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)

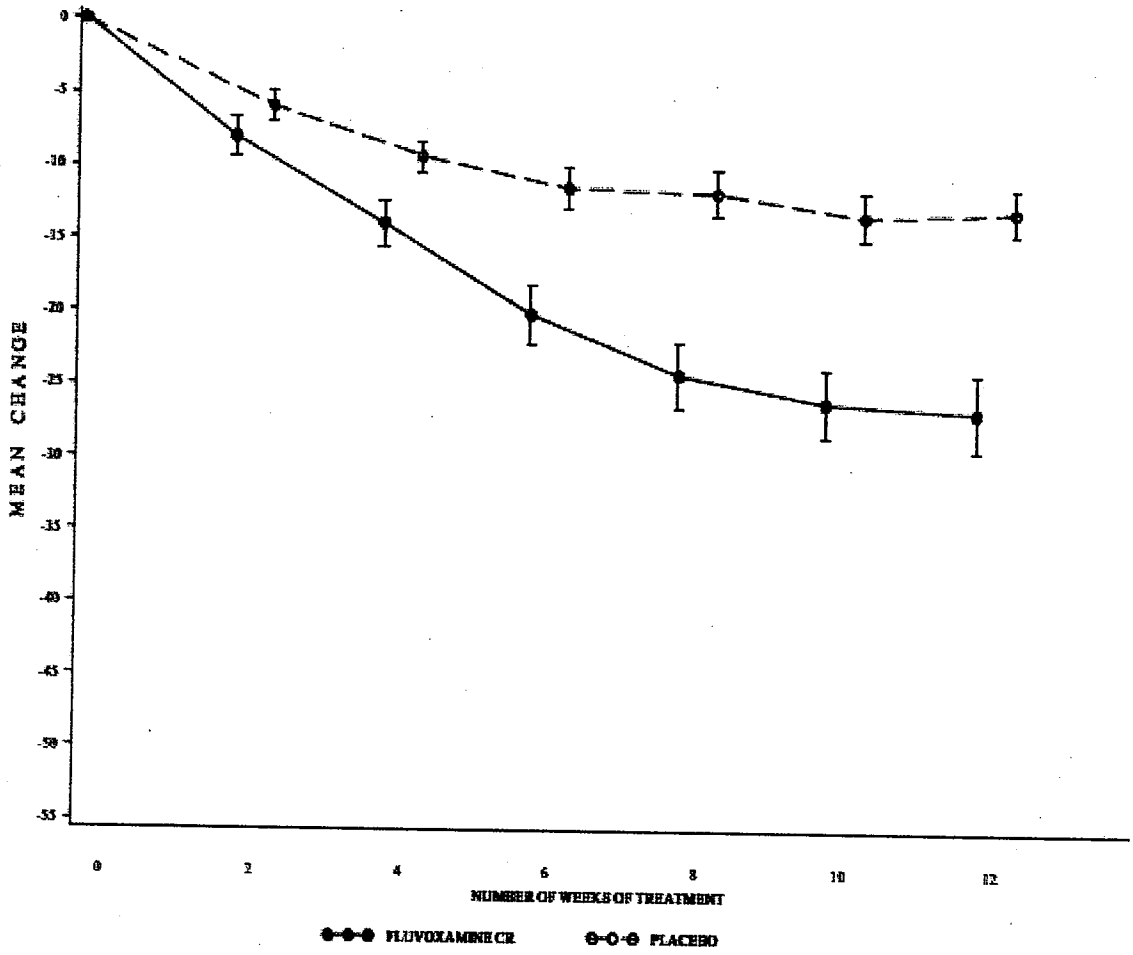
Treatment Group	Statistic	Change from Baseline					
		Week 2	Week 4	Week 6	Week 8	Week 10	Endpoint
LSAS Total Score:							
Fluvoxamine CR (n = 121)	n	108	110	110	110	110	110
	Baseline Mean	90.4	88.8	89.0	89.8	90.3	90.1
	Mean (S.E.)	-8.0 (1.3)	-13.9 (1.5)	-20.1 (2.0)	-24.2 (2.2)	-26.1 (2.4)	-26.7 (2.6)
	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]	[-28.5, -19.9]	[-30.8, -21.4]	[-31.8, -21.6]
Placebo (n = 126)	n	124	125	125	125	125	125
	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	-57, 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)

Treatment Group	Statistic	Change from Baseline					
		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.

