site/process a' ———— described in DMF —— were resolved. Additionally, the Applicant agreed to the specified limits for the drug substance particle size distribution and to the changes in the carton labels requested by the CMC reviewer in the 21 NOV 2007 deficiency letter."

has found to be acceptable

3.0 PHARMACOLOGY

The impurity issues were resolved.

I am not aware of any pharmacology/toxicology issues at this point that would preclude an approval action for this efficacy supplement.

4.0 BIOPHARMACEUTICS

Dr. Baweja confirmed in an email message dated 11 December 2007 forwarded by Rimmy Grewal that the only outstanding issue is that the sponsor must comply with the dissolution specifications detailed in the 27 February 2007 approvable letter. Ms. Grewal sent an email on 11 December 2007 asking Solvay if they would comply with the required specifications. At this point, the sponsor has not responded.

Consequently, the only issue to prevent an approval action is a biopharmaceutics issue at this point for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of this application focused on 3 short-term (12-week), double-blind, randomized, parallel group, placebo-controlled trials. Two of these studies (3107 and 3108) of identical design evaluated SAD in a dose range of 100 to 300 mg/day. A third study evaluated OCD in a dose range of 100 to 300 mg/day. The primary efficacy endpoint analyses were statistically significant in all 3 trials. There was no information bearing on a dose-response for efficacy in this program. There was no indication of any difference based on gender. The effect sizes were similar to those seen in other randomized trials of SAD and OCD. The sponsor provided no data pertaining to longer term efficacy for SAD and OCD. This has been request as a phase 4 commitment.

5.1.2 Conclusions Regarding Efficacy Data

The Division found that the sponsor provided sufficient evidence to support the claim of short-term efficacy of Luvox CR in the treatment of SAD and OCD.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data was re-reviewed for consistency. The Division requested that the sponsor send copies of the original CRFs and adverse event tabulations. Dr. Kohli-Chhabra compared the listings with the CRF pages and found the upwards of 90% of the data to be consistent as a second audit. The undersigned reviewed the data and found the consistency to be non-objectionable.

5.3 Clinical Sections of Labeling

We have made modifications to the sponsors' proposed Luvox CR labeling that was sent to the sponsor for review on 11December 2007.

6.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Solvay has submitted sufficient data to support the conclusion that Luvox CR is effective and acceptably safe in the treatment of for patients with generalized social anxiety disorder and obsessive compulsive disorder. The chemistry issues have been resolved and therefore the pharmacology/toxicology issues are now resolved. Based on the data provided in the reviews Drs. Cai, Claffey, and Fossom, I recommend that an approvable action be taken unless the sponsor commits to comply with the dissolution specifications required by Dr. Ray Baweja of the Office of Clinical Pharmacology in order to be considered for approval given satisfactory labeling negotiations before the action date of 22 December 2007.

cc:
Orig NDA 22-033
HFD-130
HFD-130/GZornberg/MMathis/TLaughren /RGrewal/SHardeman

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/s/

Gwen Zornberg
12/11/2007 12:58:31 PM
MEDICAL OFFICER

ADDENDUM TO
CDTL MEMORANDUM (December 12, 2007)
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 19, 2007

FROM: Gwen L. Zornberg, M.D., Sc.D.
Acting Team Leader
Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approvable action for Luvox CR (fluvoxamine maleate) extended release capsules) for the treatment of Social Anxiety Disorder (SAD) and Obsessive Compulsive Disorder (OCD) response

TO: Addendum to File NDA 22-033 (fluvoxamine maleate) Extended Release Capsules
Complete Response (dated June 21, 2007) to the February 27, 2007 action letter
SN 000 (new drug application dated April 28, 2006)

REVIEWERS: Chemistry, Dr. David Claffey; Biopharmaceutics, Dr. Ray Baweja; Clinical, Dr. June Cai (Dr. Kavneet Kohli-Chhabra conducted a second audit of safety data); and Pharmacology Toxicology, Dr. Linda Fossom.

1.0 BACKGROUND

Luvox CR (fluvoxamine maleate) Extended Release Capsules is an extended release formulation of Luvox (fluvoxamine maleate) immediate release tablets, which is an approved selective serotonin reuptake inhibitor for the treatment of Obsessive Compulsive Disorder (OCD). This response to the approvable action for the original NDA submission seeks a claim for the short-term use of Luvox CR as treatment for patients with generalized social anxiety disorder (SAD) and obsessive compulsive disorder (SAD in the range of 100 to 300 mg/day given daily. Luvox CR was initially submitted . This represents the response to the Approvable action letter sent February 27, 2007 for NDA 22-033 submitted April 28, 2006.

2.0 CHEMISTRY

Dr. David Claffey recommends an approvable action based on his review of ongoing quality issues dependent on the resolution of Clinical Pharmacology concerns in keeping with guidelines. Dr. Claffey had confirmed in an email dated 11 December 2007 at 9:35 a.m. that "the outstanding issues with new drug substance manufacturing site/process at ——— described in DMF ——— were resolved. Additionally, the Applicant agreed to the specified limits for the drug substance particle size distribution and to the changes in the carton labels requested by the CMC reviewer in the 21 NOV 2007 deficiency letter."

An expiry period cannot be assigned, however, as the primary stability data do not support the recently amended (December 10, 2007) drug product dissolution acceptance criteria noted below. In order to be granted an approval, this issue must be appropriately resolved.

Consequently, based on the lack of agreement remaining at this time regarding the dissolution specifications and the resultant inability to assign an expiry period, an approvable action is recommended by Dr. Claffey.

3.0 PHARMACOLOGY

The impurity issues that had been outstanding were resolved to a degree that Dr. Linda Fossom found to be non-objectionable. However, Dr. Fossom, the pharmacology/toxicology reviewer recommends that Solvay submit data on the microscopic examination of the standard battery of tissues used in the general toxicity study entitled "Fluvoxamine Maleate: 14-Day Oral (Gavage) Administration Comparative Toxicity Study in the Rat with Fluvoxamine Maleate and Fluvoxamine Maleate Spiked with ——————————————— as a post-marketing commitment.

I am not aware of any pharmacology/toxicology issues at this point that would preclude an approval action for this efficacy supplement.

4.0 BIOPHARMACEUTICS

Dr. Baweja confirmed in an email message dated 11 December 2007 forwarded by Rimmy Grewal that the only outstanding issue is that the sponsor must comply with the [redacted] with the dissolution specifications detailed in the 27 February 2007 approvable letter. Ms. Grewal sent an email on 11 December 2007 asking Solvay if they would comply with these requirements.

Ms. Rimmy Grewal (email dated December 10, 2007) requested that Solvay agree to the specification below outlined by Dr. Ray Baweja of OCP in keeping with guidelines that had been conveyed earlier in the February 27, 2007 Approvable Letter.

USP Apparatus 2:	Paddle Method
RPMs:	50 rpm
Volume:	900 mL
Medium:	pH 6.8 Phosphate Buffer
Sampling Times:	2, 4, 6, 8, and 12 hours

Time	% Released
2 hours	
4 hours:	
6 hours:	
8 hours:	
12 hours:	

Solvay responded in an email dated December 11, 2007 that they can agree to the dissolution specifications if a modification is made shifting 6 hour ranges – higher based on Solvay's assessment of the current available dataset. Solvay was informed that the agency would need to review this information that would have to be sent by Solvay for an assessment by the agency. The agreement regarding the dissolution specifications remains unresolved.

Consequently, the remaining concerns that prevent the recommendation of an approval action are biopharmaceutics and quality issues related to [redacted] dissolution specifications, and expiry assignment as the primary stability data do not support the recently amended (December 19, 2007) drug product dissolution acceptance criteria.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of this application focused on 3 short-term (12-week), double-blind, randomized, parallel group, placebo-controlled trials. Two of these studies (3107 and 3108) of identical design evaluated SAD in a dose range of 100 to 300 mg/day. A third study evaluated OCD in a dose range of 100 to 300 mg/day. The primary efficacy endpoint analyses were statistically significant in all 3 trials. There was no information bearing on a dose-response for efficacy in this program. There was no indication of any difference based on gender. The effect sizes were similar to those seen in other randomized trials of SAD and OCD. I agree with Dr. Cai's conclusion that the data support acceptable efficacy and safety in her 2 reviews dated January 22, 2007 (original NDA) and November 2, 2007 (Approvable response). The sponsor provided no data pertaining to longer term efficacy for SAD and OCD. This has been request as a phase 4 commitment in a addition to a request for data on Luvox CR in the treatment of pediatric patients (ages 12-17) diagnosed with SAD.

5.1.2 Conclusions Regarding Efficacy Data

Dr. Laughren, in the Division memorandum dated February 27, 2007, found that the sponsor had provided sufficient evidence to support the claim of short-term efficacy of Luvox CR in the treatment of SAD and OCD.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data was re-reviewed for consistency. The undersigned requested that the sponsor send copies of the original CRFs and adverse event tabulations to compare for consistency. In a second audit of the adverse event data after this issues had been highlighted in the Approvable Letter, Dr. Kohli-Chhabra compared the listings with the CRF pages and found the upwards of 90% of the data to be consistent. The undersigned reviewed the data submitted by Solvay and concurred with Dr. Kohli-Chhabra's conclusion finding the consistency of the safety data at this point in time to be non-objectionable.

5.3 Clinical Sections of Labeling

The agency will request submission of draft Luvox CR labeling. Standard language to describe the risk of hyponatremia will be employed similarly in both the Luvox and Luvox CR labeling.

6.0 FOREIGN REGULATORY ACTIONS

To the best of my knowledge, Luvox CR is not approved anywhere at this time. The sponsor will be asked to provide a review of the status of all fluvoxamine maleate actions taken or pending before foreign regulatory agencies. Solvay needs to provide English translations of current approved foreign labeling not previously submitted.

7.0 WORLD LITERATURE

Solvay will need to provide a safety update of literature to identify any changes in the safety profile.

8.0 CONCLUSIONS AND RECOMMENDATIONS

Based on the data provided in the reviews and correspondence, I recommend that an approvable action be taken on Solvay's response. Based on Dr. Cai's reviews and additional audits by Dr. Kohli-Chhabra and the undersigned, I believe that Solvay has submitted sufficient clinical data to support the conclusion that Luvox CR is effective and acceptably safe in the treatment of patients diagnosed with generalized SAD and OCD. At this point, a safety update is required when the primary deficiencies are addressed. Moreover, research on the safety and efficacy of Luvox CR in a pediatric population aged 12 to 17 years would be recommended to provide valuable clinical information.

Unresolved quality and biochemistry issues preclude and approval in my opinion until resolution is achieved. The outstanding chemistry and clinical pharmacology issues that remain unresolved turn on [redacted] agreement with the dissolution method and specifications provide in the Approvable letter, and therefore, the expiry period to be assigned must be clarified.

In addition, as a post-marketing commitment, the Division will require submission of data on the microscopic examination of the standard battery of tissues used in the general toxicity study entitled "Fluvoxamine Maleate: 14-Day Oral (Gavage) Administration Comparative Toxicity Study in the Rat with Fluvoxamine Maleate and Fluvoxamine Maleate Spiked with [redacted]

I would recommend approval conditional on satisfactory resolution on of the issues pertaining to [redacted], dissolution method and specifications, and stability data to support assignment of patent expiry. When the deficiencies are addressed, updates on safety, foreign regulatory applications and labeling, and literature in addition to agreement on Luvox CR labeling will also be required.

cc:
Orig NDA 22-033
HFD-130
HFD-130/GZornberg/MMathis/TLaughren /RGrewal/PDavid/SHardeman

DOC:Luvox CR_SADandOCD_Zornberg_AE_Memo_Addendum.doc

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/s/

Gwen Zornberg
12/19/2007 11:52:44 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA # 22,033/S-000

Sponsor:	Solvay Pharmaceuticals Inc.
Drug:	Luvox CR
Material Submitted:	Response to queries regarding AEs, response to February 27, 2007 Approvable (AE) Letter
Correspondence Date:	October 30, 2007
Date Received:	October 30, 2007
Description of Compound Drug Category:	Selective Serotonin Reuptake Inhibitor
Indications:	Generalized Social Anxiety Disorder and Obsessive Compulsive Disorder

Luvox CR Adverse Event Database Audit Summary:

I reviewed the complete data submission sent electronically by Mr. Hare of Solvay to Rimmy Grewal in an email dated 30 October 2007, regarding the audit of AEs that had been identified as inconsistent by Dr. June Cai in her review dated 2 November 2007.

Specifically, the AE data that I reviewed were derived from copies of CRF pages for pivotal and extension studies, JMP AE tabulations, and narratives for patients who experienced events that led to either study discontinuation or serious adverse events requested by the division to resolve the question regarding the quality of the data as reflected in the degree of inconsistency of safety data in this application.

The Sponsor provided this table to identify the relevant clinical studies by protocol numbers referred to in the database.

SAS Filename	Description	Protocol number
AE-103	OCD Pivotal 12- week	S1143103
AE-104	OCD 52-week extension of S1143103	S1143103/S1143104
AE-107	SAD Pivotal 12-week	S1143107
AE-108	SAD Pivotal 12-week	S1143108
AE-109	SAD 24-week extension of S1143108	S1143108/S1143109
AE-IDB	Integrated Safety Database	S1143103, S1143104, S1143107,S1143108, S1143109

Of the patients initially identified with inconsistent AEs, upon detailed review of the different sources of information most cases (i.e., 21 subjects) were found to be complete and consistent as enumerated below:

Study 103	Study 104	Study 107	Study 108	Study 109
3103-08-69001	3104-19-69034	3107-05-69626	3108-10-70055	3109-29-70074
3103-11-69048	3104-04-69128	3107-13-69652	3108-15-70070	3109-84-70161
3103-04-69101	3104-07-69215	3107-69740	3108-84-70159	
3103-14-69212	3104-69075	3107-69771	3108-85-70276	
	3104-69123			
	3104-69152			
	3104-69166			

Some inconsistencies were identified:

For the subject with ID 3104-69242, the pivotal study adverse data from the CRF tracked increased appetite, headache and common flu symptoms. However in the JMP tabulation listing for that subject, only increased appetite was identified.

