CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-033

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY
REVIEW

NDA:	22-033
Submission Code	BC-000
Submission Type	Response to AE letter
Submission Date(s):	December 28, 2007
Brand Name	Luvox Extended-Release®
Generic Name	Fluvoxamine Maleate
Formulation; Strength(s)	100 mg and 150 mg controlled-release oral capsule
Sponsor	Solvay Pharmaceuticals
Primary Reviewer	Carol Noory
Team Leader	Raman Baweja
OCP Division	Division of Clinical Pharmacology I
ORM division	Division of Psychiatry Products (DPP) HFD-130
Indication	Generalized Anxiety Disorder/ Obsessive Compulsive Disorder

On February 27, 2007, an Approvable letter was sent to Solvay Pharmaceuticals, Inc. regarding NDA 22-033 (LUVOX® 100 mg and 150 mg Controlled Release capsules). Comments cited in the letter included labeling changes and tighter release-rate specifications. On June 21, 2007 the firm responded to thecomments listed in that letter. [redacted]. On December 20, 2007, the agency notified the sponsor that t[redacted], the original dissolution specifications proposed by the agency on February 27, 2007 were recommended for the Luvox® extended-release capsules. Minor labeling changes/corrections were also recommended.

On December 28, 2007, Solvay Pharmaceuticals responded to the agency's action letter dated December 20, 2007. The sponsor accepted FDA dissolution specifications which were the same as the FDA proposed specifications of February 27, 2007. These specifications were based on the pivotal lots used in clinical pharmacology studies [redacted]. The sponsor also accepted the FDA's recommended labeling.

The dissolution method and specifications recommended by OCP for both 100 mg and 150 mg capsules are as follows:

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:	

SIGNATURES

Reviewer:	Carol Noory	Date: February 4, 2008
Team Leader:	Raman Baweja	Date: _____

cc list:

DFS: NDA 22-033

HFD-860: (NooryC, BawejaR, UppoorR, MehtaM, MarroumP)
HFD-130: (GrewalR, BenderW, LaughrenT, OliverT, ClaffeyD)

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/s/

Carol Noory
2/4/2008 10:34:20 AM
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Raman Baweja
2/4/2008 05:39:02 PM
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OFFICE OF CLINICAL PHARMACOLOGY
RESPONSE TO AE LETTER

NDA:	22-033
Submission Code	BC-000
Submission Type	Response to AE letter
Submission Date(s):	June 21, 2007
Brand Name	Luvox Extended-Release®
Generic Name	Fluvoxamine Maleate
Formulation; Strength(s)	100 mg and 150 mg controlled-release oral capsule
Sponsor	Solvay Pharmaceutical
Primary Reviewer	Carol Noory
Team Leader	Raman Baweja
OCP Division	Division of Clinical Pharmacology I
ORM division	Division of Psychiatry Products (DPP) HFD-130
Indication	Generalized Anxiety Disorder/ Obsessive Compulsive Disorder

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II. EXECUTIVE SUMMARY

A. BACKGROUND

On February 27, 2007, an Approvable letter was sent to Solvay Pharmaceuticals, Inc. regarding NDA 22-033 (LUVOX® 100 mg and 150 mg Controlled Release capsules). Deficiencies cited in the letter included labeling changes and tighter release-rate specifications. On June 21, 2007 the firm responded to the deficiencies listed in that letter.

B. RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the pertinent parts of the "Clinical Pharmacology", "Drug Interactions" and the "Dosage and Administration" Sections of

the Labeling submitted in response to the Approvable letter sent by FDA dated February 27, 2007. The labeling is acceptable as revised provided an agreement is reached between the sponsor and the Agency regarding minor corrections in the labeling (See: D below – COMMENTS TO BE SENT TO THE SPONSOR).

The drug release specifications proposed by the firm are not acceptable at this time

Therefore, the dissolution method and specifications recommended by OCP in this review are the same as that proposed in OCP's review of February 8, 2007 and are as follows:

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:	

C. COMMENTS TO THE MEDICAL DIVISION

1.
2. OCP recommends the adoption of the multi-point drug release specifications as outlined in OCP's review of February 8, 2007, and which is mentioned above.
3. OCP has made minor corrections to the labeling (See V. Detailed Labelling Recommendations later in the review)
4. The sponsor has added

   The medical officer is requested to look at this.

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_____ Draft Labeling

_____ Deliberative Process

2. Dissolution: The dissolution method and specifications for both 100 mg and 150 mg capsules are as follows:

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:	

3. Labeling: (also see V. Detailed Labelling Recommendations later in the review)

III. SIGNATURES

Reviewer: Carol Noory Date: _____

Team Leader: Raman Baweja Date: _____

cc list:
DFS: NDA 22-033

HFD-860: (NooryC, BawejaR, UppoorR, MehtaM, MarroumP)
HFD-120: (GrewalR, BenderW, LaughrenT, OliverT, FossomL, KongF, CaiJ, ClaffeyD)

IV. REVIEW

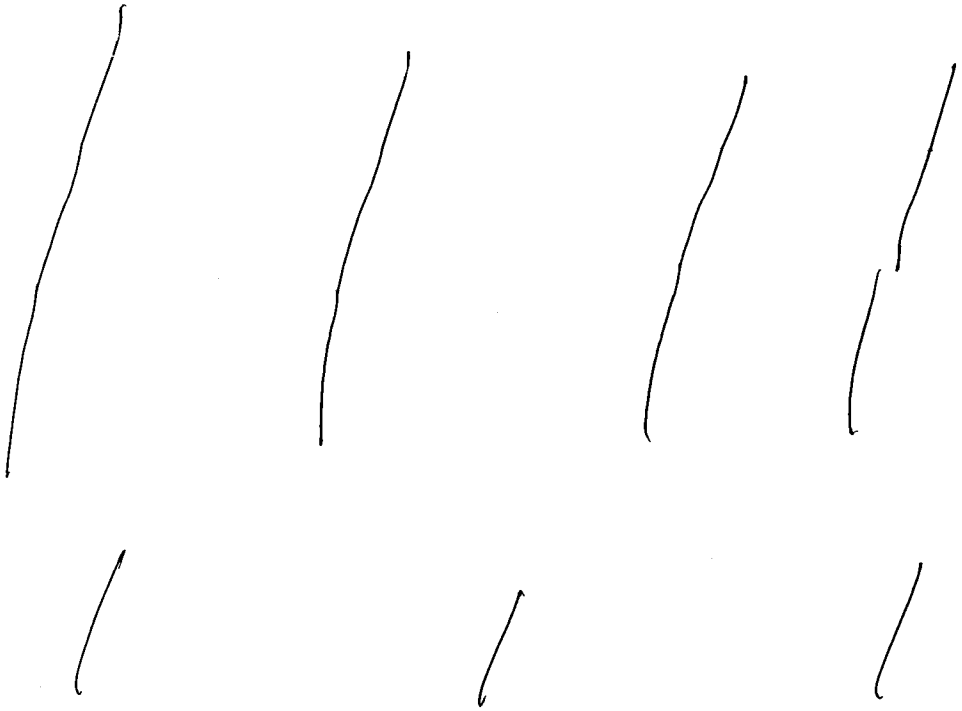
A. BACKGROUND INFORMATION

Fluvoxamine maleate is a selective serotonin reuptake inhibitor used for the treatment of Obsessive Compulsive Disorder (OCD). Fluvoxamine maleate is approved as 50, 100, and 150 mg immediate release tablets. Solvay submitted an NDA for 100 and 150 mg controlled-release capsules on April 28, 2006. An approvable letter was sent by the agency on February 27, 2007. The current submission responds to deficiencies cited in that letter.

B. CURRENT SUBMISSION

The current submission was submitted in response to the AE letter sent by the Division of Psychiatry Drug Products. The following information was submitted by the sponsor:

- Updated Labeling



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/s/

Carol Noory
12/4/2007 06:29:44 PM
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Raman Baweja
12/4/2007 06:50:06 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: FLUVOXAMINE MALEATE CR **PRIMARY REVIEWER**: Andre Jackson
NDA: 22033 **TYPE:** NDA
FORMULATION: CR CAPSULES **STRENGTH: 100 MG AND 150 MG**
APPLICANT: SOLVAY Submission Dates: April 28, 2006

INDICATIONS: GENERALIZED ANXIETY DISORDER
OCD
Generic Name: LUVOX CR

EXECUTIVE SUMMARY

Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to the chemical series, the 2 aminoethyl oxime ethers of aralkylketones. Fluvoxamine maleate (molecular weight 434.4) is a white or off white, odorless, crystalline powder which is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether. The mechanism of action of fluvoxamine maleate in Obsessive Compulsive Disorder (OCD) is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. In preclinical studies, it was found that fluvoxamine inhibited neuronal uptake of serotonin. In *in vitro* studies fluvoxamine maleate had no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors. Antagonism of some of these receptors is thought to be associated with various sedative, cardiovascular, anticholinergic, and extrapyramidal effects of some psychotic drugs.

Three controlled clinical studies were conducted to support the indications. The first study was a 10-week multicenter parallel group study done to support the OCD claim involving 250 subjects. The primary end-point was the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

The second indication generalized anxiety disorder was studied in 2 controlled clinical trials involving 600 subjects using the Liebowitz Social Anxiety Scale (LSAS) as the primary endpoint.

Fluvoxamine immediate release is approved as 50, 100 and 150 mg tablets. Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. The mean plasma half-life of fluvoxamine at steady state after multiple oral doses of 100 mg/day in healthy, young subjects was 16 hours.

Eight phase I studies were conducted by Solvay to describe the human pharmacology and bioavailability/bioequivalence of Fluvoxamine CR following oral administration to characterize the CR dosage form. Several of these studies were for formulation selection.

Oral bioavailability of Luvox CR is not affected by food. In a dose proportionality study involving fluvoxamine maleate CR at 100, 200 and 300 mg/day for 10 consecutive days in 20 normal subjects, steady state was achieved after about a week of dosing. Maximum plasma concentrations at steady state occurred within 3-8 hours of dosing and reached concentrations averaging 47, 161 and 319 ng/ml, respectively. Fluvoxamine exhibited nonlinear, dose-dependent pharmacokinetics. As the CR dose increased over the dose range from 100 mg to 300 mg per day, plasma fluvoxamine concentrations increased higher than corresponding increases in dose. Over the entire 3-fold dose range, AUC(0-24h) increased 5.8-fold and Cmax increased 5.7-fold. Females have a 62% increase in AUC and Cmax than do males under fasted conditions.

The relative bioavailability [Frel(%)] of the fluvoxamine CR formulation was 84% that of the LUVOX® Tablets. The Cmax-Cmin/Cavg for fluvoxamine CR was reduced relative to that of LUVOX® tablet.(0.77$\pm$0.3 vs 0.91$\pm$0.2).

The firm completed 3 pivotal studies related to dosage form characterization for the to-be-marketed formulation:.

1.The to-be-marketed 100mg capsule formulation was used in:
   a. the multiple dose proportionality study 1141106
   b. the single dose food effects study 1141107
   c. the pivotal clinical studies

2.The third study was a multiple dose study 1098002 comparing the 100 mg fluvoxamine CR capsule to the marketed 100 mg Luvox IR product.

RECOMMENDATIONS

1. The Clinical Pharmacology and Biopharmaceutics section of NDA 22-033 is acceptable to OCPB.

COMMENTS TO THE SPONSOR

1. Dissolution

A. Final specifications for the 100 mg and 150 mg CR capsules

Dosage form:	Capsule
Strength:	100 mg 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	Per Cent Release
2 hr	
4 hr	
6 hr	
8 hr	
12 hr	

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INTRODUCTION

Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) that was approved as LUVOX® Tablets (NDA 20-243) in the US for the treatment of OCD on 05 December 1994 and for children and adolescents on 25 March 1997.

Elan Pharmaceuticals has developed a fluvoxamine maleate controlled release formulation designed specifically for once daily administration. The controlled release formulation provides for release of the drug, using rate-controlling polymers, while maintaining therapeutic plasma concentrations over the once daily dosing interval and minimizing peak to trough fluctuations.

QUESTION BASED REVIEW

GENERAL CLINICAL PHARMACOLOGY

WHAT IS THE DEGREE OF LINEARITY OR NONLINEARITY IN THE DOSE-RESPONSE RELATIONSHIP FOR CR FLUVOXAMINE IN STUDY 1141106?

The Study was a multiple dose study done in 20 young normal adults 21-45 yrs old. 100 mg, 200 mg, and 300 mg of fluvoxamine maleate as a CR capsule was administered once-daily for 10 days.

Table 1. Pharmacokinetic parameters following administration of the 100 mg, 200 mg, and 300 mg of fluvoxamine maleate as a CR capsule.

Parameter	CR Dose (mg)	Arithmetic Mean	SD	CR Doses Compared	Ratio (%) from ANOVA	90% CI on Ratio
DN-AUC(0-24h) (ng•hr/mL)	100	8.19	3.51	200 mg/100 mg	165	143, 189
	200	13.92	7.07	300 mg/200 mg	118	94, 149
	300	19.26	11.93	300 mg/100 mg	195	142, 267
DN-Cmax (ng/mL)	100	0.47	0.19	200 mg/100 mg	165	143, 191
	200	0.81	0.40	300 mg/200 mg	114	83, 156
	300	1.07	0.66	300 mg/100 mg	189	140, 254
*DN = Dose-normalized						

Conclusion

Nonlinearity is reflected in the dose-normalized (DN) AUC(0-24h) and Cmax values. DN-AUC and DN-Cmax increased with dose; all pairwise comparisons were greater than one indicating nonlinearity

Over the entire 3-fold dose range, AUC(0-24h) increased 5.8-fold and Cmax increased 5.7-fold.

ARE THE MULTIPLE DOSE KINETICS FOR THE TO-BE-MARKETED PROTOTYPE D 100 MG CR CAPSULE SIMILAR TO THE MARKETED 100 MG LUVOX Study 1098002?

The pharmacokinetics of fluvoxamine once daily for 10 days after multiple doses of a fluvoxamine CR 100 mg capsule formulation (Prototype D) and 100 mg LUVOX® Tablets in 14 healthy male subjects ages 21-44 are shown below.

Figure 1. Mean Plasma Concentrations Versus Time Curve

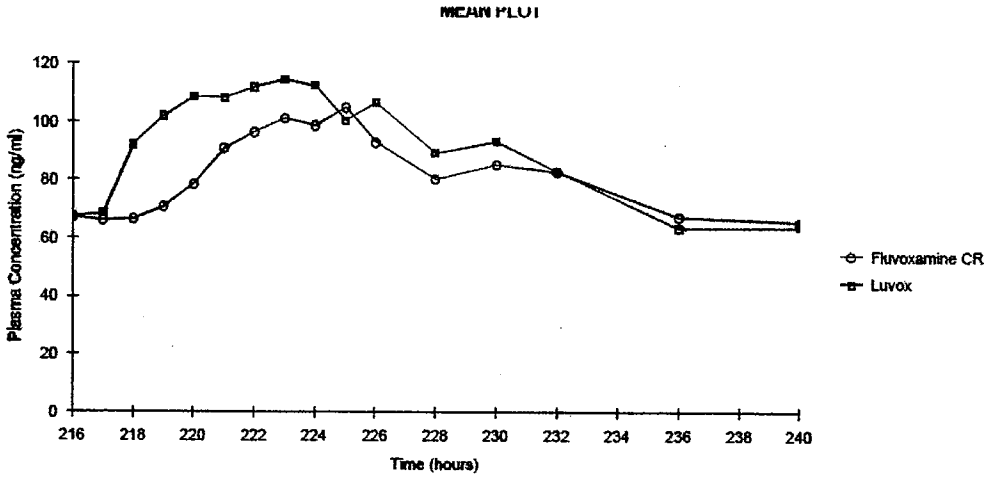

Table 1 .Summary statistics for log-transformed pharmacokinetic parameters

Parameter	TREATMENT A Fluvoxamine CR (Elan Prototype 'D') Geometric Mean (90%CI)	TREATMENT B LUVOX® Tablets Geometric Mean (90%CI)
Cmax (ng/mL)	98.45* (73.61, 131.66)	112.60 (85.39, 148.48)
AUC (0-24) (ng/mL.hr)	1627.26* (1202.56, 2201.93)	1800.03 (1341.40, 2415.47)

* $p<0.05$, statistically significant relative to LUVOX® tablets
The 90% CI are calculated using the antilog of the 90% CI for the log-transferred AUC and Cmax

Parameter	Ratio of A/B	90% CI Lower Bound	90 % CI Upper Bound
Cmax (ng/mL)	0.87	80.57	94.86
AUC (0-24) (ng/mL.hr)	0.90	85.09	96.04

A = Fluvoxamine CR (Elan Prototype 'D') ; B = LUVOX® Tablets

Conclusions:

1.The relative bioavailability [Frel(%)] of the fluvoxamine CR formulation was 91% that of the LUVOX® Tablets. The mean AUC (0-24) of the fluvoxamine CR was lower than that of LUVOX® Tablets.