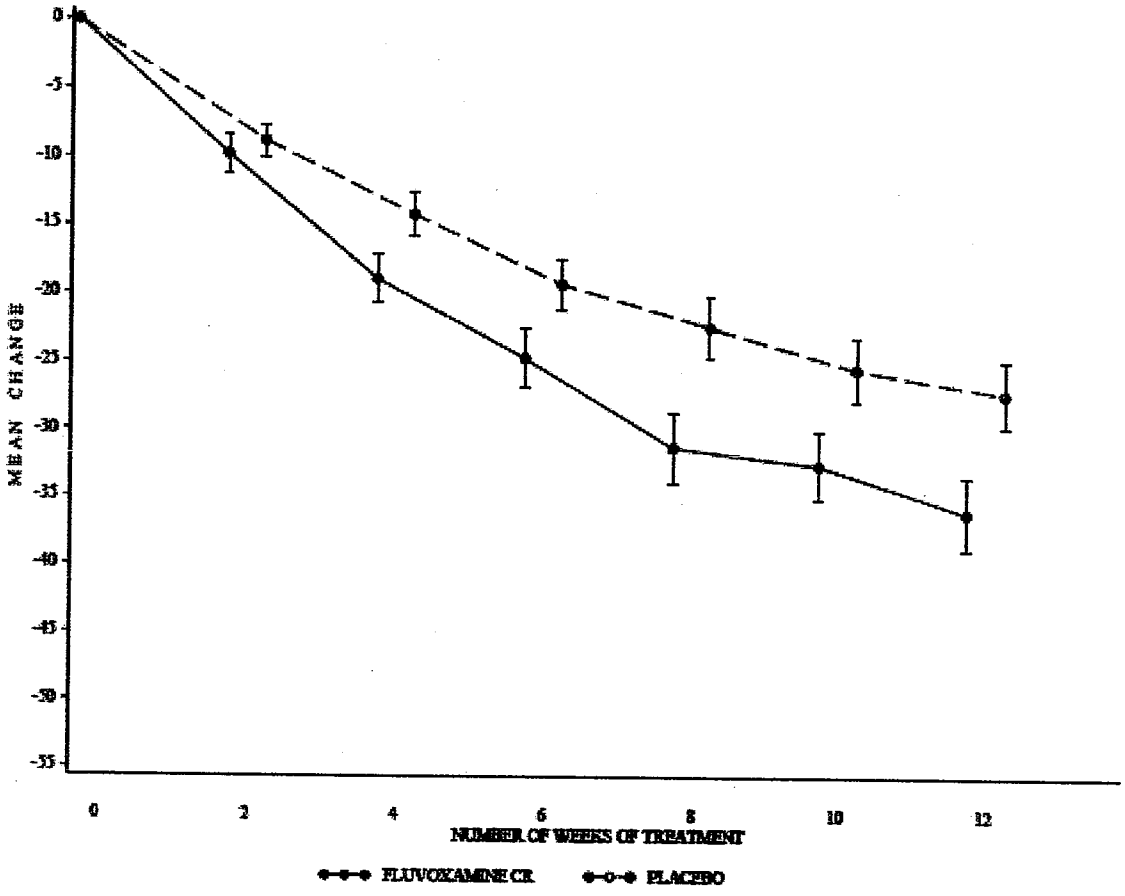
Note: P-values for fluvoxamine CR versus placebo treatment group are based on an ANOVA model fit to the rank of the change from Baseline LSAS total score with terms for treatment and pooled center.

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/µL)		
Male	<2.5	Not Applicable
Female	<2.0	Not Applicable
MCV (um)	<60	>120
MCHC (g/dL)	<20	>45
WBC (x10^3/µL)	<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/µL)	<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	Placebo n=400
		N (%)	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								
0888001 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. 0000031959 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	08 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: 128 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. 8 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%	Fluvoxamine CR 100 mg to 300 mg. Placebo 12 Weeks	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 age 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

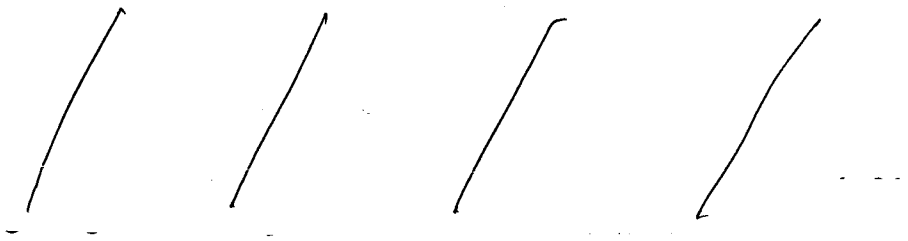
9.1 Conclusions

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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✓ Trade Secret / Confidential

_____ Draft Labeling

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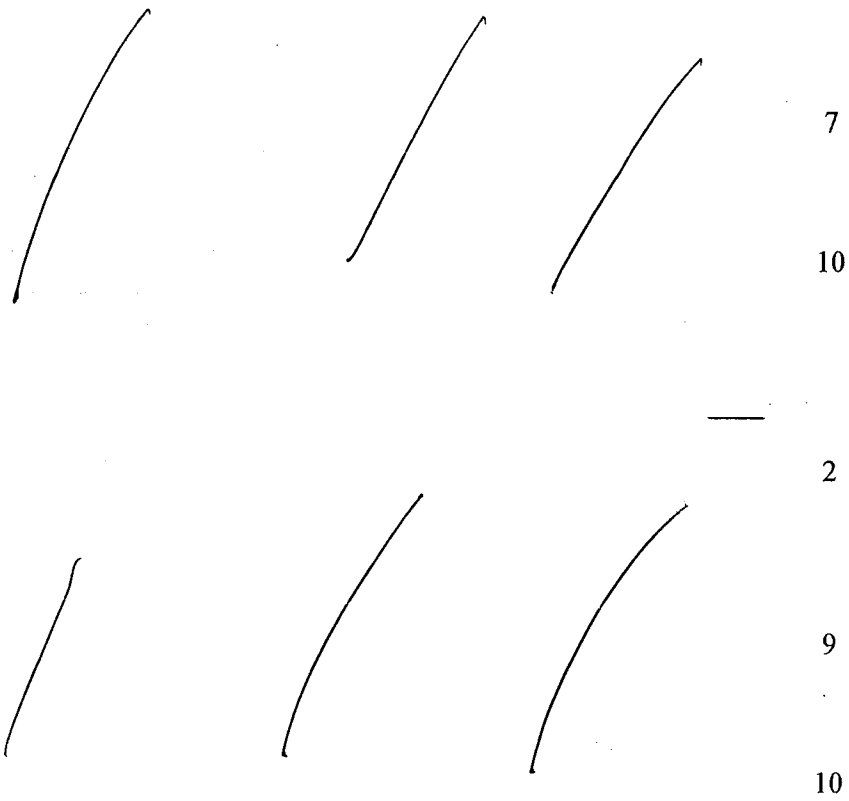

10.2 Tables of Less Common Adverse Events

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