For the subject with ID 3103-20-69015 the adverse events are listed as dizziness and syncope (fainting). However the AEs for the subject with ID 69051 were combined incorrectly (i.e., diarrhea, nausea, nightmares, pain (right flank), and suicidal ideation with plan) with the AEs from subject with ID 69015 in the AE list from the CRF, though not in the JMP AE tabulation or the narrative summary. This error has been clarified by Solvay. The sponsor stated in the response by email that, nonetheless, the AEs for subject with ID 69051 are "depicted in the individual study database and integrated database accurately."

One Phase I subject with ID 00020, that was on the list provided by Dr. Cai, had been included in the audited list. This patient has been excluded as not meeting criteria defining the data to be audited is from Phase II and Phase III studies.

Reviewer's comment:

Based on my review of all the relevant data provided by the Sponsor in response to the FDA request for data, I found that the majority of the apparent inconsistencies were resolved, and that the quality of the data appeared satisfactory.

The inconsistencies between the CRF and JMP listing for subject with ID 3104-69242 were minor. Headache and common flu symptom for this subject should be added to the JMP tabulation based on the source data review.

In contrast, the inconsistencies for subject with ID 3103-20-69015 were not minor; however, they were biased against Luvox CR versus placebo, as they falsely elevated the apparent frequency of more serious AEs compared to placebo. The Sponsor is aware and has responded to our identification of the problem.

Conclusions and Recommendations:

Please convey to the Sponsor the following:

We have reviewed all of the data that you submitted electronically on 30 October 2007 in response to our inquiry regarding the quality of the adverse event data in this application. A minority of subjects identified were found to have inconsistent AE data, though most of the discrepancies in the small number of cases that were found to be inconsistent were judged clinically to be minor.

With respect to the subject with patient ID 3104-69242, you should add headache and flu symptoms as AEs to correct the JMP tabulation in your database.

Moreover, you should correct the AEs for the two subjects with ID 3103-20-69015 and 69051 in your database for the Case Report Form AE listings. Dizziness and syncope should be listed for the subject with ID 3103-20-69015 and the AEs of diarrhea, nausea, nightmares, pain (right flank), and suicidal ideation with plan should be assigned to the subject with ID 69051.

In conclusion, the quality of the adverse event data in your application appears adequate based on the results of our review.

_____
Kavneet Kohli-Chhabra M.D
11-21-2007
Medical Reviewer
FDA CDER ODE1 DPP
HFD 130

cc: NDA 22-033
HFD 130/RGrewal
KKohli-Chhabra
WBender
DClaffey
TOliver
GZornberg
MMathis
TLaughren

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/s/

Kavneet-Ripi Kohli-Chhabra
11/21/2007 11:50:27 AM
MEDICAL OFFICER

Gwen Zornberg
11/21/2007 12:06:07 PM
MEDICAL OFFICER
I reviewed the entire body of data submitted from CRFs, narratives, and AE tabulations with Dr. Kohli-Chhabra and found her review to be thorough. I found the quality of the safety data provided by the sponsor generally to be adequate with one exception.

Review and Evaluation of Clinical Data

NDA #22033/S-000

Sponsor:	Solvay Pharmaceuticals Inc.
Drug:	Luvox® CR
Indication:	Obsessive Compulsive Disorder Social Anxiety Disorder
Material Submitted	Response to February 27, 2007 Approvable (AE) Letter
Correspondence Date	June 21, 2007
Date Received	June 26, 2007

I. Background

The sponsor submitted this NDA on April 28, 2006. The original review was completed on January 15, 2007. In response to our AP letter of February 27, 2007, the sponsor sent in this submission. The main issues we requested based on the original clinical review are as follows:

- Discrepancies in CRFs, narrative summaries, and common AE listing need to be corrected and reanalyzed.
- Additionally, the demographic analysis of AEs needs to be conducted properly by analyzing each common, drug-related adverse event incidence for each demographic variable, specifically by calculating the odds ratios of the event in each subgroup as well as the common odds ratio for the event across subgroups followed by use of the Breslow-Day Chi-Square test to test for homogeneity of the odds ratios across the subgroups, with determination of the *p*-value for this test. Furthermore, given the age distribution of these events, the following age subgroups are recommended in lieu of the multiple age categories utilized by you: age 50 years or younger versus age 51 years or older.

Additionally, we requested the sponsor to submit Safety Update and include world literature search for safety profile. The sponsor also submitted the proposed labeling.

Issues of chemistry and toxicology will be discussed by the Agency Chemistry Reviewer, David Claffey, Ph.D. and Pharmacology-Toxicology Reviewer, Linda Fossom, Ph.D. in their reviewers.

II. Clinical Data

A. Discrepancies in CRFs, narrative summaries, and common AE listing

In the original NDA reviewer, initial auditing of 5% CRF revealed missing information in AE listing and unavailability of narrative summaries. Repeated auditing of another 5% CRF revealed the similar result. (See Tables 1 and 2 in Appendix.)

An audit of the CRF's, narrative summaries, and adverse event line listings conducted after the Solvay's response to our approvable letter revealed the following: 1) Newly submitted CRF's and narrative summaries match AE listing for four audited subjects in controlled studies (see Table 3 in Appendix); 2) the newly audited CRF's in the open-label study 3104 don't match AE listing (see Table 3 in the Appendix); and 3) the previously audited CRF's in the controlled trials still don't exactly match the AE listing (see Table 4 in Appendix). These discrepancies were brought to the attention of the Clinical Team Leader for this NDA, Dr. Gwen Zornberg.

Subsequently, the CRF audit discrepancies were discussed in a teleconference between Dr. Zornberg and the sponsor on 10-31-07. Since I was not notified to attend, I cannot comment on the content of the telecon. Also, at this point, Dr. Zornberg has instructed me to expeditiously complete the review as it is considered "very late in the review cycle to be stalling on the audit of the safety data." Therefore, I defer judgment of adequacy of the audited safety information to Dr. Zornberg, who is convinced that the quality of the safety data as assessed by the CRF audit is "more than adequate" and "appears good."

B. Demographic analysis of the AEs pooled from the three placebo-controlled studies:

a) Age group analysis (≤50 years of age vs. ≥51 years of age): There was no age group differences among all the common AEs listed.
b) Race group analysis: The sponsor separated subjects into two groups – White vs. non-white. The only AE appears statistically significantly more in White is somnolence (p=0.029).
c) Gender analysis: There was no common AE that appear statistically different between the two groups.

C. Safety and Literature Update

a) Safety Update: Since Luvox CR has not been marketed, there is no postmarketing safety update. The sponsor reports that the estimated cumulative patient exposure to fluvoxamine meleate outside the U.S. is ——— This is based on an average dose of 0.125g/day and average duration of six weeks of treatment. The sponsor, however, didn't report the estimated cumulative patient exposure within the U.S. as this was pulled off the market since 2002.

The only new study report submitted this time is that of protocol # 114.2.09, which is under review by Dr. Dubitsky in NDA 22-235. Thus, it will not be reviewed here.

b) Literature Update: The sponsor reports that a thorough review of clinical and non-clinical world literature on safety of fluvoxamine maleate was conducted, using the database of MEDLINE, EMBASE, and REACTION. This clinical literature review covers the period from January 1, 1994 to December 31, 2006. A total of 364 articles were examined for relevant safety findings, covering population of all ages. The sponsor reports one change is required in the proposed labeling: The addition of amenorrhea as a potential side effect. The significance of this information was verified by Dr. Gregory Dubitsky who reviewed Luvox IR labeling several weeks ago. Thus, I have no objection of its addition. The sponsor states that no other new or different safety information found in reference to current labeling. With regard to the literature on suicidality with SSRIs, the sponsor also reports that they were carefully examined for the concern about increased risk of suicidality, particularly among children and adolescents but without clear evidence of increased suicidality. Still, the sponsor has agreed to integrate the new Black Boxed Warning and continuing close monitoring the literature with this regard.

III. Proposed Labeling

Proposed labeling was reviewed by Dr. Mitchell Mathis in the previous review cycle and will be reviewed by the current Clinical Team Leader, Dr. Gwen Zornberg.

IV. Conclusion and Recommendation

Based on the above review, from clinical point of view I recommend the division taking an approval action for this NDA.

June Cai, MD
Medical Officer, DPP
ODE1-OND-CDER, FDA
Date: Nov. 2, 2007

V. Appendix

Table 1. The First Original CRF and AE Listing Audit

PATIENT ID	CASE REPORT FORM AE'S	NARRATIVE SUMMARY	JMP AE LISTING
3103-08-69001	**Sedation.**	OK	OK
3103-14-69212	Dry mouth, general cold symptoms, hot flashes, **insomnia**, lethargy.	OK	OK
3104-03-69128	**Fractured knee.**	OK	**Not Found**
3104-14-69275	**Early insomnia**, sinus infection, **nausea, lightheadedness**, tension headache.	**Not Found**	**Missing:** nausea, lightheadedness
3107-05-69626	Nausea, **sore throat**, cold symptoms	**Not Found**	OK
3107-13-69652	Headache, flushed feeling,	OK	OK

PATIENT ID	CASE REPORT FORM AE'S	NARRATIVE SUMMARY	JMP AE LISTING
	drugged feeling.		
3108-15-70070	**Nausea**, emesis.	OK	OK
3108-85-70276	Insomnia, **anorgasmia, loss of libido.**	OK	OK
3109-84-70161	Sore throat, **tonsillectomy,** headache.	OK	**Added:** Low back pain, bladder pain, gastroenteritis, kidney pain, premenstrual tension. **Missing:** tonsillectomy.

Table 2. The Second Original CRF and AE Listing Audit

PATIENT ID	CASE REPORT FORM AE'S	NARRATIVE SUMMARY	JMP AE LISTING
3103-04-69101	Diarrhea, **dizziness, gastric reflux, insomnia, sinusitis.**	OK	OK
3103-11-69048	Daytime drowsiness, **insomnia.**	OK	OK
3103-20-69015	Diarrhea, nausea, nightmares, pain (right flank), **suicidal ideation w/plan.**	**Entirely different AE's: dizziness, syncope**	**Entirely different AE's: dizziness, syncope**
3104-07-69215	**Hot and cold flashes, feeling disoriented, dizziness, tremor, nausea, decreased concentration, photophobia**, loss of sexual interest.	OK	**Added:** chest pain, headache, infection, abnormal dreams, UTI. **Missing:** All except loss of sexual interest.
3104-19-69034	**Weight gain, increased anxiety.**	**Not Found**	**Added:** Sore throat. **Missing:** Increased anxiety
3104-20-69208	Headache, **increased weight, fatigue.**	**Not Found**	**Entirely different AE's:** Toothache, insomnia.
3108-10-70055	**Insomnia.**	OK	OK

PATIENT ID	CASE REPORT FORM AE'S	NARRATIVE SUMMARY	JMP AE LISTING
3108-84-70159	Nausea, concentration impairment, loose stools, waking up at night, increased appetite, menstrual changes, mastodinia, headache, palpitations, dog bite, **jittery**, weight gain.	OK	OK
3109-29-70074	**Fatigue**, weariness.	OK	**Added:** Tachycardia, dry mouth, rash.

Table 3. The Auditing Result of the Newly Submitted CRF and AE Listing in the Original Response to the AE Letter (The 3rd Audit)

PATIENT ID	CASE REPORT FORM AE'S	NARRATIVE SUMMARY	JMP AE LISTING
3104-69075	**Dyspepsia, Insomnia,** Nausea	OK	OK
3104-69123	**Sinus arrhythmia bradycardia, ST-wave depression** urinary tract infection,	OK	**Added:** Anorexia Insomnia
3104-69138	**Intermittent lethargy,** URI, **dyspnea, lethargy,**	**Added:** sexual dysfunction	**Added:** Dry mouth, headache, nausea, sexual dysfunction
3104-69152	Nausea, diarrhea, indigestion, decreased appetite, **burning in stomach**	OK	**Added:** Cyst, headache, pain, lethargy, skin ulcer, worsening hypertension
3104-69166	**Delayed ejaculation,** decreased appetite, lightheadedness, **insomnia,** somnolence	OK	**Added:** Migraine, headache
3104-69242	**Tingling in both arms, lightheadedness, decreased appetite, nausea**	OK	**Added: Increased appetite**
3107-69771	Itchy Eyes, itchy nose, head congestion, sinus pressure headache, **nausea,** cold symptoms	OK	OK
3107-69740	**Nausea, insomnia, diarrhea-like feeling**	OK	OK
3107-69755	Increased shakiness, decreased sleep, increased sleep, occasional palpitations, **nasal congestion**, dry mouth	OK	OK
00020	Loose stool, pressure to both ears, **high blood pressure**, headache, chest pains	OK	?

Table 4. The Changes in Previously Audited Cases (Refer to Tables 1 and 2)

PATIENT ID	CASE REPORT FORM AE'S	NARRATIVE SUMMARY	JMP AE LISTING
3104-03-69128	**Fractured knee.**	OK	**OK**
3104-14-69275	**Early insomnia**, sinus infection, **nausea, lightheadedness**, tension headache.	**Submitted OK**	**OK**
3107-05-69626	Nausea, **sore throat**, cold symptoms	**Submitted OK**	OK
3109-84-70161	Sore throat, **tonsillectomy**, headache.	OK	**Added still there**
3104-07-69215	**Hot and cold flashes, feeling disoriented, dizziness, tremor, nausea, decreased concentration, photophobia**, loss of sexual interest.	OK	**Added still there**
3104-19-69034	**Weight gain, increased anxiety.**	**Submitted OK**	**Added sore throat**
3104-20-69208	Headache, **increased weight, fatigue.**	**Submitted OK**	**OK**
3109-29-70074	**Fatigue,** weariness.	OK	**Added:** Tachycardia, dry mouth, rash.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

June Cai
11/2/2007 02:10:15 PM
MEDICAL OFFICER

Gwen Zornberg
11/6/2007 10:29:11 PM
MEDICAL OFFICER
In discussion with Drs. Mathis & David, Dr. Grewal arranged a teleconference on 31 Oct with Solvay, Bill Bender, and me. Review of all cases identified by Dr. Cai did not confirm inconsistencies of data in the CRFs & JMP AE lists. See supervisory memo.

