DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-033

NDA APPROVAL

Solvay Pharmaceuticals, Inc.
Attention: Michael Hare
Assistant Director, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Hare:

Please refer to your new drug application dated April 28, 2006, received May 1, 2006, submitted under 505(b) of the Federal Food, Drug and Cosmetics Act for Luvox CR (fluvoxamine maleate) 100mg and 150mg Extended-Release Capsules.

We acknowledge receipt of your submissions dated December 28, 2007, January 11, 2008, and January 17, 2008.

The December 28, 2007 submission constituted a complete response to our December 20, 2007 action letter.

This new drug application provides for the use of Luvox CR (fluvoxamine maleate) Extended-Release Capsules for the treatment of social anxiety disorder (SAD) and obsessive compulsive disorder (OCD).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-033."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-033**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for the indication of social anxiety disorder for ages 0-11 years because the necessary studies are impossible or highly impracticable because there are not enough patients in that age group with the disease to study. We are deferring submission of your pediatric studies for ages 12-17 years because the drug is ready for approval for use in adults and the pediatric studies have not been completed.

We note that this product is already fully labeled for use in all appropriate pediatric populations for the indication of obsessive compulsive disorder using the immediate-release formulation. Therefore, no additional pediatric studies are needed at this time.

Your deferred pediatric studies required under 505B(a) of the Food, Drug, and Cosmetic Act are required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Food, Drug, and Cosmetic Act. These commitments are listed below.

POSTMARKETING COMMITMENTS

We remind you of your following postmarketing study commitments agreed upon in your submission dated December 29, 2007 and February 20, 2008. These commitments are listed below.

1. Deferred Pediatric Studies Under PREA

   You are required to assess the safety and effectiveness of Luvox CR (fluvoxamine maleate) Extended-Release Capsules as a treatment for social anxiety disorder in pediatric patients ages 12 to 17 (children and adolescents).

   Submission of Pediatric Assessment Plan: June 2008
   Final Report Submission: 3 years from the date of approval

   Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

2. Microscopic Examination of the Standard Battery of Tissues used in the General Toxicity Study

   We note your commitment to conduct and provide a complete report of the microscopic examination of the remaining standard battery of tissues from the 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]

Final Report Submission: June 2008

3. Maintenance Study for Social Anxiety Disorder

Although your NDA for fluvoxamine maleate CR demonstrates effectiveness as a treatment for social anxiety disorder over an interval of 12 weeks, it does not provide information about the duration and conditions of treatment that are necessary to sustain effects over an extended duration. While it is widely assumed that continued treatment of symptomatically remitted patients with social anxiety disorder reduces their risk of relapse, we have no evidence that fluvoxamine maleate CR has efficacy after 12 weeks. You have agreed to conduct and submit the results of a randomized withdrawal study to address longer-term effectiveness and safety for your drug in social anxiety disorder. You have agreed to commit to conducting this study and submitting the results no later than 3 years after the date of approval for this NDA.

Final Report Submission: 3 years after the date of approval

DISSOLUTION METHOD AND SPECIFICATION

We acknowledge your agreement to adopt the following final dissolution method and specifications for all two capsule strengths, 100 mg, and 150 mg:

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

Time	% Released
2h	
4h	
8h	
12h	

EXPIRY DATE

An expiration date of 24 months has been assigned for this product based on the provided drug product stability data.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration

Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call LCDR Renmeet Grewal, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Package Insert & Medguide

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

/s/

Thomas Laughren
2/28/2008 08:05:52 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-033

SUMMARY REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 28, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Luvox CR (fluvoxamine extended release) for social anxiety disorder (SAD) and obsessive compulsive disorder (OCD)

TO: File NDA 22-033
[Note: This overview should be filed with the 12-28-07 response to the agency's 12-20-07 second approvable letter for this NDA.]

1.0 BACKGROUND

Luvox CR (fluvoxamine extended release) is an extended release formulation of fluvoxamine, an SSRI that is approved in an immediate release form for the treatment of OCD. This NDA seeks claims for the short-term treatment of social anxiety disorder (SAD) and obsessive compulsive disorder (OCD), in a dose range of 100 to 300 mg/day, given qd. The studies supporting this claim were conducted under IND 57,838, and a pre-supplemental NDA meeting was held with the sponsor on 9-22-04 to discuss CMC and biopharmaceutics issues.

This NDA was originally submitted 5-1-06, and the first approvable letter was issued 2-27-07. The sponsor came back with a complete response on 6-21-07 and, as noted, we issued a second approvable letter on 12-20-07. There were essentially two remaining issues to be resolved, i.e., dissolution specifications and establishing an expiry. The sponsor quickly responded on 12-28-07 with a complete response to these issues, including a request for a meeting to discuss these deficiencies.

We met on 1-22-08 for a premeeting to discuss the remaining deficiencies. Our 2-27-07 AE letter had identified a dissolution range of at the 6 hour time point. Although the sponsor accepted the proposed dissolution specifications, including those at the 6 hour time point, the problem was that there would be an unacceptable failure rate of manufacturing lots for

such a strict range at 6 hours, making it impossible to set a reasonable expiry. [Note: A slightly more generous range of ——, or even ——, would have allowed all lots to pass, but this was not acceptable to OCP.] The CMC group appeared to find 6 hour limits of —— acceptable, or ——, or indeed dropping the 6 hour limits altogether. It should be noted that the accepted 4 hour limits are —— and the accepted 8 hour limits are —— Thus, it is unfathomable from a clinical standpoint how limits for the 6 hour time point are an issue at all. Consequently, the clinical group opted to drop the requirement for 6 hour limits. The CMC group found this acceptable, and the sponsor has accepted the revised specifications without a 6 hour requirement.

2.0 CHEMISTRY

All of the CMC issues have been resolved, including the issue of extablishing an expiry date (see discussion under Background above).

3.0 PHARMACOLOGY

Early in the review process, there was an impurity issue that was an obstacle for the final approval of both NDA 21-519 for the sponsor's IR formulation of fluvoxamine and for this NDA for Luvox CR. This issue has now been resolved as of the last review cycle. The sponsor has committed to providing further information on a 14-day toxicity study during phase 4.

4.0 BIOPHARMACEUTICS

The only remaining issue for the biopharm group was the matter of dissolution specifications, and as noted under Background, I have recommended a slight modification of the limits that I find clinically acceptable and this makes it possible to reasonably manufacture a product that, in my view, is fully acceptable.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

There were 3 double-blind, randomized, parallel-group, flexible-dose, placebo-controlled, short-term (12 weeks) efficacy and safety trials in this program. Two of these studies (3107 & 3108) evaluated Luvox CR in adult outpatients with SAD in a dose range of 100 to 300 mg/day, and one study (3103) evaluated Luvox CR in adult outpatients with OCD in a dose range of 100 to 300 mg/day. The primary endpoint for the SAD studies was change from baseline to endpoint in

the LSAS total score, and the primary endpoint for the OCD study was change from baseline to endpoint in the Y-BOCS total score. All 3 studies were positive for Luvox CR on the primary endpoint.

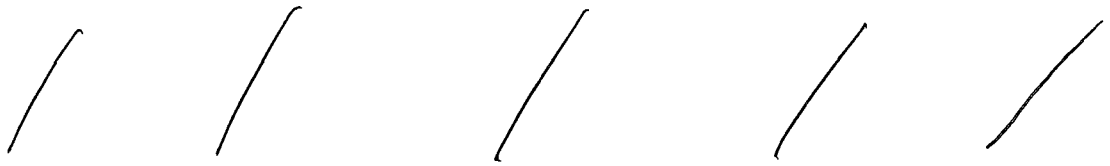
5.1.2 Comment on Other Important Clinical Issues Regarding the Efficacy Data

Evidence Bearing on the Question of Dose/Response for Efficacy

There was no information pertinent to dose/response for efficacy in this program.

Secondary Efficacy Variables

The sponsor proposed to [redacted]



Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis primarily of gender, as there were not sufficient data to conduct explorations based on age and race. There was no indication of any difference in effectiveness based on gender.

Size of Treatment Effect

The effect sizes observed in these trials were similar to those seen in other positive SAD and OCD trials.

Duration of Treatment

The sponsor presented no data pertinent to longer-term efficacy for SAD and OCD in this supplement. However, [redacted], and the sponsor has agreed to conduct a randomized withdrawal study with Luvox CR in SAD.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term efficacy of Luvox CR in the treatment of SAD and OCD. As noted, they will be permitted to include in labeling information only for the primary endpoint in these trials. The sponsor has agreed to conduct a pediatric SAD study and a maintenance study in SAD. We will not request a

pediatric OCD trial under PREA, because the sponsor has already conducted a pediatric OCD trial for immediate release fluvoxamine.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review and Overview of Findings

The safety data for this supplement were derived from a total of n=614 subject and patients exposed to Luvox CR across the 11 clinical trials comprising this program (6 phase 1 pk studies, the 3 phase 3 safety and efficacy trials, and 2 extension trials). The observed common adverse events profile was consistent with that seen with the immediate release formulation for this drug.

5.2.2 Conclusions Regarding Safety

The adverse event profile for Luvox CR in the treatment of SAD and OCD is quite similar to that seen for fluvoxamine IR for its approved indications, and can be adequately characterized in labeling. Some problems were noted in the coding and analysis of safety data by the sponsor, however, these have now been resolved.

5.3 Clinical Sections of Labeling

We made a number of modifications to the sponsor's proposed labeling, and have now reached agreement with the sponsor on final labeling.

6.0 WORLD LITERATURE

The sponsor was not able to find any literature references that were specific to fluvoxamine CR. Dr. Dubitsky (who helped in the evaluation of the safety data for this application) was able to identify 3 such references, referring to studies conducted as part of this program, and none revealed any new safety information that would change conclusions about the approvability of this application.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Luvox CR is not approved anywhere at this time.

8.0 DSI INSPECTIONS

Inspections were conducted at 6 sites, and data from all 6 were deemed to be acceptable.

10.0 LABELING AND APPROVAL LETTER

10.1 Labeling

We have now reached agreement with the sponsor on final labeling.

10.2 Foreign Labeling

Luvox CR is not approved anywhere at this time.

10.3 Approval Letter

The approval letter includes agreed upon final labeling and agreements on phase 4 commitments.

11.0 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 SAD and OCD. I believe we have satisfactorily resolved the remaining issues identified in our 12-20-07 approvable letter, and we have reached agreement with the sponsor on final labeling. Thus, I will issue an approval letter.

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

DOC: LuvoxCR_OCD_SAD_Laughren_AP_Memo.doc

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/s/

Thomas Laughren
2/28/2008 08:00:36 AM
MEDICAL OFFICER

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

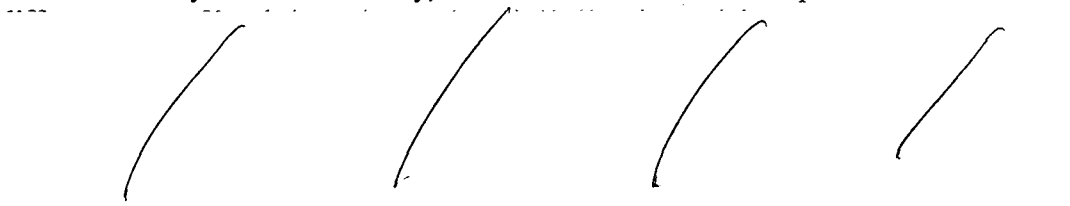
Luvox CR® (fluvoxamine maleate) is an extended release capsule formulation of fluvoxamine (immediate release), which is an approved selective serotonin reuptake inhibitor for the treatment of OCD. Solvay submitted Luvox [redacted] Dr. Cai detailed in her NDA 22-033 review the sponsor, "Solvay Pharmaceuticals 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

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



As it reads in the OCP review of Carol Noory dated 4 February 2008, on 20 December 2007 Solvay was notified that

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

are manufactured by

(DMF) and Solvay has reported to the agency that it is

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 to) 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 (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 ( ) 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

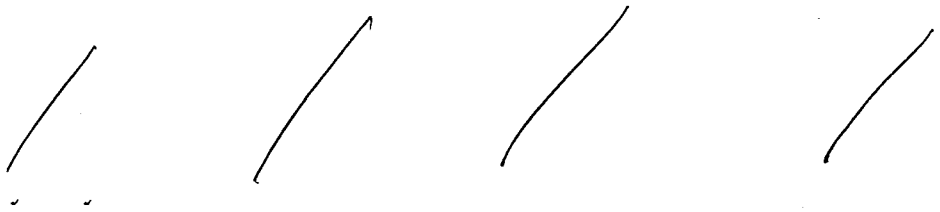
5.2.1 Clinical Data Sources for Safety Review

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

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

/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

DOC:Luvox CR_GeneralizedSADandOCD_Zornberg_AE_Memo.doc

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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 [redacted]. 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 ——————————————— :s 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 ($\leq$50 years of age vs. $\geq$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.

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

a: Estimate is made from ANOVA model with treatment and analysis center as factors.
b: Test for no difference between treatments from ranked ANOVA model with treatment and analysis center as factors. Not adjusted for multiplicity.
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

Clinical Review
June Cai, MD
Solvay Pharmaceuticals, Inc. NDA22033/N-000
Luvox®CR (Fluvoxamine meleate)

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 [redacted] drug delivery system that delivers its active moiety fluvoxamine maleate over a period of 12 hours. The [redacted] beads ranging from [redacted] mm in diameter are encapsulated in hard gelatin capsules. [redacted]

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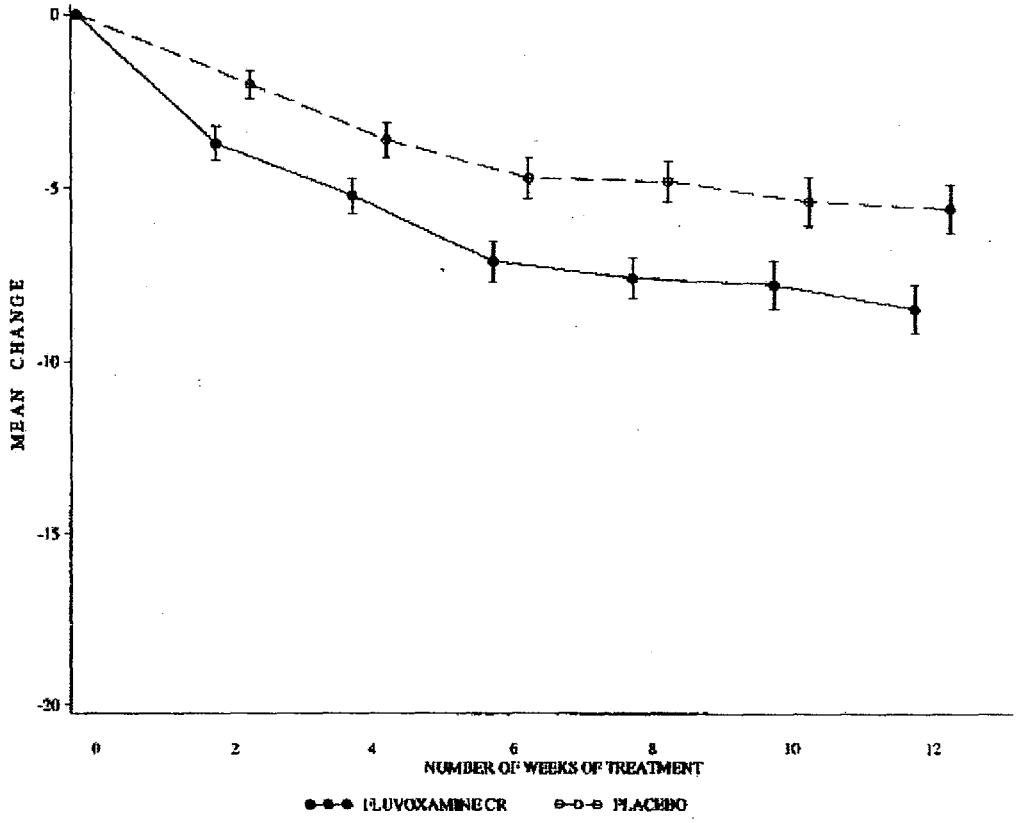
Figure 1: Mean Change from Baseline in Y-BOCS Total Score (LOCF) at Each Visit – ITT Population



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:

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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.

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.

Table 20: Mean Daily Dose by Visit for All Patients in Study 3107 (All Randomized)

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 12
Subject N	136	110	104	97	90	88	85	78	74
Mean	91.9	127.0	163.6	195.6	231.6	243.7	239.9	236.0	235.6
S.E.	1.39	2.87	4.18	5.31	6.44	6.34	6.47	7.06	7.21
Median	100	150	186	200	250	250	250	250	250
Min - Max	14 - 114	14 - 150	17 - 200	86 - 250	90 - 300	100 - 300	100 - 323	93 - 300	83 -300

Note1: Subjects who did not take any dose of Fluvoxamine CR for a specific visit are excluded from this summary table.
Note2: 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.