2.The fluxoxamine CR formulation had a reduced Cmax, Cavg, and

Cmax-Cmin/Cavg, compared to LUVOX® Tablets. However Fluvoxamine prototype D had Cmax and AUC(0-24) 90% CI within 80-125% of Luvox.

WHAT IS THE IMPACT OF DIFFERING IN VITRO DISSOLUTION PROFILES ON THE PHARMACOKINETICS OF FLUVOXAMINE 100 MG CR CAPSULES STUDY 1141109?

The study was a single dose study comparing :
Treatment A: Fluvoxamine maleate 100 mg CR capsules formulation 1 (Fast Batch, formulated with the intended upper *in vitro* release specification) and
Treatment B: Fluvoxamine maleate 100 mg CR capsules formulation 2 (Slow Batch, formulated with the intended lower *in vitro* release specification).

The firm did not supply any specific formulation or dissolution data to support the formulations.

The Study was a single dose study done in 36 young normal adults 19-42 yrs old.

Table 1. Point Estimates (Ratios A * 100/B), 90% Confidence Intervals, and ANOVA
CVs for the Primary Target Parameter Cmax as Well as for AUClast and AUC

Parameter	Point estimate A* 100/B [%]	90% Confidence Interval [%]	Intrasubject coefficient of variation [%]
AUC	105.88	100.1-112.0	14.0
AUC_{last}	106.38	100.9-112.2	13.3
C_{max}	121.10	114.7-127.8	13.4

Conclusions

1.BE was not demonstrated between the two fluvoxamine CR treatments with distinct *in vitro* performances.

2. The relative bioavailability of the test treatment (Treatment A 100 mg fluvoxamine maleate CR [Fast Batch]) as determined by AUC extrapolated to infinity was 106% that of the reference treatment (Treatment B 100 mg fluvoxamine maleate CR [Slow Batch]).

3. The test treatment has a comparable extent of absorption (as determined by AUC) but an increased rate of absorption (as determined by Cmax: 121%) compared to that of the reference treatment. The median time to reach peak concentration was reduced for the test treatment (8.5 hrs) compared to that of the reference treatment(~12 hrs).

BIOPHARMACEUTICS

WHAT IS THE RELATIVE BA OF THE PROTOTYPE CR CAPSULES Study 0698001?

The study was an open label, single dose, five treatment, five period, randomised, crossover comparing four fluvoxamine CR 100 mg prototype capsule formulations with LUVOX® Tablet 100 mg (Solvay Pharmaceuticals Inc.). Ten subjects ages 19-32 were used in the study. Only subjects who were phenotyped as extensive metabolisers ofCYP2D6 using dextromethorphan were included in the study to minimize the variability associated with the disposition of fluvoxamine.

Treatments Administered

The following were the treatments:

Treatment A:

100 mg fluvoxamine CR capsule formulation, single dose at T0 hours, fasted – formulation 1

Treatment B:

100 mg fluvoxamine CR capsule formulation, single dose at T0 hours, fasted – formulation 2

Treatment C:

100 mg fluvoxamine CR capsule formulation, single dose at T0 hours, fasted – formulation 3

Treatment D:

100 mg fluvoxamine CR capsule formulation, single dose at T0 hours, fasted – formulation 4

Treatment E:

LUVOX® 100 mg tablet, single dose at T0 hours, fasted - Solvay Pharmaceuticals Inc.

Figure 1. Mean Plasma Concentration Versus Time Curve

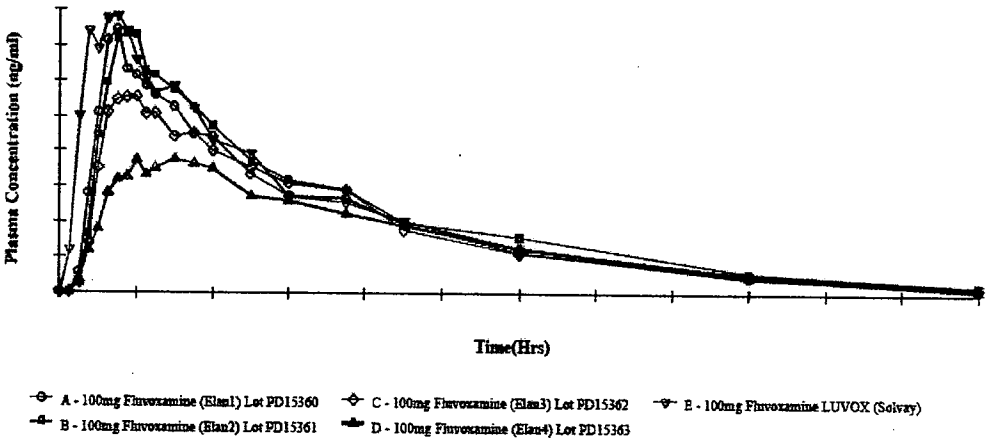

Table 1. Comparison of the relative BA for the 4 products tested compared to Luvox.

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Parameter	TREATMENT A Lot No PD15360 Mean ± Stdev	TREATMENT B Lot No PD15361 Mean ± Stdev	TREATMENT C Lot No PD15362 Mean ± Stdev	TREATMENT D Lot No PD15363 Mean ± Stdev	LUVOX® Mean ± Stdev	Criteria for acceptance (relative to Luvox®)+
AUCINF (ng/mL.h)	919.960 ± 747.132	1014.213 ± 885.705	872.731 ± 668.717	725.457 ± 450.549*	1047.194 ± 959.337	-
Frel (%)	95.201 ± 31.844	101.488 ± 24.936	91.152 ± 25.714	83.053 ± 34.432	-	≥ 80%
Cmax (ng/ml)	40.514 ± 18.491	40.611 ± 17.973	31.361 ± 15.035*	22.711 ± 9.146*	44.576 ± 23.132	-
Relative Cmax(%)	106.62 ± 52.67	101.58 ± 41.78	77.55 ± 33.95	58.35 ± 28.09	-	≤ 85%
Lambda z (hr^{-1})	0.054 ± 0.014	0.062 ± 0.013	0.049 ± 0.011	0.048 ± 0.008	0.054 ± 0.022	-
t1/ (h)	13.866 ± 4.900	14.356 ± 4.192	15.237 ± 5.395	15.168 ± 3.797	14.722 ± 6.254	-
tmax (h)	5.600 ± 0.843	6.900 ± 2.025	6.900 ± 1.663	12.400 ± 5.296*	4.200 ± 1.814	-
tmax difference (test-ref)	1.40 ± 2.27	2.70 ± 2.21	2.70 ± 2.31	8.20 ± 5.85	-	≥ 3h
AUCall (ng/mL.h)	884.426 ± 678.532	977.301 ± 800.824	838.158 ± 613.578	702.566 ± 416.032	1006.614 ± 866.971	-
C24h (ng/ml)	13.79 ± 9.45	15.95 ± 14.03	15.57 ± 11.92	13.09 ± 7.49	13.73 ± 13.03	
Relative C24h(%)	114.41 ± 37.84	126.65 ± 43.25	126.59 ± 33.81	122.79 ± 58.31	-	≥ 110%

*P ≤ 0.0125, statistically significant relative to LUVOX

+ Comparison to the criteria for acceptance was based on the individual data.

Conclusions

1.The formulations showed a prolonged tmax relative to that of the reference product (LUVOX® tablet). The tmax for formulation D was considerably longer.

2.The relative bioavailabilities of all the formulations were all >80% relative to LUVOX® tablet. All treatments had a C24h greater than that of >110% of LUVOX® tablet.

3.The sponsor selected prototype D to go into further development based upon the formulation characteristics they wanted for a CR product.

WHAT IS THE EFFECT OF FOOD ON THE TO-BE-MARKETED PROTOTYPE D FORMULATION Study 1141107?

A single-dose, three-treatment, three-period, crossover study was conducted in 28 healthy volunteers, 15 males and 13 females ages ages 20-44.

Each subject received a single dose of fluvoxamine maleate 100 mg in the form of a LUVOX tablet, a fluvoxamine maleate CR capsule under fasted conditions and fluvoxamine maleate CR capsule under fed conditions.

Each subject was phenotyped to assess metabolic status of CYP2D6 using dextromethorpan. Both extensive and poor metabolizers were enrolled into this study.

Figure 1. Mean (SEM) Plasma Fluvoxamine Concentrations for Fed and Fasting Fluvoxamine CR Treatments

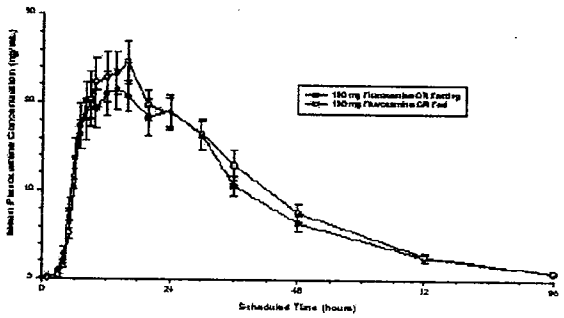


Table 1. Statistical Analysis Results for Fluvoxamine Pharmacokinetics After Fasted and Fed Fluvoxamine CR Treatments

Parameter	Treatment	Least Squares Mean from ANOVA[1]	Treatments Compared	Ratio (%) from ANOVA	90% CI on Ratio
AUC(0-inf) (ng•hr/mL)	CR Fed	784.63	CR Fed/CR Fast[2]	110	102, 118
	CR Fasted	714.79			
Cmax (ng/mL)	CR Fed	25.38	CR Fed/CR Fast	111	100, 124
	CR Fasted	22.82			

[1]Least Squares Mean values based on 28 subjects.
[2]ANOVA results indicated statistical significance ($p<0.05$).
Supporting Documentation: Table 10.2.3

Conclusion:
Food has no effect on the BA of Luvox CR capsules.

THE STUDY 1141107 WAS DESIGNED WITH MALE AND FEMALE SUBJECTS SO THE DATA WERE FURTHER ANALYZED TO ADDRESS THE QUESTION OF GENDER

WAS THERE AN EFFECT OF GENDER ON THE LUVOX CR FORMULATION Study 1141107?

Table 1. Mean (SD) Results for Fluvoxamine Pharmacokinetic Parameters Based on Gender

		Treatment Arithmetic Mean[1] (SD)[2]		
Parameter	Gender	LUVOX Fasted	Fluvoxamine CR Fasted	Fluvoxamine CR Fed
AUC(0-inf)[3] (ng•hr/mL)	Female	1150.47 (617.80)	1013.94 (573.86)	1050.17 (529.90)
	Male	793.67 (363.90)	626.36 (187.45)	725.92 (305.29)
Cmax[3] (ng/mL)	Female	46.68 (21.28)	32.58 (20.71)	34.41 (17.97)
	Male	37.72 (16.36)	19.88 (5.01)	23.86 (10.61)
Tmax (hr)	Female	7 (4-16)	14 (7-24)	17 (10-36)
	Male	8 (4-9)	16 (7-30)	14 (7-24)
T1/2 (hr)	Female	15.44 (2.88)	16.53 (2.55)	16.14 (2.71)
	Male	16.41 (2.58)	16.11 (2.83)	15.74 (3.09)

[1] Arithmetic mean based on 28 subjects (15 males and 13 females).
[2] For Tmax: Range (minimum-maximum) values depicted instead of SD.
[3] ANOVA results indicated a statistical significance ($p<0.05$) between gender when female and male values were pooled together from the three treatments. No statistical analyses were conducted for Tmax and T1/2 for gender.

Conclusion

1.Under single-dose conditions, a gender effect was demonstrated. Fluvoxamine exposure, i.e., AUC and Cmax, were both significantly increased by 62% for female subjects compared to male subjects.

WHAT IS THE EFFECT OF — BOTTLE PACKAGING VS ——— — PACKAGING ON THE BE OF THE TO-BE-MARKETED PROTOTYPE D FORMULATION STUDY 0300002?

RATIONALE-
The dissolution of the product packaged in — bottles following 6 months storage at 25^{0}C/60% RH did not meet the proposed release specifications for this product. This study was designed to evaluate the in-vivo performance of the fluvoxamine CR capsule product in both packaging configurations after storage for at least 9 months at 25^{0}C/60%RH, in order to support dissolution shelf-life specifications wider than the proposed release specifications for this fluvoxamine CR capsule product.

A single dose, 2-treatment, 2-period, crossover study was done to establish the bioequivalence between the fluvoxamine 100mg CR capsule product packaged in —— bottles with fluvoxamine 100 mg CR capsule product packaged in ————

The study was done in 22 males ages 19-45.

Figure 1. MEAN PLOT [redacted] vs [redacted] bottle storage

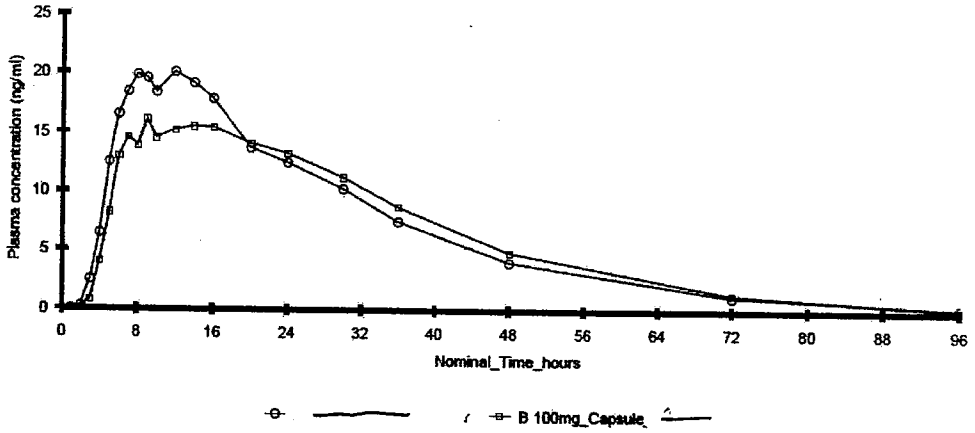


Table 1. Log-transformed Pharmacokinetic Parameters Geometric Mean (n=22 subjects) Summary Pharmacokinetic Parameters

Parameter	Treatment A - [redacted]	Treatment B - [redacted] Count Bottles
Cmax (ng/ml)	21.79	17.70*
90% CI		69 – 95
AUClast (ng/ml.h)	542.10	538.73
90% CI		91 – 108
AUCall (ng/ml.h)	554.16	553.55
90% CI		92 – 108
AUCinf (ng/ml.h)	565.10	565.64
90% CI		92 – 108

* P = 0.03, statistically significant differen

Conclusions

1. Statistical analysis of the log-transformed parameters demonstrated that the 90% confidence intervals comparing the capsules packaged in bottles and [redacted] were within 80-125% in terms of AUC but not in terms of Cmax.

FORMULATIONS

Table 1. Quantitative and qualitative formulas.