MEMORANDUM

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

DATE: 26 February 2007

FROM: Mitchell V. Mathis, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 22-033 (This overview should be filed with the 4-28-2006 original submission.)

SUBJECT: Recommendation of Approvable Action for Fluvoxamine Maleate Controlled-release Capsules (fluvoxamine CR) for the Treatment of Social Anxiety Disorder and Obsessive Compulsive Disorder

1.0 BACKGROUND

Fluvoxamine CR is a selective serotonin reuptake inhibitor (SSRI) developed by Solvay Pharmaceuticals as an extended-release capsule for once daily administration in the treatment of Social Anxiety Disorder (SAD) and Obsessive Compulsive Disorder (OCD).

Solvay's fluvoxamine maleate immediate-release tablets (brand name Luvox®) were approved under NDA 20-243 on 5 December 1994 to treat OCD. In September 1997, the NDA was withdrawn as a result of negotiations with the sponsor under the FDA Application Integrity Policy (AIP). In April 2003 Solvay was removed from AIP. While there are multiple generic fluvoxamine maleate formulations available, this is the first application for a controlled-release formulation.

This NDA has been reviewed by June Cai, M.D., Medical Officer, DPP, Fanhui Kong, Ph.D., Office of Biostatistics, David Claffey, Ph.D., Chemist, Linda Fossom, Ph.D., Pharmacology/Toxicology, and Andre Jackson, Office of Clinical Pharmacology and Biopharmaceutics.

2.0 CHEMISTRY

Dr. Claffey has identified several CMC concerns that need to be addressed prior to taking an approval action:

- Resolution of the deficiencies in the drug master files for both the drug substance (DMF 5169) and the drug product (DMF [redacted]
- Adequate responses to information requested of the Sponsor on 22 Dec 2006.
- Receipt from the Office of Compliance of an acceptable recommendation for the [redacted] site [redacted]

In addition, Chemistry recommends that specific information be conveyed to the Sponsor; this information is listed under section 9.2.1 of this review.

3.0 PHARMACOLOGY

Pharmacology/Toxicology recommends an APPROVABLE action for this NDA. Their review reiterates that the two impurities/degradants with specifications above the threshold for qualification in the drug product must be adequately qualified (see page 10 of Dr. Fossom's Review). Comments to be conveyed to the sponsor from Pharmacology/Toxicology are included in section 9.2.3 below.

4.0 CLINICAL PHARMACOLOGY

The Clinical Pharmacologists have provided dissolution specifications which they would like to be conveyed to the sponsor (see section 9.2.4 below).

5.0 CLINICAL DATA

5.1 Overview of Studies Pertinent to Safety and Efficacy

Three pivotal studies were submitted in support of two indications, two (3107 and 3108) for SAD and one (3103) for OCD. In addition, two Phase 3 extension studies (3104 and 3109) and six Phase 1 studies were included in the safety database.

A total of 579 patients were randomized (288 to treatment and 291 to placebo) for both studies 3107 and 3108. These trials were conducted in the United States (3107 was conducted solely in the U.S.), Europe, and South Africa. Of those randomized, 541 were included in the ITT analysis data set (267 in the treatment group and 274 in the placebo group). More than ¾ of the patients were Caucasian and over half male. The majority of the patients were between 18 and 50 years of age.

In study 3103, 253 patients were randomized (127 to treatment and 126 to placebo) across 20 centers throughout the United States. Of these, 237 patients were included in the ITT analysis data set (117 in the treatment group and 120 in the placebo group). Over ¾ of the patients were Caucasian and over half female. The majority of the patients were between 18 and 50 years of age.

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 fluvoxamine maleate CR compared with placebo in subjects with SAD or OCD. Eligible subjects were randomly assigned to receive flexible doses of drug (range of 100 to 300 mg/day) or placebo (Table 1). Patients randomized to the drug group started with 100 mg/day. The dose was then increased in increments 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; no dose adjustment was permitted during Week 6 to Week 12 of the double-blind phase.

Table 1: Studies Supporting the Efficacy and Safety of Luvox® CR in the Treatment of 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 randomized.
Source: Dr. Kong's review.

5.2 Efficacy Data

5.2.1 Summary of Studies Pertinent to Efficacy Claim for SAD

Studies 3107 and 3108 were 12-week, multicentered, randomized, double-blind, placebo-controlled, parallel-group evaluations of safety and efficacy in adult patients with SAD. The primary efficacy measure was change from baseline to endpoint in the Liebowitz Social Anxiety Scale (LSAS).

In both of these studies, the efficacy of fluvoxamine maleate CR was demonstrated by LOCF analysis of change from baseline in the primary efficacy measure (Table 2). No key secondary efficacy measures were pre-specified.

Table 2: Statistical Comparisons between Treatment and Placebo for Primary Efficacy Variable LSAS Total Score in Studies 3107 and 3108–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	

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: Dr. Kong's review.

5.2.2 Summary of Data Pertinent to Efficacy Claim for OCD

Study 3103 was a 12-week, multicentered, randomized, double-blind, placebo-controlled, parallel-group evaluation of safety and efficacy in adult patients with OCD. The primary efficacy measure was change from baseline to endpoint in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

The efficacy of fluvoxamine maleate CR was demonstrated by LOCF analysis of change from baseline in the primary efficacy measure (Table 3). No key secondary efficacy measures were pre-specified (Table 3).

Table 3: Statistical Comparisons between Treatment and Placebo for Primary Efficacy Variable Total Y-BOCS score–LOCF ITT Population for Week 12

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.
Source: Dr. Kong's review.

5.3 Weeks 2-10 and Time to Onset of Action

An analysis of statistical comparisons between drug and placebo for primary efficacy variables demonstrates that fluvoxamine maleate CR was statistically distinguishable from placebo prior to the last observation at 12 weeks for both SAD and OCD (Tables 4, 5, and 6). The results from studies 3107 and 3103 are consistent from Week 6 to the end of study, while the results from study 3108 were not as consistent. However, even in Studies 3107 and 3103, the p-values are only

nominal and not adjusted for multiplicity caused by multiple observations, so caution must be exercised in making inferences regarding time of onset.

Table 4: 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.

Source: Dr. Kong's review

Table 5: 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.

Source: Dr. Kong's review.

Table 6: 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 (ITT population)	(N=117)	(N=120)
N (ITT for Y-BOCS Total Score)	117	120
Baseline Mean (Raw)	113	119
	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.
Source: Dr. Kong's review.

5.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analyses presented by the Sponsor and reviewed by Drs. Cai and Kong support the efficacy claim of fluvoxamine maleate CR in the treatment of SAD and OCD.

Additionally, in all three studies, the OC and MMRM analyses produced statistically significant efficacy results for the primary endpoints. P-values from the MMRM analyses were below 0.0001 for all three studies.

Team Leader comment: We should include the results from the IR formulation in labeling as additional supporting data for the single CR study in OCD.

6.0 Safety Data

6.1 Safety Findings from the Placebo-Controlled Trials

The controlled-trial safety database for fluvoxamine CR is comprised of the pool of the three Phase 3 studies discussed above. This database consists of 403 subjects receiving flexible dose fluvoxamine CR and 400 placebo patients. The safety profile of fluvoxamine CR is similar to that of fluvoxamine immediate-release. There is considerable safety experience with the fluvoxamine immediate-release formulation, and exposures with fluvoxamine CR are less than or comparable at comparable doses.

6.1.2 Safety Findings and Issues of Particular Interest

6.1.2.1 Common and Drug-Related Adverse Events

In the fixed dose trials, the following events were reported in at least 5% of the fluvoxamine CR group and at a rate twice that of placebo: nausea, insomnia, somnolence, asthenia, diarrhea, anorexia, abnormal ejaculation, dyspepsia, decreased libido, anxiety, tremor, sweating, and anorgasmia.

Team Leader Comment: Note that the review team (Dr. Cai and Dr. Dubitsky) has audited the Case Report Forms (CRFs) and found that the AEs listed in the CRFs do not match those found in the AE line listings provided by the sponsor. Therefore, the accuracy of common drug-related adverse events is questionable and must be verified with the sponsor prior to approval (see section 9.2.2 below).

6.1.2.2 Adverse Events Leading to Dropout

The adverse events among fluvoxamine CR-treated patients that most frequently led to dropout were nausea, insomnia, and somnolence. Most patients who withdrew from the studies with these events did so within the first four weeks of treatment.

6.1.2.3 Serious Adverse Events (SAEs) in Clinical Trials

The sponsor defines a serious adverse event as any event that resulted in death, was life-threatening, resulted in significant disability/incapacity, required hospitalization, or caused a congenital anomaly. Pregnancy recorded during the trials was also reported as serious.

There were no deaths among subjects in the clinical trials which were likely related to fluvoxamine CR.

There were no serious adverse events in any of the Phase 1 studies. In the Phase 3 studies there were 18 SAEs identified by the sponsor, none of which are reasonably attributable to fluvoxamine CR (see Dr. Cai's review page 43).

6.1.2.4 Laboratory Findings

There were no significant differences between combined treatment and placebo groups with regard to serum chemistries, hematology, or urinalysis.

6.1.2.5 ECG Findings

There were no significant changes in ECG measures between drug and placebo groups among the three pivotal studies.

6.1.2.6 Vital Signs Findings

Examination of the combined safety database from the three pivotal studies from baseline to week 12 showed no significant differences between drug and placebo groups with regard to blood pressure, heart rate, body temperature, or body weight.

6.2 Conclusion Regarding Safety

Short-term treatment with fluvoxamine CR appears to have been reasonably safe in the populations studied. There were no unexpected adverse events.

7.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

This NDA was not presented to the PDAC.

8.0 DSI INSPECTIONS

A DSI audit was conducted of six clinical sites. Although the final report is pending, data from each of these sites is recorded as acceptable in a DSI Memo to File dated 10 January 2007.

9.0 LABELING AND ACTION LETTER

9.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed labeling will require extensive modification and negotiation and should be included with the Action Letter.

9.2 Deficiencies and Comments to be Conveyed to Sponsor

9.2.1 Chemistry

Dr. Claffey has identified several CMC concerns that need to be addressed prior to taking an approval action:

- Resolution of the deficiencies in the drug master files for both the drug substance (DMF 5169) and the drug product (DMF).
- Adequate responses to information requested of the Sponsor on 22 Dec 2006.
- Receipt from the Office of Compliance of an acceptable recommendation for the site .

The Chemists have also requested that the following be added to the Action Letter:

The following deficiencies were forwarded to the sponsor (via fax) on 22 Dec 06 and remain outstanding:

1. Please note that a deficiency letter has been sent to DMF (22 Dec 2006).
2. Provide a letter of authorization to access DMF 5169.
3. The term for the dosage form is not acceptable, we recommend that it be replaced with 'extended-release.'
4. Provide information about the testing carried out by prior to the final commercial packaging operation. Who is responsible for the release testing of the final commercial product packaged in marketed packaging? Provide release specification and representative CoAs for the final commercial product.
5. Please lower the specified limit for the impurity in drug substance specification to the recommended ICH Q3A qualification limit of .
6. An appearance test and particle size test should be added to the drug substance specification.
7. The drug product label needs to reflect regulatory requirement with respect to the inclusion of a manufactured by/for designation (21 CFR 201.1).
8. Please provide updated mockups of the proposed drug product labels.

9.2.2 Clinical

As noted above, the clinical review team (Dr. Cai and Dr. Dubitsky) has audited the Case Report Forms (CRFs) and found that the AEs listed in the CRFs do not match those found in the AE line listings provided by the sponsor. Therefore, the accuracy of common drug-related adverse events is questionable and must be verified with the sponsor prior to approval. This will be noted in the annotated draft labeling returned to the sponsor with the Action Letter.

Additionally, common drug-related AEs should be analyzed and reported for each demographic sub-group, including age.

9.2.3 Pharmacology/Toxicology

The review team has asked that the following be communicated to the sponsor:

There are several impurities/degradants in the drug substance and/or CR drug product with specifications above the threshold(s) for qualification. Although you have not addressed this issue in your current NDA, similar issues were addressed under your NDA 21-519 for Luvox IR tablets.

Based on the toxicology studies available for review under that NDA, we have determined that only the specifications for the —— (i.e.,——) and —— (i.e.,——) have been set too high in the CR product and cannot be considered to be qualified by nonclinical studies that have previously been submitted. Consequently, you will need to qualify these 2 impurities/degradants, as described below, prior to approval.

Only an additional (adequate) Ames test will be required to qualify the —— to its higher specification in the CR drug product (—— compared with —— for the IR product under NDA 21-519 and a threshold for qualification of —— It should be noted that you were informed in the AE letter for NDA 21-519 dated 11/16/06, that the Ames tests that had been submitted up to that time (with —— at concentrations up to ——) would be considered adequate to qualify the specification of —— proposed for the IR product, but not higher specifications.

Apparently, no studies that could serve to qualify —— have been provided (under NDA 21-519 or the current NDA). Qualification of —— will require: 1) a general toxicology study in one species of 14-90 days duration, which should include microscopic, as well as macroscopic, evaluation of the standard battery of tissues; 2) *in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tK assay [with colony sizing]); and 3) an embryofetal development study in one species.