Fewer than 50% of subjects were on 300mg/day from Week 6. The table below displays dose titration by visits in all randomized subjects.

Table 21: 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**
LuvoxCR	**136**	**110**	**104**	**97**	**90**	**88**	**85**	**78**	**74**
100 mg	136(100)	41 (37)	18 (17)	9 (9)	4 (4)	2 (2)	2 (2)	2 (3)	2 (3)
150 mg	0	69 (63)	32 (31)	19(20)	12(13)	11 (13)	11 (13)	11(14)	11(15)
200 mg	0	0	54 (52)	28(29)	21(23)	14 (16)	14 (16)	13(17)	13(18)
250 mg	0	0	0	41(42)	23(26)	21 (24)	19 (22)	22(23)	16(22)
300 mg	0	0	0	0	30(33)	40 (45)	39 (46)	34(44)	32(43)
Placebo	**136**	**133**	**129**	**123**	**117**	**113**	**106**	**96**	**88**
100 mg	136(100)	22 (17)	8 (6)	4 (3)	2 (2)	1 (<1)	1 (<1)	1 (1)	1 (1)
150 mg	0	111(83)	21 (16)	8(7)	2 (2)	2 (2)	2 (2)	1 (1)	1 (1)
200 mg	0	0	100(76)	19 (15)	11(9)	5 (4)	5 (5)	4 (4)	3 (3)
250 mg	0	0	0	92 (75)	26(21)	17 (15)	14 (13)	14(15)	13(15)
300 mg	0	0	0	0	77(66)	88 (78)	84 (79)	76(79)	70(80)

Duration of exposure in Study 3108 is shown in the following table.

Table 22: Duration of Exposure in Study 3108

		Fluvoxamine CR	**Placebo**
Duration of Exposure (Days)	**Mean (SD)**	61.4 (2.7)	73.6 (1.7)
	Median	83	84
	Range	1-97	7-90

The sponsor reports that the mean dose over the duration of Study 3108 for fluvoxamine CR group is 163mg/day, then provides the following information on mean daily dose of fluvoxamine CR by visit in all randomized (not ITT population) in the response to 74-day letter.

Table 23: Mean Daily Dose of Fluvoxamine CR by Visit for Patients in Study S3108 (All Randomized)

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 12
Subject N	149	131	120	111	109	105	104	97	92
Mean	94.2	115.9	145.7	173.9	198.9	209.4	205.9	207.1	204.3
S.E.	1.18	2.56	3.67	5.18	6.45	6.62	6.55	6.71	6.75
Median	100	100	150	150	200	200	200	200	200
Min - Max	22 - 107	14 - 150	50 - 200	38 - 250	100 - 300	75 - 300	67 - 300	93 - 300	100 -300

Note: Subjects who did not take any dose of Fluvoxamine CR for a specific visit are excluded from this summary table.
Note: 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.

Fewer than 30% of the subjects were able to receive daily dose of 300mg/day. The next table displays dose titration by visits in all randomized subjects.

Table 24: Dose Titration by Visits in All Randomized Subjects of Study 3108

Dosages	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 8**	**W 10**	**W 12**
Luvox CR	**149**	**131**	**120**	**111**	**109**	**105**	**104**	**97**	**92**
100 mg	149(100)	75 (57)	37 (31)	22 (20)	14 (13)	10 (10)	10(10)	9 (9)	9 (10)
150 mg	0	56 (43)	49 (41)	34 (31)	31 (28)	26 (25)	26(25)	26(27)	24(26)
200 mg	0	0	34 (28)	30 (27)	22 (20)	18 (17)	18(17)	18(19)	18(20)
250 mg	0	0	0	25 (23)	22 (20)	25 (24)	25(24)	22(23)	22(23)
300 mg	0	0	0	0	20 (18)	26(25)	25(24)	22(23)	19(21)
Placebo	**151**	**147**	**146**	**141**	**138**	**133**	**129**	**123**	**111**
100 mg	151(100)	51 (35)	22 (15)	12 (9)	8 (6)	7 (5)	7 (5)	7 (6)	7 (6)
150 mg	0	96 (65)	55 (38)	34 (24)	24 (17)	20 (15)	19 (15)	18(15)	18(16)
200 mg	0	0	69 (47)	40 (28)	29 (21)	19 (14)	18 (14)	18(15)	17(15)
250 mg	0	0	0	55 (39)	31 (22)	25 (19)	25 (19)	24(20)	19(17)
300 mg	0	0	0	0	46 (33)	62 (47)	60 (47)	56(46)	50(45)

Prior and Concomitant Medications

In Study 3107, a total of 95 subjects (79%) of subjects in fluvoxamine CR group and 104 (83%) of those in placebo group used concomitant medications; In *Study 3108, a* total of 101 subjects (69%) of subjects in fluvoxamine CR group and 113 (76%) of those in placebo group used concomitant medications. The most commonly used ones are listed in the following two tables.

Table 25: Most Commonly Prescribed Concomitant Drugs in Study 3107

	Fluvoxamine CR N=121	Placebo N=126
Ibuprofen	29 (24%)	24 (19%)
Multivitamins	25 (21%)	27 (21%)
Paraceamol	15 (12%)	18 (14%)
Acetylsalicylic Acid	11 (9%)	15 (12%)
Progestrogene and Estrogen, Fixed Combinations	9 (7%)	7 (6%)
Progestrogene and Estrogen in Combination	5 (4%)	4 (3%)

Table 26: Most Commonly Prescribed Concomitant Drugs in Study 3108

	Fluvoxamine CR N=146	Placebo N=148
Paraceamol	31 (21%)	34 (23%)
Acetylsalicylic Acid	16 (11%)	17 (11%)
Progestrogene and Estrogen, Fixed Combinations	12 (8%)	19 (13%)
Ibuprofen	6 (5%)	18 (12%)

Other than the hormonal combinations, these commonly used ones do not seem to have significant anxiogenic or anxiolytic effects.

The number of subjects who used other agents, including some psychotropics or possible anxiogenic and anxiolytic agents, is considerably low in both trials.

In Study 3107, 2% (3/121) subjects in the active treatment group used benzodiazepine derivatives (one used clonazepam and two used diazepam); no one in placebo group used any. On the other hand, one subject used beta-blocker in placebo group but none in fluvoxamine CR group did. More subjects in placebo group (6, 5%) than those in fluvoxamine CR group (3, 2%) used sympathomimetics such as phenylephrine, pseudoephedrine, Dimetapp, Contac 700, and Artifed. Two (2%) subjects in placebo group used Tretinoin for acne and another subject (1%) used Fentanyl.

In *Study 3108,* caffeine was used by one subject of each treatment group. Up to 3% (5/146) subjects in the active treatment group used benzodiazepine derivatives (one of each used alprazolam, bromazepam, clorazepate dipotassium, diazepam, and oxazepam) but none in placebo group. Similarly, in active treatment group one subject (<1%) was on unspecified anxiolytics and four subjects (3%) needed zolpidem while none needed any of these medications in placebo group. On the other hand, levothyroxine sodium was used by four subjects (3%) in fluvoxamine CR group and only one in placebo group. One subject used sertraline and another thioridazine in placebo group. More subjects in placebo group (4%) than those in the active

treatment group (<1%) took corticosteroids as well as estrogen (10, 7% versus 6, 4%) in Study 3108.

For information on the use of prohibited medications during the study, please see Protocol Deviation subsection below. The overall number of subjects who took them is small. In my opinion, the impact of these concomitant medications on efficacy is probably small.

Protocol Deviation

A total of 24 (10%) protocol deviations occurred in ITT population during Study 3107 and 42 (14%) in Study 3108. In both studies, fluvoxamine CR group had higher incidences of protocol deviation than placebo group (17% versus 3% in Study 3107 and 20% versus 9% in Study 3108. The types of deviation in both Study 3107 and Study 3108 are similar (see tables below).

Table 27: Protocol Deviations in ITT Population of Study 3107**

Types of Protocol Deviations	Study 3107			Study 3108		
	Luvox CR	Placebo	Overall	Luvox CR	Placebo	Overall
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total Subjects	121	126	247	146	148	294
Number of Deviations	20 (17)	4 (3)	24(10)	29 (20)	13 (9)	42 (14)
Non-compliance*	18 (15)	3 (2)	21 (9)	21 (14)	5 (3)	26 (9)
Screening MADRS≥18	0	2 (2)	2 (<1)	1 (<1)	0	1 (<1)
Used Prohibited Drugs	3 (2)	0	3 (1)	9 (6)	8 (5)	17 (6)

*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.
**Subjects may be counted in more than one protocol deviation category.

- In both studies, "noncompliance" was the leading cause of protocol deviation - the rates in fluvoxamine CR groups are much higher than those in placebo groups. These subjects took 80% lower doses than their prescribed. One subject from fluvoxamine CR group in Study 3108 discontinued from the study due to noncompliance, but none discontinued from fluvoxamine CR group in Study 3107.
- Two subjects in placebo group met one of the exclusion criteria with MADRS ≥ 18 at Screening in Study 3107; one subject in the fluvoxamine CR group met one of the exclusion criteria with MADRS 18 at Screening in Study 3108
- Taking prohibited medications – After excluding Center 14 where 11 subjects enrolled, three subjects took prohibited medication (one took clonazepam for unknown period and two took diazepam for one day each) in Study 3107. The table below lists the prohibited medications taken by subjects in different treatment groups in Study 3108 (see also "Prior and Concomitant Medications" above).

Table 28: List of Prohibited Medication Taken during Study 3108 (by ITT)

Fluvoxamine CR	Placebo
benzodiazepine derivatives	other hypnotics and sedatives such as valerian extract, hyoscine, and passiflora extract
diphenylpropylamine derivatives (Propofan)	kava-kava rhizome
psychostimulants (Piracetam and guronsan)	diltiazem hydrochloride
	sertraline
Cyclopyrrolones (zopiclone), selective beta-blockers (metoprolol succinate and acebutolol hydrochloride), thioridazine, and prochlorperazine mesilate	

Subject Disposition

Only 56% subjects completed the study, 50% in the fluvoxamine CR group and 61% in the placebo in Study 3107; the completion rate is slightly higher in Study 3108 (66%) with 60% in fluvoxamine CR group and 72% in placebo group. Major reasons for dropout are presented in the Safety section.

Table 29: Subject Disposition throughout Studies 3107 and 3108 (ITT)

	Study 3107			Study 3108		
	Luvox CR	**Placebo**	**Total**	**Luvox CR**	**Placebo**	**Total**
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Randomized	139	140	279	149	151	300
ITT	121 (87)	126 (90)	247 (89)	146 (98)	148 (98)	294 (98)
Completed	70 (50)	85 (61)	155 (56)	90 (60)	108 (72)	198 (66)

The table below displays ITT subject enumeration throughout the two SAD studies.

Table 30: Subject Enumeration throughout the Studies 3107 and 3108 (ITT)

	Study 3107		Study 3108	
Timing	**Fluvoxamine CR**	**Placebo**	**Fluvoxamine CR**	**Placebo**
Baseline (Day 1 – 7)	121	126	146	148
Week 2 (Day 8 – 15)	108	124	126	148
Week 4 (Day 23 -- 29)	94	116	111	138
Week 6 (Day 37 –43)	84	107	107	132
Week 8 (Day 51 – 57)	77	96	95	125
Week 10 (Day 65 – 71)	73	90	91	113
Week 12 (Day 72 – 84)	70	85	90	108

Efficacy Results

Due to protocol deviations (non-compliant with Good Clinical Practice, the sponsor excluded Center 14 for efficacy analysis. The study result is presented as follows. The following table presents the analysis of primary variable, change of LSAS total score from baseline to endpoint (LOCF) in Study 3107.

Table 31: Liebowitz Social Anxiety Scale Total Score Change from Baseline to Endpoint (LOCF) in ITT Population of Study 3107 (Per Sponsor)

Treatment Group	Statistic	Change from Baseline					
		Week 2	Week 4	Week 6	Week 8	Week 10	Endpoint
LSAS Total Score:							
Fluvoxamine CR (n = 121)	n	108	110	110	110	110	110
	Baseline Mean	90.4	88.8	89.0	89.8	90.3	90.1
	Mean (S.E.)	-8.0 (1.3)	-13.9 (1.5)	-20.1 (2.0)	-24.2 (2.2)	-26.1 (2.4)	-26.7 (2.6)
	Median	-4	-11	-18	-20	-20	-20
	Min., Max.	-51, 14	-74, 22	-81, 33	-86, 15	-94, 21	-94, 20
	95% CI	[-10.5, -5.5]	[-16.8, -11.0]	[-24.0, -16.2]	[-28.6, -19.9]	[-30.8, -21.4]	[-31.8, -21.6]
Placebo (n = 126)	n	124	126	126	126	126	126
	Baseline Mean	89.0	89.4	89.7	89.4	89.6	88.6
	Mean (S.E.)	-5.9 (1.1)	-9.3 (1.1)	-11.4 (1.4)	-11.7 (1.5)	-13.3 (1.6)	-12.9 (1.6)
	Median	-3	-7	-7	-9	-10	-10
	Min., Max.	-82, 19	-67, 17	-70, 16	-86, 23	-86, 24	-86, 24
	95% CI	[-8.1, -3.7]	[-11.5, -7.1]	[-14.1, -8.7]	[-14.6, -8.8]	[-16.4, -10.2]	[-16.0, -9.8]
Treatment Effect P-Value		0.284	0.048*	0.001**	<0.001**	<0.001**	<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 LSAS total score with terms for treatment and pooled center.

Note: Endpoint is defined as the last post Baseline value collected while on study medication.

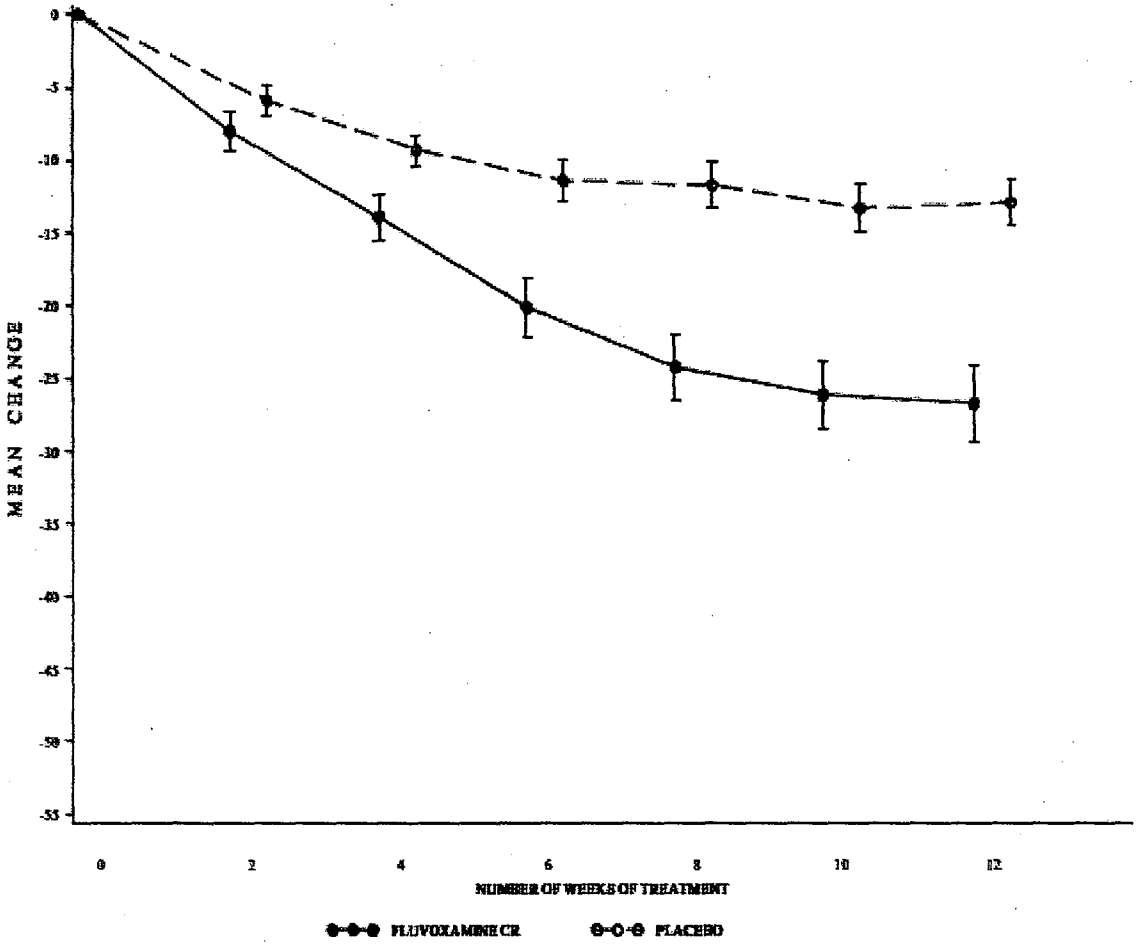
Note: Efficacy measurements collected outside the assigned visit windows or efficacy measurements collected more than three days after discontinuation of study medication were excluded from the efficacy analyses for that visit.