	Target 100 mg	Target 150 mg	
Component Material	***mg/ capsule and (%)***	***mg/ capsule and (%)***	***Function and Ref.***
Fluvoxamine Maleate	100 mg	150 mg	Active Ingredient- Solvay DMF
Talc			
(sugar spheres)			
Ammonio Methacrylate Copolymer Type B**			
Dibutyl Sebacate			
Hard Gelatin Capsule	For Encapsulation	For Encapsulation	For Encapsulation

DISSOLUTION DATA

Firms Proposed Dissolution Method and Specifications:

Dosage form:	Capsule
Strength:	100 mg 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

Time (hour)	Percent (%)Release	Purpose
2		
4		
6		
8		
12		

NMT=Not more than, NLT=Not less than

PANEL 6.5.1

Release Data – Prototype Biostudy Batches – Biopharmaceutical Lots

Dosage Form and Strength, Methodology	Lot Number	Dissolution Apparatus	Media/ Temperature	Speed of Rotation	Collection Time (Hours)	Units Tested	Range Min	Range Max	% Release Mean	% Release CV
Capsule 100 mg	PD15363 *	USP II	Phosphate Buffer pH 6.8 37.0°C±0.5°C	50 rpm	0.5	N=12			3.2	27.6
					1				8.9	22.3
					2				25.7	13.0
					4				51.6	6.6
Method 400/1					6				71.0	5.3
					8				82.7	4.7
					10				90.9	4.6
					22				102.8	1.8
Capsule 100 mg	PD15538 **	USP II	Phosphate Buffer pH 6.8 37.0°C±0.5°C	50 rpm	0.5	N=12			4.8	21.6
					1				10.3	12.6
					2				35.5	9.6
					4				58.9	7.4
Method 400/3					6				75.4	4.3
					8				86.5	3.8
					10				92.9	2.8
					22				100.8	2.2

* Used in study 0098001.

**Used in study 1098002; this batch is supported by a formal stability program on lot PD15363. The composition and manufacturing process is equivalent for both batches.

Lot number PD 15538 was used in Study 1098002 which compared Fluvoxamine CR to 100 mg Luvox

Release Data – CTM Batches*

Dosage Form and Strength, Methodology	Lot Number	Dissolution Apparatus	Media/ Temperature	Speed of Rotation	Collection Time (Hours)	Units Tested	Range Min	Range Max	% Release Mean	% Release CV
Capsule 100 mg XPP10031/3-0	DE5252	USP II	Phosphate Buffer pH 6.8 37.0°C±0.5°C	50 rpm	1	N=6			4.3	83.7
					2				11.4	48.4
					4				39.6	9.9
					6				54.1	15.8
					8				73.2	11.1
					10				86.2	5.1
					12				91.4	2.6

*All used in study S1143104; batches were reallocated from pivotal stability for use as clinical supply.

Lot number DE 5252 was used in PK studies S1141106 and S1141107

PANEL 6.5.7

Release Data – CTM Batches*

Dosage Form and Strength, Methodology	Lot Number	Dissolution Apparatus	Media/ Temperature	Speed of Rotation	Collection Time (Hours)	Units Tested	Range Min	Range Max	% Release Mean	% Release CV
Capsule 150 mg XPP10032/3-0	DE5186	USP II	Phosphate Buffer pH 6.8 37.0°C±0.5°C	50 rpm	1	N=6			2.9	59.9
					2				15.7	25.8
					4				41.1	3.0
					6				54.7	2.8
					8				70.9	6.1
					10				85.2	3.4
					12				92.5	2.1
Capsule 150 mg XPP10032/3-0	DE5207	USP II	Phosphate Buffer pH 6.8 37.0°C±0.5°C	50 rpm	1	N=6			3.2	68.0
					2				12.7	26.2
					4				43.6	8.0
					6				56.7	6.9
					8				76.1	4.1
					10				88.8	2.2
					12				96.1	4.6
Capsule 150 mg XPP10032/3-0	DE5208	USP II	Phosphate Buffer pH 6.8 37.0°C±0.5°C	50 rpm	1	N=6			3.1	47.8
					2				7.5	57.9
					4				36.5	11.5
					6				55.7	8.8
					8				72.5	12.3
					10				85.3	7.0
					12				91.1	3.9

*All used in study S1143104; batches were reallocated from pivotal stability for use as clinical supply.

Lots DE5188, DE5207 and DE5208 were all used in the Clinical study S1143104 for obsessive compulsive behavior.

Capsule 150 mg XFC51007/0	DE6890	USP II	Phosphate Buffer pH 6.8 37.0°C±0.5°C	50 rpm	1 2 4 6 8 10 12	N=6			3.4 22.3 45.8 64.5 79.6 88.7 93.7	5.4 7.1 4.8 4.7 1.7 2.1 1.6

Lot DE6890 was used in the Clinical study S1143107

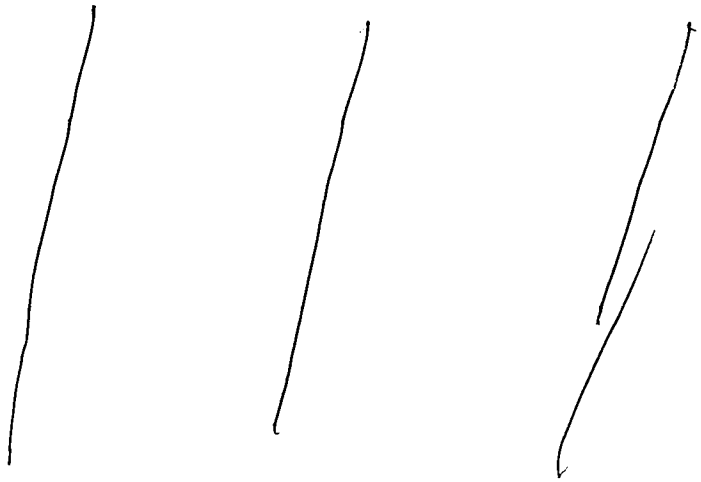
ANALYTICAL SECTION

Assay Validation - Fluvoxamine

Parameter	Fluvoxamine
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection
Number of Freeze-thaw	4 Cycles QC's 4ng/ml, 800 ng/ml
Benchtop Stability at RT	4 hrs
Long term at –20° C	8 WEEKS
Extraction Recovery Low High	114% @ 0.5 ng/ml 126% @ 2 ng/ml 114% @ 1000 ng/ml Internal standard 91%

% Recovery								
N	7	7	7	7	7	7	7	7
Mean	114.83	126.12	101.79	117.83	116.31	116.03	115.71	114.16
SD	17.07	12.36	7.84	4.76	5.58	3.76	5.41	8.91
% CV	14.89	9.80	7.70	4.05	4.80	3.24	4.67	7.80

FIRM'S PROPOSED LABEL



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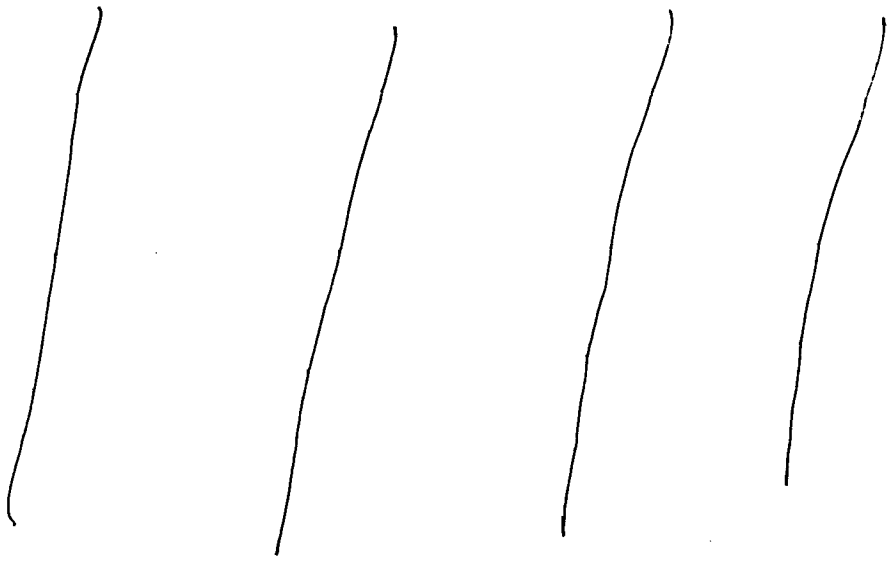

SIGNATURES

Andre Jackson_____
Reviewer, Psychopharmacological Drug Section, DCP I
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RD/FTinitialized by Raman Baweja, Ph.D._____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 22-033, HFD-860(Mehta, Baweja, Jackson)

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Briefing Attendees: Andre Jackson, Ray Bawejs, Mehul Metha, Christoffer Tornoe, Mitch Mathis, Nhi Aye Kin, Kofi Kumi

APPENDIX

DETAILED STUDY REPORTS

Study-S1141106-The Multiple-Dose Pharmacokinetics of Fluvoxamine

TITLE: The Multiple-Dose Pharmacokinetics of Fluvoxamine in Healthy Male Volunteers After Administration of 100-, 200- and 300-mg Once-Daily Dose of Fluvoxamine Maleate in Controlled-Release Capsules
STUDY INITIATION DATE: 21 June 1999
STUDY COMPLETION DATE: 6 August 1999

STUDY OBJECTIVES

To determine the multiple-dose pharmacokinetics and dose proportionality of fluvoxamine after once-daily administration of 100 mg, 200 mg, and 300 mg of fluvoxamine maleate as a CR capsule in healthy male subjects.
To evaluate safety and tolerability of multiple-dose administration of fluvoxamine CR
capsule in healthy male subjects.

Overall Study Design and Plan - Description
This was an open-label, ascending, multiple-dose study to determine the pharmacokinetics and dose proportionality of 100 mg, 200 mg, and 300 mg fluvoxamine maleate after administration of fluvoxamine maleate CR capsules. The
study was conducted in healthy male subjects.

METHODS
Demographics

DEMOGRAPHY
SAFETY POPULATION

DEMOGRAPHIC	STATISTIC	TOTAL (N=20)
AGE (YRS)	n	20
	MEAN +/- SD	34.9 +/- 8.17
	MEDIAN	33.2
	RANGE	21.2 TO 45.3
ETHNICITY	CAUCASIAN	10 (50%)
	AFRICAN AMERICAN	3 (15%)
	HISPANIC	7 (35%)
	TOTAL	20 (100%)
WEIGHT (KG)	n	20
	MEAN +/- SD	77.5 +/- 8.26
	MEDIAN	77.6
	RANGE	62.6 TO 99.8
HEIGHT (CM)	n	20
	MEAN +/- SD	172.4 +/- 5.52
	MEDIAN	172.7
	RANGE	160.0 TO 188.0

Fluvoxamine Plasma Sample Collection and Handling

Whole blood samples (7 mL) were obtained prior to and at 1, 2, 3, 4, 5, 6, 7, 8, 9,10, 12, 14, 16, 20, and 24 hours after administration of the 100 mg and 200 mg doses of fluvoxamine maleate CR on Days 7 and 17, respectively. On Day 27, blood samples were obtained prior to and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 48, 72, and 96 hours after administration of the 300 mg dose of fluvoxamine maleate CR.

In addition, predose blood samples were collected on the mornings of Days 1, 5, 6, 15, 16, 25, and 26 prior to drug administration. A total of 58 blood samples (total volume 406 mL) were obtained by venipuncture from each subject for pharmacokinetic analysis.

Pharmacokinetic Data Analysis

The following pharmacokinetic parameters were determined for fluvoxamine at the 100 mg, 200 mg, and 300 mg per day dose levels using observed data and noncompartmental methods. All pharmacokinetic samples were collected within the allowable time deviation (□3 minutes) set in the protocol, subsequently nominal

times were used for all pharmacokinetic parameter calculations.

□the individual subject and mean plasma concentrations of fluvoxamine

□the area under the plasma concentration-time curve within a 24-hour dosing interval after multiple dosing, AUC(0-24h), was calculated by applying the linear trapezoidal rule up to Tmax and the log-linear trapezoidal rule thereafter

□the area under the plasma concentration-time curve, AUC(0-last), up to the last observable concentration, Clast, at time, tlast, was calculated by applying the linear trapezoidal rule up to Tmax and the log-linear trapezoidal rule thereafter

□the terminal rate constant, Kel, was based on concentrations that were judged to be in the terminal phase upon visual inspection and examination of residuals by log-linear regression (a minimum of three points were used in the estimate)

□the area under the plasma concentration-time curve extrapolated to infinity, AUC(0-inf), was estimated by the following equation for the 300 mg/day dose: AUC(0-inf) = AUC(0-last) + Clast/Kel □the percent of AUC(0-inf) extrapolated, %AUCext, was estimated by the following equation for the 300 mg/day dose: %AUCext = [AUC(0-inf) - AUC(0-last)]/AUC(0-inf) □100

□the maximum plasma concentration of the drug, Cmax, and the time of its occurrence, Tmax
□time required to achieve steady state conditions
□the minimum plasma concentration, Cmin, regardless of sampling time
□the mean plasma concentration within a dosing interval, Cav, was estimated by the following equation (where □= dosing interval of 24 hours):
Cav = AUC(0-24h)/□

Statistical Analysis of Pharmacokinetic Parameters
Descriptive statistics (sample size "n", arithmetic mean, geometric mean, standard deviation "SD", standard error of the mean "SEM", coefficient of variation, minimum, and maximum) were provided for the pharmacokinetic parameters. Steady state conditions were assessed within each dose level using an ANOVA repeat-measures model with fixed effects for day and repeated effect for subject. Predose concentrations for each dose (Days 5, 6, and 7; or 15, 16, and 17; or 25, 26, and 27) were used in the analysis. Concentration data was natural logtransformed for the analysis.
The primary endpoint in this study was the relationship between the pharmacokinetic parameters for fluvoxamine and the dose of fluvoxamine maleate. The endpoint was evaluated by 1) determining the extent of pharmacokinetic differences between fluvoxamine maleate CR doses using analysis of variance (ANOVA) methods, and 2) determining the dose proportionality of AUC and Cmax using orthogonal linear and quadratic contrasts incorporated into the ANOVA model. The general form of the statistic model employed for analysis of the pharmacokinetic parameters was an ANOVA with fixed factor for dose and repeated factor for subject. AUC and Cmax were natural log-transformed for analysis. Differences between dose were tested using contrasts in ANOVA and expressed as ratios with 90% confidence intervals of the higher dose to the lower dose. The 90% confidence intervals were generated using a standard t-test confidence interval approach. Dose proportionality was assessed using linear (-1, 0, 1) and quadratic (-1, 2, -1) contrasts on the dose.
P-values and 95% confidence intervals of the contrast estimates were presented. The analysis was produced using PROC MIXED in SAS with an unstructured covariance matrix. An effect in the analysis was considered significant if the p-value was less than 0.05. Both dose-normalized and log-transformed AUC and Cmax were analyzed.

The time to reach the maximal observed concentration, Tmax, was analyzed using descriptive statistics.

Assessment of Steady State
Analysis of trough concentrations on Days 5-7 (100 mg), 15-17 (200 mg), and 25-27 (300 mg) demonstrated that fluvoxamine achieved steady state prior to the final dose administration from which pharmacokinetic parameters were calculated.

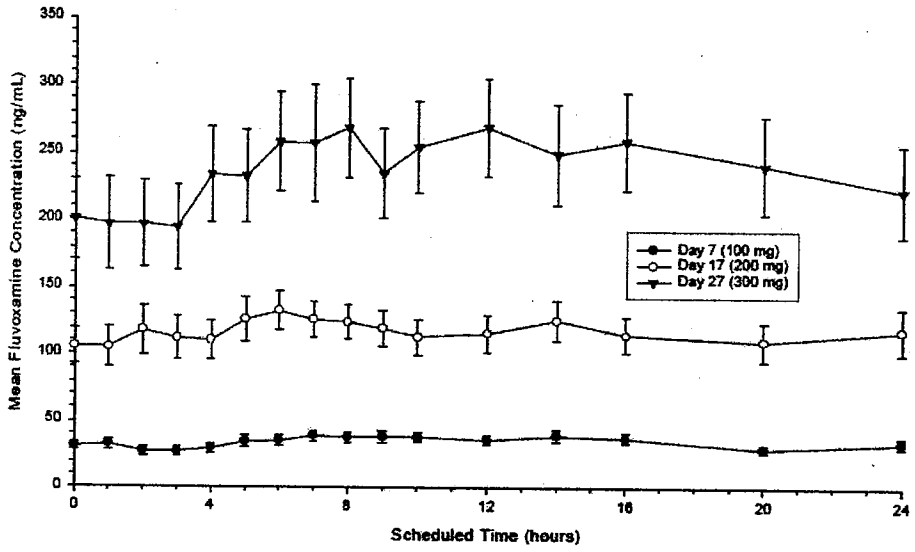
Initially, steady state was attained after five consecutive days of once daily 100 mg fluvoxamine CR administration. Plot 1 illustrates individual and mean fluvoxamine trough values for Days 5-7, 15-17, and 25-27. Individual trough concentrations and statistical analysis for steady state (i.e., p-values) are located in Tables 10.2.2 and 10.2.5, respectively.