9.2.4 Clinical Pharmacology/Biopharmaceutics

Dr's Jackson and Baweja have recommended the folowying be conveyed to the sponsor regarding dissolution specifications:

1. Dissolution—Final specifications for the 100 mg and 150 mg CR capsules
   a. Dosage Form: Capsules
      Strength: 100mg and 150 mg
      Apparatus Type: USP Apparatus II (Rotating Paddles)
      Media: Phosphate Buffer pH 6.8
      Volume: 900 mL
      Speed of Rotation: 50 rpm
      Sampling Times: 2, 4, 6, 8, and 12 hours

      Specifications:

Time (hrs)	Criteria (% Released)
2	
4	
6	
8	
12	

9.2.5 DMETS

The Division of Medication Errors and Technical Support found the proprietary name LUVOX CR to be acceptable, but they will require the name be re-evaluated 90 days prior to a final approval

action. They also had several carton and container label comments which should be incorporated into the Action Letter.

10.0 Phase 4 Commitments

Although we agreed that studies of fluvoxamine in pediatric patients could be deferred, we should ask the sponsor to study the effect of fluvoxamine CR in adolescent patients with SAD and OCD as a Phase 4 commitment.

SAD and OCD are chronic illnesses and long term efficacy should be assessed post approval.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that fluvoxamine maleate CR is effective and reasonably safe in the treatment of SAD and OCD. I recommend that we issue an approvable action letter.

Multiple requests for additional information are outlined in section 9 of this memo and should be conveyed to the sponsor.

Phase 4 commitments should be requested for pediatric and maintenance studies as outlined in section 10 above.

Annotated Draft Labeling as revised by the Division should be attached to the Action Letter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mitchell Mathis
2/26/2007 02:59:00 PM
MEDICAL OFFICER
Approvable--TL Memo

CLINICAL REVIEW

Application Type	NDA-22033
Submission Number	000
Submission Code	N
Letter Date	April 28, 2006
Stamp Date	May 01, 2006
PDUFA Goal Date	March 1, 2007
Reviewer Name	June Cai, MD
Review Completion Date	January 15, 2007
Established Name	Fluvoxamine maleate
(Proposed) Trade Name	Luvox® CR
Therapeutic Class	Serotonin reuptake inhibitor
Applicant	Solvay Pharmaceuticals Inc.
Priority Designation	S
Formulation	Capsules
Dosing Regimen	100mg, 150mg
Indication	Obsessive Compulsive Disorder Social Anxiety Disorder
Intended Population	Adults

Table of Contents

1 Executive Summary

1.1 Recommendation on Regulatory Action

I recommend the Division take an Approvable action on this NDA for the use of fluvoxamine CR to treat adult generalized anxiety disorder and obsessive-compulsive disorder.

The following clinical issues should be addressed prior to taking a final approval action on this application:

- The discrepancies in CRFs, narrative summaries, and common AE listing need to be corrected and reanalyzed.

- Additionally, the demographic analysis of AEs needs to be conducted properly by analyzing each common, drug-related adverse event incidence for each demographic variable, specifically by calculating the odds ratios of the event in each subgroup as well as the common odds ratio for the event across subgroups followed by use of the Breslow-Day Chi-Square test to test for homogeneity of the odds ratios across the subgroups, with determination of the *p*-value for this test. Furthermore, given the age distribution of these events, the following age subgroups are recommended in lieu of the multiple age categories utilized by the sponsor: age 50 years or younger versus age 51 years or older. This request should be communicated in the approvable letter for this application.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activity is considered necessary for fluvoxamine CR at this point.

1.2.2 Required Phase 4 Commitments

According to the Pediatric Research Equity Act (PREA), the sponsor should conduct studies in pediatrics as Phase 4 commitments. In this case, since both disorders are more common in older children and teenagers, the (age – 17 years old)

1.2.3 Other Phase 4 Requests

The sponsor should consider trials to study long term efficacy of fluvoxamine CR for treatment of generalized social anxiety disorder and OCD because they are chronic illnesses.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Fluvoxamine maleate controlled-release (Fluvoxamine CR) is a selective serotonin reuptake inhibitor (SSRI) consisting of a multiparticulate drug delivery system that delivers its active moiety fluvoxamine maleate over a period of 12 hours. Its immediate-release formulation was approved and used worldwide since 1995.

This submission includes three pivotal studies for two indications: Two studies (3107 and 3108) for generalized social anxiety disorder (GSAD) and one study (Study 3103) for obsessive compulsive disorder (OCD). Overall, a total of 579 subjects were included in the two controlled studies of SAD and 253 subjects were in the controlled study of OCD.

In addition, two Phase 3 extension studies (3104, of Study 3103, and 3109, of Study 3108) and six Phase 1 studies were also included for safety analysis.

1.3.2 Efficacy

There were two efficacy studies (Studies 3107 and 3108) for generalized social anxiety disorder (GSAD) and one efficacy study (Study 3103) for obsessive compulsive disorder (OCD). All three studies are Phase 3, double-blind, placebo-controlled, 12-week studies with dosage ranging from 100mg to 300mg. The primary variable for GSAD studies was the mean change from baseline to endpoint in Liebowitz Social Anxiety Scale (LSAS); whereas the mean change from baseline to endpoint in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score was the primary variable for OCD study.

Each individual study demonstrates efficacy of fluvoxamine CR for treatment of the intended indication compared to placebo.

Though two studies are generally required for a new indication, in this case, fluvoxamine immediate-release was previously approved for OCD based on two positive studies. Therefore, one study is sufficient for approval of the CR formulation for OCD.

1.3.3 Safety

The primary integrated safety database for this review is comprised of the pool of three Phase 3, double-blind, placebo-controlled, 12-week studies (3103, 3107, and 3108). However, events at the more serious end of the spectrum (that is, deaths, other serious adverse events, and dropouts due to adverse experiences) are examined from not only the above mentioned three Phase 3 pivotal trials but also the two extension trials (3109 and 3104) and six Phase 1 pharmacokinetic studies that evaluated fluvoxamine prototype D capsules (1098001, 1098002, 1141106, 1141107, 0300002, and 1141109). A total of 614 subjects received fluvoxamine CR and provided safety data altogether (Phases 1-3).

There were no significant previously unrecognized adverse events associated with fluvoxamine maleate immediate-release. However, there are deficiencies in the submission. These include discrepancies among the CRFs, narrative summaries, and common adverse event line listing; improperly analyzed common, drug-related adverse events by demographic subgroups; and no categorical analysis of ECG as well as unclear correction formulation of QT interval analysis.

1.3.4 Dosing Regimen and Administration

Starting fluvoxamine CR 100mg and increase to maximum dose 300mg. The titration should be 50mg each week if tolerated, according to clinical trials. However, [redacted], this titration schedule is somewhat complicated for patients to switch between the capsules of two different doses, 100mg and 150mg.

1.3.5 Drug-Drug Interactions

No drug-drug interaction study has been conducted. However, there have been observations of some significant drug-drug interactions with fluvoxamine maleate immediate-release formulation. Detailed information can be seen in its labeling.

1.3.6 Special Populations

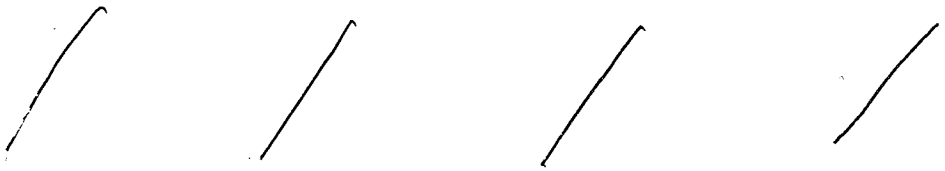
There were no studies conducted in a special population as part of fluvoxamine CR development program. Though the sponsor tried to include subjects who are age 65 or older, there were not enough number of subjects in this age group to adequately assess the efficacy and safety in this population.

2 Introduction and Background

2.1 Product Information

Chemically, fluvoxamine maleate is 5-methoxy-4'-(trifluoromethyl) valerophenone-(E)-(O)-(2-aminoethly) oxime maleate (1:1) with an empirical formula of $C_{15}H_{21}O_2N_2F_3 \cdot C_4H_4O_4$ and a molecular weight of 434.41. It belongs to the chemical series 2-aminoethyl oxime ethers of aralkylketones and is chemically unrelated to other SSRIs and clomipramine, a serotonin-selective tricyclic agent that has been the first-line therapy for many years.

Fluvoxamine maleate controlled-release (Fluvoxamine CR) is a selective serotonin reuptake inhibitor (SSRI) consisting of a ——— drug delivery system that delivers its active moiety fluvoxamine maleate over a period of 12 hours. The ——— beads ranging from —mm in diameter are encapsulated in hard gelatin capsules. ———



The trade name for its immediate release form is Luvox® (see Section 2.3 and 2.5 regarding regulatory and clinical history of Luvox®); Luvox® CR is the trade name for fluvoxamine CR.

This submission covers the clinical development program that utilized three dose strengths of fluvoxamine CR: 50mg, 100mg, and 150mg capsules; however, the sponsor only seeks approval for the strengths of 100mg and 150mg to be used daily for the treatment of both obsessive compulsive disorder (OCD) and generalized social anxiety disorder (SAD) in adults aged 18 to 65 year-old.

2.2 Currently Available Treatment for Indications

Treatment for OCD includes both psychotherapy (a combination of the behavioral therapy known as exposure and response prevention, and cognitive therapy) and drug therapy.

For most OCD patients, pharmacological treatment is indicated. Since clomipramine is associated with frequent anticholinergic side effects, postural hypotension, somnolence, and weight gain, the SSRIs, such as fluoxetine, fluvoxamine, paroxetine, and sertraline, that have shown as efficacious as clomipramine but with fewer side effects have been used as the first-line treatment for OCD. Length of treatment with these SSRIs is for at least 10 weeks before they are considered ineffective. After a failed trial with one SSRI, either another SSRI is recommended or the patient can be switched to clomipramine. Continued therapy with an SSRI is commonly needed because of relatively high relapse rate with initial treatment.

Other drugs have been used in combination with SSRIs with variable success. Neuroleptic agents are effective in patients with OCD and coexisting tic-spectrum disorders.

Treatment for SAD also includes both cognitive behavioral psychotherapy and drug therapy. A variety of drug classes have been used for this indication. These include SSRIs, benzodiazepines, beta blockers, serotonin norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs). Some other agents such as clonidine, pregabalin, and among others have been investigated as well. The SSRIs that are approved for this indication are paroxetine, sertraline, and venlafaxine.

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety, Luvox® (fluvoxamine maleate) immediate release is a selective serotonin reuptake inhibitor (SSRI). The sponsor submitted Luvox [redacted] It was approved by the Agency for use in the treatment of obsessive-compulsive disorder (OCD) on December 5, 1994 under NDA 20-243.

The sponsor, Solvay Pharmaceuticals Inc., was placed under the Application Integrity Policy (AIP) by the CDER Center Director on Sept. 24, 1997 for the following reasons: falsified stability data, falsified and missing data for drug interaction studies after approval, and other Chemistry, Manufacturing, and Controls (CMC) information that was deemed to be falsified or missing. The sponsor thus withdrew the NDA 20-243 in May 2002 and resubmitted as NDA 21-519 for treatment of OCD in adults and children on June 28, 2002. On April 9, 2003, AIP was removed. The approvable action was taken for the most recent resubmission of fluvoxamine maleate immediate-release tablet application on November 16, 2006.

According to the sponsor, fluvoxamine maleate has been registered in more than 80 countries and has been used in more than 50 million patients world wide since its introduction in Switzerland in 1983. Effective strengths have been shown from 25mg to 200mg per day in the treatment of OCD in pediatric outpatients; starting dose in adults with depression (in Europe) and OCD is 50mg per day that could be titrated up to 300mg per day.

During the most recent review, major labeling changes recommended by the medical reviewer for Luvox® (immediate release) approval include adding class blacking box warning regarding suicidality in children and adolescents; listing drugs that are contraindicated to use concurrently, including alosetron, tizanidine, ramelteon, [redacted], as well as MAOI's within 14 days of treatment; [redacted] caution its use during late pregnancy and risks of serotonin syndromes.

[redacted]

2.4 Important Issues with Pharmacologically Related Products

Fluvoxamine CR belongs to SSRI class. These compounds are thought to have ability to inhibit neuronal uptake of serotonin (5HT) in the central nervous system as well as a relatively weaker effect on norepinephrine or dopamine neuronal reuptake. Many compounds are approved for treatment of depression; some are also for treatment of anxiety disorders such as panic disorder, OCD, and generalized anxiety disorder. They must not be used within 14 days of using any monoamine oxidase inhibitors (MAOIs). All patients should be monitored for symptoms and signs of serotonin syndrome. In children and adolescents as well as young adults up to age 25 years old, closer monitoring for suicidal thoughts and behaviors are also necessary.

2.5 Presubmission Regulatory Activity

. This NDA (#22-033) is the — submission of fluvoxamine maleate CR.

2.6 Other Relevant Background Information

Fluvoxamine maleate has been registered in 80 countries worldwide. However, this is the first application for fluvoxamine maleate CR.

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable)

The sponsor intended to develop — strengths — 100 and 150 mg) of the controlled release tablets , however, at present, the sponsor only applies approval for 100mg and 150mg capsules

For detailed CMC information, please see the review conducted by the Agency Chemistry Reviewer, David Claffey, Ph.D.

3.2 Animal Pharmacology/Toxicology

The Agency Pharmacology-Toxicology Reviewer, Linda Fossom, Ph.D. verbally communicates that no significant pharmacology/toxicology issue exists with this application other than possible impurity issue. Please see Dr. Fossom's review for details.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

This submission includes mainly three clinical trials for two indications: One for OCD (Study 3103) and two for SAD (Studies 3107 and 3108). A total of 579 subjects were included in the two controlled studies of SAD and 253 subjects were in the controlled study of OCD. Additionally, the sponsor also includes data of another placebo-controlled and a fixed dose study, Study 3109, an extension study of Study 3108. However, the subjects were those who had shown at least minimal response to fluvoxamine CR treatment. Two of these studies (Studies 3108 and 3109) were also conducted in Europe and South Africa. The table in the next subsection delineates more detailed information of these studies.