Data Source: Table 10.2.1.1

Statistic significance becomes evident from Week 4. More evident changes are seen from Week 4 to Week 8 but not from Week 8 to 12. It is possible that higher dose is associated with better efficacy.

The following figure illustrates the total LSAS score changes from baseline to endpoint (LOCF) in ITT population of Study 3107.

Figure 2: Liebowitz Social Anxiety Scale Total Score Mean Change from Baseline to Each Visit and Endpoint (LOCF) in ITT Population of Study 3107 (Per Sponsor)



The positive efficacy result has been confirmed by the Agency Statistician Reviewer, Dr. Kong who evaluated the result with or without Center 14 and it is positive under both circumstances. Thus, excluding Center 14 does not necessarily affect the efficacy result, according to Dr. Kong.

The change of LSAS total score from baseline to endpoint (LOCF) in Study 3108 is shown in the following table.

Table 32: Liebowitz Social Anxiety Scale Total Score Change from Baseline to Endpoint (LOCF) in ITT Population of Study 3108 (Per Sponsor)

		Change from Baseline					
Treatment Group	Statistic	Week 2	Week 4	Week 6	Week 8	Week 10	Endpoint
LSAS Total Score:							
Fluvoxamine CR (n = 146)	n	126	126	126	126	126	126
	Baseline Mean	95.9	96.7	96.3	97.5	97.3	97.4
	Mean (S.E.)	-9.8 (1.4)	-18.9 (1.8)	-24.7 (2.2)	-31.3 (2.6)	-32.6 (2.5)	-36.1 (2.7)
	Median	-7	-15	-25	-27	-31	-33
	Min., Max.	-94, 17	-91, 22	-112, 22	-127, 22	-128, 33	-129, 29
	95% CI	[-12.5, -7.1]	[-22.4, -15.4]	[-29.0, -20.4]	[-36.4, -26.2]	[-37.5, -27.7]	[-41.4, -30.8]
Placebo (n = 148)	n	148	148	148	148	148	148
	Baseline Mean	93.9	94.4	94.1	93.9	95.2	95.8
	Mean (S.E.)	-8.8 (1.2)	-14.2 (1.6)	-19.3 (1.9)	-22.4 (2.2)	-25.5 (2.4)	-27.3 (2.4)
	Median	-6	-11	-16	-16	-20	-24
	Min., Max.	-64, 30	-104, 29	-110, 20	-133, 26	-133, 23	-133, 29
	95% CI	[-11.2, -6.4]	[-17.3, -11.1]	[-23.0, -15.6]	[-26.7, -18.1]	[-30.2, -20.8]	[-32.0, -22.6]
Treatment Effect P-Value		0.618	0.029*	0.066	0.007**	0.017*	0.020*

* Significant at the 0.050 level. ** Significant at the 0.010 level.

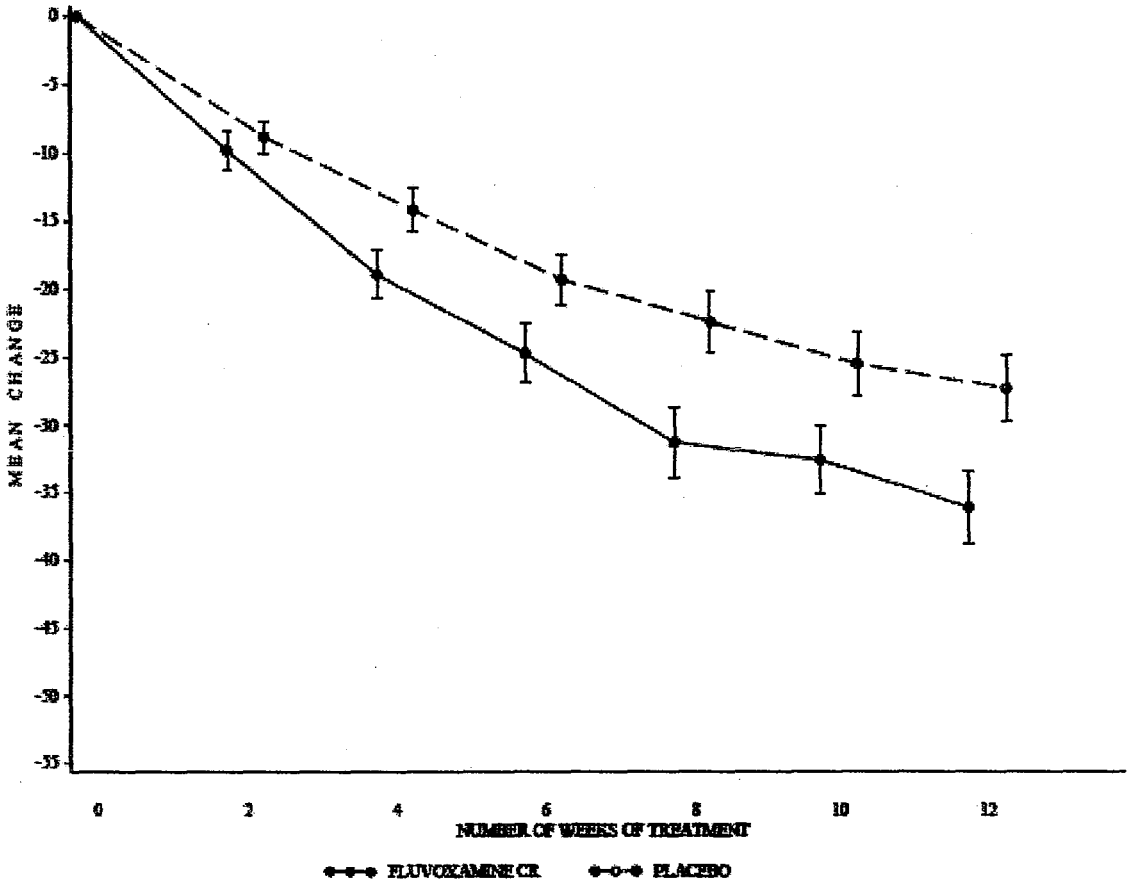
Note: P-values for fluvoxamine CR versus placebo treatment group are based on an ANOVA model fit to the rank of the change from Baseline LSAS total score with terms for treatment and pooled center.

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.

Statistic significance becomes evident from Week 8. Longer time of treatment doesn't necessarily increase efficacy in this study. It is interesting that efficacy also showed in Week 4 but not in Week 6. Considering dosage increased to maximum 300mg/day by Week 6 and then maintained till the end of the study, it is possible that 300mg/day gives more definitive effect.

Figure 3: Liebowitz Social Anxiety Scale Total Score Mean Change from Baseline to Each Visit and Endpoint (LOCF) in ITT Population of Study 3108 (Per Sponsor)



Demographic Effects

Age: In *Study 3107*, only four (2%) subjects in the age group of 65 years old and older in ITT population. Thus, efficacy in elderly population can't be considered. Similarly, in *Study 3108*, only three (1%) subjects in the age group of 65 years old and older and they were all randomized to placebo group. Thus, efficacy in elderly population can't be considered.

Gender: The Agency Statistic Reviewer, Dr. Kong explored the gender effect on the efficacy by testing the significance of the treatment effect at a nominal level of 0.05 after the adjustment of gender alone, and gender by treatment interaction on the change from baseline in LSAS total score using LOCF data. Dr. Kong agreed with the sponsor's conclusion that there is no treatment effect difference between the two groups in *Study 3107*.

However, in *Study 3108*, male patients have a larger improvement on LSAS score when take the treatment than female patients. Based on Dr. Kong's analysis, gender is quite significant in the ANCOVA analysis (p=0.01) of the primary endpoint, so is the interaction of gender and treatment indicator (0.05) which is contrast to the sponsor's conclusion. However, according to Dr. Kong, including gender factor does not change the significance level of the treatment. Thus, this indicates the treatment effect is stable regardless a possible difference in treatment effect between male and female patients.

Table 33: Mean Change from Baseline in Male and Female Subjects in Study 3108

	Fluvoxamine CR	Placebo
Male	N=60	N=74
Mean Change From Baseline	-41.2	-26.7
Female	N=66	N=74
Mean Change From Baseline	-31.4	-27.9

Ethnicity: In both Study 3107 and Study 3108, most subjects are Caucasian (80% in Study 3107 and >90% in Study 3108). In either study, there were not enough subjects in other ethnic groups to be considered.

6.1.3 Efficacy Conclusions

6.1.3.1 OCD

Study 3103 provides sufficient evidence to support approval of this indication. Two studies are generally required for a new indication. However, 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.

6.1.3.2 SAD

The presented clinical trials (Study 3107 and 3108) support the efficacy results for treatment of SAD. Although there seems to be gender effect on Study 3108 efficacy result, it is not replicated in Study 3107. Therefore, in my opinion, it is not clinically meaningful.

7 Integrated Review of Safety

7.1 Methods and Findings

The primary integrated safety database for this review is comprised of the pool of the three Phase 3, double-blind, placebo-controlled, 12-week studies (3103, 3107, and 3108). A total of 832 patients were randomized (415 received fluvoxamine CR) and were included in the safety

analyses. However, 12 fluvoxamine CR patients and 17 placebo patients were excluded from the safety analyses because either 1) study medication was not taken, 2) there were no post-baseline safety data, or 3) safety data was not deemed to be reliable (this pertains only to the 14 patients from Center 14 in study 1143107). Thus, 403 fluvoxamine CR and 400 placebo patients comprised the safety population for this database. The examination of the common adverse event profile for Luvox CR and dropout rate is based on this study pool.

The sponsor didn't integrate laboratory, vital sign, and ECG data to submit initially but only presented separately by study. However, in response to our request of these integrated data via the 74-day letter, the sponsor submitted them in October, 2006. They are thus examined below. Considering the extensive safety experience to date with immediate-release fluvoxamine products and the fact that exposures attained with Luvox CR are less than or comparable to those with the immediate-release products at comparable doses, this safety review will be somewhat abbreviated in that analyses of laboratory, vital sign, and ECG data will focus only on patients with outlier values in these parameters.

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).

7.1.1 Deaths

The sponsor reports no deaths in Phase 1 and 3 studies but one among all three trials. The subject (S#2769517) was a 51 year-old female randomized to fluvoxamine CR group in Study 3107 and received fluvoxamine CR up to 200mg/day. Her medical history included asthma, seasonal allergies, eczema, and menopause. Concomitant medications were Motrin, Ciloxan (ciprofloxacin ophthalmic ointment), and Slo-bid (theophylline). During the study, she experienced the following AEs: Somnolence (day 2), sweating (days 2 and 31), nausea (day 2), decreased concentration (day 31), anorexia (day 31), headache (days 64 and 70), and mild eye infection (day 68). At study termination, her physical examination and vital signs were within normal limits. Her MCV was slightly high (100.2 fL) at Screening and at termination (101.4fL). There were no other reported abnormal lab values despite her serum potassium was 5.5 mEq/L and alkaline phosphatase was 117 U/L at Screening. Four days after completing the study, she experienced severe heart failure and died the same day.

Considering that the subject completed the study with a normal physical examination and apparently developed acute heart failure four days later, I agree with the sponsor that this subject's death seems unlikely due to fluvoxamine CR.

7.1.2 Other Serious Adverse Events

The sponsor defines a serious adverse event as any adverse occurrence that:

- resulted in death.
- was life-threatening.
- resulted in persistent or significant disability or incapacity.
- required inpatient hospitalization or prolongation of hospitalization.
- was a congenital anomaly or birth defect.

Events that jeopardized patient safety or required intervention to prevent one of the above outcomes could also have been considered serious. In addition, pregnancies during drug administration were to be reported as serious.

There were no serious adverse events in any Phase 1 studies. In the Phase 3 studies, there were 18 serious adverse events (13 on fluvoxamine CR and 5 on placebo), including the fatal event described above. The sponsor summarized all these events in the **Table 34: Subjects with SAEs in All Phase 3 Studies**.

Table 34: Subjects with SAEs in All Phase 3 Studies

Study	Subject ID Gender/Age (yrs)	Preferred Term	Severity Relationship	Action Taken Outcome
Fluvoxamine CR				
S1143107	107-2769517 Female/ 51	Heart Failure	Severe Unlikely	None Death
S1143109	2470087 Male/41	Psychosis	Severe Unknown	Discontinued AE still present[1], no further treatment
	3170212 Male/63	Cholelithiasis	Mild Unrelated	None Recovered without sequelae
S1143103	103-0269187 Male/28	Suicide Attempt	Severe Unrelated	Discontinued Recovered without sequelae
	103-0369159 Female/29	Accidental Injury	Severe Unrelated	None Recovered without sequelae
	103-1269079 Male/34	Asthma	Severe Unlikely	None Recovered without sequelae
	103-2069017 Female/46	Hostility	Moderate Unrelated	None Recovered without sequelae
	103-2069051 Male/41	Depression	Severe Unlikely	Discontinued Recovered without sequelae
S1143104	269105 Female/32	Anxiety	Severe Unlikely	Discontinued Recovered without sequelae
	369128 Female/42	Accidental Injury	Severe Unrelated	None Recovered without sequelae
	1169046 Female/54	Carcinoma	Severe Unlikely	Discontinued Unknown
	1269182 Male/34	Syncope	Severe Possible	None Recovered without sequelae
	1669065 Female/30	Unintended Pregnancy	Severe Unrelated	Discontinued Lost to follow-up
Placebo				
S1143108	108-5170264 Male/49	Nasal Septum Disorder	Moderate Unrelated	None Recovered without sequelae
S1143109	14700025 Female/38	Unintended Pregnancy	Severe Unrelated	Discontinued AE still present[1], no further treatment
	8470161 Female/29	Pharyngitis	Severe Unrelated	None Recovered without sequelae
S1143103	103-1269182 Male/34	Neoplasm (Lipoma)	Severe Unrelated	None Recovered without sequelae
	103-1769030 Female/21	Unintended Pregnancy	Mild Unrelated	Discontinued AE still present[1], treatment continuing

[1] Status at last subject contact.

In review of the case report forms (CRF's) of all 13 fluvoxamine CR patients who experienced a serious adverse event, including the fatal case, in my judgment, none of these events are reasonably attributable to fluvoxamine CR though the investigator considered one of these was possibly related to the study drug. This subject (S#69182) was a 34 year old male in Study 3104 taking fluvoxamine CR up to 250mg/day. He stopped medication on Day 179 due to a return of

OCD symptoms, and then experienced loss of consciousness (coded as syncope) five days after (Day 184) his last dose of study medication.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

As mentioned before, in the primary safety database of the three pivotal studies, 415 patients were randomized to receive fluvoxamine CR and 417 were randomized to receive placebo, but 403 versus 400 are counted as safety population from the each treatment group, respectively (see table below). The sponsor provides the following table showing subject disposition, including an enumeration of dropouts by reason for discontinuation.

Table 35: Subject Disposition in the Phase 3 Study Pool (per Sponsor)

		Treatment Group		
	Statistic	Fluvoxamine CR	Placebo	Overall
Number of Subjects Randomized	n	415	417	832
Subjects Who Completed the Study	n (%)	249 (60)	289 (69)	538 (65)
Subjects Who Withdrew from the Study	n (%)	166 (40)	128 (31)	294 (35)
Reasons for Withdrawal:				
Lack of Efficacy	n (%)	3 (<1)	29 (7)	32 (4)
Adverse Experience	n (%)	99 (24)	18 (4)	117 (14)
Lost to Follow-Up	n (%)	13 (3)	22 (5)	35 (4)
Protocol Violation	n (%)	14 (3)	16 (4)	30 (4)
Withdrew Consent[1]	n (%)	22 (8)	22 (8)	44 (8)
Other[2]	n (%)	15 (4)	21 (5)	36 (4)
Subjects in the Safety Population	n (%)	403 (97)	400 (96)	803 (97)
Reasons for Exclusion from the Safety Population				
Did Not Take Study Medication	n (%)	5 (1)	5 (1)	10 (1)
No Post-Baseline Safety Data	n (%)	1 (<1)	4 (<1)	5 (<1)
Subjects in Center 14	n (%)	6 (1)	8 (2)	14 (2)

[1]Category only applies to Studies S1143107 and S1143108.
[2]The category of Other included subjects who were non-compliant, were unable to attend appointments, withdrew consent, one subject who was withdrawn by sponsor, one subject who took prohibited medication, and 14 subjects who were enrolled in Center 14 in Study S1143107.
Note: Percentages are based on the total number of subjects randomized.