Clinical study began: July 7, 1999
Sample analysis completed: November 22, 1999
Longest Possible Storage-139 days

Parameter	Fluvoxamine
Method	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL
Linearity (Standard curve samples)	0.5-1000 ng/ml
Quality Control (QC) Samples	4, 120, & 600 ng/mL
Precision of Standards (%CV)	2.7 %@0.5 ng/ml 4.5%@ 1000 ng/ml
Precision of QC Samples (%CV)	16.6%@4 ng/ml 9.9%@120 ng/ml 9.5%@ 600 ng/ml
Accuracy of Standards (%)	99%@0.5 ng/ml 103%@ 1000 ng/ml
Accuracy of QC Samples (%)	102%@4 ng/ml 96%@120 ng/ml 96%@ 600 ng/ml

RESULTS

Mean (SEM) Plasma Fluvoxamine Concentrations on Day 7 (100 mg), Day 17 (200 mg), and Day 27 (300 mg)



Statistical Analysis Results on Multiple-Dose Pharmacokinetic Parameters: AUC(0-24h) and Cmax

Parameter	CR Dose (mg)	Arithmetic Mean	SD	CR Doses Compared	Ratio (%) from ANOVA	90% CI on Ratio
AUC(0-24h) (ng•hr/mL)	100	818.54	350.62	200 mg/100mg	329	286, 379
	200	2783.42	1413.63	300 mg/200mg	177	140, 224
	300	5777.72	3579.76	300 mg/100mg	584	426, 800
Cmax (ng/mL)	100	47.38	19.45	200 mg/100mg	331	286, 383
	200	161.71	80.24	300 mg/200mg	171	125, 235
	300	319.49	197.99	300 mg/100mg	566	421, 761

Fluvoxamine exhibited nonlinear, dose-dependent pharmacokinetics. As the CR dose increased over the dose range from 100 mg to 300 mg per day, plasma fluvoxamine concentrations increased higher than corresponding increases in dose.
This is reflected in the mean steady state AUC(0-24h) and Cmax values the Table

Over the entire 3-fold dose range, the ANOVA indicated that AUC(0-24h) increased 5.8-fold and Cmax increased 5.7-fold. Initially over the lower end of the dosage range, as dose doubled from 100 mg to 200 mg fluvoxamine CR per day, AUC(0-24h) and Cmax increased 3.3-fold. Over the upper end of the dose range, the deviation from dose proportionality was less. As dose increased 1.5-fold from 200 mg to 300 mg, AUC(0-24h) increased 1.8-fold and Cmax increased 1.7-fold.

Fluctuation of fluvoxamine (peak to trough concentrations) within the dosing interval remained relatively constant across the 100 mg, 200 mg, and 300 mg

doses at 70% to 80%. Tmax values were similar across the CR doses, but variable when comparing individual values within the same CR dose indicated by mean (range) values of 9 (1-16), 9 (2-24), and 11 (1-24) hours for the 100 mg, 200 mg, and 300 mg CR doses, respectively. Oral clearance (CLss/F) and T1/2 mean (SD) values for the 300 mg dose were 1.15 (1.99) L/hr/kg and 29.97 (21.02) hours, respectively.

PANEL 7.3. Statistical Analysis Results of Key Pharmacokinetic Parameters for Dose Proportionality

Parameter	CR Dose (mg)	Arithmetic Mean	SD	CR Doses Compared	Ratio (%) from ANOVA	90% CI on Ratio
DN-AUC(0-24h) (ng•hr/mL)	100	8.10	3.51	200 mg/100 mg	165	[3, 180]
	200	13.92	7.07	300 mg/200 mg	118	[4, 149]
	300	19.26	11.93	300 mg/100 mg	195	[2, 257]
DN-Cmax (ng/mL)	100	0.47	0.19	200 mg/100 mg	165	[3, 191]
	200	0.81	0.40	300 mg/200 mg	114	[3, 156]
	300	1.07	0.66	300 mg/100 mg	189	[0, 254]

*DN = Dose-normalized

Deviations from linearity were statistically significant over the entire dose range of 100 mg to 300 mg indicated by an increase in DN-AUC(0-24h) and DN-Cmax of 2-fold and 1.9-fold, respectively.

Comment:

1. Nonlinearity is reflected in the dose-normalized (DN) AUC(0-24h) and Cmax values. DN-AUC and DN-Cmax increased with dose; all pairwise comparisons were greater than one indicating nonlinearity (Panel 7.3).

2. Statistical significance regarding nonlinearity was also evident in the low dose range comparison of 100 mg to 200 mg with DN-AUC(0-24h) and DN-Cmax increasing 1.7-fold. The upper dose range comparison of 200 mg to 300 mg, although not statistically significant, had evidence of nonlinearity with an increase of 1.2-fold and 1.1-fold for DN-AUC(0-24h) and DN-Cmax, respectively.

Study 1098001- Study to Determine the Pharmacokinetics of Fluvoxamine After Multiple Doses of a Fluvoxamine CR 100 mg Capsule (Prototype C)

TITLE: A Pilot Study to Determine the Pharmacokinetics of Fluvoxamine After Multiple Doses of a Fluvoxamine CR 100 mg Capsule (Prototype C) and a 100 mg LUVOX® Tablet in Healthy Male Volunteers

STUDY INITIATION DATE: 13 November 1998

STUDY COMPLETION DATE: 20 December 1998

STUDY OBJECTIVES
To determine the pharmacokinetics of fluvoxamine after multiple-doses of a fluvoxamine CR 100 mg capsule formulation (Prototype C) and 100 mg LUVOX® Tablet in healthy male subjects and to monitor the subjects for safety.

Overall Study Design and Plan – Description
This was an open-label, multiple-dose, two-treatment, two-period, balanced randomized, crossover study to determine the pharmacokinetics of fluvoxamine after multiple doses of a fluvoxamine CR 100 mg capsule formulation (Prototype C) and reference tablet. The study was conducted in healthy male subjects. Sixteen (16) subjects were planned for this study, with a minimum of 12 subjects expected to complete both treatment periods. Only subjects who were phenotyped as extensive metabolizers by CYP2D6 using dextromethorphan were included in the study to minimize the variability associated with the disposition of fluvoxamine. The duration of the study was approximately 30 days from Day 1 of administration.

Sixteen (16) healthy subjects were planned to receive fluvoxamine 100 mg/day in the form of either LUVOX® Tablets or as CR Capsule Formulation Prototype C for 10 consecutive days. Each subject was confined to the clinic for the duration of each treatment period (Days -1 to 12 and Days 17 to 29).

A light supper was provided at approximately 21.00 hours. On the morning of Days 1-10
and 18-27, each subject was administered a 100 mg dose of fluvoxamine maleate, which was swallowed whole with 180 mL of tap water. Subjects were required to fast overnight until four hours after drug administration on Days 10 and 27. Subjects were to remain upright for four hours after dosing on Days 10 and 27.

Pre-dose blood samples were collected on the mornings of Days 1 to 10 and 18 to 27, prior to drug administration.
In addition, blood samples (7 mL each) were obtained at the following times following administration of both the reference and test treatments on Days 10 and 27: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36 and 48 hours

Demographic Data

Demographic Information

Trait		Overall
Gender	Male	12
Race	Caucasian	12
Frame Size	Small	1
	Medium	8
	Large	3
Age	Mean	26
	S.D.	8
	Minimum	19
	Maximum	43
	N	12
Weight (lb)	Mean	169.2
	S.D.	27.5
	Minimum	133.6
	Maximum	222.0
	N	12.0
Height (in)	Mean	70.0
	S.D.	3.2
	Minimum	64.6
	Maximum	75.3
	N	12.0

Treatments Administered

The primary objective of this study was pharmacokinetic evaluation so this study was not blinded. The following were the treatments:
Reference Treatment : 100 mg LUVOX® (fluvoxamine maleate) Tablet
Test Treatment: 100 mg Fluvoxamine CR formulation (Prototype C)

Primary Pharmacokinetic Variables

The following pharmacokinetic parameters were derived from the plasma concentration data: Cmax, AUC(0-24), tmax, tmin, Cmin, Cavg. For comparison between the two treatments, Cmax-Cmin, Cmax/Cmin, Cmax-Cmin/Cmin, Cmax-Cmin/Cavg and Frel[%] were also calculated.
Linear regression analysis was performed on the individual trough plasma concentrations to determine whether the plasma concentrations on the prespecified
sampling day (Days 10 and 27) reflected steady state (Appendix 12.1.8.2). Following linear regression, data with a slope which was statistically significantly different from zero was deemed to have not attained steady state, otherwise steady state was assumed.
An analysis of variance (ANOVA) was performed on AUC (0-24) and Cmax

transformed to the log base 10. ANOVA was also conducted on the nontransformed
pharmacokinetic parameters, Cmax, AUC(0-24), tmax, tmin, Cmin, Cavg, Cmax-Cmin, Cmax/Cmin, Cmax-Cmin/Cmin, Cmax-Cmin/Cavg, and Frel [%] .

Bioanalytical Analysis

Screening of subjects – extent of CYP2D6 metabolism with dextromethorphan
All subjects were screened (pre-study) to establish their extent of CYP2D6 metabolism with dextromethorphan. Only healthy subjects who were phenotyped as extensive metabolizers by CYP2D6 with dextromethorphan were included in the study to decrease the variability associated with the disposition of fluvoxamine. Samples were analysed for dextromethorphan and dextrorphan by HPLC with fluorescence detection [redacted]

Samples were analysed according to Test Method [redacted], which is a procedure recently adapted in [redacted] from literature supplied by Solvay Pharmaceutical, Inc., for the extraction of dextromethorphan and dextrorphan from human urine. The method involves [redacted]

Assay validation has been carried out over the concentration range of 0.05 - 5.0 ug/ml for dextromethorphan and 0.5 - 50 ug/ml for dextrorphan. This included intra-day accuracy and precision, inter-day accuracy and precision, selectivity, and recovery.

This assay has a limit of quantification of 0.05 □g/ml dextromethorphan and 0.5 ug/ml dextrorphan. The intra-assay reproducibility data for dextromethorphan ranged from 99.31% to 111.18% across the calibration range. The intra-assay precision for dextromethorphan measured by the coefficient of variation (%CV) ranged from 2.03% to 14.57% across the calibration range. The intra-assay reproducibility data for dextrorphan ranged from 99.39% to 112.74% across the calibration range. The intra-assay precision for dextrorphan measured by the coefficient of variation (%CV) ranged from 2.50% to 12.87% across the calibration range.

Plasma Analysis Results

Clinical study began: November 14, 1998
Sample analysis completed: January 7, 1999
Longest Possible Storage-54 days

Parameter	Fluvoxamine
Method	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL
Linearity (Standard curve samples)	0.5-500 ng/ml
Quality Control (QC) Samples	4, 120, & 600 ng/mL
Precision of Standards (%CV)	3 %@0.5 ng/ml 6 %@ 1000 ng/ml
Precision of QC Samples (%CV)	12%@4 ng/ml 15%@120 ng/ml 7%@ 600 ng/ml
Accuracy of Standards (%)	99%@0.5 ng/ml 99%@ 1000 ng/ml
Accuracy of QC Samples (%)	98%@4 ng/ml 98%@120 ng/ml 102%@ 600 ng/ml

RESULTS

Figure 1 . **Mean Plasma Concentrations Versus Time Curve**

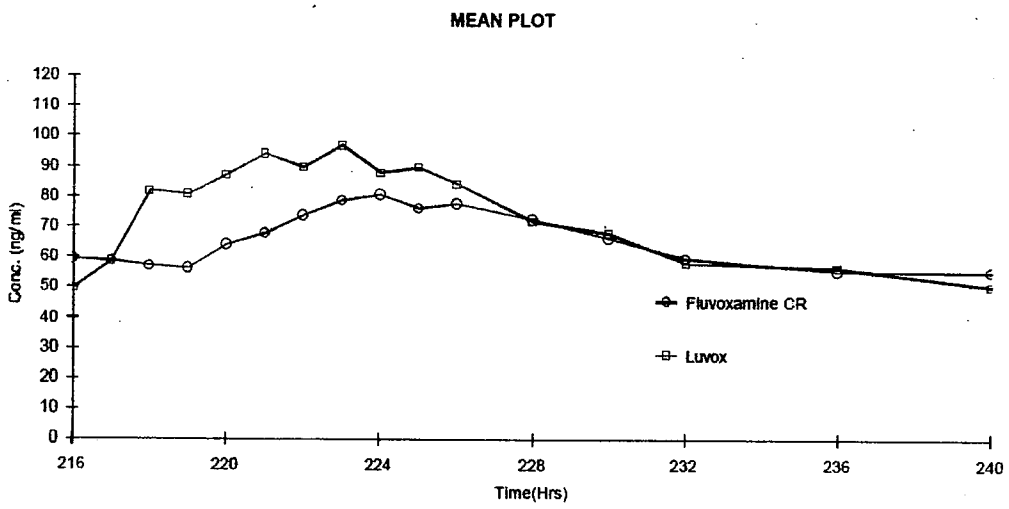


Table 1 .Summary statistics for non-transformed pharmacokinetic parameters

parameters

Parameter	TREATMENT A Fluvoxamine CR (Elan Prototype 'C') Mean ± SD	TREATMENT B LUVOX® Tablets Mean ± SD
Cmax (ng/mL)	91.85 ± 63.67 *	107.00 ± 73.52
AUC(0-24) (ng/mL.hr)	1543.18 ± 1136.99	1738.55 ± 1392.42
Frel [%] (Trt A/Trt B)	93.97 ± 15.77	-
Cmin (ng/mL)	44.51 ± 34.78	43.76 ± 41.15
Cmax – Cmin (ng/mL)	47.35 ± 29.41 *	63.23 ± 33.90
Cmax-Cmin/Cavg	0.85 ± 0.22 *	1.13 ± 0.38
Cmax-Cmin/Cmin	1.32 ± 0.51 *	2.26 ± 1.09
Cavg (ng/mL)	64.30 ± 47.37	72.44 ± 58.02
Cmax/Cmin	2.32 ± 0.51 *	3.26 ± 1.09
tmax (hr)	224.90 ± 1.97# (8.90 ± 1.97)	222.80 ± 2.15# (6.80 ± 2.15)
tmin (hr)	225.10 ± 10.51# (9.1 ± 10.51)	227.30 ± 11.94# (11.3 ± 11.94)

*p<0.05, statistically significant relative to LUVOX® tablets

#Numbers in parentheses represent tmax and tmin as indicated from time of dosing on intensive sampling day.

Table 2 .Summary statistics for log-transformed pharmacokinetic parameters

Parameter	TREATMENT A Fluvoxamine CR (Elan Prototype 'C') Geometric Mean	TREATMENT B LUVOX® Tablets Geometric Mean
Cmax (ng/mL)	70.07*	82.65
AUC(0-24) (ng/mL.hr)	1119.04	1205.64

*p<0.05, statistically significant relative to LUVOX® tablets

Comments:

1. The relative bioavailability (Frel [%]) of the fluvoxamine CR formulation was 92.8%(geometric means) that of the LUVOX® Tablet. The mean AUC(0-24) of the fluvoxamine CR formulation was not different from that of LUVOX® tablets.