4.2 Table of Clinical Studies

Table 1: Design and Subject Numbers in Phase 3 Controlled Clinical Trials

Trials & Indication	Study Design	Planned Subjects	Fluvoxamine CR		Placebo		Total Subjects Of Each Study	
			Randomized	ITT	Randomized	ITT	Randomized	ITT
S1143107 GSAD	Flexible dose	250	139	121	140	126	279	247
S1143108 GSAD	Flexible dose	250	149	146	151	148	300	294
Subjects in Short Term GSAD Studies		**500**	**288**	**267**	**291**	**274**	**579**	**541**
S1143109 GSAD	Fixed dose extension	300	57	56	55	53	112	109
S1143103 OCD	Flexible dose	250	127	117	126	120	252	237

All four are randomized, multicenter, parallel group, double-blind, placebo-controlled studies for 12 weeks long and total daily doses are 100mg to 300mg.

4.3 Review Strategy

Efficacy review divides into two sections according to the two indications. Study 3109 is an extension study of Study 3108. Thus, its data are not considered for acute efficacy. Moreover, the sponsor is not claiming for long term effects for treatment of generalized anxiety disorder in the drafted labeling.

Safety review combines data from all clinical trials for these two indications because both of these disease entities are part of anxiety disorders and neither is associated with a particular physical illness.

4.4 Data Quality and Integrity

Consult to Division of Scientific Investigations (DSI) was initiated and inspection was conducted in 6 sites. According to the DSI official report, data generated are acceptable despite deficiencies do exist among them. (See DSI report in DFS.)

Additionally, Dr. Gregory Dubitsky helped audit 10% of the Case Report Forms (CRFs) and checked the appropriateness of the coding of verbatim terms to preferred terms (see below). Deficiencies of data are detailed in the Section 7.2.8 "Assessment of Completeness and Quality of Data."

4.5 Compliance with Good Clinical Practices

The sponsor reports that subjects at Study Center 14 in Study 3107 were not reliably monitored for their vital signs. Thus, the validity of data was questionable and the sponsor has excluded the data from this center in the analysis. For other site-specific issues, please see the official DSI report of this NDA.

Specific protocol deviations are presented in the correlated study efficacy review in subsections 6.1.1.4 and 6.1.2.4. The most common cause of protocol deviations in all three pivotal studies was non-compliance to the dosage prescribed. Other leading causes were incorrect study drug doses taken (in OCD trial), including subjects with higher depression scores (GSAD trials), and prohibited medications were prescribed (in all trials).

Overall, these pivotal studies appear to be conducted with good ethical standards.

4.6 Financial Disclosures

The sponsor reports that only [redacted] MD who participated in Study [redacted] received more than $25,000 in support of an [redacted] t Program that developed [redacted] y. Financial disclosures of two other investigators of this study cannot be obtained because they left the study sites.

Financial disclosure was unavailable for 4 of the 156 investigators of Study 3108/3109 because they no longer work at study sites; The sponsor states that two investigators were unable to be contacted to obtain corrections but does not specify what kind of correction is needed.

Among 235 investigators of Study 3103, 29 (12.3%) of them no longer work at study site; 2 retired before signing and 1 never saw any patient for the study.

In general, the sponsor has provided adequate information of clinical investigators' financial disclosure.

5 Clinical Pharmacology

Below are summaries of clinical pharmacology data reported by the sponsor. For more detailed information, please refer to the review by Agency's Biopharmaceutical Science Reviewer, Andrew Jackson, PhD.

5.1 Pharmacokinetics

According to Dr. Jackson (personal communication via email), since this is a change in formulation IR to CR, there was no ADME data to review.

In the submission, the sponsor specifies that like Luvox, fluvoxamine CR exhibits a similar non-linear dose-dependent pharmacokinetics. Additionally, the sponsor also states the following: Bioavailability of *Luvox CR 100mg capsules* is 84% compared to *Luvox 100mg tablets*. Its $AUC_{(0\text{-}inf)}$ is $\geq$ 80% compared with Luvox. Unlike Luvox, fluvoxamine CR has a higher trough concentrations (C_{24h} 110% compared with Luvox), and a lower and later peak concentrations in the blood (mean Cmax was 38% lower compared with Luvox, Tmax delayed by $\geq$ 3 hours). Food has minimum impact on the PK parameter of this formulation (Luvox CR 100mg capsule).

The steady state was achieved within 5 days following administration of 100mg once daily doses of fluvoxamine CR capsule, about 1.5 days longer than the marketed 100mg tablet Luvox. It has extensive tissue distribution and approximately 80% is bound to plasma protein, mostly albumin.

Titration from 100mg to 300mg daily dose, female subjects had consistently higher plasma concentrations than males within each treatment group; however, there was large variability within a treatment group with coefficients of variation ranging from 51% to 128%.

According to the current labeling, fluvoxamine maleate is extensively metabolized by the liver. The main metabolite in human is fluvoxamine acid which together with its N-acetylated analog, accounted for 60% of the excretion product. A total of nine metabolites were identified and they constitute about 85% of the urinary excretion. The oxidation metabolite, fluvoxehanol accounted for 10%. Approximately 2% of fluvoxamine was excreted in urine unchanged.

The mean elimination half life of fluvoxamine CR is actually similar to Luvox tablet: At dose 100mg, the half life is 16.3 hours versus 16.0 hours.

No drug-drug interaction studies or drug-disease interaction studies have been done with fluvoxamine CR so far.

5.2 Pharmacodynamics

Fluvoxamine inhibits neuronal serotonin uptake. It has no significant affinity of other receptors, such as histaminic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors that are thought to be associated with sedative, cardiovascular, anticholinergic, and extrapyramidal effects as in other psychotropic medications other psychotropic medications.

However, the sponsor reports that no pharmacodynamic studies related to efficacy or safety were conducted using fluvoxamine CR capsules.

5.3 Exposure-Response Relationships

Given that all three pivotal studies are design for flexible dosing, exposure-response relationship cannot be established from these studies.

6 Integrated Review of Efficacy

6.1 Indications

The sponsor seeks approval of two indications in this submission. I shall divide this section into two subsections, 6.1.1 for OCD and 6.1.2 for SAD. The headings under these two subsections will be numbered accordingly.

6.1.1 OCD

OCD is a chronic anxiety disorder with both obsessive thoughts that are intrusive and compulsive behaviors that are often adopted to reduce obsessions. Lifetime prevalence is approximately 2% to 3% in the general population. Mean age of onset is 20 year-old. Adult patients recognize their thoughts and behaviors are excessiveness and unreasonable but cannot resist or control them. Examples of common obsessions are fear of contamination, repeated doubts, a need to keep things in a particular order; common impulsions include repeated checking, washing hands, excessive praying or counting, and among others. Symptoms often exacerbate and relapse during distress.

6.1.1.1 Methods

The sponsor submits one double-blind, placebo-controlled study (#3103) for this indication (see Sections 4.1 and 4.2 also), given that the studies for fluvoxamine maleate immediate-release for

this indication was submitted and approved in the past. Thus, the following general sections include specific study information from this single study review.

6.1.1.2 General Discussion of Endpoints

The sponsor's primary study objective was to establish the efficacy and safety of fluvoxamine maleate CR, 100mg/day and 300mg/day, compared to placebo for treatment of OCD in adult outpatients for 12 weeks.

The primary efficacy variable for this study was the change from baseline to endpoint (Week 12 or early termination) in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score.

The Y-BOCS is widely used clinically and in research for obsessive compulsive disorder. It is regarded as "gold standard" for assessing obsessive-compulsive symptoms. It is administered by clinician with a semi-structured interview. It is divided into two subscales: the Obsession subscale and the Compulsions subscale. For each subscale, five aspects of pathology related to the specific focus, obsessions or compulsions, are rated 0 (no symptom) to 4 (extremely symptomatic), assessed mainly based on the amount of patient's distress, time consumed on the symptom, and severity of dysfunction. Detailed probes and anchor points are provided for each item. Scores of each item and subscales are summed to yield a total score that ranges from 0 to 40 (each subscale scores 0 to 20), with higher score indicating more severe of the disease. In this study, the sponsor defines those with a mean baseline Y-BOCS of 23 or higher as moderate to severe OCD (patients with OCD scores 25 on average); people who don't have OCD typically scores less than 8.

The total score intraclass correlation co-efficients ranged from 0.80 to 0.99. The scale also demonstrates moderate convergence with other questionnaires measuring obsessive compulsive symptoms, such as Maudsley Obsessional Compulsive Inventory and the Compulsive Activity Checklist: $\gamma = 0.33 - 0.62$. It also showed more strongly related to measures of depression and general anxiety than to other measures of obsessive-compulsive symptoms; however, the total score distinguishes patients with OCD from patients with other anxiety disorders and non-patient individual.

The sponsor's secondary efficacy variables are the changes from baseline to endpoint (Week 12 or early termination) in the Clinical Global Impression- Severity of Illness (CGI-S) and CGI - Global Improvement (CGI-I) scores. Both CGI-S and CGI-I are rated by clinician investigators on a 7-point scale, ranging from 0 (not assessed to 7 (most extremely ill) with 4 indicating no change.

The sponsor didn't assign a key secondary efficacy variable.

Subjects were evaluated with Y-BOCS and CGI-S at Screening, Baseline (Day 1), and then every two weeks (the end of Weeks 2, 4, 6, 8, 10, and 12); the CGI-I was performed at a similar biweekly schedule except for Screening and Baseline.

6.1.1.3 Study Design

Study 3103 is a 12-week, randomized, double-blind, placebo-controlled, Phase 3, flexible dose, study conducted in 20 centers for treatment of adult outpatients 18 years or older with OCD. It was planned to include 250 patients and a total of 253 subjects were randomized: 127 were in fluvoxamine CR group and 126 in placebo group. Screening period ranges from 1 to 14 days. Qualified subjects were then randomized and given a total active treatment period for 12 weeks.

Dose Schedules

Subjects were started on Fluvoxamine CR 100mg if in the active drug group; the dosage was increased on a weekly basis by 50mg over the first six weeks based on clinical response and eventually reached 300mg per day by Week 4 for those who needed and could tolerate. All patients are maintained on the effective doses from Weeks 6 to 10.

Those who couldn't tolerate 100mg during the first week or were discontinued from the study; after Week 1, the dose was allowed to be lowered based on the tolerance. However, if the dose needs to be decreased after Week 6 due to an intolerable adverse event, the subject was also discontinued from the study. No dose increase was permitted after a decrease.

Protocol Amendment and Study Flow Chart

There was one protocol amendment in April 1999, a few months after the protocol date. The changes involved all the followings:

- Change of IND number per assignment by the Agency
- Change of the Therapeutic Area Director and the sponsor contact
- Removal of the Social Adjustment Scale-Self Report (SAS-SR) as a safety assessment from the study for which the reason was the scale being updated and validated
- Addition of SF-36 (Health Status Survey) as safety measure conducted at Baseline and end of Week 12 or at termination
- An optional 40 week extension was provided to the subjects as open-label trial as the sponsor believed that the open-label extension would enhance the enrollment in the double-blind study
- The seven-day follow-up visit was removed because no subjects received study medication during the visit
- Reduction of time window from 3 months to 1 month for diabetic control and thyroid or anti-thyroid medications that require stabilization for the sponsor considered this shortened stabilization was not likely to confound the drug evaluation. Additionally, the sponsor grouped insulin and oral anti-hypoglycemics as diabetic control medications
- Addition of Gingko Biloba and St. John's Wort to the list of drugs requiring a washout prior to screening
- Redefinition of medications prohibited during the study – these include "5HT1D agonists for migraines (i.e., sumatriptan and zolmitriptan), cholinesterase inhibitors (i.e. Cognex and Aricept), and both prescription and non-prescription weight loss agents"

- Permission of using Ambien (zolpidem) as sleeping aid on as needed basis with approval of the Medical Monitor unless it was taken 48 hours prior to a clinic visit
- Removal of thyroid analyses TSH and T4 from serum chemistry panel at the termination visit as they were listed as error by the sponsor
- Clarification of unblinding treatment code and the definition of endpoint
- Increased number of study centers
- Updated flow chart (See table below.)

Table 2: Flow Chart for Study 3103 (Post Amendment)

Assessments	Week	Screen	Baseline	1	2	3	4	5	6	8	10	12
	Day	-14 to -1	1	8	15	22	29	36	43	57	71	85***
Clinic visit		X	X	X	X		X		X	X	X	X
Safety Visit						X		X				
Consent		X										
Inclusion/Exclusion		X										
Medical/Psych Hx		X										
Physical exam		X										X
12-lead ECG		X										X
Clinical Labs ****		X	X*						X			X
PK sample									X			X
β- HCG (females)		X	X*									X
Urine drug screen		X										
Vital Signs/Weight**		X	X	X	X		X		X	X	X	X
Y- BOCS		X	X		X		X		X	X	X	X
CGI –S		X	X		X		X		X	X	X	X
CGI –I					X		X		X	X	X	X
Ham-D		X										
Neurological Soft Signs Exam		X										
SF-36			X									X
Adverse Events			X	X	X	X	X	X	X	X	X	X
Concomitant Meds		X	X	X	X	X	X	X	X	X	X	X

* Repeated if screening period is more than 10 days duration
** Height is obtained at screen only.
*** Or upon early termination
****Clinical labs included routine CBC+ differential and chemistry panel, urinalysis but didn't include GGT.

Criteria for Subject Selection

Male or female subjects who were age 18 or older (no age upper limit) were recruited. Female subjects required a negative serum pregnancy test (beta-HCG) at the Screening visit; females of childbearing potential must not be planning a pregnancy and have been using a medically acceptable method of birth control.

Other key inclusion criteria are:
- Meeting DSM-IV diagnosis of OCD
- Scores at least 21 on the Y-BOCS at the Screening and Baseline visits
- Scores ≤ 16 on the 17 item Hamilton Depression Scale (Ham-D) at the Screening visit

- Caffeine-related disorder and nicotine related disorders were allowed though substance abuse and dependence disorders were excluded (see exclusion criteria below)

Major exclusion criteria are:

1) Psychiatric disorders

Current DSM-IV diagnoses of any major Axis I psychiatric and Axis II disorders, except for Cluster C personality disorders, as well any significant risk of suicide.