Overall, a greater proportion of fluvoxamine CR patients dropped out compared to placebo: 40% (166/415) versus 31% (128/417). Included among the dropouts are the 14 subjects from Center

14 in Study 3107 whose participation was prematurely terminated by the sponsor due to GCP concerns.

The most common reason for dropout in the fluvoxamine CR group was due to adverse experiences (24% vs. 4% for placebo). In the placebo group, lack of efficacy was the second most common reason (7%, next to withdraw of consent 8%) for dropout whereas less than 1% of fluvoxamine CR patients dropped out for this reason.

7.1.3.2 Adverse events associated with dropouts

Specific treatment-emergent signs and symptoms (TESS) which led to discontinuation of study medication in the Phase 3 study pool and are calculated based on the safety population with a reporting rate of at least 1% in the fluvoxamine CR group and at least twice the placebo rate are displayed in Table 36 below.

Table 36: TESS Leading to Dropout in the Phase 3 Study Pool

Preferred Term of Adverse Events	Fluvoxamine CR (N=403)	Placebo (N=400)
Nausea	7%	<1%
Insomnia	5%	1%
Somnolence	5%	0%
Dizziness	4%	0%
Asthenia	3%	<1%
Anxiety	3%	<1%
Headache	2%	<1%
Diarrhea	2%	0%
Anorexia	1%	0%
Depression	1%	<1%
Nervousness	1%	<1%
Thinking Abnormal	1%	<1%
Any TESS Leading to Dropout	24%	4%

The adverse experiences that most frequently led to dropout in the fluvoxamine CR-treated patients were nausea, insomnia, and somnolence. These dropouts appear to be related to treatment period: Most fluvoxamine CR patients who withdrew due to an adverse event did so within the first four weeks of treatment.

There is a statistically significant difference for overall dropouts due to any TESS by different indications (SAD versus OCD) with higher dropout rates in the SAD sample (26% for drug versus 3% for placebo) compared to the OCD sample (19% for drug versus 6% for placebo). Nevertheless, the clinical significance of this difference is unclear and there were no major differences in dropout incidence by individual adverse events between the two indications.

Only one subject dropped out due to an adverse experience in Phase 1 studies: Subject 20 in Study 1106 discontinued due to moderate hypertension (162/98) on the second day of fluvoxamine CR treatment. Blood pressure readings on days 3 and 4 were also elevated (to 178/108) and he was treated with a single dose of nitroglycerin. He was withdrawn on day 5. Several days later, blood pressure readings were reduced (140/90) but still had not returned to the pre-treatment level (130/80).

7.1.3.3 Other significant adverse events

None.

7.1.4 Other Search Strategies

Though utilizing a specific scale for evaluation of sexual dysfunction scores and the MADRS for severity of depressive symptoms, the sponsor did not conduct special searches. The sponsor's search and analysis of suicidal events is ongoing.

7.1.5 Common Adverse Events[1]

This section is mostly reviewed by Dr. Gregory Dubitsky considering the time constraints of the review period.

7.1.5.1 Eliciting adverse events data in the development program

Treatment-emergent signs and symptoms (TESS) were defined as any adverse events that occurred following initiation of study medication or worsening of any pre-existing medical condition that was documented at baseline (day 1). In the Phase 3 studies, these events were generally based on spontaneous reports from the patient or investigator as opposed to an adverse event checklist.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All adverse events were coded using the coding symbols for a modified thesaurus of standard adverse reaction terms (COSTART) dictionary. I audited the acceptability of this coding by examining the investigator (verbatim) and preferred (COSTART) terms for all adverse events listed in the file "ae_idb.xpt" submitted with the 4-28-06 submission of this application, sorted first by investigator term then by preferred term.

The following coding irregularities were noted:

[1] Dr. Dubitsky also audited Case Report Forms (CRFs) for this review and found that the AEs in CRFs do not match the narrative summary or AEs listed in JMP database (see Section 7.2.8 Assessment of Quality and Completeness of Data). Thus, the true incidences of these events are questionable.

1) The investigator term "quinsy" was coded to the preferred term "nausea" for one patient. The preferred term "infection" would be more appropriate since quinsy is a peritonsillar abscess.

2) The investigator term "sexual dysfunction" was coded to the preferred term "libido decreased" for nine patients. It is not clear that these events were actually decreased libido since sexual dysfunction could represent a number of other events, such as impotence or premature ejaculation.

3) The investigator term "gastrointestinal virus" was coded to the preferred term "gastrointestinal disorder" for one patient. The preferred term "infection" would be more appropriate. Note: The investigator term "stomach virus" was coded to "infection" elsewhere.

4) The investigator term "reflux" was coded to the preferred term "gastrointestinal disorder" for one patient. The preferred term "dyspepsia" may be more appropriate.

7.1.5.3 Incidence of common adverse events

The incidence of common adverse events was determined from the pool of Phase 3 studies in SAD and OCD. Since both indications are anxiety disorders, no major differences in the adverse event profile would be expected a priori.

7.1.5.4 Common adverse event tables

Table 37 presents the incidence of TESS which occurred in at least 2% of fluvoxamine CR patients at a rate greater than that in the placebo group for the pool of the three Phase 3 studies.

Table 37: Common Adverse Events (2% Table) Pool of SAD and OCD Phase 3 Studies

Preferred Term	Fluvoxamine CR (n=403) n (%)	Placebo (n=400) n (%)
Subjects With At Least One TESS	378 (94)	329 (82)
Nausea	151 (37)	45 (11)
Headache	139 (34)	120 (30)
Insomnia	132 (33)	62 (16)
Somnolence	106 (26)	38 (10)
Asthenia	98 (24)	37 (9)
Diarrhea	60 (15)	25 (6)
Dizziness	57 (14)	30 (8)
Anorexia	56 (14)	10 (3)
Dry Mouth	44 (11)	34 (9)
Nervousness	37 (9)	30 (8)
Dyspepsia	36 (9)	17 (4)
Libido Decreased	33 (8)	17 (4)
Anxiety	31 (8)	16 (4)
Tremor	29 (7)	2 (<1)
Sweating	25 (6)	7 (2)
Constipation	22 (5)	14 (4)
Abnormal Ejaculation	20 (10)	4 (2)
Anorgasmia	19 (5)	3 (<1)
Pharyngitis	18 (4)	11 (3)
Vomiting	17 (4)	9 (2)
Abnormal Dreams	15 (4)	13 (3)
Yawn	15 (4)	2 (<1)
Thinking Abnormal	13 (3)	6 (2)
Agitation	11 (3)	3 (<1)
Hypertonia	10 (2)	4 (1)
Apathy	8 (2)	0 (0)
Taste Perversion	8 (2)	2 (<1)
Tooth Disorder	7 (2)	5 (1)

Note: Percentages for "Abnormal Ejaculation" are based on the total number of male subjects in the safety population for each study grouping.

7.1.5.5 Identifying common and drug-related adverse events

Common and drug-related adverse events are defined here as those TESS which were reported by at least 5% of fluvoxamine CR-treated at a rate at least twice the placebo rate in the Phase 3 study pool. Based on Table 7.1.5.4, the following are common, drug-related adverse events:

Nausea, insomnia, somnolence, asthenia, diarrhea, anorexia, abnormal ejaculation, dyspepsia, libido decreased, anxiety, tremor, sweating, and anorgasmia.

7.1.5.6 Additional analyses and explorations

Analysis by demographics

TESS were analyzed by demographic subgroup as follows:

- gender (males and females).
- age (18-30, 31-40, 41-50, 51-64, and 65 and older).
- ethnicity (Caucasian and non-Caucasian).

However, the sponsor's analysis simply identified common events for which the proportion of patients reporting each event by subgroup differed by at least 5%, regardless of the placebo reporting rates. The sponsor should be requested to conduct and provide the results of the following standard analysis of adverse event incidence by demographic subgroup: for each common, drug-related adverse event identified above and for each demographic variable, the odds ratios of the event in each subgroup should be computed as well as the common odds ratio for the event 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 can be communicated in the action letter for this application.

Analysis by indications

The following table compares the common and drug-related AEs in pivotal studies for the two indications, SAD and OCD. No significant difference is seen among the shared TESS from these studies. TESS that met the definition for common and related TESS in one indication but not in the other included dyspepsia, dizziness, insomnia and yawning (Generalized SAD studies) and accidental injury, vomiting, myalgia, anxiety, decreased libido, and pharyngitis (OCD studies)

Table 38: Common and Drug-Related Adverse Events in Three Pivotal Studies of GSAD and OCD

	GSAD Studies		OCD Studies	
Preferred Term	Fluvoxamine CR (n= 279) n (%)	Placebo (n=276) n (%)	Fluvoxamine CR (n= 124) n (%)	Placebo (n=124) n (%)
Nausea	109 (39)	29 (11)	42 (34)	16 (13)
Insomnia	89 (32)	37 (13)	-	-
Somnolence	72 (26)	24 (9)	34 (27)	14 (11)
Asthenia	67 (24)	27 (10)	31 (25)	10 (8)
Dizziness	42 (15)	18 (7)	-	-
Anorexia	40 (14)	4 (1)	16 (13)	6 (5)
Diarrhea	38 (14)	15 (5)	22 (18)	10 (8)
Dyspepsia	26 (9)	11 (4)	-	-
Tremor	22 (8)	2 (<1)	7 (6)	0
Abnormal Ejaculation	16 (11)	4 (2)	4 (8)	0 (0)
Sweating	16 (6)	6 (2)	9 (7)	1 (<1)
Anorgasmia	13 (5)	3 (1)	6 (5)	0 (0)
Yawn	13 (5)	2 (<1)	-	-
Libido Decreased	-	-	9 (7)	4 (3)
Anxiety	-	-	8 (6)	2 (2)
Vomiting	-	-	8 (6)	2 (2)
Myalgia	-	-	7 (6)	4 (3)
Pharyngitis	-	-	7 (6)	1 (<1)
Accidental Injury	-	-	6 (5)	3 (2)

Note1: Percentages for "Abnormal Ejaculation" are based on the total number of males in the safety population for each study grouping.
Note2: "-" sign indicates that these AEs do not meet the criteria for TESS as with an incidence of =5% in the fluvoxamine CR treatment group and an incidence in the fluvoxamine CR treatment group that was =2 times that of the placebo treatment group for the specific study pool.

7.1.6 Less Common Adverse Events

TESS that were reported by 1% of subjects in the fluvoxamine CR treatment group and more common in the fluvoxamine CR treatment group than in the placebo treatment group in the combined safety data of the three pivotal studies are presented in Table 51 in the Appendix 10.2.1. These include migraine, abnormal liver function tests, ecchymosis, twitching, vasodilation, laryngitis and menorrhagia. Among the five subjects who had liver enzyme increase, only one subject dropped out from the study. It will be reviewed more in detail in Section 7.1.7 Laboratory Findings.

Table 52 (see Appendix 10.2.2) presents TESS reported by <1% of subjects in the fluvoxamine CR treatment group but reported by more subjects in the fluvoxamine CR treatment group than in the placebo treatment group in the combined data of the three pivotal studies. Of this list, it is unclear if the case of intentional injury is a suicidal attempt. Since the sponsor is conducting more extensive and in-depth surveys of suicidal related events, it should be clarified in that

project. After review further details, other potentially concerning cases such as deafness, eye hemorrhage, and corneal lesion, none of them was serious or led to drop-out. One subject's deceased hearing lasted for 20 days; another had unilateral hearing decrease which is doubtfully drug-related. The case of syncope was described in dropout section and heart failure was described in death section – neither case was drug related in my judgment.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The database for laboratory findings is the combined data from the three pivotal studies. The sponsor initially submitted the data by study but then submit the combined data on blood tests from the three pivotal studies upon our request in the 74-day letter on October 25, 2006. However, laboratory outliers and urinalysis data are not submitted as the integrated data. There is no discrepancy for planned approach and the presentation. Of note, GGT was not included as clinical laboratory measure in the OCD trial (Study 3103). As mentioned in 7.1, this part of review will focus only on patients with outlier values in these parameters, considering the extensive safety experience to date with immediate-release fluvoxamine products and the fact that exposures attained with Luvox CR are less than or comparable to those with the immediate-release products at comparable doses.

Below is the laboratory reference used to identify markedly abnormal results by the sponsor:

Table 39: Laboratory Ranges Used to Identify Markedly Abnormal Results

Laboratory Parameter	Lower Limit	Upper Limit
Hematology:		
Hemoglobin (g/dL)		
Male	<11.5	Not Applicable
Female	<9.5	Not Applicable
Hematocrit (%)		
Male	<37	Not Applicable
Female	<32	Not Applicable
Erythrocytes ($x10^6/\mu L$)		
Male	<2.5	Not Applicable
Female	<2.0	Not Applicable
MCV (um)	<60	>120
MCHC (g/dL)	<20	>45
WBC ($x10^3/\mu L$)	<2.80	>16.00
Eosinophils (%)	Not Applicable	>10
Basophils (%)	Not Applicable	>15
Lymphocytes (%)	Not Applicable	>80
Monocytes (%)	Not Applicable	>40
Neutrophils (Total) (%)	<15	Not Applicable
Platelet Count ($x10^3/\mu L$)	<75	>700
Clinical Chemistry:		
Alkaline Phosphatase (U/L)	Not Applicable	>390
SGOT (AST) (U/L)	Not Applicable	>150
SGPT (ALT) (U/L)	Not Applicable	>165
Total Bilirubin (mg/dL)	Not Applicable	>2.0
LDH	Not Applicable	>3.0 x normal
Glucose (mg/dL)	<30	>250
Urea Nitrogen (mg/dL)	Not Applicable	>30
Creatinine (mg/dL)	Not Applicable	>2.0
Sodium (mmol/L)	<120	>165
Potassium (mmol/L)	<2.5	>6.5
Chloride (mmol/L)	<80	>125
GGT (U/L)		
Male	Not Applicable	>100
Female	Not Applicable	>90
Albumin (g/dL)	<2.0	>9.0

For the numbers of patients exposed to the drug who had baseline laboratory values and follow-up assessments, please see relevant analyses for outliers.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The laboratory tests specified in the protocols of the three pivotal studies are Studies 3103, 3107, and 3108 are examined. These include hematologic tests (complete blood count plus differential) and chemistry panel (sodium, potassium, chloride, glucose, blood urea nitrogen, and creatinine, as well as liver panel which includes SGOT, SGPT, GGT (except in Study 3103), LDH, albumin, total bilirubin, and alkaline phosphatase.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

In examination of the mean changes of the laboratory test values from baseline to Week 12 in the two treatment groups, there was no significant changes in any of the laboratory tests mentioned above (see 7.1.7.2) in the drug group compared to placebo.

7.1.7.3.2 Marked outliers and dropouts for laboratory abnormalities

Table 40 below displays the proportions of drug and placebo patients who met the above criteria for markedly abnormal blood chemistry values. There is no statistically significant difference between the two treatment groups.

There were two subjects in fluvoxamine CR group developed elevated SGPT but neither had jaundice or liver failure.

Subject 69623 is a 37 year-old Caucasian male whose SGPT increased from 23 U/L at baseline to 204 U/L at endpoint but decreased to 101 U/L during the follow-up period.

Subject #69550 of Study 3107 is the only one among these subjects who had elevated liver enzymes discontinued from the study. He was a 33 year-old Filipino male whose SGPT increased from 18 U/L to 197 U/L and his GGT increased from 83 U/L to 418 U/L. Four days after the event, he took his last dose of medication and three days later, he withdrew from the study. Upon follow-up, his SGPT level decreased to 23 U/L and GGT down to 108 U/L.

Table 40: Overall Incidence of Markedly Abnormal Blood Chemistry Parameters – Safety ITT (Studies 3103, 3107, and 3108)

Laboratory Parameters	Fluvoxamine CR N= 403	Placebo N= 400
Sodium	0/356	0/353
Potassium	1/356 (0.3%)	0/350
Chloride	0/356	0/353
Glucose	1/356 (0.3%)	1/353 (0.3%)
Urea Nitrogen (BUN)	0/356	1/353
Creatinine	0/356	0/353
GGT	5/243 (2%)	3/242 (1%)
SGOT (AST)	0/356	1/353
SGPT (ALT)	2/356 (0.6%)	0/353
Total Bilirubin	0/356	3/353(0.9%)
Alkaline Phosphatease	0/356	0/353
LDH	0/356	0/352
Albumin	0/356	0/353

Note: Percentages mentioned above are based on the total number of subjects in the Safety Population with a post-Baseline measurement collected up to 30 days after discontinuation from study medication. N represents the total number of subjects in the Safety Population with a post-Baseline measurement collected up to 30 days after discontinuation from study medication for each parameter. All markedly abnormal values occurring at a post-Baseline visit from the start of study medication up to 30 days after discontinuation from study medication are included in these summaries.