2. The test formulation had a reduced Cmax compared to the LUVOX® tablets. The Cavg and Cmin of the test formulation were not different from the LUVOX® tablets. The Cmax-Cmin/Cavg for fluvoxamine CR was reduced relative to that of LUVOX® Tablet.

3. There was no difference in the tmax of the two treatments tested. The tmin of fluvoxamine CR and LUVOX® Tablets was also not different.

Study 1098002- Study to Determine the Pharmacokinetics of Fluvoxamine After Multiple Doses of a Fluvoxamine CR 100 mg Capsule (Prototype D)

A Pilot Study to Determine the Pharmacokinetics of Fluvoxamine After Multiple Doses of a Fluvoxamine CR 100 mg Capsule (Prototype D) and a 100 mg LUVOX□Tablet in Healthy Male Volunteer

STUDY INITIATION DATE: 10 November 1998
STUDY COMPLETION DATE: 09 December 1998

STUDY OBJECTIVES
To determine the pharmacokinetics of fluvoxamine after multiple doses of a fluvoxamine CR 100 mg capsule formulation (Prototype D) and 100 mg LUVOX® Tablets in healthy male subjects and to monitor the subjects for safety.

METHODS

DEMOGRAPHICS

Trait		Overall
Gender	Male	14
Race	Caucasian	14
Frame Size	Small	3
	Medium	5
	Large	6
Age	Mean	31
	S.D.	8
	Minimum	21
	Maximum	44
	N	14
Weight (lb)	Mean	169.8
	S.D.	21.1
	Minimum	138.5
	Maximum	195.8
	N	14.0
Height (in)	Mean	70.1
	S.D.	2.6
	Minimum	66.2
	Maximum	74.1
	N	14.0

Overall Study Design and Plan – Description

This was an open-label, multiple-dose, two-treatment, two-period, balanced randomised, crossover study to determine the pharmacokinetics of fluvoxamine after multiple doses of a fluvoxamine CR 100 mg capsule formulation (Prototype D) and reference tablet. Sixteen (16) healthy male subjects were planned for this study, with a minimum of 12 subjects expected to complete both treatment periods. Only subjects who were phenotyped as extensive metabolisers of CYP2D6 using dextromethorphan were included in the study to minimise the variability associated with the disposition of fluvoxamine.

The duration of the study was approximately 30 days from Day 1 of administration. Subjects received fluvoxamine 100 mg/day in the form of either LUVOX® Tablets or as Fluvoxamine CR Capsule Formulation Prototype D for 10 consecutive days. Eachsubject was confined to the clinic for the duration of each treatment period (Days -1 to 12 and Days 17 to 29).

In addition, blood samples (7 mL each) were obtained at the following times following administration of both the Reference and Test treatments on Days 10 and 27: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36 and 48 hours

Pharmacokinetic Data Analysis

Non-compartmental pharmacokinetic analysis was performed on plasma concentration data of fluvoxamine using WinNonLin-Pro Version 1.5. The data analysis was conducted on all 14 subjects who completed the study.

The following pharmacokinetic parameters were derived from the plasma concentration data: Cmax, AUC (0-24), tmax, tmin, Cmin, Cavg. For comparison between the two treatments, Cmax-Cmin, Cmax/Cmin, Cmax-Cmin/Cmin, Cmax-Cmin/Cavg and Frel [%] were also calculated.

Statistical Analysis of Pharmacokinetic Parameters
Descriptive statistics (mean, standard deviation and coefficient of variation) were provided for each pharmacokinetic parameter (Appendix 12.2.6.4).
Linear regression analysis was performed on the individual trough plasma concentrations to determine whether the plasma concentrations on the pre-specified sampling day (Days 10 and 27) reflected steady state (Appendix 12.1.8.3). Following linear regression, data with a slope which was statistically significantly different from zero was deemed to have not attained steady state, otherwise steady state was assumed. An analysis of variance (ANOVA) was performed on AUC (0-24) and Cmax transformed to the log base 10. ANOVA was also conducted on the non-transformed pharmacokinetic parameters, Cmax, AUC(0-24), tmax, tmin, Cmin, Cavg, Cmax-Cmin, Cmax/Cmin, Cmax-Cmin/Cmin, Cmax-Cmin/Cavg and Frel[%]

Plasma Analysis Results

Study
Clinical study began:Nov 11, 1998
Sample analysis completed: December 18, 1998
Longest Possible Storage-37 days

Parameter	Fluvoxamine
Method	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL
Linearity (Standard curve samples)	0.5-500 ng/ml
Quality Control (QC) Samples	4, 120, & 600 ng/mL
Precision of Standards (%CV)	2.5%@0.5 ng/ml 4.3 %@ 1000 ng/ml
Precision of QC Samples (%CV)	8%@4 ng/ml 11%@20 ng/ml 8%@ 120 ng/ml
Accuracy of Standards (%)	100%@0.5 ng/ml 99%@ 1000 ng/ml
Accuracy of QC Samples (%)	96%@4 ng/ml 100%@20 ng/ml 99%@ 120 ng/ml

Samples were analysed for dextromethorphan and dextrorphan by HPLC with fluorescence detection [redacted]
Samples were analysed according to Test Method TM098, which is a procedure recentlyadapted in [redacted] from literature supplied by Solvay Pharmaceutical, Inc.,for the extraction of dextromethorphan and dextrorphan from human urine. The methodinvolves [redacted]

[redacted] Assay validation has been carried out over the concentration range of 0.05 - 5.0 ug/ml for dextromethorphan and 0.5 - 50 ug/ml for dextrorphan. This included intra-day accuracy and precision, inter-day accuracy and precision, selectivity, and recovery. This assay has a limit of quantification of 0.05 ug/ml dextromethorphan and 0.5 ug/ml dextrorphan. The intra-assay reproducibility data for dextromethorphan ranged from 99.31% to 111.18% across the calibration range. The intra-assay precision for dextromethorphan measured by the coefficient of variation (%CV) ranged from 2.03% to 14.57% across the calibration range. The intra-assay reproducibility data for dextrorphan ranged from 99.39% to 112.74% across the calibration range. The intra-assay precision for dextrorphan measured by the coefficient of variation (%CV) ranged from 2.50% to 12.87% across the calibration range.

RESULTS

Mean Plasma Concentrations Versus Time Curve

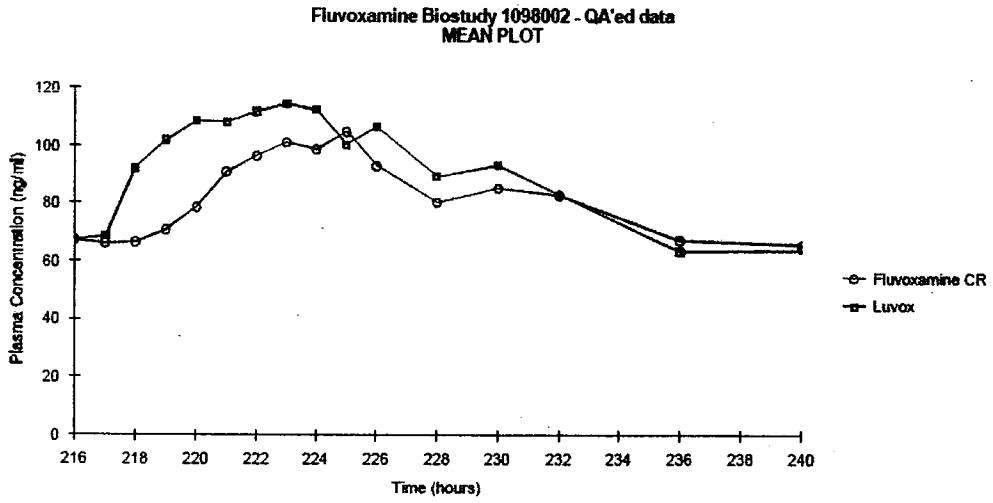


Table 1. Summary statistics for non-transformed pharmacokinetic parameters

Parameter	TREATMENT A Fluvoxamine CR (Elan Prototype 'D') Mean ± SD	TREATMENT B LUVOX® Tablets Mean ± SD
Cmax (ng/mL)	114.87 ± 58.09 *	129.59 ± 62.86
AUC(0-24) (ng/mL.hr)	1929.09 ± 1048.27 *	2109.30 ± 1085.63
Frel [%] (Trt A/Trt B)	91.01 ± 10.83	-
Cmin (ng/mL)	57.41 ± 34.39	54.56 ± 32.69
Cmax – Cmin (ng/mL)	57.45 ± 27.40 *	75.03 ± 34.30
Cmax-Cmin/Cavg	0.77 ± 0.27	0.91 ± 0.18
Cmax-Cmin/Cmin	1.26 ± 0.92	1.59 ± 0.51
Cavg (ng/mL)	80.38 ± 43.68 *	87.89 ± 45.23
Cmax/Cmin	2.26 ± 0.92	2.59 ± 0.51
tmax (hr)	223.79 ± 1.19 *	222.43 ± 2.24
tmin (hr)	224.14 ± 10.24	224.79 ± 10.23

* $p<0.05$, statistically significant relative to LUVOX® tablets.

Numbers in parentheses represent tmax and tmin as indicated from time of dosing on intensive sampling day.

Table 2 .Summary statistics for log-transformed pharmacokinetic parameters

Parameter	TREATMENT A Fluvoxamine CR (Elan Prototype 'D') Geometric Mean	TREATMENT B LUVOX® Tablets Geometric Mean
Cmax (ng/mL)	98.45*	112.60
AUC(0-24) (ng/mL.hr)	1627.26*	1800.03

* $p<0.05$, statistically significant relative to LUVOX® tablets

Comments:

1.The relative bioavailability [Frel(%)] of the fluvoxamine CR formulation was 91% that of the LUVOX® Tablets. The mean AUC (0-24) of the fluvoxamine CR was lower than that of LUVOX® Tablets.

2.The fluxoxamine CR formulation had a reduced Cmax, Cavg, Cmax-Cmin/Cavg, Cmax-Cmin and tmax compared to LUVOX® Tablets.

Study-0398002- Bioavailability of Four Elan Fluvoxamine CR 100 mg Tablet Formulations Relative to LUVOX® 100 mg Tablet

A Single Dose Study in Healthy Volunteers to Compare the Bioavailability of Four Elan
Fluvoxamine CR 100 mg Tablet Formulations Relative to LUVOX® 100 mg Tablet (Solvay
Pharmaceuticals Inc.)

STUDY INITIATION DATE: 09 July 1998
STUDY COMPLETION DATE: 02 September 1998

INTRODUCTION

Elan Pharmaceutical Technologies is developing a once-daily formulation of fluvoxamine maleate (fluvoxamine CR). Currently, doses of fluvoxamine maleate greater than 100 mg are dosed twice daily. Elan's controlled release formulation will facilitate once daily dosing resulting in ease of titration and patient compliance. This is one of the pilot studies to evaluate four tablet formulations.

STUDY OBJECTIVES
The objectives of this study were:
- To compare the bioavailability of four Elan fluvoxamine CR 100 mg prototype tablet formulations relative to LUVOX® 100 mg Tablets.
- To characterize the plasma concentration profile of the CR formulation compared to LUVOX® Tablets.
- To ensure the safety of the test formulations by monitoring the volunteers for adverse events.

Overall Study Design and Plan - Description
The study was an open label, single dose, five treatment, five period, randomised, crossover comparing four Elan fluvoxamine CR 100 mg prototype tablet formulations with LUVOX® Tablet 100 mg (Solvay Pharmaceuticals Inc.). Fifteen (15) subjects were planned to be dosed as one group to ensure completion of ten (10). All subjects were screened to exclude poor metabolisers of CYP 2D6 using dextromethorphan, in order to minimize the variability in the disposition of fluvoxamine. The duration of stay in the clinic was approximately 16 hours prior to dosing and 96 hours after dosing with a ten day washout interval between each treatment period. The total duration of the study was approximately 45 days from Day 1 of administration.
During each treatment period of the study, subjects received either one of the Elan 100 mg fluvoxamine CR prototype tablets or one LUVOX® 100 mg Tablet (SolvayPharmaceuticals Inc.) according to the table of randomisation (Appendix

12.1.5). Subjects were required to remain sitting or ambulatory for four hours after dosing. At a designated time between 0800 and 1000 hours to be called T0, the study drug was to be administered with 240 ml of tap water after at least a 10 hour overnight fast. Lunch was to be served at T0+4 hours, an evening meal at T0+9 hours, and a light supper at T0+12 hours. Breakfast, lunch, dinner and supper were provided at approximately 09.30 hours, 13.00 hours, 18.00 hours and 21.00 hours respectively on Days 2, 3 and 4. The same daily menu was to be followed in each treatment period.

Disposition of Subjects
Ten male subjects were enrolled in the study. All subjects were extensive metabolisers of dextromethorphan.

Demographics

Subj. No:	V. No:	Sequence	Age	Height	Weight	Frame	Smoker	Sex
1	1367	D,C,E,B,A	36	181	88	Large	Yes	MALE
2	758	C,B,D,A,E	32	180	87.5	Large	Yes	MALE
3	1387	E,D,A,C,B	37	176	83	Large	Yes	MALE
4	1352	E,A,D,B,C	24	186	83.2	Medium	Yes	MALE
5	1383	A,B,E,C,D	35	193.5	102	Large	Yes	MALE
7	1361	A,E,B,D,C	36	184.5	80	Medium	No	MALE
9	943	E,D,A,C,B	22	180.5	77.5	Medium	No	MALE
12	1015	A,E,B,D,C	23	181	77	Medium	Yes	MALE
13	1371	D,E,C,A,B	23	181	69	Small	No	MALE
14	960	B,A,C,E,D	23	187	89	Large	Yes	MALE

The following were the treatments:
Treatment A : 100 mg fluvoxamine CR tablet formulation, single dose at T0 hours, fasted -
Treatment B : 100 mg fluvoxamine CR tablet formulation, single dose at T0 hours, fasted -
Treatment C : 100 mg fluvoxamine CR tablet formulation, single dose at T0 hours, fasted -
Treatment D : 100 mg fluvoxamine CR tablet formulation, single dose at T0 hours, fasted -
Treatment E : LUVOX® 100 mg Tablet, single dose at T0 hours, fasted - Solvay Pharmaceuticals Inc.

Plasma Sampling

Venous blood samples (5ml) were to be obtained via an indwelling cannula or by direct venepuncture of the ante-cubital veins at the following times following each drug administration for a total of 21 samples:0 (predose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36, 48, 72 and 96 hours.

Pharmacokinetic Data Analysis
Non-compartmental pharmacokinetic analysis was performed on plasma concentration
data of fluvoxamine using WinNonLin-Pro Version 1.5. The data analysis was conductedon all 6 subjects who completed the study. The following pharmacokinetic parameters were derived from the plasma concentration data: AUC(0-∞), Frel [%], Cmax, tmax, C24h, AUCall, lambda z and t½. For comparison with the reference product LUVOX® Tablet, Frel [%], relative Cmax, difference in tmax and relative C24h for each formulation were also calculated. The calculations of these comparative parameters were carried out within each subject and then averaged. These averaged results were then used to assess if the formulation met the criteria for acceptance.

Statistical Analysis of Pharmacokinetic Parameters
Descriptive statistics (mean, standard deviation and coefficient of variation) were provided for each pharmacokinetic parameter (Appendix 12.2.9).
An analysis of variance (ANOVA) was performed on AUCall, AUC(0-∞) and Cmax data transformed to the log base 10. ANOVA was also conducted on the non-transformed pharmacokinetic parameters, Cmax, AUCall, AUC(0-∞), tmax, C24h, Lambda z and t1/2.
Criteria for Acceptance
The following criteria were applied to determine the acceptability of the prototype CR formulations.
- Relative bioavailability (Frel [%]) > 80% compared to LUVOX® 100 mg tablet.
- Peak concentrations (Cmax) < 85% and occurring > 3h (tmax) later compared to LUVOX® 100 mg tablet.
- 24-hour concentrations (C24h) > 110% of LUVOX® 100 mg tablet.