Subjects who had the following psychiatric diagnoses within the past six months are also excluded:

- ADHD
- Major depressive disorder (MDD) except for secondary depression
- Panic disorder of any type, PTSD, generalized anxiety disorder, social phobia
- Factitious disorders and dissociative disorders
- Eating disorders
- Impulse control disorders NOS and trichotillomania that is not part of OCD

DSM-IV diagnoses of the following psychiatric disorders in life time, again, with the exception of secondary depression are excluded:

- Schizophrenia or psychotic disorders
- Bipolar disorders
- Alcohol or substance abuse or dependence, unless in full remission for at least six months prior to Day 1 (Baseline)
- Various types of Paraphilias
- Pervasive developmental disorders including autistic disorder and Asperger's disorder, as well as Rett's syndrome and tic disorders
- Dementia

Additionally, eligibility for those with a comorbid diagnosis of sleep disorders, learning and communication disorders, ADHD, NOS, cognitive disorder NOS, and disruptive behavioral disorders was determined by the medical monitor.

Subjects with documented history of non-response to pharmacological treatment for OCD with clomipramine, fluoxetine, sertraline, paroxetine, citalopram, venlafaxine or fluvoxamine (defined as no clinically meaningful improvement after at least six weeks therapy with a therapeutically relevant dose) were also excluded.

2) Current evidence of clinically significant medical diseases, such as hematopoietic, cardiovascular, hepatic, renal, gastrointestinal, endocrine, neurological or autoimmune diseases; Clinically significant laboratory abnormalities at Screening (any result more than 25% outside of the normal range was to be approved prior to study entry by the Study Medical Monitor); Or,

subjects with any medical condition or receiving any drug therapy which might confound evaluation of the study medication, specifically,

- Cardiovascular: History or current evidence of a myocardial infarction (recent - within three months of Day 1, i.e. Baseline), any heart blocks, arrhythmias (other than sinus arrhythmias or premature beats), or any ECG abnormality which in the judgment of the Investigator or the Study Medical Monitor was considered clinically significant

- Neurological: History of brain trauma resulting in loss of consciousness for greater than 15 minutes or loss of consciousness and hospitalization; and subjects with a history of brain surgery; Presence or history of seizure disorder (except for childhood febrile seizures), cerebrovascular disease or brain trauma and subjects requiring treatment with anticonvulsants

- Endocrinological: Subjects with insulin dependent diabetes mellitus (IDDM) considered clinically unstable (Le., glycosylated hemoglobin (HbA1C) higher than 9%, fasting glucose
  levels over 200 mg/dl) at any time during the six months prior to Day 1 (Baseline). Subjects with diabetes who were controlled by diet and/or oral hypoglycemic therapy were eligible if stable for one month or greater before Day 1 (Baseline)

- Oncologic: History of life-threatening neoplasm (treated within five years prior to Screening) other than carcinoma in situ of the cervix or basal cell carcinoma of the skin

- Metabolic: History or presence of malabsorption syndrome, or major gastrointestinal surgery which could possibly interfere with the absorption, distribution, metabolism or excretion of the study medication

- Subjects with a prior allergic response to fluvoxamine

- Subjects with a clear, prior history of developing a serotonergic syndrome in response to a selective serotonin reuptake inhibitor (SSRI) or clomipramine

- In addition, there were certain prior therapies that caused the subject to be excluded from the study. These subjects would have been screened but not randomized. (These medications are discussed in detail in Section 5.4.7.)

3) History of noncompliance with clinic visits or treatment or the following non-compliant behavior happens during the study:

- Missed the total daily dose for three or more consecutive days
- Discrepancy in prescribed dose versus returned medication of more than 20% over the dosing interval on two or more occasions
- Missed two or more scheduled visits by more than three days during the study

4) Intolerability during the study:

- Unable to tolerate two capsules of double blind medication at bedtime during Week 1
- Unable to tolerate two capsules of double blind medication at bedtime after Week 6 for the remainder of double blind treatment

Data Analysis

The sponsor specified in the protocol that the following hypothesis was tested at α=0.05 on the primary efficacy variables: There is no treatment effect difference between fluvoxamine CR and placebo. The successful result is considered significant treatment effect ($p \leq 0.05$) in primary variable. Descriptive statistics, such as number of patients, means, standard deviations, and 95% confidence intervals are summarized for efficacy result.

ANOVA with treatment and center as fixed factors is used as the main analysis where center is interpreted as a block effect. For positive treatment results, ANOVA with treatment, center, and treatment by center interaction as fixed factors will be performed to test the homogeneity of treatment effect across centers at $\alpha = 0.15$. The normality assumption for ANOVA is verified by Shapiro-Wilk test, and homogeneity of variance, by Levene test. All statistical tests for comparing the treatment groups were two-sided. If $p \leq 0.05$, the result is considered statistically significant.

All efficacy assessments were obtained within three days of last dose of double-blind study drugs; those obtained more than three days past last dose (including those of three days after Week 12) were excluded from the Intent-to-Treat efficacy patient population.

In my opinion, the length of the study is adequate and the dose regimen is acceptable. Criteria for subject selection are reasonable. The overall design of the study provides reasonable assessment of benefit and meets CFR 314.126 as a well-controlled study.

6.1.1.4 Efficacy Findings

Subject Baseline Characteristics

The following table illustrates the subject demographics of ITT of this study:

Table 3: Subject Demographics (ITT) of Study 3103

Subjects	Fluvoxamine CR N (%)	Placebo N (%)	Total N

Total			117	120	237
Age	Mean [SD]		37.8 [1.1]	37.2 [1.1]	37.5 [0.7]
	Median		36	38	36
	Range		19-70	18-69	18-70
	group	18-64	113 (97)	118 (98)	231(97.5)
		≥65	4 (3)	2 (2)	6 (2.5)
Gender	Male		47 (40)	40 (33)	87 (36.6)
	Female		70 (60)	80 (67)	150(63.4)
Ethnicity	Asian, American Indian & Alaska Natives		4 (3)	5 (4)	9 (3.8)
	Black		5 (4)	7 (6)	12 (5)
	Caucasian		99 (85)	94 (78)	193 (81)
	Hispanic		5 (4)	11 (9)	16 (6.8)
	Other*		4 (3)	3 (3)	7 (3)

*Category Other includes Indian, Black/Puerto Rican, Hispanic/Caucasian, Iranian, Black/Caucasian, and Middle Eastern.

Baseline Severity

The baseline disease characters and severity between two treatment groups are comparable and are shown in the following table.

Table 4: Baseline Primary Diagnosis and Duration (ITT) in Study 3103

Baseline Disease Characters & Comorbidity		Fluvoxamine CR (N=117)	Placebo (N=120)
Y-BOCS Total Score	Mean	26.6	26.3
	Median	26	25
	Range	21-38	21-36
CGI-S	Mean	4.7	4.6
	Median	5	5
	Range	4-6	3-7
Duration of OCD (Years)	Mean	22.4	21.1
	Median	20	20
	Range	2-55	1-55
Current Episode of OCD (Years)	Mean	16.5	16.9
	Median	15	14
	Range	0-55	0-55
Presence of Axis I Disorders		5 (4%)	8 (7%)

Subject Disposition

According to the sponsor, three subjects in the fluvoxamine CR treatment group (69044, 69117, 69243) and two subjects in the placebo treatment group (69081, 69267) did not take study drug. Additionally, seven subjects in the fluvoxamine CR group and four in the placebo group had no post-baseline assessment. Thus, a total of 117 subjects were treated with fluvoxamine CR and 120 received placebo. The table below displays subject disposition throughout the study.

Table 5: Subject Disposition throughout Study 3103 (ITT)

	Fluvoxamine CR	Placebo	Total
	N (%)	N (%)	N (%)
Subjects Randomized	127	126	253
Subject Treated (ITT)	117 (92)	120 (95)	237 (94)
Subject Completed	78 (61)	93 (74)	171 (68)

The following table displays ITT subject enumeration in Study 3103.

Table 6: Subject Enumeration throughout Study 3103 (ITT)

Timing*	Fluvoxamine CR	Placebo
Baseline (Day 1 – 7)	117	120
Week 2 (Day 8 – 15)	112	118
Week 4 (Day 23 -- 29)	103	107
Week 6 (Day 37 –43)	99	99
Week 8 (Day 51 – 57)	81	95
Week 10 (Day 65 – 71)	83	94
Week 12 (Day 79 – 85)	78	93

Protocol Deviation

Overall, a total of 20 (8%) protocol deviations occurred in ITT population. The fluvoxamine CR group had higher incidences of than placebo group (10% versus 7%). The table below displays the major categories and incidences in ITT population.

- Compliance was the leading cause of protocol deviation.
- Incorrect dose was prescribed to two subjects, one in each treatment group, after Week 6, which was not allowed per the protocol.
- Prescribing prohibited medications (sertraline for depression and suicidal ideation with a plan, lorazepam for insomnia, and butalbital for headaches) happened in three patients: One in fluvoxamine group and two in placebo group.

Table 7: Protocol Deviation in ITT Population of Study 3103

Protocol Deviations	Fluvoxamine CR (n=127)	Placebo (n=126)	Overall (n=253)

Total Number of Subjects	12 (10%)	8 (7%)	20 (8%)
Compliance* <80% or >120%	10 (9%)	6 (5%)	16 (7%)
Incorrect Dose Taken	1 (<1%)	1 (<1%)	2 (<1%)
Used Any Prohibited Medication	1 (<1%)	2 (2%)	3 (1%)

*Treatment compliance was assessed as the total dose taken by a subject divided by the total dose scheduled to be taken, expressed as a percentage. Subjects who took less than 80% or more than 120% of their prescribed dose were considered noncompliant per the protocol.

The sponsor also reports that an additional subject in fluvoxamine CR group was taking a protocol prohibited drug, Levsinex (hyoscyamine sulfate) for stomach virus. However, these incidences pose insignificant effects on the efficacy result.

Dose Information

Duration of exposure is shown in the following table.

Table 8: Duration of Exposure in Study 3103

		Fluvoxamine CR	Placebo
Duration of Exposure (Days)	**Mean (SD)**	66.6 (2.5)	70.8 (2.4)
	Median	83	84
	Range	1-98	3-100

The following table displays dose titration by visits in all randomized subjects.

Table 9: Dose Titration by Visits in All Randomized Subjects

Dosages	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 8**	**W 10**	**W 12**
Luvox CR	**124**	**110**	**107**	**107**	**103**	**100**	**96**	**85**	**84**
100 mg	124(100)	16 (15)	7 (7)	5 (5)	3 (3)	3 (3)	3 (3)	3 (4)	3 (4)
150 mg	0	94 (85)	17(16)	13(12)	9 (9)	7 (7)	7 (7)	6 (7)	6 (7)
200 mg	0	0	83(78)	15(14)	10(10)	9 (9)	8 (8)	7 (8)	7 (8)
250 mg	0	0	0	74(69)	17(17)	9 (9)	10(10)	10(12)	10(12)
300 mg	0	0	0	0	64(62)	72(72)	68(71)	59(69)	58(69)
Placebo	**123**	**116**	**113**	**106**	**103**	**100**	**96**	**96**	**95**
100 mg	123(100)	7 (6)	5 (4)	4 (4)	2 (2)	3 (3)	3 (3)	3 (3)	3 (3)
150 mg	0	109(94)	9 (8)	3 (3)	1 (<1)	0	0	0	0
200 mg	0	0	99(88)	10 (9)	4 (4)	2 (2)	1 (1)	1 (1)	1 (1)
250 mg	0	0	0	89(84)	11(11)	4 (4)	3 (3)	3 (3)	3 (3)
300 mg	0	0	0	0	85(83)	91(91)	89(93)	89(93)	88(93)

In active drug group, a total of 12 subjects required dose reduction during the study (Week 3: 1; Week 4: 4; Week 5: 2; Week 6: 5), while only five subjects required dose reduction in the

placebo group (Week 3: 4; and Week 5: 1). About 70% of the subjects reached 300mg from Week 6 and mostly stayed on this dose.

Upon responding to our 74-day letter, the sponsor submitted the mean daily dose of fluvoxamine CR by visit in all randomized patients (instead of ITT population). See table below.

Table 10: Mean Daily Dose of Fluvoxamine CR by Visit for Patients in Study 3103 (All Randomized)

	Week 1	Week 2	Week 3	Week 4	Week5	Week 6	Week 8	Week 10	Week12
Subject N	124	110	107	107	103	100	95	85	84
Mean	94.0	138.7	183.7	222.9	258.4	264.1	256.0	264.4	260.5
S.E.	1.47	2.24	3.07	4.46	6.05	5.98	6.34	6.08	6.70
Median	100	150	200	250	300	300	300	300	300
Min - Max	14 - 117	43 - 188	50 - 229	100 - 292	61 - 407	43 - 350	100 - 300	100 - 300	14 -300

Note 1: Subjects who did not take any dose of Fluvoxamine CR for a specific visit are excluded from this summary table.
Note 2: Subject 69187 is also excluded due to unclear study medication stop date at week 8.
Note 3: Mean daily dose is calculated as total dose taken during a visit window divided by number of days in the visit window regardless on drug or not

Prior and Concomitant Medications

Up to 85% (100/117) of subjects in fluvoxamine CR group and 92% (110/120) of those in placebo group used concomitant medications. The number of subjects and types of medications used by the two treatment groups are comparative. The most common ones are shown in the following table. None of these seem to have significant anxiolytic effect. All others were less than 9% and few were psychotropic medications.