The outliers for hematology parameters were examined for each of the pivotal studies separately. There was only one significant difference between drug and placebo: In Study 3108, 4/128 subjects (3%) had outlying values for eosinophil count versus 0/136 in the placebo group (p=0.05). The sponsor did not have explanations for these changes in their study report. However, considering that all these cases were from one of the three pivotal studies and not replicated in other two, this phenomenon is probably not drug-related.

There is no consistent major difference in percentage of people with abnormal urinalysis values (PH, gravity, glucose, and protein) between the drug and placebo across the three pivotal studies.

7.1.7.4 Additional analyses and explorations

Not applicable.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The database for vital signs is also the combined data from the three pivotal studies. The sponsor initially submitted the data by study but then submit the combined data on blood tests from the three pivotal studies upon our request in the 74-day letter on October 25, 2006. However, as with the laboratory data, the sponsor did not submit the integrated data for outliers.

There is no discrepancy for planned approach and the presentation except that there were blood pressure measurement problems with subjects of Center 14 in Study 3108 that the sponsor

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Similar to the laboratory tests, the vital signs specified in the protocols of the three pivotal studies are Studies 3103, 3107, and 3108 are examined. These include sitting and standing systolic blood pressure, heart rate, and weight. Temperature was only evaluated in Study 3103.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Examination of the mean changes of the vital signs from baseline to Week 12 showed no significant changes in any of them comparing the drug group and placebo.

7.1.8.3.2 Marked outliers and dropouts for vital sign abnormalities

Table below displays the criteria for markedly abnormal changes in blood pressure, heart rate, and body weight as well as number of subjects who had these markedly abnormal values in the two treatment groups in the three pivotal studies. No significant differences in number of subjects who had markedly abnormal vital sign values are seen between the two treatment groups.

Table 41: Number of Subjects With Markedly Abnormal Changes in Vital Signs in the Three Pivotal Studies

Criteria for Markedly Abnormal Vital Signs*		Fluvoxamine CR n=403 N (%)	Placebo n=400 N (%)
Systolic Blood Pressure (mmHg)			
Sitting	≥180 mmHg and ≥20 mmHg increase	1 (<1)	1 (<1)
	≤90 mmHg and ≥20 mmHg decrease	9 (2)	12 (3)
Standing	≥180 mmHg and ≥20 mmHg increase	2 (<1)	1 (<1)
	≤90 mmHg and ≥20 mmHg decrease	12 (3)	13 (3)
Diastolic Blood Pressure (mmHg)			
Sitting	≥105 mmHg and ≥15 mmHg increase	6 (1)	3 (<1)
	≤50 mmHg and ≥15 mmHg decrease	11 (3)	9 (2)
Standing	≥105 mmHg and ≥15 mmHg increase	9 (2)	5 (1)
	≤50 mmHg and ≥15 mmHg decrease	7 (2)	3 (<1)
Heart Rate (bpm)			
Sitting	≥120 bpm and ≥15 bpm increase	0	0
	≤50 bpm and ≥15 bpm decrease	3 (<1)	3 (<1)
Standing	≥120 bpm and ≥15 bpm increase	2 (<1)	5 (1)
	≤50 bpm and ≥15 bpm decrease	1 (<1)	2 (<1)
Body Weight (kg)			
≥7% increase		18 (4)	14 (4)
≤7% increase		13 (3)	6 (2)

*Temperature is listed separately in the following paragraph.

The criterion for markedly abnormal changes in temperature is ≥101°F and 2° increase. No significant changes in temperature in subjects of Study 3103.

Both treatment groups had the similar dropout rates that due to hypertension.

7.1.8.4 Additional analyses and explorations

There are no important additional analyses or explorations.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program

The main database for ECG is also from the three pivotal studies. The sponsor initially submitted the data by study but then submit the combined data on mean changes in ECG parameters from baseline to Week 12/endpoint from the three pivotal studies upon our request in the 74-day letter on October 25, 2006. However, as with the laboratory data, the sponsor did not submit the integrated data for outliers.

The number of baseline and on-study ECG obtained from three pivotal studies are summarized in the table of markedly abnormal outliers in subsection 7.1.9.3.2 below.

According to the sponsor, there has been no new pre-clinical study of fluvoxamine CR effect on cardiovascular system.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

ECG parameters that specified in the protocols of the three pivotal studies (Studies 3103, 3107, and 3108) are examined. These include P-R interval, QRS, Q-T interval, and QTc. The analyses are focused on the mean changes from baseline to endpoint and markedly abnormal outliers.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Examination of the mean changes of the ECG parameters from baseline to Week 12 showed no significant changes in P-R interval, QRS, Q-T and QTc comparing the drug group and placebo. However, the sponsor didn't provide QTc analysis method, in protocols, study reports, or in the Integrated Safety Summary, including the integrated safety data submitted in October, 2006.

7.1.9.3.2 Marked outliers and dropouts for ECG abnormalities.

The following table pools the data from the three pivotal studies submitted to display the total numbers of subjects who had markedly abnormal ECG changes, according to the criteria set in

the protocol, in the two treatment groups after baseline. The sponsor did not specify the correction formulation of QTc in the protocols or study reports, however, it appears to be based on Bazett's. The sponsor agrees to submit this information soon.

Table 42: Overall Incidence of Markedly Abnormal Rhythm Disturbances - Safety Population - Studies 3103, 3107, and 3108

		Fluvoxamine CR N= 403	Placebo N= 400
Total Number of Subjects with Post-Baseline ECG		343	342
Criteria for Markedly Abnormal ECG Parameters	**PR > 0.21 sec**	1 (<1%)	8 (2%)
	QTc > 0.45 sec	11 (3.2%)	5 (1.3 %)
	QRS > 0.12 sec	4 (1.2 %)	1 (<1%)

Note: Percentages are based on the total number of subjects with a post-Baseline ECG evaluation.

Overall, more subjects in fluvoxamine CR group had QTc prolongation (3.2%) and increased QRS (1.2%) compared to those in placebo (1.3% and <1%, respectively). However, neither is statistically significant. Breaking down by indications, the incidence of abnormal clinically significant ECG values was higher in the SAD studies than in the OCD study.

No subjects dropped out due to ECG abnormalities in Phase 3 studies.

7.1.9.4 Additional analyses and explorations

The sponsor didn't conduct ECG categorical analysis and didn't present any Q-T interval or QTc of over 500msec or above.

7.1.10 Immunogenicity

No data seem to reflect potential of immunogenicity.

7.1.11 Human Carcinogenicity

No human carcinogenicity data is provided in this application. The sponsor reports no evidence of carcinogenicity in rat studies and no evidence of mutagenic potential in mouse micronucleus test, in-vitro chromosome aberration test or the Ames microbial mutagen test with or without metabolic activation. For more detailed information, please see the Agency Pharmacology-toxicology Review.

7.1.12 Special Safety Studies

No special safety study is available.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Premarketing clinical experience has not revealed any tendency for drug-seeking behavior. However, discontinuation effects of fluvoxamine CR capsules have not been systemically evaluated in clinical trials.

The potential for abuse, tolerance and physical dependence with fluvoxamine maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena was found.

7.1.14 Human Reproduction and Pregnancy Data

No neonate was exposed to fluvoxamine CR. Its effects on labor and delivery in humans are unknown. The teratogenic effect of this drug is classified as Pregnancy Category C.

7.1.15 Assessment of Effect on Growth

Not applicable for this NDA.

7.1.16 Overdose Experience

The only overdose case in the fluvoxamine CR trials was subject (#69187) who was in the fluvoxamine CR treatment group in Study 3103. The subject was taking 300 mg of fluvoxamine CR per day) and ingested nine PROZAC® capsules and two blister cards of study medication (fluvoxamine CR) which appears to be as much as 6000 mg of fluvoxamine CR on Day 47. The subject was treated with activated charcoal, potassium, and IV fluids. The subject was withdrawn from the study on Day 50 despite no other TESS were reported at the time of this event or subsequent to this event.

According to the sponsor, this subject's overdose of study medication was a suicide attempt. but resolved with no sequelae three days after the onset. Termination physical examinations including vital signs, as well as all laboratory values were within normal limits, except low lymphocyte percentage (13.5%).

Among the 535 overdose reports since market introduction of fluvoxamine (immediate release formula), 47 of them were fatal. Many of these (36 patients) overdosed with fluvoxamine also overdosed with other drugs. The rest were suspected to be associated with an overdose of fluvoxamine alone. However, information on the ingested dose of fluvoxamine was available in only two patients (4200 mg and 6000 mg) and postmortem plasma levels in four patients (3000 ng/ml – 6300 ng/ml). Nevertheless, there have also been reports that patients recovered completely from much higher overdoses (up to 12000 mg).
Symptoms commonly associated with fluvoxamine maleate overdose include coma, somnolence, respiratory difficulties, tachycardia, hypokalemia, hypotension, nausea, and vomiting. Other notable signs and symptoms seen are bradycardia, ECG abnormalities (such as heart arrest, QT interval prolongation, first degree atrioventricular block, bundle branch block, and junctional rhythm), convulsions, tremor, and increased reflexes, and diarrhea.

7.1.17 Postmarketing Experience

Fluvoxamine CR has not been marketed in the U.S. or elsewhere. However, the immediate-release formulation has been marketed since 1995 in the U.S. and since 1984 worldwide. For detailed information on important postmarketing reports, please refer to its labeling.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary clinical safety data source is combined data from the three placebo-controlled Phase 3 studies.

7.2.2 Study type and design/patient enumeration

A total of 132 healthy volunteers participated in Phase I studies. They were also exposed to 100mg to 300mg of fluvoxamine CR.

There was no study categorized as Phase 2 by the sponsor.

The table below summarizes all the studies and subject enumerations:

Table 43: All Studies and Subject Enumerations

Protocol No. Indication Location	Study Design	Study Start Study End Investigators Publications	Mean Age (Range) (yrs) Gender %	Treatments Dose	Batch Numbers	Randomized	Safety	ITT
Clinical Pharmacology: Bioavailability and bioequivalence								
0898001 Healthy males Vol. 36, p. 153	Open Label, Single Dose, Five Treatment, Five Period, Randomized, Crossover	06 Jul 1998 03 Sep 1998 — None	24 (19-32) male: 100%	Fluvoxamine CR 100 mg Four prototype capsule formulations LUVOX® 100 mg Subjects received a single 100 mg dose of each formulation	PD15360 PD15361 PD15362 PD15363 89184	10	10	NA
8002 Healthy males Vol. 36, p. 154	Open Label, Multiple Dose, Two Treatment, Two Period, Randomized, Crossover	10 Nov 1998 09 Dec 1998 — None	31 (21-44) male: 100%	Fluvoxamine CR 100 mg LUVOX® 100 mg Subjects received a single 100 mg dose of each formulation once daily for 10 consecutive days.	PD15538 89184	14	14	NA
S1141107 Healthy males and females Vol. 36, p. 155	Open Label, Single Dose, 3 Treatment Period, Balanced, Randomized, Crossover	13 Sep 1999 18 Dec 1999 — None	32 (20.3-44.8) male: 54% female: 46%	Fluvoxamine CR 100 mg fasting Fluvoxamine CR 100 mg fed LUVOX® 100 mg fasting	DE5252 DE5252 89814	28	28	NA

Protocol No. Indication Location	Study Design	Study Start Study End Investigators Publications	Mean Age (Range) (yrs) Gender %	Treatments Dose	Batch Numbers	Randomized	Safety	ITT
0300002 Healthy males Vol. 36, p. 156	Open Label, Single Dose, Two Period, Randomized, Crossover	24 May 2000 Stop 09 Jun 2000 — None	28 (19-45) years male: 100%	Fluvoxamine CR 100 mg capsule packaged in — bottles; — —	DE5251	24	24	NA
S1141109 Healthy Males Vol. 36, p. 157	Open label, randomized, single-dose, 2-sequence, 2-period, crossover design	24 Jul 2003 Stop Date: 08 Oct 2003 — None	25 (19-42) male: 100%	Trmt A: Fluvoxamine 100mg capsule — Trmt B: Fluvoxamine 100mg capsule —	Lot No. 0000031950 Lot No. 0000031960	36	36	36
Clinical Pharmacology:--Dose Proportionality/Pharmacokinetics								
S1141108 Healthy males Vol. 36, p. 159	Open Label, Ascending, Multiple Dose, Single Group	21 Jun 1999 06 Aug 1999 — None.	35 (21-45) male: 100%)	Fluvoxamine CR 100 mg/day Days 1-7 150 mg/day Days 8-10 200 mg/day Days 11-17 250 mg/day Days 18-20 300 mg/day Days 21-27	Combinations of: DE5315 (50 mg) and DE5252 (100 mg)	20	20	NA

Controlled Phase III Studies								
S1143107 Generalized SAD Vol. 36, p. 161	Randomized, multicenter, parallel group, flexible dose, double blind, placebo controlled	06 Jul 1999 21 Jan 2000 None	37.2 (18-68) males: 64% females: 36% 12 weeks	Fluvoxamine CR 100-300 mg Placebo	DE5314 DE5185 DE5186 DE5187 DE5057 DE5058 DE5059	Fluvoxamine CR: 139 Placebo: 140 Total: 279	Fluvoxamine CR: 131 Placebo: 126 Total: 257	Fluvoxamine CR: 121 Placebo: 126 Total: 247
S1143108 Generalized SAD Vol. 48, p. 6	Randomized, multicenter, parallel group, flexible dose, double blind, placebo controlled	10 Sep 199 10 May 2000 al. None	37.9 (18-69) males: 48% females: 52% 12 Weeks	Fluvoxamine CR 100 mg to 300 mg Placebo	DE5314 DE5185 DE5186 DE5187DE6951 DE6891DE6890 DE7004 DE7005DE7006 DE5057DE5058 DE5059	Fluvoxamine CR: 149 Placebo: 151 Total: 300	Fluvoxamine CR: 148 Placebo: 150 Total: 298	Fluvoxamine CR: 146 Placebo: 148 Total: 294
S1143103O CD Vol. 82, p. 6 Item 6, Vol. 21, p. 4 (PK substudy)	Randomized, multicenter, parallel group, flexible dose, double blind, placebo controlled	29 Apr 199 24 Feb 2000 None	37 (18-70) males: 36% females 64% 12 weeks	Fluvoxamine CR 100 mg to 300 mg Placebo	DE5314 DE5185DE5186 DE5187 DE5057 DE5058DE5059	Fluvoxamine CR: 127 Placebo: 126 Total: 253	Fluvoxamine CR: 124 Placebo: 124 Total: 248	Fluvoxamine CR: 117 Placebo: 120 Total: 237
Controlled Phase III Extension Study								
S1143109 SAD Vol. 73, p. 4	Randomized, double-blind, placebo controlled, parallel group, fixed dose extension study	08 Dec 1999 14 Jul 2000 et. al. None	37.1 20-65 Male 51% Female 49% 12 Weeks	Fluvoxamine CR 100 mg to 300 mg, Placebo	DE5314 DE5185DE5186 DE5187DE6951 DE6891 DE6890 DE5057, DE5058, DE5059, DE7004, DE7005, DE7006	Fluvoxamine CR: 57 Placebo: 55 Total: 112	Fluvoxamine CR: 57 Placebo: 55 Total: 112	Fluvoxamine CR: 56 Placebo: 53 Total: 109
Uncontrolled Phase III Extension Study								
S1143104 OCD Vol. 80, p. 4	Open label, flexible dose extension study	29 Jul 1999 29 Nov 2000 None	37.9 (18-70) Male 33% Female 67% 40 Weeks	Fluvoxamine CR 100 mg to 300 mg2	DE5314 DE5185DE5186 DE5187	156[1]	151	-

Note: Subjects in S1143104 began treatment at 100 mg/day. The dose could be titrated up to a maximum of 300 mg/day during Weeks 1 through 6 of the study in increments of 50 mg/day in intervals of at least one week (7 days ± 3 days). However, after Week 1, and through the end of Week 6, the dose could be decreased by 50 mg/day in the event of an intolerable adverse event that would otherwise cause the subject to drop out of the study

[1] Of these subjects, 73 had been in the fluvoxamine CR treatment group and 83 had been in the placebo treatment group in Study S1143103.