Study-0398002
Clinical study began: July 10, 1998
Sample analysis completed: September 3, 1998
Longest Possible Storage-55 days

Parameter	Fluvoxamine
Method	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL
Linearity (Standard curve samples)	0.5-1000 ng/ml
Quality Control (QC) Samples	4, 120, & 600 ng/mL
Precision of Standards (%CV)	2.5%@0.5 ng/ml 6.8%@ 1000 ng/ml
Precision of QC Samples	14%@4 ng/ml

(%CV)	12%@120 ng/ml 8%@ 600 ng/ml
Accuracy of Standards (%)	98%@0.5 ng/ml 93%@ 1000 ng/ml
Accuracy of QC Samples (%)	97%@4 ng/ml 95%@120 ng/ml 90%@ 600 ng/ml

RESULTS

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10.1.2 **Mean Plasma Concentration Versus Time Curve**

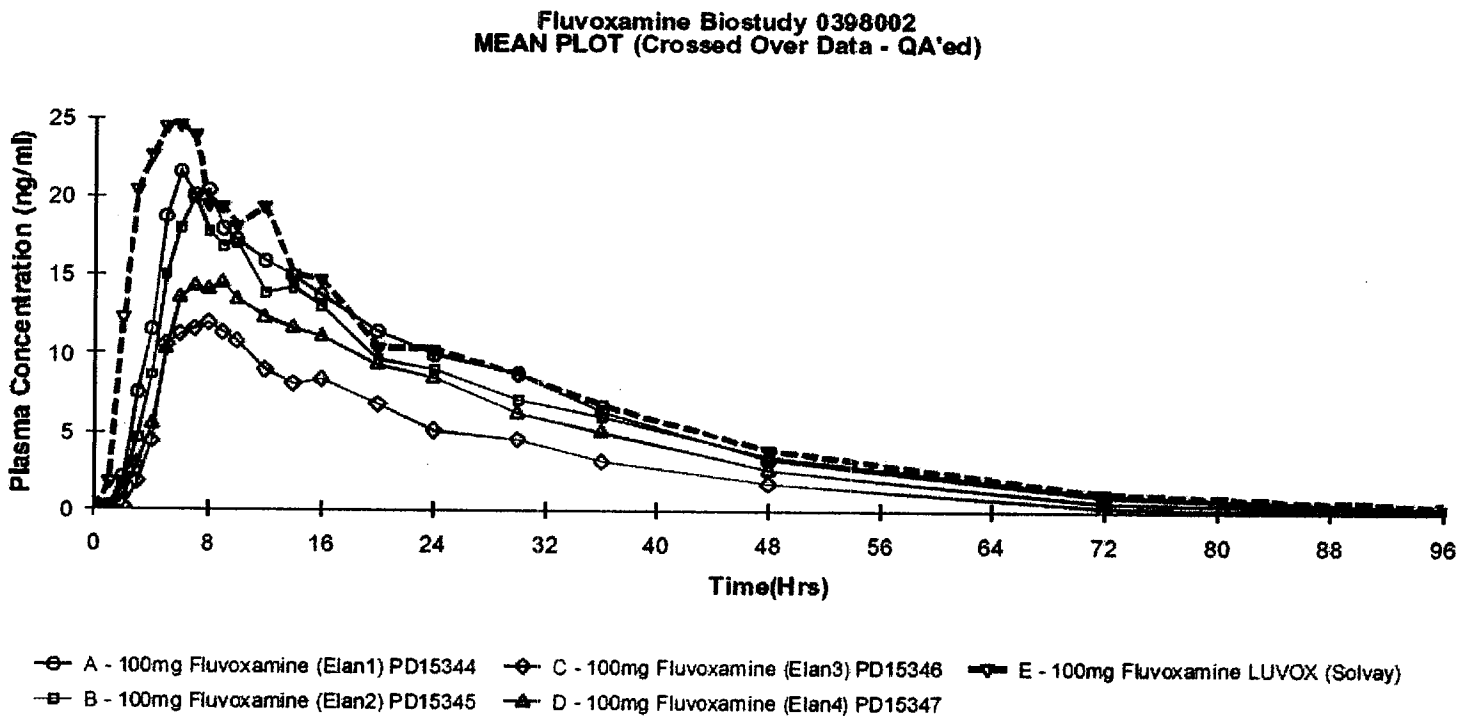


Table 10.1.1.2 – Summary Statistics for Non-Transformed Pharmacokinetic Parameters

	TREATMENT					SELECTION CRITERIA RELATIVE TO LUVOX
	Treatment A Lot No. PD15344 Mean ± Stdev	**Treatment B** Lot No. PD15345 Mean ± Stdev	**Treatment C** Lot No. PD15346 Mean ± Stdev	**Treatment D** Lot No. PD15347 Mean ± Stdev	**LUVOX** *	
AUCinf (ng/ml.h)	549.70 ± 288.93	511.49 ± 372.93	297.14 ± 162.27*	417.72 ± 232.12*	638.82 ± 393.86	-
Frel (%)	92.90 ± 16.84	80.83 ± 22.05	53.10 ± 17.02	75.42 ± 35.40	-	≥ 80%
Cmax (ng/ml)	23.12 ± 7.20	20.70 ± 10.97	13.46 ± 5.06*	16.45 ± 6.91*	28.59 ± 10.35	≤ 85%
Lambda z (h^{-1})	0.06 ± 0.02	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	-
t1/2 (h)	13.10 ± 3.09	13.38 ± 2.87	13.61 ± 2.68	13.89 ± 3.80	14.28 ± 3.41	-
tmax (h)	6.33 ± 1.51	7.50 ± 1.22	7.67 ± 2.34	9.17 ± 3.13*	5.33 ± 1.63	3h
AUCall (ng/ml.h)	542.01 ± 284.97	500.94 ± 365.08	286.98 ± 154.99*	407.87 ± 225.59*	623.93 ± 383.74	-
C24h (ng/ml)	10.02 ± 6.46	9.05 ± 6.99	5.18 ± 2.55	8.53 ± 4.87	10.37 ± 7.13	≥ 110%

* $P \leq 0.0125$ statistically

* Comparison to the criteria for acceptance was based on the individual data.

10.1. Pharmacokinetic Data

10.1.1 Summary Statistics of Pharmacokinetic Parameters

Table 10.1.1.1 – Summary Statistics for Log-Transformed Pharmacokinetic Parameters

PK Parameter	TREATMENT				
	Treatment A Lot No. PD15344 Geometric mean	**Treatment B Lot No. PD15345** Geometric mean	**Treatment C Lot No. PD15346** Geometric mean	**Treatment D Lot No. PD15347** Geometric mean	**LUVOX** Geometric mean
AUCinf (ng/ml.h)	481.26	406.77	266.69 *	361.69	525.62
Cmax (ng/ml)	22.04	18.07	12.59*	15.05*	26.37
AUCall (ng/ml.h)	474.13	398.61	258.04*	353.31	514.35

* $P \leq 0.0125$ statistically significant relative to LUVOX

COMMENTS:
1. A test formulation was considered acceptable for further development by the firm if it met the following criteria: relative bioavailability to LUVOX® 100 mg tablet: ≥80%; relative peak
concentrations to LUVOX® 100 mg tablet: ≤85%, delayed tmax by ≥3h; relative C24h to
LUVOX® 100 mg tablet: ≥110%

2. The relative bioavailabilities of Treatment A and Treatment B were greater than 80% relative to LUVOX® tablet. On the basis of the selection criteria (Frel ≥80%) Treatments A and B are within the acceptable limits. The Cmax data for Treatment B, Treatment C and Treatment D were less than 85% relative to LUVOX® tablets and within the selection criteria. Values observed for the parameter, C24h for Treatment A, Treatment B, Treatment C, and Treatment D were either similar to or less than the C24h reported for LUVOX® tablets. Therefore, none of the four treatments fulfilled the selection criteria of C24h≥ 110% relative to LUVOX® tablets.

3. The tmax for Treatment A, Treatment B and Treatment C were slightly prolonged compared to that of LUVOX® tablets and did not meet the selection criteria of extending tmax ≥3 hours beyond that of LUVOX® tablets. Treatment D showed a significantly longer tmax compared to LUVOX® tablets and was within the criteria for selection. Although all of the Elan fluvoxamine CR 100 mg prototype tablet formulations had reduced peak concentrations and prolonged tmax relative to LUVOX100 mg tablet, none fully met the acceptance criteria set for further development. All treatments were safe and well tolerated in this population.

Study-0698001 Relative Bioavailability of Four Elan Fluvoxamine CR 100 mg Prototype Capsule Formulations Relative to LUVOX□100 mg Tablet

TITLE: A Single Dose Study in Healthy Male Volunteers to Compare the Relative Bioavailability of Four Elan Fluvoxamine CR 100 mg Prototype Capsule Formulations Relative to LUVOX□100 mg Tablet (Solvay Pharmaceuticals Inc.)
STUDY INITIATION DATE: 06 Jul 1998
STUDY COMPLETION DATE: 03 Sep 1998

Primary Objective
To compare the relative bioavailability of four Elan fluvoxamine CR 100 mg prototype capsule formulations relative to LUVOX® 100 mg tablet (Solvay Pharmaceuticals Inc.)

Secondary Objective

To characterize the plasma concentration profile of the CR formulation compared to LUVOX® 100 mg tablet (Solvay Pharmaceuticals Inc.) and to monitor the subjects for safety.

Overall Study Design and Plan – Description

The study was an open-label, single-dose, five-treatment, five-period, randomised, crossover trial comparing four Elan fluvoxamine CR 100 mg prototype formulations with LUVOX® 100 mg (Solvay Pharmaceuticals Inc.). Fifteen subjects were planned to complete 10. Only subjects who were phenotyped as extensive metabolisers of CYP2D6 using dextromethorphan were included in the study to minimize the variability associated with the disposition of fluvoxamine. The duration of the study was 45 days from Day 1 of administration. Vital signs, ECG and clinical laboratory were performed at screening and in the post study assessment. During the trial, vital signs were taken at 0, 1, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72 and 96 hours after dosing, ECG was taken at 24 hours post dosing and adverse events were monitored throughout.

Demographics

Demographic Data

Subject Number	Initials	Gender	Age (Years)	Height (cm)	Weight (Kg)	Frame	Smoking Habits	Race
1		M	27	167	69.8	Medium	Non-Smoker	Caucasian
2		M	20	170	61.7	Medium	Non-Smoker	Caucasian
3		M	28	171	71.9	Medium	Non-Smoker	Caucasian
4		M	29	175	69.6	Medium	Non-Smoker	Caucasian
5		M	21	171	74.5	Medium	Non-Smoker	Caucasian
6		M	19	185	78.3	Medium	Non-Smoker	Caucasian
7		M	19	183	77.6	Medium	Non-Smoker	Caucasian
8		M	26	173	71.3	Medium	Non-Smoker	Caucasian
9		M	32	178	76.6	Medium	Non-Smoker	Caucasian
11		M	21	182	59.7	Small	Non-Smoker	Caucasian
Mean			24	176	71.1			
Std. Dev.			5	6	6.3			
Range:								
Minimum			19	167	59.7			
Maximum			32	185	78.3			
N			10	10	10.0			

Pharmacokinetic Sampling

Venous blood samples (5 mL) were obtained via an indwelling cannula or by direct venepuncture of the ante-cubital veins before dosing and at the following times following each drug administration: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36, 48, 72, and 96 hours.

Pharmacokinetic Data Analysis

Non-compartmental pharmacokinetic analysis was performed on plasma concentration data of fluvoxamine using WinNonLin-Pro Version 1.5. The data analysis was conducted on all ten subjects who completed the study.

The following pharmacokinetic parameters were derived from the plasma concentration data: AUCinf, Cmax, tmax, C24h, AUCall, Lambda z and t½. For

comparison with the reference product LUVOX®, Frel [%], relative Cmax, difference in tmax and relative C24h for each formulation were also calculated. The calculation of these comparative parameters were made within each subject and then averaged. The average results were then used to assess if the formulation met the criteria for acceptance.

Statistical Analysis of Pharmacokinetic Parameters
Descriptive statistics (mean, standard deviation and coefficient of variation) were provided for each pharmacokinetic parameter (Appendix 12.2.6.4).
An analysis of variance (ANOVA) was performed on AUCall, AUCinf and Cmax data transformed to the log base 10. ANOVA was also conducted on the non-transformed pharmacokinetic parameters, Cmax, AUCall, AUCinf, tmax, C24h, Lambda z and t½.

The following criteria were applied to determine the acceptability of the prototype CR formulations:
- Relative bioavailability (Frel [%]) > 80% compared to LUVOX® 100 mg tablet.
- Peak concentrations (Cmax) < 85% and occurring > 3h later (tmax) compared to LUVOX® 100 mg tablet.
- 24-hour concentrations (C24h) > 110% of LUVOX® 100 mg tablet.

Treatments Administered
The following were the treatments:
Treatment A:
100 mg fluvoxamine CR capsule formulation, single dose at T0 hours, fasted - 1
Treatment B:
100 mg fluvoxamine CR capsule formulation, single dose at T0 hours, fasted - 2
Treatment C:
100 mg fluvoxamine CR capsule formulation, single dose at T0 hours, fasted - 3
Treatment D:
100 mg fluvoxamine CR capsule formulation, single dose at T0 hours, fasted - 4
Treatment E:
LUVOX® 100 mg capsule, single dose at T0 hours, fasted - Solvay Pharmaceuticals Inc.

Analytical
Study-0698001

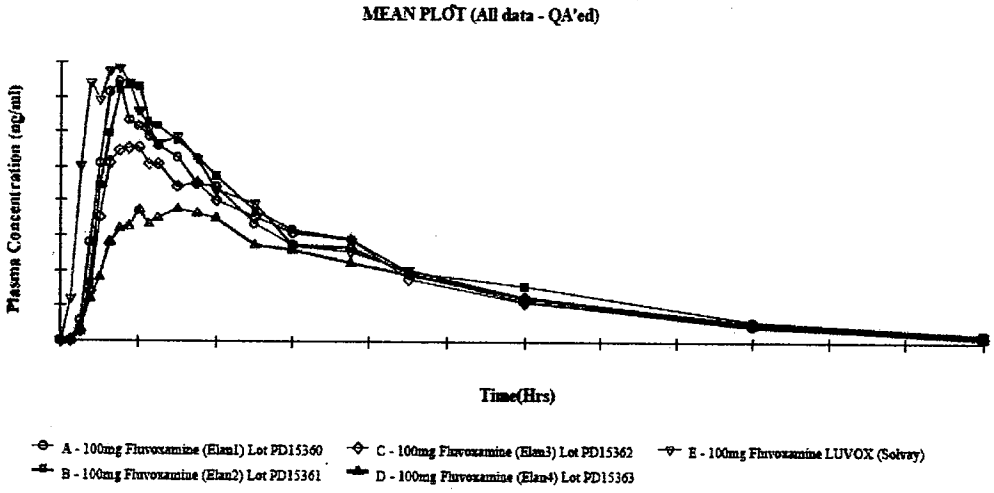
Clinical study began: July 7, 1998
Sample analysis completed: September 3, 1998
Longest Possible Storage-58 days

Parameter	Fluvoxamine
Method	LC-MS/MS

Sensitivity/LOQ	0.5 ng/mL
Linearity (Standard curve samples)	0.5-1000 ng/ml
Quality Control (QC) Samples	4, 120, & 600 ng/mL
Precision of Standards (%CV)	2.4%@0.5 ng/ml 6.8%@ 1000 ng/ml
Precision of QC Samples (%CV)	23%@4 ng/ml 6%@120 ng/ml 15%@ 600 ng/ml
Accuracy of Standards (%)	98%@0.5 ng/ml 93%@ 1000 ng/ml
Accuracy of QC Samples (%)	107%@4 ng/ml 99%@120 ng/ml 89%@ 600 ng/ml

Results

Mean Plasma Concentration Versus Time Curve



Summary statistics for log-transformed pharmacokinetic parameters

Parameter	TREATMENT A Lot No PD15360 Geometric Mean	TREATMENT B Lot No PD15361 Geometric Mean	TREATMENT C Lot No PD15362 Geometric Mean	TREATMENT D Lot No PD15363 Geometric Mean	TREATMENT E LUVOX Geometric Mean
Cmax (ng/ml)	37.88	37.45	28.03	21.00	39.61
AUCinf (ng/ml.h)	734.16	804.16	715.54	631.56	815.88
AUCall (ng/ml.h)	716.13	788.69	699.63	615.61	798.32