Table 11: Most Commonly Prescribed Concomitant Drugs

	Fluvoxamine CR	Placebo
Ibuprofen	43 (37%)	43 (36%)
Ketoprofen	40 (34%)	35 (29%)
Paraceamol	25 (21%)	24 (20%)
Multivitamine	23 (20%)	33 (28%)
Acetylsalicylic Acid	14 (12%)	9 (8%)
Progestrogene and Estrogen, combinations	14 (12%)	21 (18%)
Sympathomimetics	9 (8%)	9 (8%)

Results

The following table shows the change in primary variable (Y-BOCS total score) between the two treatment groups (LOCF). The group received fluvoxamine CR shows statistically significant changes in Y-BOCS at endpoint from baseline compared to placebo group; the changes can be seen as early as Week 2 and shows most significantly at Week 8.

Table 12: Y-BOCS Total Score Change from Baseline at Each Visit (LOCF) -- ITT Population

Treatment Group		Change from Baseline					
		Week 2	Week 4	Week 6	Week 8	Week10	Endpoint
Fluvoxamine CR (N = 117)	n	112	113	113	113	113	113
	Baseline Mean	26.6	26.5	26.3	26.1	26.1	26.3
	Mean (S.E.)	-3.7 (0.5)	-5.2 (0.5)	-7.1 (0.6)	-7.6 (0.6)	-7.8 (0.7)	-8.5 (0.7)
	Median	-2	-4	-6	-7	-6	-7
	Min., Max.	-28, 7	-28, 7	-28, 7	-28, 6	-30, 6	-31, -6
	95% CI	[-4.7, -2.7]	[-6.2, -4.2]	[-8.3, -5.9]	[-8.8, -6.4]	[-9.2, -6.4]	[-9.9, -7.1]
Placebo (N = 120)	n	118	119	119	119	119	119
	Baseline Mean	26.3	26.3	26.3	26.2	26.2	26.3
	Mean (S.E.)	-2.0 (0.4)	-3.6 (0.5)	-4.7 (0.6)	-4.8 (0.6)	-5.4 (0.7)	-5.6 (0.7)
	Median	-1	-2	-4	-3	-4	-4
	Min., Max.	-20, 8	-20, 8	-28, 10	-30, 8	-30, 8	-30, -8
	95% CI	[-2.8, -1.2]	[-4.6, -2.6]	[-5.9, -3.5]	[-6.0, -3.6]	[-6.8, -4.0]	[-7.0, -4.2]
Treatment Effect P-Value		0.023*	0.018*	0.002**	<0.001**	0.005**	0.001*

* Significant at the 0.050 level. ** Significant at the 0.010 level.
Note: P-values for fluvoxamine CR versus placebo treatment group are based on an ANOVA model fit to the rank of the change from Baseline YBOCS total score with terms for treatment and pooled center.
Note: Endpoint is defined as the last post-Baseline value collected while on study medication.
Note: Efficacy measurements collected outside the assigned visit windows or efficacy measurements collected more than three days after discontinuation of study medication were excluded from the efficacy analyses for that visit.

The following figure illustrates the efficacy result.

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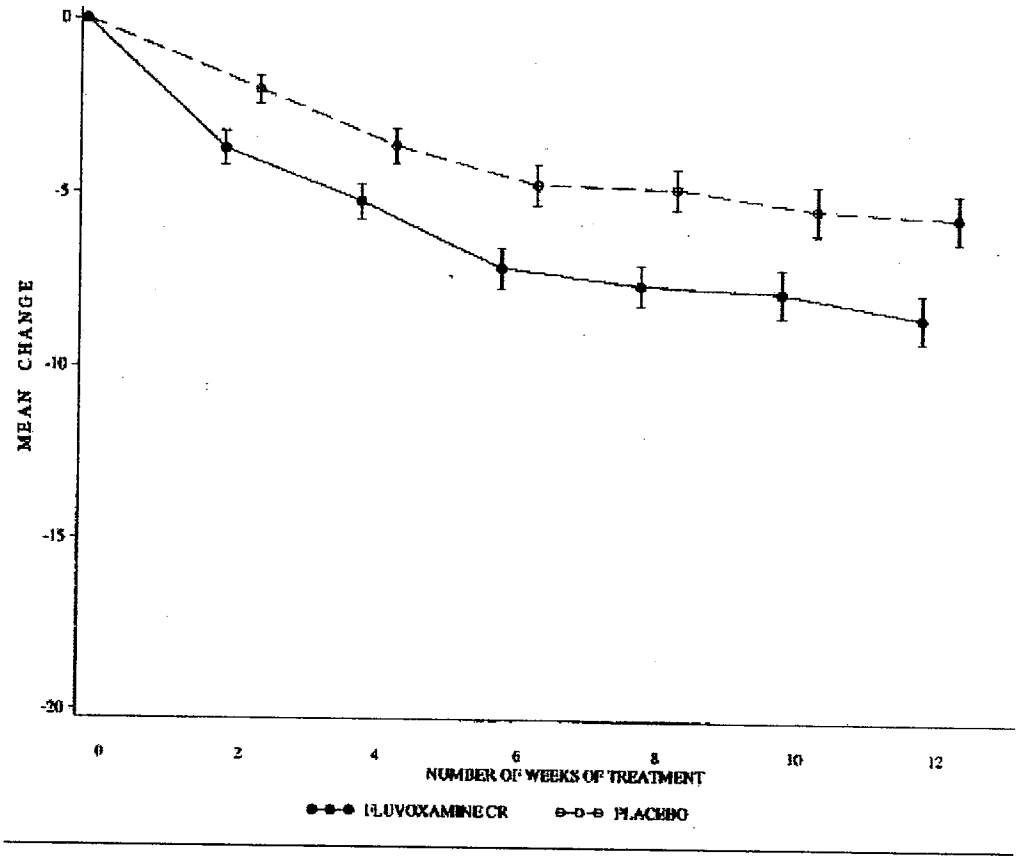
Figure 1: Mean Change from Baseline in Y-BOCS Total Score (LOCF) at Each Visit – ITT Population



Demographic Factors on Efficacy

Age: Most of the subjects are in the age range of 18 to 64 year-old. Only about 3% subjects are age 65 years or older. Thus, there are not enough age effects on the efficacy.

Gender: There is not statistically significant difference between the two gender groups for treatment effect (p=0.069) based on ANOVA analysis.

Ethnicity: Most subjects are Caucasian. There are not enough subjects in other ethnic groups to determine ethnic effects on efficacy.

Statistician's Analysis

Please see the Agency Statistician Reviewer, Dr. Fanhui Kong's review for details. In summary, Dr. Kong concludes that the sponsor's data and analysis supports the efficacy claim.

6.1.2 SAD

6.1.2.1 Methods

The sponsor submits two double-blind, placebo-controlled study (#3107 and #3108) for this indication (see Sections 4.1 and 4.2 also). There was no submission of fluvoxamine maleate immediate-release for this indication. Integrated review of these two studies will be summarized in the following subsections. The long lists of investigators of these studies will be presented in the Appendix 10.1.1 – 10.1.4.

6.1.2.2 General Discussion of Endpoints

The primary variable for both SAD studies is change from baseline (Day 1) at endpoint (Week 12 or early termination) in the Liebowitz Social Anxiety Scale (LSAS).

LSAS includes four subscales: Fear-Social, Avoidance-Social, Fear-Performance, and Avoidance-Performance. Fear scores are generated from fear items across social and performance situations; likewise, avoidance scores are summed from social and performance situations. There are a total of 24 items, 13 of which describing performance situations and the rest 11 describing social interactional situations. Each item is rated separately for fear (ranging from 0 to 3, with 3 being most severe) and avoidance. Three additional spaces are provided for individually created items.

LSAS is assessed by a clinician who conducts a semi-structured interview as determined by DSM criteria through the evaluation of fear and avoidance in a wide variety of social and performance situation. It covers a broad range of potentially fearful situations and separates symptoms of anxiety from avoidance. It has been used widely in clinical and research. According to the author (M. R. Liebowitz), formal training is not required. It has demonstrated good internal consistency with alpha ranged from 0.82 to 0.92 across the various subscales.

However, the scale lacks items assessing cognitive or physiological symptoms associated with SAD. Thus, it does not detect symptomatic improvement in a patient with decrease in psychological arousal symptoms while confronted with a phobic stimulus but without a decrease in avoidance behavior. The scale is found to be associated strongly with some scales measuring social phobia, such as Social Interaction and Anxiety Scale (r=0.75), Social Phobia and Anxiety Inventory (r=0.87), and the Brief Social Phobia Scale (r=0.76) but lower with others, such as Social Avoidance and Distress Scale (=0.33) and the Fear of Negative Evaluation Scale (r=0.18).

Both studies have the same secondary efficacy variables which are change from Baseline (Day 1) at endpoint (Week 12 or early termination) in CGI Global Improvement, CGI Severity of Illness, and Sheehan Disability Scale.

Additionally, the sponsor also uses the same following assessments in both studies. They include The Montgomery-Asberg Depression Rating Scale (MADRS), administered at Screening and

study end (Week 12 or early termination) to assess the effect of treatment on depressive symptoms, and The Arizona Sexual Dysfunction Scale used to evaluate the effects of fluvoxamine CR treatment on sexual function.

The sponsor has not assigned any of these measurements as key secondary variable.

6.1.2.3 Study Design

Both studies 3107 and 3108 are double blind, placebo controlled, flexible dose trials for 12 weeks. Both trials used doses up to 300mg/day.

The primary objective of both studies is to assess the efficacy and safety of fluvoxamine CR (100 – 300mg/day) compared to that of placebo in the treatment of adult outpatients with Generalized Social Anxiety Disorder.

Dose Schedule

The dose schedules of Study 3107 and Study 3108 are the same:

Subjects randomized to fluvoxamine CR group began treatment at 100mg/day at bedtime, which is the minimum dose allowed at any time during the study. Those who tolerated were given dose increment of 50mg/day weekly (7 days +/- 3 days) at the end of Weeks 1 to 5, up to a maximum dose of 300mg/day. Dosage remained constant from Week 6 through 12.

After Week 1 and through the end of Week 5, the dosage could be decreased once by 50mg/day in case of intolerable adverse event; if such cases, the dosage of previous level would remain throughout the study; no increase of dosage is permitted after a decrease.

Those who were unable to tolerate the initial dose during the first week and those who require dose decrease after Week 6 were discontinued from the study.

The following two tables depict the study flow charts for these two studies:

Table 13: Flow Chart of Study 3107

Week	Screen	Baseline	1	2	3	4	5	6	8	10	12	Early Termination[1]
Day	-14 to -1	1	8	15	22	29	36	43	57	71	85	
Clinic Visit	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation for Dose Adjustment			X	X	X	X	X					
Informed Consent	X											
Physical Examination	X										X	X
Inclusion/Exclusion	X	X										
Medical/Psychiatric History	X											
12-lead ECG	X										X	X
Clinical Labs	X	X[2]									X	X
β- HCG (females)	X	X[2]									X	X
Urine Drug Screen	X	X[3]										
Vital Signs/Weight	X	X	X	X	X	X	X	X	X	X	X	X
Modified SCID-I	X											
Liebowitz Social Anxiety Scale	X	X		X		X		X	X	X	X	X
CGI Severity of Illness		X		X		X		X	X	X	X	X
CGI Global Improvement				X		X		X	X	X	X	X
PGI Improvement				X		X		X	X	X	X	X
Sheehan Disability Scale		X		X		X		X	X	X	X	X
AZ Sexual Dysfunction Scale		X		X		X		X	X	X	X	X
Montgomery-Asberg Depression Rating Scale	X										X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X

[1] If early termination visit is more than three days after last dose of study medication, efficacy evaluations should not be performed.
[2] Clinical labs to be repeated if Screening period is more than 10 days in length.
Chemistry: glucose, sodium, potassium, chloride, BUN, creatinine, alkaline phosphatase, total bilirubin, GGT, SGOT (AST), SGPT (ALT), LDH, (TSH and T_4, at Screening visit only. HbA_{1c} for IDDM subjects at Screening only).
Hematology: hemoglobin, hematocrit, erythrocyte count, WBC with differential and platelet count, MCH, MCHC, MCV
Urinalysis: pH, glucose, protein, specific gravity and microscopic examination.
[3] Urine drug screen will be repeated within 14 days if subject tested positive for benzodiazepines or barbiturates at Screening visit.

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Table 14: Flow Chart of Study 3108

Week	Screen	Baseline	1	2	3	4	5	6	8	10	12	Early
Day	-14 to -1	1	8	15	22	29	36	43	57	71	85	Term [3]
Assessment:												
Clinic visit	X	X	X	X	X	X	X	X	X	X	X	X
Eval. For Dose Adjust.			X	X	X	X	X					
Consent	X											
Physical exam	X										X	X
Inclusion/Exclusion	X	X										
Medical/Psych Hx	X											
12-lead ECG	X										X	X
Clinical Labs	X	X[1]									X	X
β- HCG (females)	X	X[1]									X	X
Urine drug screen	X	X[2]										
Vital Signs/Weight	X	X	X	X	X	X	X	X	X	X	X	X
SCID-I	X											
LSAS	X	X		X		X		X	X	X	X	X
CGI –Sev. Of Illness		X		X		X		X	X	X	X	X
CGI –Global Imprvmt				X		X		X	X	X	X	X
PGI-Global Imprvmt				X		X		X	X	X	X	X
SDS		X		X		X		X	X	X	X	X
AZ Sexual Dysfunc.		X		X		X		X	X	X	X	X
MADRS	X										X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X

[1] Clinical labs to be repeated if screening period is more than 10 days in length
Chemistry: glucose, sodium, potassium, chloride, urea, creatinine, alkaline phosphatase, total bilirubin, GGT, SGOT (AST), SGPT (ALT), LDH, (TSH and T_4, at screening visit only. HbA_{1c} for IDDM subjects at screening only).
Hematology: hemoglobin, hematocrit, erythrocyte count, WBC with differential and platelet count, MCH, MCHC, MCV
Urinalysis: pH, glucose, protein, specific gravity and microscopic examination.
[2] Urine drug screen will be repeated in 14 days if subject tested positive for benzodiazepines or barbiturates at screening visit.
[3] If early termination visit is more than 3 days after last dose of study medication, efficacy evaluations should not be performed.