7.2.3 Demographics

Table 44: Baseline Demographic Information in the Generalized SAD and OCD Phase III Studies: Combined Data - Safety Population

Subjects			Fluvoxamine CR N (%)	Placebo N (%)
Total			**403**	**400**
Age	Mean [SD]		38 [0.6]	37.4 [0.5]
	Median		37	36
	Range		18,70	18-69
	group	18-64	398 (99)	392 (98)
		≥65	5 (1)	8 (2)
Gender	Male		196 (49)	202 (51)
	Female		207 (51)	198 (50)
Ethnicity	Asian, American Indian & Alaska Natives		13 (3)	12 (3)
	Black		22 (5)	20 (5)
	Caucasian		342 (85)	337 (84)
	Hispanic		14 (3)	20 (5)
	Other*		12 (3)	11 (3)

*Other includes Filipino, Haitian-American, and Pacific Islander.

7.2.4 Extent of exposure (dose/duration)

Total number of patient-exposure years for fluvoxamine CR is 157.7, and 103.6 for placebo.

The sponsor summarizes the dose/duration of all Phase 3 studies with fluvoxamine CR in Table 45 below.

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Table 45: Mean Daily Fluvoxamine CR Dose by Duration Categories for all Patients in Phase III Studies S1143103, S1143104, S1143107, S1143108, and S1143109 All Randomized Patients

	Mean Daily Fluvoxamine CR Dose			
Duration Category	<100mg n (%)	100 - 200mg n (%)	201 - 300mg n (%)	> 300mg n (%)
Total patients	488			
Number of patients within each mean daily dose category	54 (11.1%)	236 (48.4%)	197 (40.4%)	1 (0.2%)
0-4 wks	33 (6.8%)	97 (19.9%)	0	0
5-12 wks	5 (1.0%)	79 (16.2%)	98 (20.1%)	1 (0.2%)
13-26 wks	1 (0.2%)	11 (2.3%)	37 (7.6%)	0
27-52 wks	15 (3.1%)	46 (9.4%)	48 (9.8%)	0
>52 wks	0	3 (0.6%)	14 (2.9%)	0

Note: Subjects who entered core study and continued into extension study are considered as one subject in this summary table.
Note: Subjects whose treatment duration is unknown are excluded from this summary table.
Note: Percentages are based on total number of patients who took Fluvoxamine CR.
Note: Besides subjects who were randomized in Fluvoxamine CR in core studies S1143103, S1143107, and S1143108, subjects who were randomized in placebo treatment group in study S1143103 but treated with Fluvoxamine CR in extension study S1143104 are included in this summary table.

7.2.5 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.5.1 Other studies

No secondary clinical data source used for this NDA.

7.2.5.2 Postmarketing experience

There is no postmarketing experience with fluvoxamine CR.

7.2.5.3 Literature

The sponsor states that at the time of the original submission of this application, there was no published literature on fluvoxamine CR.

Dr. Dubitsky helped conduct a literature search using PubMed on 1-13-07 using the search term "fluvoxamine controlled release." This search revealed a total of nine published articles. I then reviewed the abstracts for all nine articles.

Three of these articles appear to describe the three key efficacy studies contained in this application:

1) Hollander E, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. J Clin Psychiatry 2003;64(6):640-7. (Study 3103)

2) Davidson J, et al. Fluvoxamine controlled release formulation for the treatment of generalized social anxiety disorder. J Clin Psychopharmacol 2004;24(2):118-25. (Study 3107)

3) Westenberg HG, et al. A double-blind placebo-controlled study of controlled release fluvoxamine for the treatment of generalized social anxiety disorder. J Clin Psychopharmacol 2004;24(1):49-55. (Study 3108)

The safety findings of these published trials are expected to be contained in the safety database for this application.

Among the remaining six articles, only one described a clinically significant safety finding:

Sperber AD. Toxic interaction between fluvoxamine and sustained release theophylline in an 11-year-old boy. Drug Saf 1991;6(6):460-2.

The interaction between fluvoxamine and theophylline is well-known and is discussed under the WARNINGS section of labeling for fluvoxamine immediate-release. Likewise, it is contained in the proposed labeling for Luvox CR.

Thus, there are no known safety findings described in the literature which would preclude approval of this application or merit addition to Luvox CR labeling.

7.2.6 Adequacy of Overall Clinical Experience

A total of 778 patients were included in all Phase 3 (Studies 3103, 3107, and 3108) and their extension studies (Studies 3104 and 3109). Of note, subjects from both extension studies were also subjects from Studies 3103 and 3108, respectively. (See table in section 7.2.1.1 for details.)

Only 15 subjects were exposed to fluvoxamine CR for a year. The table in section 7.2.1.3 shows more detailed information on dose exposure.

Thus, the exposure to the study drug is not adequate according to ICH guideline. However, because the immediate-release formulation of this drug has been used on the market worldwide

since 1995, this extensive exposure to the fluvoxamine maleate should be taken into consideration, albeit a different formulation.

7.2.7 Adequacy of Special Animal and/or In Vitro Testing

There was only one animal study to examine the potential for fluvoxamine CR to cause gastric irritation. From a clinical perspective, this study appears to be adequate.

7.2.8 Adequacy of Routine Clinical Testing

Overall, the routine clinical testing in clinical trials was adequate in my opinion.

7.2.9 Adequacy of Metabolic, Clearance, and Interaction Workup

Information pertaining to the metabolism, clearance, and potential for interactions is contained in the labeling for the immediate-release formulation. There was no further information relevant to these areas contained in this application.

7.2.10 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The safety evaluations performed in these studies appear to be adequate to detect and evaluate adverse events associated with the clinical use of fluvoxamine CR given the extensive clinical trial and postmarketing experience with the immediate-release formulation.

7.2.11 Assessment of Quality and Completeness of Data

The most important deficiencies are discrepancies among the submitted CRFs, narrative summaries, and AE line listing. This creates problems in accuracy and reliability of common adverse events. Furthermore, the demographic analysis of common AEs is also problematic. (See 7.1.5.6.)

Below are the results of AE coding audit and examples of CRF audits.

ADVERSE EVENT CODING AUDIT (12-30-06)

Based on the "ae_idb.xpt" CRT file in the 4-28-06 submission to NDA 22-033.

The following coding irregularities were noted:

1) the investigator term "quinsy" was coded to the preferred term "nausea" for one patient. The preferred term "infection" would be more appropriate since quinsy is a peritonsillar abscess.

2) the investigator term "sexual dysfunction" was coded to the preferred term "libido decreased" for nine patients. It is not clear that these events were actually decreased libido since sexual dysfunction could represent a number of other events, such as impotence or premature ejaculation.

3) the investigator term "gastrointestinal virus" was coded to the preferred term "gastrointestinal disorder" for one patient. The preferred term "infection" would be more appropriate. Note: The investigator term "stomach virus" was coded to "infection" elsewhere.

4) the investigator term "reflux" was coded to the preferred term "gastrointestinal disorder" for one patient. The preferred term "dyspepsia" may be more appropriate.

Examples of CRF Audits

Table 46: The First CRF Audit (5% of 169 CRF's = 9)

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, **drugged feeling.**	OK	OK
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 47: The Second CRF Audit (5% of 169 CRF's = 9)

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
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.

7.2.12 Additional Submissions, Including Safety Update

As discussed above, the data in the sponsor's submission on October 25, 2006 in responding to our 74-day letter were integrated to the review. There has been no submission for Safety Update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

As mentioned above, there are discrepancies among CRFs, narrative summaries, and the line listing of AEs in JMP files. These need to be reanalyzed and corrected before common adverse event rates can be correctly concluded. In addition, the demographic analysis of common adverse events is not properly conducted. Further more, the sponsor needs to provide QTc analysis method to make the data interpretable.

Finally, the sponsor has no study data to support tolerability with increasing 100mg of fluvoxamine CR at a time.

The sponsor needs to complete these tasks before this NDA can be approved.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

All three Phase 3 short term, placebo-controlled pivotal studies were reviewed individually for evidence of efficacies in both indications. However, these three studies were combined to give pooled data for review of common adverse events, laboratory changes, and changes in ECG. Additionally, all six Phase 1 studies and two Phase 3 extension studies were reviewed together with the above mentioned three pivotal studies for deaths, serious adverse events, and dropouts due to adverse events.

7.4.1.2 Combining data

Due to similar study designs and because the two indications belong to the same disease category, Anxiety Disorders, data from Studies 3103, 3107, and 3108 were combined for review of common adverse events and changes in laboratory values and ECG. Studies of all phases were reviewed for deaths, SAEs, and dropouts due to AEs. (Also see above subsection 7.4.1.1.)

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Since the studies are flexible dose studies, dose dependency for adverse findings cannot be explored.

7.4.2.2 Explorations for time dependency for adverse findings

The only time dependency for adverse findings explored is dropouts due to AEs. They mostly happened during the first four weeks.

7.4.2.3 Explorations for drug-demographic interactions

The exploration for drug-demographic interactions conducted by the sponsor is not proper. The sponsor will need to perform reanalysis for this. (See 7.1.5.6.)

7.4.2.4 Explorations for drug-disease interactions

There were no explorations for drug-disease interactions. No study regarding subjects with any organ disease or failure is presented.

7.4.2.5 Explorations for drug-drug interactions

There is no study for drug-drug interaction in the submission and no evidence of drug-drug interactions from the cases in pivotal studies.

7.4.3 Causality Determination

Adverse events of 5% or more and twice of the incidence of placebo group are considered drug-related.

8 Additional Clinical Issues

8.1 Dosing Regimen and Administration

The dosing regimen is acceptable. Since the three pivotal studies are all flexible dose studies, there is no dose-response relationship that can be determined.

In the pivotal trials, the dose increments made were 50mg weekly. Dose titration for fluvoxamine maleate immediate-release is also 50mg each time. However, according to the Agency Chemistry Review Team, the sponsor [redacted] Thus, titration schedule will be somewhat complicated for patients to switch between the capsules of two doses, 100mg and 150mg.

8.2 Drug-Drug Interactions

As mentioned above, 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.

8.3 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.

8.4 Pediatrics

The sponsor seeks full waiver in pediatric group age less than – year-old due to infrequent diagnosis of SAD and OCD in this population.

The sponsor also seeks deferral for pediatric population ag to 17 year-old due to

8.5 Advisory Committee Meeting

None.

8.6 Literature Review

No literature articles were referenced in this review.

8.7 Postmarketing Risk Management Plan

Based on the extensive clinical experience with fluvoxamine maleate immediate-release formulation and the clinical trial data with fluvoxamine CR, there is no risk management plan needed at this point.

8.8 Other Relevant Materials

None.

9 Overall Assessment

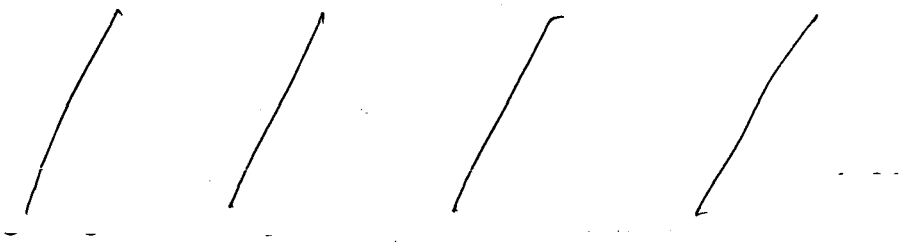
9.1 Conclusions

The above review of the efficacy and safety data supports the sponsor's claimed indications.

9.2 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. This is based on the above review of the efficacy and safety data supporting the sponsor's claimed indications.

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

- 

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

- Finally, 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.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

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

9.3.2 Required Phase 4 Commitments

Though studies in pediatrics (age ~ 17 years old) were allowed to postpone upon the sponsor's request, it is still important that the sponsor will conduct these studies as Phase 4 commitments.

9.3.3 Other Phase 4 Requests

Considering both SAD and OCD are chronic illnesses, it is important to study long term efficacy for treatment of these disorders.

9.4 Labeling Review

Changes need to be made in almost all sections of the labeling, except the "Black Box Warning" and "Indications and Usage." Please see Line-by-Line Labeling Review in Appendix 10.3 for details.

9.5 Comments to Applicant

Thank you for the submission. I sincerely hope that the quality of data presentation will be improved in the future.

10 Appendices

10.1 Review of Individual Study Reports

10.1.1 Study 3103

Since this study is the only study for indication OCD, this study is reviewed in Section 6.1.1 in detail.

Below is the list of investigators and study centers for this study.

Table 48: Investigators and Study Centers of Study 3103

Center	Investigator Name	Investigator Address	Patients
			23
			16
			12
			7
			13
			5

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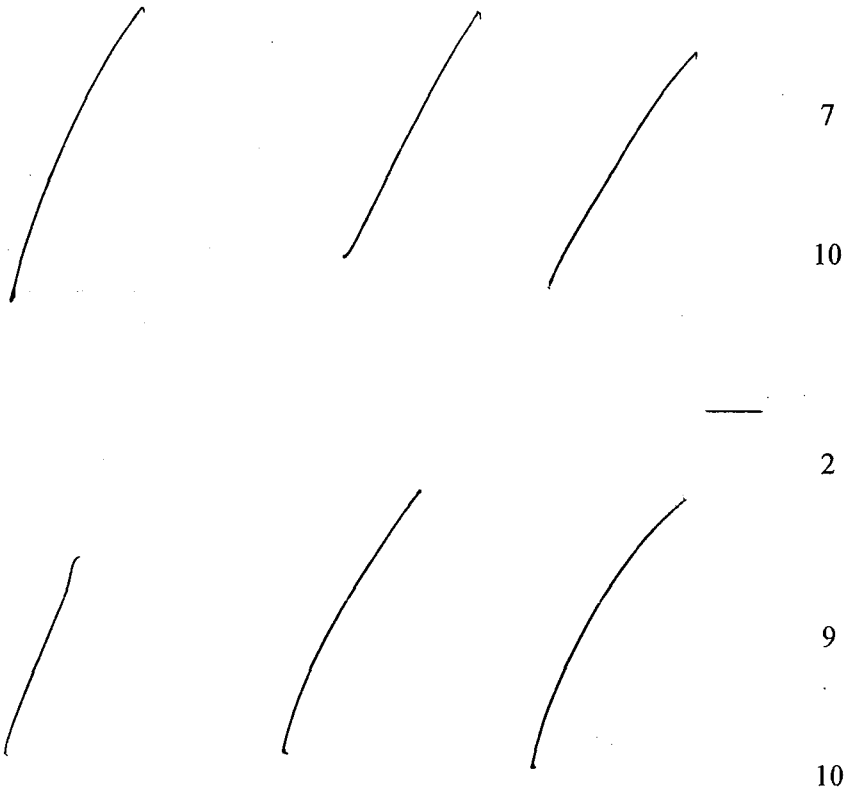

10.2 Tables of Less Common Adverse Events

10.2.1. Tables for Adverse Events of At Least 1% in Fluvoxamine CR Group

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Table 51: Overall Incidence of Treatment-Emergent Adverse Events Occurring In ≥1% of the Subjects in the Fluvoxamine CR Treatment Group and Are More Than Those in Placebo Group - Safety Population - Studies S1143107, S1143108, and S1143103

	Fluvoxamine CR	Placebo
Total Number of Subjects in the Safety Population	403	400
Total Number of Male Subjects in the Safety Population	196 (49%)	202(51%)
Total Number of Female Subjects in the Safety Population	207 (51%)	198(50%)
Preferred Terms which Occurred in At Least 1% of Subjects in the Fluvoxamine CR Treatment Group[1]:		
Body as a Whole		
Accidental Injury	11 (3%)	10 (3%)
Asthenia	98 (24%)	37 (9%)
Headache	139 (34%)	120 (30%)
Cardiovascular System		
Migraine	5 (1%)	3 (<1%)
Palpitation	9 (2%)	6 (2%)
Tachycardia	6 (1%)	4 (1%)
Digestive System		
Anorexia	56 (14%)	10 (3%)
Constipation	22 (5%)	14 (4%)
Diarrhea	60 (15%)	25 (6%)
Dyspepsia	36 (9%)	17 (4%)
Liver Function Tests Abnormal	5 (1%)	1 (<1%)
Nausea	151 (37%)	45 (11%)
Tooth Disorder	7 (2%)	5 (1%)
Vomiting	17 (4%)	9 (2%)
Hemic and Lymphatic System		
Ecchymosis	5 (1%)	2 (<1%)
Nervous System		
Abnormal Dreams	15 (4%)	13 (3%)
Agitation	11 (3%)	3 (<1%)
Anxiety	31 (8%)	16 (4%)
Apathy	8 (2%)	0
Dizziness	57 (14%)	30 (8%)
Dry Mouth	44 (11%)	34 (9%)
Hypertension	6 (1%)	4 (1%)
Hypertonia	10 (2%)	4 (1%)
Insomnia	132 (33%)	62 (16%)
Libido Decreased	33 (8%)	17 (4%)
Nervousness	37 (9%)	30 (8%)
Paresthesia	10 (2%)	6 (2%)
Somnolence	106 (26%)	38 (10%)
Thinking Abnormal	13 (3%)	6 (2%)

Tremor	29 (7%)	2 (<1%)
Twitching	5 (1%)	0
Vasodilatation	5 (1%)	3 (<1%)
Respiratory System		
Bronchitis	7 (2%)	6 (2%)
Laryngitis	5 (1%)	1 (<1%)
Pharyngitis	18 (4%)	11 (3%)
Yawn	15 (4%)	2 (<1%)
Skin and Appendages		
Sweating	25 (6%)	7 (2%)
Special Senses		
Taste Perversion	8 (2%)	2 (<1%)
Urogenital System		
Abnormal Ejaculation	20 (10%)	4 (2%)
Anorgasmia	19 (5%)	3 (<1%)
Menorrhagia	3 (1%)	1 (<1%)

Note: Percentages for "Abnormal Ejaculation" and "Impotence" are based on the total number of male subjects in the Safety Population. Percentages for "Dysmenorrhea" and "Menorrhagia" are based on the total number of female subjects in the Safety Population. Percentages for all other adverse events are based on the total number of subjects in the Safety Population.
Note: Each subject is counted at most once within each body system and preferred term. Adverse events were coded to body system and preferred term using the COSTART dictionary.
Note: Treatment-emergent adverse events include all adverse events reported after start of study medication and through a subject's study discontinuation visit and all serious adverse events reported after start of study medication or spontaneously reported within 30 days after the permanent discontinuation visit.