*p ≤ 0.0125, statistically significant relative to LUVOX

Summary statistics for non-transformed pharmacokinetic parameters

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Parameter	TREATMENT A Lot No PD15360 Mean ± Stdev	TREATMENT B Lot No PD15361 Mean ± Stdev	TREATMENT C Lot No PD15362 Mean ± Stdev	TREATMENT D Lot No PD15363 Mean ± Stdev	LUVOX® Mean ± Stdev	Criteria for acceptance (relative to Luvox®)+
AUCINF (ng/ml.h)	919.960 ± 747.132	1014.213 ± 885.705	872.731 ± 688.717	725.457 ± 450.549*	1047.194 ± 959.337	-
Frel (%)	95.201 ± 31.844	101.486 ± 24.936	91.152 ± 25.714	83.053 ± 34.432	-	≥ 80%
Cmax (ng/ml)	40.514 ± 16.491	40.611 ± 17.973	31.381 ± 15.035*	22.711 ± 9.146*	44.576 ± 23.132	-
Relative Cmax(%)	106.62 ± 52.67	101.58 ± 41.78	77.55 ± 33.95	58.35 ± 26.09	-	≤ 85%
Lambda z (h^{-1})	0.054 ± 0.014	0.052 ± 0.013	0.049 ± 0.011	0.048 ± 0.008	0.054 ± 0.022	-
t1/ (h)	13.868 ± 4.900	14.356 ± 4.192	15.237 ± 5.395	15.168 ± 3.797	14.722 ± 6.254	-
tmax (h)	5.600 ± 0.843	6.900 ± 2.025	6.900 ± 1.663	12.400 ± 5.296*	4.200 ± 1.814	-
tmax difference (test-ref)	1.40 ± 2.27	2.70 ± 2.21	2.70 ± 2.31	8.20 ± 5.85	-	≥ 3h
AUCall (ng/ml.h)	884.426 ± 678.532	977.301 ± 800.824	838.158 ± 613.578	702.566 ± 416.032	1008.614 ± 868.971	-
C24h (ng/ml)	13.79 ± 9.45	15.95 ± 14.03	15.57 ± 11.92	13.09 ± 7.49	13.73 ± 13.03	
Relative C24h(%)	114.41 ± 37.64	126.65 ± 43.25	126.59 ± 33.81	122.79 ± 58.31	-	≥ 110%

* P ≤ 0.0125, statistically significant relative to LUVOX

+ Comparison to the criteria for acceptance was based on the individual data.

COMMENTS:

1. A test formulation was considered acceptable for further development if it met the following criteria: relative bioavailability to LUVOX® 100 mg tablet > 80%; relative peak concentrations to LUVOX® 100 mg tablet < 85%, delayed by > 3h; relative C24h to LUVOX® 100 mg tablet > 110%.

2. The relative bioavailabilities of all the Elan formulations met the acceptance criteria (≥80% of the LUVOX® tablet). The Cmax of treatments C and D were significantly reduced compared to the reference and met the acceptance criteria of reducing the peak concentration to ≤85% of LUVOX® tablet.

3. The concentrations at 24 h (C24h) of all treatments met the acceptance criteria of ≥110% of LUVOX® tablet. The tmax of treatment D was significantly longer

than that of the reference and met the acceptance criteria of delaying the time to maximum concentration by more than 3 h beyond that of LUVOX® tablet. The tmax of treatments B and C was just marginally shorter than the required 3 h extension beyond that of the reference.

4. In conclusion, all the Elan formulations showed a prolonged tmax relative to that of the reference product (LUVOX® tablet), although only Treatment D met the acceptance criteria. Two formulations had a reduced Cmax and met the acceptance criteria and a further two did not meet the criteria. The relative bioavailabilities of all the formulations were all >80% relative to LUVOX® tablet. All treatments had a C24h greater than that of >110% of LUVOX® tablet.

Study -0798005- Effect of Food on the Relative Bioavailability of a

Fluvoxamine CR 100 mg Formulation C

A Pilot Study to Determine the Effect of Food on the Relative Bioavailability of a Fluvoxamine CR 100 mg Prototype Formulation
STUDY INITIATION DATE: 11 October 1998
STUDY COMPLETION DATE: 04 November 1998

STUDY OBJECTIVE
The objective of the study was to assess the effect of food on the relative bioavailability
of a fluvoxamine CR 100 mg prototype formulation and to monitor the subjects for
safety.

Overall Study Design and Plan – Description
This was an open-label, single-dose, two-treatment, two-period, randomised, crossover study which assessed the effect of food on a fluvoxamine CR 100 mg prototype formulation. Sixteen (16) healthy volunteers were dosed as one group on two separate occasions. Only subjects who were phenotyped as extensive metabolizers by CYP2D6 using the dextromethorphan procedure described in Appendix 1 of the protocol (Appendix 12.1.1) were included in this study in order to minimise the variability associated with the disposition of fluvoxamine. Full vital signs and safety assessments (clinical laboratories, ECGs and adverse event monitoring) were performed at screening, at various times during the study, and during the post-study examination.In each treatment period, subjects were to receive the 100 mg fluvoxamine CR prototype formulation under either fasting or fed conditions

A light supper was provided at approximately 21.00 hours on Day -1 of each treatment

period. Subjects then fasted overnight for a period of at least ten hours. Subjects who were randomised to the Test treatment received a high fat breakfast (see below) thirty minutes prior to dosing and completely consumed this breakfast by five minutes prior to dosing.
2 eggs (fried in butter)
2 strips bacon
2 slices toast with butter
4oz hash browns
1 glass whole milk (240 ml)

Treatments Administered
The primary objective of this study was pharmacokinetic evaluation so this study was not blinded. The treatments were as follows:
Treatment A:
100 mg fluvoxamine CR capsule formulation, single dose at T0 hours, fasting
Treatment B:
100 mg fluvoxamine CR capsule formulation, single dose at T0 hours, fed

DEMOGRAPHICS

Demographic Summary for All Subjects

Trait		Female	Male	Overall
Gender	Female	.	.	3
	Male	.	.	13
Race	Caucasian	3	13	16
Frame Size	Small	.	2	2
	Medium	2	8	10
	Large	1	3	4
Age	Mean	23	28	27
	S.D.	3	7	6
	Minimum	20	19	19
	Maximum	26	38	38
	N	3	13	16
Weight (kg)	Mean	65.7	72.6	71.3
	S.D.	4.9	5.3	6.8
	Minimum	60.3	62.7	60.3
	Maximum	69.9	79.9	79.9
	N	3.0	13.0	16.0
Height (cm)	Mean	167	169	169
	S.D.	2	6	5
	Minimum	165	162	162
	Maximum	168	178	178
	N	3	13	16

Drug Concentration Measurements
Pharmacokinetic Sampling

Venous blood samples (7 ml) were obtained by direct venipuncture of the ante-cubital veins at the following times following each drug administration (expressed as Hours): 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36, 48, 72 and 96 hours. (Total blood volume = 294 mL per subject)

Pharmacokinetic Data Analysis
Non-compartmental pharmacokinetic analysis was performed on plasma concentration data of fluvoxamine using WinNonLin-Pro Version 1.5. The data analysis was conducted on all 16 subjects.
The following pharmacokinetic parameters were derived from the plasma concentration data: AUC(0-inf), Cmax, tmax, AUCall, Lambda_z, and t½. For comparison with the reference fasted treatment, Frel [%] was also calculated. The calculation of this relative parameter was carried out on an individual subject basis and the mean of all of these individual results averaged.

Statistical Analysis of Pharmacokinetic Parameters
Descriptive statistics (mean, standard deviation and coefficient of variation) were provided for each pharmacokinetic parameter (Appendix 12.2.6.4).
An analysis of variance (ANOVA) was performed on AUCall, AUC(0-∞), and Cmax data transformed to the log base 10. ANOVA was also conducted on the non-transformed pharmacokinetic parameters, Cmax, AUCall, AUC(0-∞), tmax, Lambda_z, and t½ (Appendix 12.1.8.2). Geometric mean values (fed/fasted ratios) were calculated for Cmax, AUC(0-∞), and AUCall. The 90% confidence intervals were determined for the log-transformed ratios (fed/fasted) of Cmax, AUC(0-∞), and AUCall.

Study -0798005

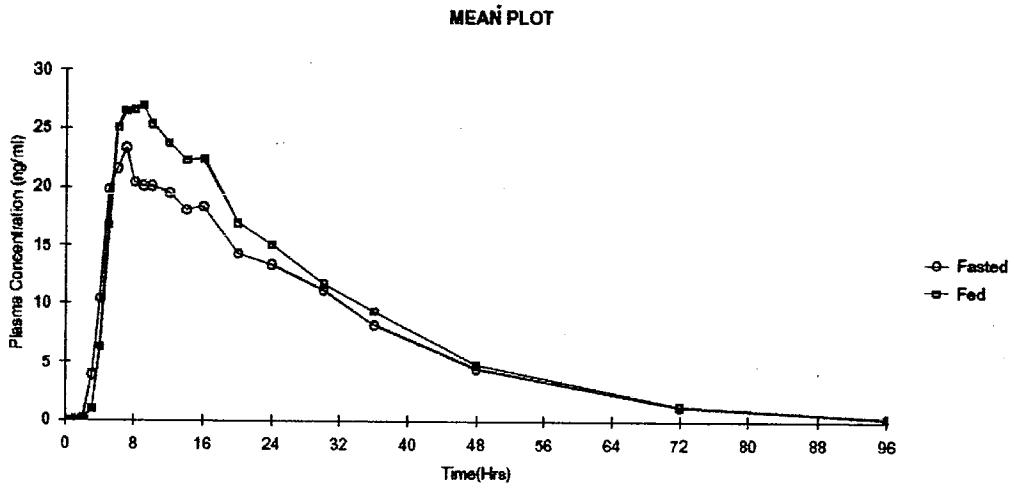
ANALYTICAL
Study -0798005
Clinical study began: October 12, 1998
Sample analysis completed: November 16, 1998
Longest Possible Storage-35 days

Parameter	Fluvoxamine
Method	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL
Linearity (Standard curve samples)	0.5-200 ng/ml
Quality Control (QC) Samples	4, 120, & 600 ng/mL
Precision of Standards	2.4%@0.5 ng/ml

(%CV)	9.2%@ 200 ng/ml
Precision of QC Samples (%CV)	12%@4 ng/ml 9%@120 ng/ml 10%@ 600 ng/ml
Accuracy of Standards (%)	99%@0.5 ng/ml 102%@ 1000 ng/ml
Accuracy of QC Samples (%)	106%@4 ng/ml 102%@120 ng/ml 100%@ 600 ng/ml

RESULTS

Mean Plasma Concentration versus Time Curve



Summary statistics and mean percent ratio (fed/fasted) for log transformed pharmacokinetic parameters

PK PARAMETER	Fasted Lot No PD15537 Mean	Fed Lot No PD15537 Mean	Mean Percent (Fed/Fasted) (%)
AUC(0-∞) (ng/mL.h)	604.398	696.888	115.30
AUCall (ng/mL.h)	596.820	685.043	114.78
Cmax (ng/mL)	25.435	29.108	114.44

Summary statistics for non-transformed pharmacokinetic parameters

PK PARAMETER	Fasted Lot No PD15537 Mean ± SD	Fed Lot No PD15537 Mean ± SD
AUC(0-∞) (ng/mL.h)	667.434 ± 328.065	760.028 ± 319.427
Frel [%]	-	118.816 ± 29.194
Cmax (ng/mL)	26.628 ± 8.149	31.450 ± 12.793
Lambda_z (h^{-1})	0.056 ± 0.016	0.053 ± 0.011
t½ (h)	13.219 ± 3.378	13.613 ± 3.036
tmax (h)	7.125 ± 2.655	8.000 ± 2.066
AUCall (ng/mL.h)	658.195 ± 320.196	747.626 ± 315.366

COMMENTS:

1.The geometric mean values for AUCinf of fluvoxamine CR administered fasted or fed did not differ by more than 15%. In addition, the geometric mean values for Cmax of fluvoxamine CR administered fasted or fed did not differ by more than 14%. The tmax, half life and lambda z values were similar when the fed treatments were compared to fasted confirming that food had a minimal effect on the pharmacokinetics of fluvoxamine from this formulation.

2.The 90% confidence intervals for AUCinf (104-128%) suggest that a food effect cannot be determined in terms of AUC. However, the absence of a food effect on Cmax is indicated by the confidence intervals of the geometric mean data for Cmax (100-131%).

Study-S1141107- Single-Dose Pharmacokinetics of Fluvoxamine, Administered as the100-mg LUVOX® Tablet (Fasting) and the Controlled-Release 100-mg Capsule (Fasting and Fed Conditions)

The Single-Dose Pharmacokinetics of Fluvoxamine, Administered as the 100-mg LUVOX® Tablet (Fasting) and the Controlled-Release 100-mg Capsule (Fasting and Fed Conditions) in Healthy Male and Female Volunteers

STUDY INITIATION DATE: 13 Sep 1999

STUDY COMPLETION DATE: 18 Dec 1999

STUDY OBJECTIVES

To determine and compare the pharmacokinetics of fluvoxamine after a single dose of a fluvoxamine CR 100 mg capsule formulation and a 100 mg LUVOX tablet in healthy subjects.
To determine the effect of food on the pharmacokinetics of fluvoxamine after a single dose of a fluvoxamine CR 100 mg capsule formulation in healthy subjects.

Overall Study Design and Plan – Description
This was an open-label, single-dose, three-treatment, three-period, balanced randomized, crossover study conducted in 28 healthy volunteers, 15 males and 13 females. Each subject received a single dose of fluvoxamine maleate 100 mg in the form of a LUVOX tablet, a fluvoxamine maleate CR capsule under fasted conditions, and fluvoxamine maleate CR capsule under fed conditions. Each dose was separated by at least a 7-day washout. During the screening period, each subject was phenotyped to assess metabolic status of CYP2D6 using dextromethorpan. Both extensive and poor metabolizers were enrolled into this study. All subjects were admitted to the clinical research unit in the evening on Days –1, 7, and 14 and remained confined until the mornings of Days 5, 12, and 19, respectively. On the mornings of Days 1, 8, and 15, each subject was administered a 100-mg dose of fluvoxamine maleate as a tablet or capsule. For two of the study periods, subjects were required to fast from 10 hours before until 4 hours after drug administration. For one study period, subjects received a high-fat breakfast prior to dosing.

Treatments Administered
Fluvoxamine CR 100 mg capsules and LUVOX 100 mg tablets were used in this study.

Demographic Data

Subject Demographic and Baseline Characteristics

Variables	Total (N=28)	Male (n=15)	Female (n=13)
Age (years): Mean (SD)	32.1 (8.64)	29.8 (7.02)	34.8 (9.81)
Range	20.3 – 44.7	20.4 – 43.5	20.3 – 44.7
Ethnicity N(%):			
Caucasian	24 (86%)	12 (80%)	12 (92%)
African-American	2 (7%)	2 (13%)	0
American Indian/Native Alaskan	2 (7%)	1 (7%)	1 (8%)
Metabolic Phenotype N(%):			
Extensive Metabolizer	27 (96%)	14 (93%)	13 (100%)
Poor Metabolizer	1 (4%)	1 (7%)	0
Weight (kg): Mean (SD)	73.0 (9.95)	77.9 (7.71)	67.4 (9.49)
Range	56.2 – 91.2	65.8 – 91.2	56.2 – 88.0
Height (cm): Mean (SD)	173.1 (9.29)	178.8 (6.77)	166.5 (7.23)
Range	152.4 – 193.0	167.6 – 193.0	152.4 – 172.7

Supporting Documentation: Appendix 12.2.4

PHARMACOKINETIC SAMPLING

Whole blood samples (7 mL) were obtained prior to the dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36, 48, 72, and 96 hours following dose administration.