Criteria for Subject Selection

The inclusion and exclusion criteria of both studies are basically similar. They are summarized as follows:

Key inclusion criteria

- Male or female subjects must be between ages 18 to 70 years old. Female subjects required a negative serum pregnancy test (beta-HCG) at the Screening visit; females of childbearing potential or less than one year post-menopausal must be using a medically acceptable method of birth control [oral contraceptives for at least three months, a dose of medroxyprogesterone

(Depo-Provera®) for at least two months or implantation of an IUD or levonorgestrel (Norplant®) for at least two months prior to the start of double-blind; or barrier methods (combination condom and spermicide use or diaphragm) and have a negative serum beta human chorionic gonadotropin assay pregnancy test prior to Baseline (Day 1)].

- Have a predominant DSM-IV diagnosis of Generalized Social Anxiety Disorder (300.23); based on the modified version of the Structured Clinical Interview for the DSM-IV (SCID), the diagnosis is made when the SCID documents ≥ 4 phobic situations in the six months prior to the screening visit and two of them must be interactional situations. Of note, the decision of predominant diagnosis is based on Investigators' clinical judgment.
- Scored at least 60 on LSAS at Screening
- Have clinical and laboratory safety findings considered not clinically abnormal or clinically significant. Any result more than 25% outside the normal range must be approved prior to study entry by the Medical Monitor.

Major exclusion criteria

1) Psychiatric disorders

Current DSM-IV diagnoses of any major Axis I psychiatric and Axis II disorders, except for Cluster C personality disorders, as well any significant risk of suicide.

Subjects who had the following predominant psychiatric diagnoses within the past six months are also excluded:

- Major depressive disorder and Dysthymia
- Panic disorder with two or more unexpected panic attacks
- Obsessive Compulsive Disorder
- Substance abuse or dependence (with the exception of nicotine) or positive urine toxicology

Subjects with MADRS ≥ 18 at Screening are excluded.

Subjects who have current or a history of the following psychiatric disorders

- Schizophrenia or other psychotic disorders
- Bipolar disorders

Additionally, eligibility for those with a comorbid diagnosis of sleep disorders, learning and communication disorders, ADHD, NOS, cognitive disorder NOS, and disruptive behavioral disorders was determined by the medical monitor.

Subjects with documented history of non-response to pharmacological treatment for OCD with clomipramine, fluoxetine, sertraline, paroxetine, citalopram, venlafaxine or fluvoxamine (defined as no clinically meaningful improvement after at least six weeks therapy with a therapeutically relevant dose) were also excluded.

2) Current evidence of clinically significant medical diseases, such as hematopoietic, cardiovascular, hepatic, renal, gastrointestinal, endocrine, neurological or autoimmune diseases; Clinically significant laboratory abnormalities at Screening (any result more than 25% outside of the normal range was to be approved prior to study entry by the Study Medical Monitor); Or, subjects with any medical condition or receiving any drug therapy which might confound evaluation of the study medication, specifically,

- Cardiovascular: History or current evidence of a myocardial infarction (recent - within three months of Day 1, i.e. Baseline), any heart blocks, arrhythmias (other than sinus arrhythmias or premature beats), or any ECG abnormality which in the judgment of the Investigator or the Study Medical Monitor was considered clinically significant

- Neurological: History of brain trauma resulting in loss of consciousness for greater than 15 minutes or loss of consciousness and hospitalization; and subjects with a history of brain surgery; Presence or history of seizure disorder (except for childhood febrile seizures), cerebrovascular disease or brain trauma and subjects requiring treatment with anticonvulsants

- Endocrinological: Subjects with insulin dependent diabetes mellitus (IDDM) considered clinically unstable (Le., glycosylated hemoglobin (HbA_{1C}) higher than 9%, fasting glucose levels over 200 mg/dl) at any time *during the 90 days prior to Day 1* (Baseline). Subjects with diabetes who were controlled by diet and/or oral hypoglycemic therapy were eligible if stable for one month or greater before Day 1 (Baseline)

- Oncologic: History of life-threatening neoplasm (treated within five years prior to Screening) other than carcinoma in situ of the cervix or basal cell carcinoma of the skin

- Metabolic: History or presence of malabsorption syndrome, or major gastrointestinal surgery which could possibly interfere with the absorption, distribution, metabolism or excretion of the study medication

- Subjects with a prior allergic response to fluvoxamine

- Subjects with a clear, prior history of developing a serotonergic syndrome in response to a selective serotonin reuptake inhibitor (SSRI) or clomipramine

- In addition, there were certain prior therapies that caused the subject to be excluded from the study. (See items 3) and 4).)

3) Subjects whose treatment regimen would not remain constant for the duration of study or those have had any recent adjustment of any medication dosages; Structured psychotherapy has to be started at least six months prior to baseline and remain unchanged in frequency or character for the duration of the study.

4) The use of the following treatment throughout the study: ECT, cholinesterase inhibitors, antipsychotics, anxiolytics, antidepressants, MAOIs, lithium, anticonvulsants, barbiturates, benzodiazepines, beta-blockers, diltiazem, digoxin, warfarin, $5HT_{1D}$ agonists, theophylline, illicit drugs, methadone, as well as any investigational agent, astemizole, cisapride or terfenadine, and any weight loss agents.

Additionally, the timeline for some of them to be stopped before the trial are as follows:

- At least 14 days prior to baseline for any antidepressants (except 30 days for fluoxetine), benzodiazepines, beta adrenergic blockers, MAOIs, or other psychotropic medications as well as cisapride or terfenadine, This list included but was not limited to Gingko Biloba, Ginseng, and St. John's Wort
- At least 30 days prior to baseline for antihypertensives, insulin, and oral anti-hypoglycemics, any investigational agent, cognitive behavioral therapy or formal behavioral therapy which intent was to treat social anxiety disorder symptoms
- At least 60 days prior to baseline for astemizole,
- At least 90 days prior to baseline for thyroid replacement or anti-thyroid medications, ECT

5) History of noncompliance with clinic visits or treatment or the following non-compliant behavior happens during the study:

- Missed the total daily dose for three or more consecutive days
- Discrepancy in prescribed dose versus returned medication of more than 20% over the dosing interval on two or more occasions
- Missed two or more scheduled visits by more than three days during the study

6) Intolerability during the study:

- Unable to tolerate two capsules of double blind medication at bedtime during Week 1 Unable to tolerate two capsules of double blind medication at bedtime after Week 6 for the remainder of double blind treatment
- Risk of suicide in the judgment of the investigator

Protocol Specified Analysis

Similar to the analysis for OCD trial (Study 3103), in both Study 3107 and Study 3108, the Intent-to-Treat Efficacy Patient Population (ITT Efficacy Patient Population) is defined as subjects randomized into the trial who take at least one capsule of study medication, who have a Baseline (Day 1) efficacy evaluation, and have at least one post-baseline efficacy evaluation (of any type). All efficacy assessments were obtained within three days of last dose of double-blind study drugs; those obtained more than three days past Week 12 were excluded.

Also like the OCD trial, in both SAD trials, the sponsor specified that the following hypothesis was tested at α=0.05 on the primary efficacy variables: There is no treatment effect difference between fluvoxamine CR and placebo. The successful result is considered significant treatment effect ($p \leq 0.05$) in primary variable. Descriptive statistics, such as number of patients, means, standard deviations, and 95% confidence intervals are summarized for efficacy result.

Moreover, as in Study 3103, ANOVA with treatment and center as fixed factors is used as the main analysis where center is interpreted as a block effect in both SAD trials. For positive treatment results, ANOVA with treatment, center, and treatment by center interaction as fixed factors will be performed to test the homogeneity of treatment effect across centers at $\alpha = 0.15$. The normality assumption for ANOVA is verified by Shapiro-Wilk test, and homogeneity of variance, by Levene test. All statistical tests for comparing the treatment groups were two-sided. If $p \leq 0.05$, the result is considered statistically significant.

The same approach and analysis have been applied to both primary and secondary variables. The primary variable for SAD study is the change of LSAS total scores from Baseline to endpoint (Week 12 or early termination). The sponsor didn't specify any secondary variables as key secondary parameter.

The design of studies provides reasonable assessment of benefit and meets CFR 314.126 as a well-controlled study.

Protocol Amendment

There was no amendment to study protocol #3107.

Study protocol #3108 was amended twice: Amendment One was to add study sites in South Africa; Amendment Two was to add domestic study sites and safety report coverage; The Therapeutic Area Director replacement was also included in this amendment. No change of study protocol otherwise.

6.1.2.4 Efficacy Findings

Baseline Demographics

Baseline demographics of ITT population of Study 3107 and 3108 are displayed in the following two tables.

Table 15: Baseline Demographics of ITT Population of Study 3107

Subjects			Fluvoxamine CR N (%)	Placebo N (%)	Total N
Total			**121**	**126**	**247**
Age	Mean [SD]		37.6 [1.1]	38.0 [1.0]	37.8 [0.7]
	Median		37	37	37
	Range		18-67	18-68	18-68
	group	18-64	120 (99)	123 (98)	243(98)
		≥65	1 (1)	3 (2)	4 (2)
Gender	Male		74 (61)	87 (69)	161 (65)
	Female		47 (39)	39 (31)	86 (35)
Ethnicity	Asian, American Indian & Alaska Natives		4 (3)	4 (3)	8 (3)
	Black		7 (6)	11 (9)	18 (7)
	Caucasian		100 (83)	100 (79)	200 (81)
	Hispanic		7 (6)	7 (6)	14 (6)
	Other		3 (2)	4 (3)	7 (3)

Table 16: Baseline Demographics of ITT Population of Study 3108

Subjects			Fluvoxamine CR N (%)	Placebo N (%)	Total N
Total			**146**	**148**	**294**
Age	Mean [SD]		38.6 [0.9]	37.2 [0.9]	37.9 [0.6]
	Median		39	35	37
	Range		19-63	18-69	18-69
	group	18-64	146 (100)	145 (98)	291(99)
		≥65	0	3 (2)	3 (1)
Gender	Male		68 (47)	74 (50)	142 (48)
	Female		78 (53)	74 (50)	152(52)
Ethnicity	Asian, American Indian & Alaska Natives		4 (3)	3 (2)	7 (2)
	Black		7 (5)	2 (1)	9 (3)
	Caucasian		130 (89)	138 (93)	268 (91)
	Hispanic		1 (<1)	1 (<1)	2 (<1)
	Other		4 (3)	4 (3)	8 (3)

While both studies seem to have more balanced gender representations, there are few subjects who were 65 years old and above and the majority subjects are Caucasians.

Baseline Disease Severity

Social Anxiety Disorder is a persistent and chronic disease. It often co-exists with other Axis I diagnoses. The following table displays the disease severity and comorbidities of subjects in Study 3107. The two treatment groups are comparable except for the category of Axis I diagnosis of depression (both major depression and Dysthymia) that are more in fluvoxamine CR group while generalized anxiety disorder and other/unspecified axis I diagnoses are slightly more in placebo group.

Table 17: Baseline Disease Characters of ITT Population of Study 3107

Baseline Disease Characters & Comorbidity		**Fluvoxamine CR** (N=121)	**Placebo** (N=126)
LSAS Total Score	Mean (SD)	89.3 (1.6)	89.1 (1.7)
	Median	85	86
	Range	61-134	59-137
CGI-S	Mean (SD)	4.6 (0.1)	4.6 (0.1)
	Median	5	5
	Range	4-7	4-6
Duration of SAD (Years)	Mean (SD)	22.2 (1.3)	23.0 (1.2)
	Median	20	24
	Range	2-59	1-60
Presence of Axis I Disorders		9 (7%)	7 (6%)
Major Depression		2 (2%)	0
Generalized Anxiety Disorder		0	2 (2%)
Dysthymia		5 (4%)	2 (2%)
Past Substance Abuse		1 (<1%)	0
Other/Unspecified		2 (2%)	3 (2%)
Presence of Axis II Disorders			
Avoidant Personality Disorder		1 (<1%)	0
Other/Unspecified		0	0

The table below displays the disease severity and comorbidities of subjects in Study 3108. The two treatment groups are fairly comparable but there are more subjects with Axis I diagnoses in placebo group, especially the category of other/ unspecified Axis I diagnoses and major depression.

Table 18: Baseline Disease Characters of ITT Population of Study 3108

Baseline Disease Characters & Comorbidity		**Fluvoxamine CR** (N=146)	**Placebo** (N=147)
LSAS Total Score	Mean	94.9 (1.6)	93.9 (1.5)
	Median	96	94
	Range	56-136	48-142
CGI-S	Mean (SD)	4.8 (0.1)	4.7 (0.1)
	Median	5	5
	Range	3-7	3-7
Duration of SAD (Years)	Mean (SD)	20.6 (1.1)	20.2 (1.0)
	Median	20	17
	Range	1-53	1-52
Presence of Axis I Disorders		10 (7%)	17 (11%)
	Major Depression	2 (1%)	4 (3%)
	Generalized Anxiety Disorder	2 (1%)	3 (2%)
	Dysthymia	4(3%)	4 (3%)
	Past Substance Abuse	1 (<1%)	0
	Other/Unspecified	1 (<1%)	7 (5%)
Presence of Axis II Disorders			
	Avoidant Personality Disorder	3	6
	Other/Unspecified	4	2

Dose Information

The following table shows duration of exposure in Study 3107.

Table 19: Duration of Exposure in Study 3107

		Fluvoxamine CR	**Placebo**
Duration of Exposure (Days)	**Mean (SD)**	56 (2.9)	68.2 (2.1)
	Median	82	83
	Range	1-91	1-96

The sponsor reports that the mean dose over the duration of the study for fluvoxamine CR group is 174mg/day. In respond to our 74-day letter, the sponsor provides the following data on mean daily dose by visit for all randomized (not ITT population) patients in Study 3107.