10.2.2. Table for Adverse Events of Less Than 1% in Fluvoxamine CR Group

The table below summarizes overall incidence of adverse events which occurred in at most 1% of the subjects in the fluvoxamine CR treatment group and are more than those in placebo group.

Table 52: Overall Incidence of Treatment-Emergent Adverse Events Occurring In <1% of the Subjects in the Fluvoxamine CR Treatment Group and Are More Than Those in Placebo Group - Safety Population - Studies S1143107, S1143108, and S1143103

	Fluvoxamine CR	Placebo
Total Number of Subjects in the Safety Population	403	400
Total Number of Male Subjects in the Safety Population	196 (49%)	202 (1%)
Total Number of Female Subjects in the Safety Population	207 (51%)	198 (0%)
Preferred Terms which Occurred in Less Than 1% of Subjects in the Fluvoxamine CR Treatment Group		
Body as a Whole		
Chills	4 (<1%)	2 (<1%)
Hernia	1 (<1%)	0

Intentional Injury	1 (<1%)	0
Lab Test Abnormal	1 (<1%)	0
Malaise	2 (<1%)	0
Photosensitivity Reaction	1 (<1%)	0
Suicide Attempt	1 (<1%)	0
Unexpected Benefit	1 (<1%)	0
Cardiovascular System		
Cardiovascular Disorder	1 (<1%)	0
Heart Failure	1 (<1%)	0
Syncope	1 (<1%)	0
Digestive System		
Dysphagia	2 (<1%)	1 (<1%)
Eructation	2 (<1%)	0
Gastritis	2 (<1%)	1 (<1%)
Gastrointestinal Disorder	4 (<1%)	2 (<1%)
Gingivitis	2 (<1%)	0
Increased Salivation	2 (<1%)	0
Tongue Disorder	1 (<1%)	0
Tongue Edema	1 (<1%)	0
Tooth Caries	1 (<1%)	0
Ulcerative Stomatitis	2 (<1%)	0
Metabolic and Nutritional Disorders		
Dehydration	1 (<1%)	0
Glycosuria	1 (<1%)	0
Hyperglycemia	1 (<1%)	0
Hypoglycemia	1 (<1%)	0
Peripheral Edema	2 (<1%)	1 (<1%)
Musculoskeletal System		
Joint Disorder	1 (<1%)	0
Leg Cramps	1 (<1%)	0
Myasthenia	2 (<1%)	1 (<1%)
Nervous System		
Ataxia	1 (<1%)	0
CNS Stimulation	1 (<1%)	0
Confusion	1 (<1%)	0
Emotional Lability	2 (<1%)	1 (<1%)
Euphoria	2 (<1%)	0
Hallucinations	1 (<1%)	0
Hyperkinesia	2 (<1%)	0
Incoordination	2 (<1%)	0
Manic Reaction	1 (<1%)	0
Myoclonus	1 (<1%)	0
Neuralgia	2 (<1%)	0
Sleep Disorder	1 (<1%)	0
Speech Disorder	1 (<1%)	0

Respiratory System		
Epistaxis	3 (<1%)	1 (<1%)
Skin and Appendages		
Alopecia	1 (<1%)	0
Eczema	2 (<1%)	0
Herpes Simplex	2 (<1%)	1 (<1%)
Pustular Rash	1 (<1%)	0
Skin Carcinoma	1 (<1%)	0
Urticaria	2 (<1%)	0
Special Senses		
Abnormality of Accommodation	1 (<1%)	0
Amblyopia	3 (<1%)	2 (<1%)
Cataract NOS	1 (<1%)	0
Conjunctivitis	2 (<1%)	1 (<1%)
Corneal Lesion	1 (<1%)	0
Deafness	2 (<1%)	0
Dry Eyes	1 (<1%)	0
Ear Disorder	2 (<1%)	1 (<1%)
Ear Pain	3 (<1%)	2 (<1%)
Eye Disorder	2 (<1%)	0
Eye Hemorrhage	2 (<1%)	0
Hyperacusis	1 (<1%)	0
Mydriasis	1 (<1%)	0
Taste Loss	3 (<1%)	0
Urogenital System		
Breast Pain	2 (<1%)	0
Dysuria	3 (<1%)	1 (<1%)
Urethritis	1 (<1%)	0
Urinary Frequency	3 (<1%)	0
Urinary Incontinence	1 (<1%)	0
Urinary Retention	1 (<1%)	0
Urinary Urgency	1 (<1%)	0

Note: Percentages for all other adverse events are based on the total number of subjects in the Safety population.
Note: Each subject is counted at most once within each body system and preferred term. Adverse events were coded to body system and preferred term using the COSTART dictionary.
Note: Treatment-emergent adverse events include all adverse events reported after start of study medication and through a subject's study discontinuation visit and all serious adverse events reported after start of study medication or spontaneously reported within 30 days after the permanent discontinuation visit.

10.3 Line-by-Line Labeling Review

The following review of labeling focuses on clinical aspects:

A. Black Box Warning

9 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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
1/22/2007 03:56:57 PM
MEDICAL OFFICER

Mitchell Mathis
2/20/2007 11:39:55 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-033

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-033
Drug Name:	Luvox® (Fluvoxamine CR)
Indication(s):	Obsessive Compulsive Disorder and Generalized Social Anxiety Disorder
Applicant:	Solvay Pharmaceuticals, Inc.
Date(s):	May 1, 2006
Review Priority:	Standard
Biometrics Division:	Biometrics I (HFD-710)
Statistical Reviewer:	Fanhui Kong
Concurring Reviewers:	Peiling Yang, H.M. James Hung
Medical Division:	Division of Psychiatry Products
Clinical Team:	June Cai, Mitchell Mathis, Thomas Laughrem
Project Manager:	Gujral Renmeet

Keywords: Luvox® CR, OCD, Generalized SAD, Ranked ANOVA, LOCF, MMRM

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

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

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

1.2 Brief Overview of Clinical Studies

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

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

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

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

1.3 Statistical Issues and Findings

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

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

2. INTRODUCTION

2.1 Overview

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

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

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

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

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

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

2.2 Data Sources

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

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

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

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

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

3.1.1 Dispositions

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

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

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

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

3.1.2 Demographic Characteristics

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

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

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

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

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

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

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

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

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

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

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3.1.3 Patient Discontinuation

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

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

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

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

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

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

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

3.1.4 Baseline Disease Characteristics

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

3.1.5 Statistical Issues

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

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

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

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

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

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

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

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

Source: Reviewer.

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

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

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

Source: Reviewer.

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

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

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

Source: Reviewer.

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

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

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

Source: Reviewer.

3.1.6 Statistical Results

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

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

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

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

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

3.2 Evaluation of Safety

See medical review for detail.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

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

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

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

Source: FDA analysis.

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

4.2 Other Special/Subgroup Populations

Not available.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

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

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

5.2 Conclusions and Recommendations

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

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

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/s/

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Peiling Yang
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James Hung
1/22/2007 04:42:11 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-033

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-033 SUPPL # HFD # HFD-130

Trade Name Luvox CR

Generic Name fluvoxamine maleate

Applicant Name Solvay

Approval Date, If Known February 28, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505b1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-243 Luvox (fluvoxamine maleate) Immediate Release Tablets; AP Date 9-3-03; WD by Solvay due to AIP violations

NDA# 21-519 Luvox (fluvoxamine maleate) Immediate Release Tablets; AP Date 12-20-07; Sponsor relied on data from NDA 20-243 to support approval

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Social Anxiety Disorder (SAD): Trial 3107 & Trial 3108
Obsessive Compulsive Disorder (OCD): Trial 3103

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Social Anxiety Disorder (SAD): Trial 3107 & Trial 3108
Obsessive Compulsive Disorder (OCD): Trial 3103

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 57,838	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 57,838	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!

YES ☐	! NO ☐
Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Renmeet Grewal, Pharm.D.
Title: Senior Regulatory Project Manager
Date: 2/28/08

Name of Office/Division Director signing form: OND/ODE1/DPP, Mitchell Mathis, M.D.
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Mitchell Mathis
2/29/2008 04:36:00 PM
For Dr. Laughren

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-033 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: December 31, 2007 **PDUFA Goal Date:** February 29, 2008

HFD 130 **Trade and generic names/dosage form:** Luvox CR (fluvoxamine maleate) extended release capsules)

Applicant: Solvay Pharmaceuticals **Therapeutic Class:** Anti Anxiety

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

X Yes. Please proceed to the next question.

☐ No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** _____

Each indication covered by current application under review must have pediatric studies: ***Completed, Deferred, and/or Waived.***

Number of indications for this application(s): _____

Indication #1: Generalized Social Anxiety Disorder

Is this an orphan indication?

☐ Yes. PREA does not apply. Skip to signature block.

X No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

X No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- **☐ Products in this class for this indication have been studied/labeled for pediatric population**
- **☐ Disease/condition does not exist in children**
- **☐ Too few children with disease to study**
- **☐ There are safety concerns**
- **☐ Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr.__0___ Tanner Stage_____
Max_____ kg_____ mo._____ yr.____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- X **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__17___ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): __3 years from the date of approval_____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Renmeet Grewal
2/29/2008 04:00:24 PM

For Internal Use Only

Meeting Cancellation Form

(Use this form to cancel a meeting that was granted and scheduled after which time the sponsor or FDA has subsequently cancelled.)

Please remember to update the Meeting Status field in IMTS for this cancellation.

Complete the information below and check form into DFS.

Application Type	NDA
Application Number	22-033
DATE Meeting Cancelled (per communication with requester)	Tuesday, January 22, 2008
Scheduled Meeting Date	Thursday, January 24, 2008
Reason for Cancellation	The agency let the sponsor know the 6 hour time point for the dissolution specs could be dropped. Therefore the meeting was no longer needed.
Project Manager	Renmeet Grewal, Pharm.D.

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/s/

Renmeet Grewal
1/31/2008 03:05:27 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-033

Solvay Pharmaceuticals, Inc.
Attention: Michael F. Hare
Manager, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Hare:

We acknowledge receipt of your resubmission dated December 28, 2007, received December 31, 2007 to your new drug application for Fluvoxamine maleate extended release tablets.

We consider this a complete, class 1 response to our December action letter. Therefore, the user fee goal date is February 29, 2008.

If you have any question, call Renmeet Grewal, Pharm.D., Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Renmeet Grewal, Pharm.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Renmeet Grewal
1/31/2008 11:57:32 AM

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Monday, December 10, 2007 2:19 PM
To: 'Hare, Michael'
Cc: Grewal, Renmeet
Subject: NDA 22-033 dissolution specification

Importance: High

Hi Michael,
Please respond to my email stating you agree to the following specifications regarding NDA 22-033 Luvox CR (fluvoxamine) Capsules which are the same specifications relayed to you 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:	

Please respond to this email by COB today.

Thank you,
Rimmy

Renmeet Grewal, Pharm.D., LCDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

Renmeet Grewal
12/10/2007 02:33:01 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-033

INFORMATION REQUEST LETTER

Solvay Pharmaceuticals, Inc.
Attention: Michael F. Hare
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Hare:

Please refer to your June 21, 2007, correspondence to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox CR(fluvoxamine maleate) extended release capsules.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response as soon as possible in order to continue our evaluation of your NDA:

1. Based on the particle size distribution data for the drug substance lots which you listed in Attachment 20 of the 21 JUN 2007 submission, we recommend the following acceptance criteria for the drug substance particle size distribution specification:

   

   These ranges bracket the proven acceptable ranges and are within the 99% confidence interval described in the Application.

2. Revise the drug product label as below so that the dosage form designation (extended release capsules) follows 'fluvoxamine maleate' in the carton labels. For example:

LuvoxCR (fluvoxamine maleate) extended release capsules	Or	Luvox CR (Fluvoxamine maleate) extended release capsules

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
11/21/2007 11:07:29 AM

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Friday, November 16, 2007 9:47 AM
To: 'Hare, Michael'
Cc: Bender, William
Subject: NDA 21-519 and NDA 22-033; request for final reports for PT studies

Good Morning Michael,

In your response to our Approvable Letters for NDA 21-519 and NDA 22-033, you submitted audited draft reports for 4 nonclinical studies to be used to support qualification of impurities/degradants in your drug substance and/or drug products (your submissions: NDA 21-519, N-000, AZ, letter-dated 6/20/07; and NDA 22-033, N-000, AZ, letter-dated 6/21/07).

We cannot complete our reviews of those submissions without consulting the final study reports. If you have already provided these final reports, please let us know where and when they were submitted; otherwise you must submit them immediately. You are reminded that you should also provide a list of all differences between the audited draft and final versions.

Sincerely,
Rimmy

Renmeet Grewal, Pharm.D., LCDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

Renmeet Grewal
11/16/2007 01:31:34 PM
CSO

Grewal, Renmeet

From: Grewal, Renmeet
Sent: Wednesday, October 24, 2007 11:57 AM
To: 'Hare, Michael'
Subject: NDA 22-033

Dear Michael,

We have identified the following discrepancies between the adverse reactions reported in the CRFs, the JMP AE listing and the narratives as presented in the table below.

1. Please reconcile the differences in reported AEs between the 3 types of documentation, and for each patient, provide explanations for the discrepancies observed between what has been reported in CRFs, the JMP AE lists and the narratives included in this application.

2. Please review the remaining CRFs, narratives and AE lists related to identify any additional inconsistencies that are clinically meaningful.

3. Please provide a general explanation for the disparities that we have discovered in the audit of your application, as the accuracy of the safety data is of the utmost concern to us as the review process is being completed.

As you alluded to in your voicemail left today, it is in your best interest to provide the data required as expeditiously as possible to finalize the review of your application. Please send us a complete response to these questions by Wednesday, 31 October 2007.

Patient ID	Case Report Form AE's	Narrative Summary	JMP AE Listing
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**
00020	LOOSE STOOL, PRESSURE TO BOTH EARS, **HIGH BLOOD PRESSURE**, HEADACHE, CHEST PAINS	Ok	?
3109-84-70161	Sore throat, **tonsillectomy**, headache.	OK	**Added still there**
3103-20-69015	Diarrhea, nausea, nightmares, pain (right flank), **suicidal ideation w/plan.**	**Entirely different AE's: dizziness, syncope**	**Same listing 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 still there**
3104-19-69034	**Weight gain, increased anxiety.**	**Submitted OK**	**Added sore throat**
3109-29-70074	**Fatigue**, weariness.	OK	**Added:** Tachycardia, dry mouth, rash.

Renmeet Grewal, Pharm.D., LCDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 796-1080
Email: renmeet.grewal@fda.hhs.gov
Fax: (301) 796-9838

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/s/

Renmeet Grewal
10/24/2007 05:12:45 PM
CSO

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 10, 2007

TO: Renmeet Grewal, Pharm.D., Regulatory Project Manager
June Cai, M.D., Clinical Reviewer
Division of Psychiatry Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Sherbet Samuels, R.N., M.P.H.

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-033

APPLICANT: Solvay Pharmaceuticals, Inc.

DRUG: Luvox (Fluvoxamine) CR capsules

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Obsessive Compulsive Disorder and Generalized Social Anxiety Disorder.

CONSULTATION REQUEST DATE: September 11, 2006

DIVISION ACTION GOAL DATE: January 11, 2007

PDUFA DATE: March 1, 2007

I. BACKGROUND:

Luvox (Fluvoxamine) is currently marketed for the treatment of Obsessive Compulsive Disorder and Depression. The sponsor, Solvay Pharmaceuticals, Inc. submitted a New Drug Application (NDA # 22-033) for the use of Luvox (Fluvoxamine) in the treatment of Obsessive Compulsive Disorder and Generalized Social Anxiety Disorder.

Drs. Mohammed Bari, Robert Dupont, Jon Heiser, and Peter Londborg sites were selected for inspection due to large enrollment. The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, validity of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. Protocol S1143103 entitled "A Multicenter, Double-Blind, Randomized, Parallel Group Study of the Efficacy and Safety of a Flexible Dose Regimen of Fluvoxamine CR versus Placebo in Outpatients with Obsessive Compulsive Disorder" and protocols S1143107 and S1143108 both entitled "A Twelve-Week, Randomized, Double-blind, Placebo Controlled, Flexible Dose Study of Fluvoxamine CR in the Treatment of Generalized Social Anxiety Disorder" were inspected. Dr. Dupont's conduct of protocol S1143107 was inspected in 2001 in support of NDA 21-309 submitted by the applicant, which was later withdrawn.

Summary Report of U.S. Inspections

II. RESULTS (by protocol/site):

Name of CI and site #	City, State	Protocol	Insp. Date	EIR Received Date	Final Classification
Mohammed Bari, M.D./1	National City, CA	S1143103	Nov.7-16, 2006	Nov. 30, 2006	VAI
Robert Dupont, M.D./8	Rockville, MD	S1143107	May 1-7, 2001	May 25, 2001	VAI
Jon Heiser, M.D./13	New Port Beach, CA	S1143107	Nov. 16-21, 2006	EIR Pending	EIR Pending
Robert Dupont, M.D./92	Rockville, MD	S1143108	Nov. 30-Dec. 5, 2006	EIR Pending	EIR Pending
Jon Heiser, M.D./94	New Port Beach, CA	S1143108	Nov. 16-21, 2006	EIR Pending	EIR Pending
Peter Londborg, M.D./95	Seattle, WA	S1143108	Nov. 15-Dec. 4, 2006	EIR Pending	EIR Pending

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. Data unreliable.

A. Protocol # S1143103

1. Mohammed Bari, M.D. (Site Number 1)
Synergy Clinical Research Center
11908 Sweetwater Road,
National City, CA 91950

a. What was inspected: Dr. Bari enrolled 23 subjects. The inspection encompassed an audit of 15 subjects' records. Primary endpoint efficacy data were verified for 15 subjects.

b. Limitations of inspection: Our investigator was unable to copy requested electronic case report forms (e-CRFs) because the dedicated computer used to retrieve the e-CRFs did not allow printing.

c. General observations/commentary: The inspection found inadequate and inaccurate case histories. Specifically:

1. For Subject 69058, the source dosing compliance and accountability record for Day 85, return date 9/16/99, indicates that two capsules were lost with four remaining. However, the e-CRF indicates that six capsules remain with none lost.

2. For Subject 69059, a note to file, dated 8/17/99, indicates that the patient did not return the blister card at the Day 22 visit on 8/17/99 and would return the card on 8/24/99. However, the source dosing compliance/accountability record and e-CRF list 8/17/99 as the date of return.

3. For Subject 69141, the source dosing compliance and accountability record for Day 29, return date 9/24/99, indicates that two capsules were lost. However, the e-CRF accountability record indicates that none were lost while an e-CRF comment section states that two capsules were lost.

4. For Subject #69170:

i. The source dosing compliance and accountability record for Day 8, return date 10/5/99, indicates that one capsule was lost with five remaining and a photocopy of the associated blister card indicates that five remain. However, a note to file and the e-CRF indicates that six remain with none lost.

ii. The source accountability record for Day 15, return date 10/12/99, indicates that one capsule was lost with five remaining and a photocopy of the associated blister card indicates that five remain. However, the e-CRF indicates that six remain with none lost.

d. Data from this site are acceptable.

B. Protocol # S1143107

1. Robert Dupont, M.D. (Site Number 8)
   Institute for Behavior & Health, Inc.
   6191 Executive Boulevard
   Rockville, MD 20852

Observations noted below for this clinical investigator are based on the inspection conducted in May 2001 in support of [redacted].

a. What was inspected: Dr. Dupont enrolled 33 subjects. The inspection encompassed an audit of 28 subjects' records. Primary endpoint efficacy data were verified for 28 subjects.

b. Limitations of inspection: none

c. General observations/commentary: The inspection found that a subject was terminated due to an adverse event, but there was no documentation to indicate that the subject was followed up as required by the protocol. The inspection also found that there was no documentation for 5 out of 431 study kits that were returned to the sponsor.

d. Data from this site are acceptable.

2. Jon Heiser, M.D. (Site Number 13)
   Pharmacology Research Institute
   1000 Dove Street, Suite 200
   Newport Beach, CA 92660-2814

Observations noted below for this clinical investigator are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. What was inspected: Dr. Heiser enrolled 23 subjects. The inspection encompassed an audit of 12 subjects' records. Primary endpoint efficacy data were verified for 12 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No significant deviations from FDA regulations were observed.

d. Data from this site are acceptable.

C. Protocol S1143108

Observations noted below for all three clinical investigators are based on communications from field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

1. Robert Dupont, M.D. (Site Number 92)
   Institute for Behavior & Health, Inc.
   6191 Executive Boulevard
   Rockville, MD 20852

a. What was inspected: Dr. Dupont enrolled 10 subjects. The inspection encompassed an audit of 8 subjects' records. Primary endpoint efficacy data were verified for 10 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No significant deviations from FDA regulations were observed. However, it was noted that for subject 70240, an adverse event description at Week 10, reads "stopped breathing, while dreaming, woke self up". The clinical investigator noted it probably meant sleep apnea. This adverse event was not noted in the data line listings. In addition, for subject 70290, an adverse event description at the Final Visit noted "side pain" off and on for 3 days. The data line listing did not note any description related to "side pain".

d. Data from this site are acceptable.

2. Jon Heiser, M.D. (Site Number 94)
   Pharmacology Research Institute
   1000 Dove Street, Suite 200
   Newport Beach, CA 92660-2814

a. What was inspected: Dr. Heiser enrolled 11 subjects. The inspection encompassed an audit of 9 subjects' records. Primary endpoint efficacy data were verified for 9 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No significant deviations from FDA regulations were observed. Data listings provided by the sponsor for subject 69831, Liebowitz Social Anxiety Scale (LSAS), dated 10/28/99, did not match the CRF.

d. Data from this site are acceptable.

3. Peter Londborg, M.D. (Site Number 95)
   Seattle Research Center
   901 Boren Avenue, Suite 1800
   Seattle, WA 98104

a. What was inspected: Dr. Londborg enrolled 10 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for 10 subjects.

b. Limitations of inspection: none

c. General observations/commentary: The inspection found inaccurate record keeping. Specifically:

CGI global improvement for subject #70304 at visit 4 (2/3/00) is documented as "4" in the source documents. However, it is reported as "5" (minimally worse) in the CRF and data listings.

CGI Severity for subject #70304 at visit 4 (2/3/00) is documented as "5" in the source documents. However it was reported as "4" (moderately ill) in the CRF and data listings.

An adverse event with start date of 2/10/00 for subject 70363 was reported as "decreased appetite" in the source documents, but the CRF noted the adverse event as "increased appetite".

d. Data from this site are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As noted above, inspection of Drs. Bari and Londborg found inadequate and inaccurate record keeping. The inspection of Dr. Dupont's site for protocol S1143107 found failure to adhere to protocol and failure to maintain adequate records of the disposition of the drug. The inspection of Drs. Dupont (protocol S1143108) and Heiser revealed that these investigators appear to have conducted the studies noted in accordance with FDA regulations. Data from these four clinical investigators are acceptable in support of NDA 22-033.

As previously mentioned, observations noted above regarding Drs. Dupont (protocol S1143108), Heiser, and Londborg sites are based on communications from the field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Sherbert Samuels
1/12/2007 11:22:53 AM
CSO

Constance Lewin
1/12/2007 11:29:49 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-033

INFORMATION REQUEST LETTER

Solvay Pharmaceuticals, Inc.
Attention: Michael F. Hare
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Hare:

Please refer to your May 1, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox (fluvoxamine maleate) extended release capsules.

We also refer to your submissions dated October 5, 2006 and October 9, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response as soon as possible in order to continue our evaluation of your NDA.

1. Please note that a deficiency letter has been sent to DMF [redacted] December 22, 2006). These deficiencies will need to be resolved before this application can be approved.
2. Provide a letter of authorization to access DMF 5169.
3. The term [redacted] for the dosage form is not acceptable, we recommend that it be replaced with 'extended-release'.
4. Provide information about the [redacted]. 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 [redacted] impurity in drug substance specification to the recommended ICH Q3A qualification level [redacted]. Similarly the limit for individual unidentified substances should be lowered from [redacted] o the ICH Q3A recommended identification limit of 0.10%.
6. An appearance test and particle size test and [redacted] t acceptance limit that appropriately defines the particle size distribution based on the lots used for manufacture of clinical batches 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.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
12/22/2006 10:14:45 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-033

Solvay Pharmaceuticals, Inc.
Attention: Michael F. Hare
Manager, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Mr. Hare:

Please refer to your April 28, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox CR (fluvoxamine maleate) Controlled-Release 100 mg &150 mg capsules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on June 30, 2006 in accordance with 21 CFR 314.101(a).

Clinical:
Please provide the following information:

1) For the pool of all Phase 3 studies with Luvox CR, please provide a table enumerating all patients by their total duration of exposure to Luvox CR and their mean dose of Luvox CR. This should be in the format shown below. Each cell should contain the number of patients who had the specified duration of exposure and a mean dose over that period of exposure in the specified range. Please note that patients should be enumerated only once in this table so that the sum of all cells equals the total number of unique patients in Phase 3 studies who were treated with Luvox CR.

Duration	Mean Daily Luvox CR Dose			
	<100mg	100-200mg	201-300mg	>300mg
0-4 wks.				
5-12 wks.				
13-26 wks.				
27-52 wks.				
>52 wks.				

2) Also for the pool of all Phase 3 studies with Luvox CR, please provide the total number of patient-exposure years for both Luvox CR and placebo. This should be computed by summing the total durations of exposure to Luvox CR (or placebo) for all patients in this study pool.

3) For studies 3103, 3107, and 3108 separately, please provide the mean daily dose of Luvox CR for all Luvox CR patients in-study for each study visit.

4) Kindly integrate analyses regarding mean change from baseline and outlier data for laboratory values, vital sign measures, and ECG parameters for the three pivotal studies (3107, 3108, and 3103). For example, please combine data from the following pages (of Studies 3107 and 3108) from volumes 31 with those of Study 3103 from Volume 30 of your submission altogether:

Laboratory Analyses
• page 23 and page 161 of volume 31 and page 24 of volume 30

Vital Sign Analyses
• page 80 and page 300 of volume 31 with page88 of volume 30

ECG Analyses
• page 106 and page 334 of volume 31 with page 124 of volume 30

Office of Clinical Pharmacology & Biopharmaceutics:
As requested in an e-mail communication from Dr. Andre Jackson, of this Agency, on June, 6, 2006, please provide the following information for studies Biostudy 1098001; Study 1098002; Study S1141106; Study 0398002; Study 0798005; Study 0698001; Study 0300002; Study S1141109 and Study S1141107:

1. Dates samples were collected.
2. Dates samples were analyzed.
3. QC -amount added -amount found-precision and accuracy
4. Calibrators-amount added -amount found-precision and accuracy

Be sure that each study has all of the above information.

Please confirm you will perform an analysis on the suicide data on the studies conducted using the fluvoxamine controlled release capsules.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission. If you have any questions, call Renmeet Gujral, Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
7/11/2006 12:05:03 PM

MEETING MINUTES
IND ?

Date: September 22, 2004
Location: Conference Room E; WOC2
Time: 1:00 – 2:00 PM EST
Firm: Solvay and Elan Pharmaceuticals
Type: Face-to-Face
Meeting: Type C-Pre-NDA Meeting
Drug: Luvox CR (fluvoxamine maleate) Controlled-Release Capsules
Indication: Obsessive Compulsive Disorder and Generalized Anxiety Disorder
Meeting Chair: Thomas Oliver, Ph.D., CMC Psychopharm Team Leader, DNDP, HFD-120
Meeting Recorder: Paul David, R.Ph., Senior Regulatory Project Manager

Participants:
FDA:
Drs. Thomas Oliver, Chhagan Tele, Andre Jackson, Sally Yasuda, and Mr. Paul David

Solvay Pharmaceuticals:

Willem J. Bolink, Ch.E.,	Vice-President of Chemical and Pharmaceutical Development, Weesp, The Netherlands
C. Rob van den Akker, M.S., R.Ph.,	CMC Project Leader, Weesp, The Netherlands
Karen D. Quinn, Ph.D.,	Manager Regulatory Affairs-CMC, Baudette, MN

Elan Pharmaceuticals:

Roger Wayne Wiley, R.Ph.,	Senior Director, Regulatory Affairs, Gainesville, GA
Mairead Fogarty, B.Sc,	Director, Technical Services, Athalone, Ireland
Geraldine Carr, M.Sc.,	Associate Director, Regulatory Affairs, Athalone, Ireland

Meeting Objective
The sponsor requested a meeting with the office of clinical pharmacology and biopharmaceutics (OCPB) and chemistry review teams to discuss 2 questions related to their NDA resubmission.

Background

The sponsor requested this Type C meeting in a submission dated July 14, 2004. The meeting briefing packages were submitted on September X and X, 2004.

Purpose:
The sponsor has the following 2 questions:

1. Does the Agency agree that the equivalence data presented for the pivotal clinical lots and the lots representing the final proposed manufacturing process are adequate to support resubmission of the NDA?
2. Does the Agency agree the overall stability data package is sufficient to support the resubmission of the NDA for the proposed commercial product? The stability data package includes — months of pivotal stability from the original process and 12 months of supportive stability data fro product produced by the final manufacturing process.

Solvay was informed, prior to the meeting that the briefing package did not contain sufficient information to respond to their two questions. Both Solvay and the Agency agreed that the purpose of this meeting would be to discuss what information should be provided in order for the Agency to respond to their questions.

Discussion:

- Solvay made a presentation of the manufacturing process and how it differs from the originally proposed manufacturing process.
- The Agency replied that Solvay should submit component composition comparisons between the previous manufacturing method and the current manufacturing method. This would delineate all of the differences between the clinical lots used in the pivotal studies and the batches targeted for commercial distribution.
- The sponsor should submit information (comparisons between the previous manufacturing method and the current manufacturing method) on the — equipment and particle size.
- The sponsor had no release and/or stability data for the — beads. The NDA will need to contain release/stability data on — beads. The sponsor acknowledged they would be following ICHQ7A guidelines.
- — contains — . Your NDA should provide information how you control —) suspected mutagens) in —
- Provide information about the compatibility studies of the excipients used in the drug product formulations.
- Provide information about the characterization of potential impurities in the drug product.
- The sponsor proposes to market two capsule strengths, i.e., 100 mg and 150 mg. To date, the sponsor only has release data on two batches of 100 mg strength. Typically, the NDA would contain data from three batches of each strength. This issue will be discussed in the near future, after the component/composition data mentioned above is received by the Agency.
- The Agency noted that there have been — of capsules in the new manufacturing process. The sponsor should address these — issues and provide photostability data in the NDA.
- The Agency stressed that they would consider the stability data generated from the to be marketed commercialization process to be the primary data. Data from previous manufacturing processes would be considered as supportive data.
- The Agency recommended that the NDA, at submission, contain 12 months of stability data. Stability updates received within 3 months of the PDUFA date, would be reviewed within that cycle. Updates received after that 3-month date, would receive no such guarantee for that cycle.
- The Agency stated that this product would carry a MedGuide based upon the PDAC's recent recommendations regarding this class of drug. As such, the sponsor would be obligated to submit unit of use packaging. The sponsor replied that they intend to package this drug as unit of use —
- The sponsor will need to submit individual capsule data consistent with the USP description of analysis for controlled release formulations. The information requested in the USP can not be obtained from the mean data submitted by the firm.
- The sponsor stated that they will submit the entire NDA at the time of resubmission.

Conclusions:

1. Solvay will submit the additional information so that the Agency could respond to their questions.
2. Minutes will be provided to sponsor within 30 days from the date of this meeting in accordance with MAPP 4512.1.

Minutes Preparer **Concurrence, Chair (or designated authority)**

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

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/s/

Thomas Oliver
10/8/04 10:11:38 AM