PHARMACOKINETIC DATA ANALYSIS

The following pharmacokinetic parameters were calculated for fluvoxamine after each treatment using observed data for 28 subjects and noncompartmental methods: AUC(0-inf), %AUCext, AUC(0-last), AUC(0-96h), Cmax, CL/F, Kel, T1/2,
and Vz/F.

STATISTICAL DATA ANALYSIS

Descriptive statistics (n, arithmetic mean, geometric mean [for AUC and Cmax only], standard deviation [SD], standard error of mean [SEM], median, minimum, and maximum) were provided for all pharmacokinetic parameters indicated above for each treatment group, and for each treatment by gender group. The geometric mean was calculated using log-transformed, nonzero data and back-transforming the mean result (exponentiating) to obtain the final value.
For the equivalence testing between formulations (a single dose of fluvoxamine CR 100-mg capsule formulation versus a LUVOX 100-mg tablet, each under fasted conditions), the following analysis was performed:
- The equivalence tests were performed on natural log-transformed AUC and Cmax with the LUVOX 100-mg tablet as the reference formulation and the fluvoxamine CR 100-mg capsule under fasted conditions as the test formulation.
- Tmax was analyzed by nonparametric methods[6].

For the comparison of the food effect (after a single dose of fluvoxamine CR 100-mg capsule under fed conditions vs. fasting conditions) the following analysis was performed:
- The equivalence tests were performed on natural log-transformed AUC and Cmax. Fasting was the reference condition, and fed was the test condition.
- Tmax was analyzed by nonparametric methods.[

ANALYTICAL

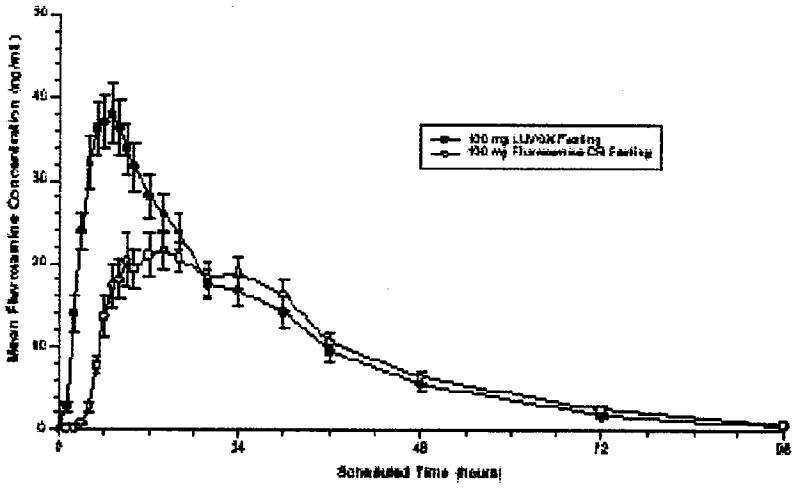
Clinical study began: September 20, 1999
Sample analysis completed: February 2, 2000
Longest Possible Storage-137 days

Parameter	Fluvoxamine
Method	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL
Linearity (Standard curve samples)	0.5-1000 ng/ml

Quality Control (QC) Samples	4, 120, & 600 ng/mL
Precision of Standards (%CV)	1.52 %@0.5 ng/ml 5.23%@ 1000 ng/ml
Precision of QC Samples (%CV)	13.7%@4 ng/ml 11.3%@120 ng/ml 12.8%@ 600 ng/ml
Accuracy of Standards (%)	99%@0.5 ng/ml 101%@ 1000 ng/ml
Accuracy of QC Samples (%)	99%@4 ng/ml 100%@120 ng/ml 94%@ 600 ng/ml

RESULTS

Mean (SEM) Plasma Fluvoxamine Concentrations for LUVOX Fasting and Fluvoxamine CR Fasting Treatments



Mean (SD) Values of Key Fluvoxamine Pharmacokinetic Parameters

Parameter	Treatment	Arithmetic Mean[1]	SD[1,2]
AUC(0-inf) (ng•hr/mL)	LUVOX Fasted[3]	959.33	520.71
	CR Fasted[3]	806.31	450.92
	CR Fed	876.47	447.49
Cmax (ng/mL)	LUVOX Fasted[3]	41.88	18.99
	CR Fasted[3]	25.78	15.66
	CR Fed	28.76	15.18
Tmax (hr)	LUVOX Fasted[4]	6	4–16
	CR Fasted[4]	15	7–30
	CR Fed	16	7–36
T1/2 (hr)	LUVOX Fasted	15.96	2.71
	CR Fasted	16.31	2.66
	CR Fed	15.93	2.87

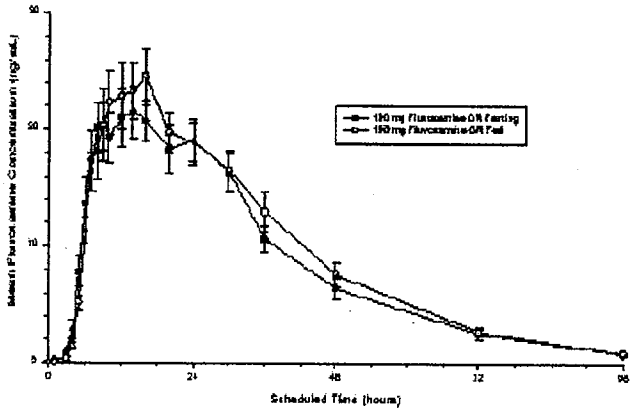
[1] Mean (SD) values based on 28 subjects.
[2] For Tmax: Range (minimum-maximum) values depicted instead of SD.
[3] ANOVA results indicate statistical significance ($p<0.05$) between LUVOX and fluvoxamine CR fasted treatments. An ANOVA was not conducted on T1/2.
[4] Signed rank test results indicate statistical significance ($p<0.05$) between LUVOX and fluvoxamine CR fasted treatments.

Statistical Analysis Results for Fluvoxamine Pharmacokinetics After Fasted and Fed Fluvoxamine CR Treatments

Parameter	Treatment	Least Squares Mean from ANOVA[1]	Treatments Compared	Ratio (%) from ANOVA	90% CI on Ratio
AUC(0-inf) (ng•hr/mL)	CR Fed	784.63	CR Fed/CR Fast[2]	110	102, 118
	CR Fasted	714.79			
Cmax (ng/mL)	CR Fed	25.38	CR Fed/CR Fast	111	100, 124
	CR Fasted	22.82			

[1] Least Squares Mean values based on 28 subjects.
[2] ANOVA results indicated statistical significance ($p<0.05$).
Supporting Documentation: Table 10.2.3

Mean (SEM) Plasma Fluvoxamine Concentrations for Fed and Fasting Fluvoxamine CR Treatments



Mean (SD) Results for Fluvoxamine Pharmacokinetic Parameters Based on Gender

Parameter	Gender	Treatment Arithmetic Mean[1] (SD)[2] LUVOX Fasted	Fluvoxamine CR Fasted	Fluvoxamine CR Fed
AUC(0-inf)[3] (ng*hr/mL)	Female	1150.47 (617.80)	1013.94 (573.86)	1050.17 (529.90)
	Male	793.67 (363.90)	626.36 (187.45)	725.92 (305.29)
Cmax[3] (ng/mL)	Female	46.68 (21.28)	32.58 (20.71)	34.41 (17.97)
	Male	37.72 (16.36)	19.88 (5.01)	23.86 (10.61)
Tmax (hr)	Female	7 (4-16)	14 (7-24)	17 (10-36)
	Male	6 (4-9)	16 (7-30)	14 (7-24)
T1/2 (hr)	Female	15.44 (2.88)	16.53 (2.55)	16.14 (2.71)
	Male	16.41 (2.58)	16.11 (2.83)	15.74 (3.09)

[1] Arithmetic mean based on 28 subjects (15 males and 13 females).
[2] For Tmax: Range (minimum-maximum) values depicted instead of SD.
[3] ANOVA results indicated a statistical significance ($p<0.05$) between gender when female and male values were pooled together from the three treatments. No statistical analyses were conducted for Tmax and T1/2 for gender.

Pharmacokinetics Conclusions

1. Under single-dose fasting conditions the relative BA for the CR formulation was 91% compared to Luvox.
2. Under single-dose conditions, no food effect was demonstrated after fluvoxamine CR administration.
3. Under single-dose conditions, a gender effect was demonstrated. Fluvoxamine exposure was significantly increased for female subjects compared to male subjects by 62%.

4. Exposure to fluvoxamine was greater for female subjects compared to male subjects. The magnitude of the gender effect was similar for all three treatments. This was reflected in AUC(0-inf) and Cmax values. Compared to males, mean AUC(0-inf) for females were 1.4-, 1.6-, and 1.4-fold higher with LUVOX fasting, fluvoxamine CR fasting, and fluvoxamine CR fed treatments, respectively. Similarly, mean Cmax values were 1.2-, 1.6-, and 1.4-fold higher for females compared to males for the same treatments.

Study-0300002- Bioequivalence Between a 100 mg Fluvoxamine CR Capsule Product Packaged in —— Bottles and in ————

A Single Dose Study in Healthy Male Volunteers to Establish the Bioequivalence Between a 100 mg Fluvoxamine CR Capsule Product Packaged in —— Bottles and in ————
STUDY INITIATION DATE: 24 May 2000
STUDY COMPLETION DATE: 09 Jun 2000

BACKGROUND

The dissolution of the product packaged in —— bottles following 6 months storage at 25oC/60% RH did not meet the proposed release specifications for

this product. This study was designed to evaluate the in-vivo performance of the fluvoxamine CR capsule product in both packaging configurations after storage for at least 9 months at 25oC/60%RH, in order to support dissolution shelf-life specifications wider than the proposed release specifications for this fluvoxamine CR capsule product.

STUDY OBJECTIVES

The primary objective of this study was to establish the bioequivalence between fluvoxamine CR capsule product packaged in [redacted] bottles or [redacted] Safety
and tolerability were also assessed.

OVERALL STUDY DESIGN AND PLAN – DESCRIPTION

This was an open-label, single-dose, 2-treatment, 2-period, randomised, crossover study to establish the bioequivalence between fluvoxamine CR capsule product packaged in [redacted] bottles with fluvoxamine CR capsule product packaged [redacted] The study was conducted in healthy male volunteers who were extensive metabolisers of dextromethorphan.
Subjects were dosed as one group on two separate occasions. In order to minimise the intersubject variability associated with the disposition of fluvoxamine, subjects were included in the study only if they were phenotyped as extensive metabolisers of dextromethorphan by CYP2D6

TREATMENTS ADMINISTERED

Treatment A: Fluvoxamine CR 100 mg capsule, ([redacted]
Treatment B: Fluvoxamine CR 100 mg capsule, [redacted] packed)
A 10.5 hour overnight fast was observed prior to dosing. The subjects remained fasting for 4 hours postdosing. The subjects were not allowed to consume any water 1 hour predose through 2 hours postdose. Subjects were required to remain sitting or ambulatory for 4 hours after dosing.

DEMOGRAPHIC DATA

APPEARS THIS WAY

Trait		Overall
Gender	Male	24
Race	Asian	1
	Caucasian	23
Frame Size	Small	1
	Medium	21
	Large	2
Age	Mean	28
	S.D.	7
	Minimum	19
	Maximum	45
	N	24
Weight (kg)	Mean	77.0
	S.D.	9.1
	Minimum	60.4
	Maximum	104.0
	N	24.0
Height (cm)	Mean	180
	S.D.	7
	Minimum	167
	Maximum	193
	N	24

PHARMACOKINETIC SAMPLING

Venous blood specimens (5 mL) were obtained by direct venepuncture of the antecubital veins at the following times following each drug administration (expressed as Day:Hours:Minutes):
1:00:00 (predose), 1:01:00, 1:02:00, 1:03:00, 1:04:00, 1:05:00, 1:06:00, 1:07:00, 1:08:00, 1:09:00, 1:10:00, 1:12:00, 1:14:00, 1:16:00, 1:20:00, 2:00:00, 2:06:00, 2:12:00, 3:00:00, 4:00:00, 5:00:00.

PHARMACOKINETIC DATA ANALYSIS

The following pharmacokinetic parameters were derived from the plasma concentration data: Cmax, AUCall, AUClast, AUCinf, tmax, lambda_z, t1/2, Frel(%) and relative Cmax %.

STATISTICAL DATA ANALYSIS

Descriptive statistics (n, arithmetic mean, coefficient of variation CV%, SD, SE, median, minimum, maximum) for AUCinf, AUCall, AUClast, Cmax, tmax, lambda_z, and t1/2, were provided for assessment of pharmacokinetic parameters obtained between the 2 treatments.
For equivalence testing, two one-sided t-tests for the natural log-transformed target parameters (AUCinf, AUClast, AUCall and Cmax) were performed.
The equivalence of the target parameters were concluded when the 90% confidence intervals for the ratios of Test Treatment B (I ——— count bottles) to Test Treatment A ——— means (population geometric means) fell within the equivalence range, [0.80, 1.25] for AUCinf, AUClast and Cmax.

ANALYTICAL

Study-0300002

Clinical study began: May 25, 2000
Sample analysis completed: June 27, 2000
Longest Possible Storage- 33 days

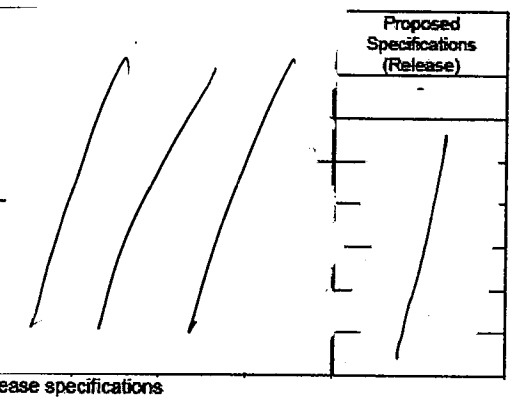
Parameter	Fluvoxamine
Method	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL
Linearity (Standard curve samples)	0.5-1000 ng/ml
Quality Control (QC) Samples	4, 120, & 600 ng/mL
Precision of Standards (%CV)	1.86%@0.5 ng/ml 6.01 %@ 1000 ng/ml
Precision of QC Samples (%CV)	12.6%@4 ng/ml 17.2%@120 ng/ml 9.5%@ 600 ng/ml
Accuracy of Standards (%)	100%@0.5 ng/ml 100%@ 1000 ng/ml
Accuracy of QC Samples (%)	90%@4 ng/ml 97%@120 ng/ml 102%@ 600 ng/ml

RESULTS

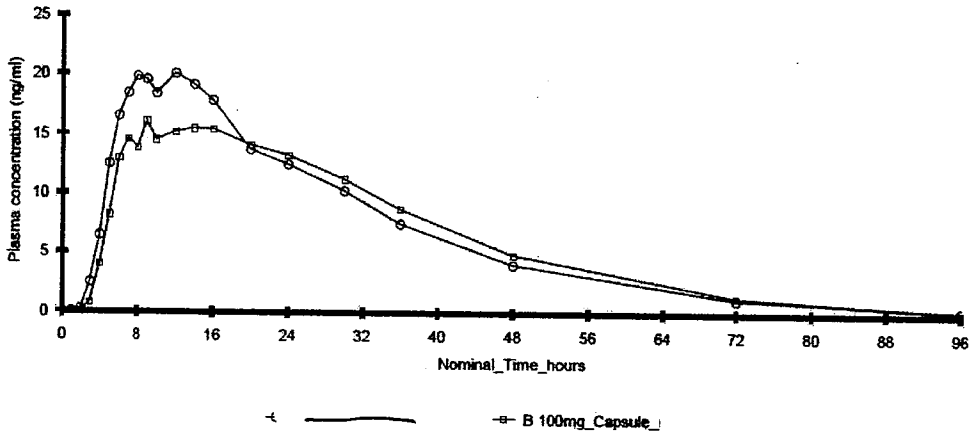
Table 1
Dissolution of 100mg fluvoxamine capsules – NDA stability program
Mean ± SD

Time Hours	Bottles				Proposed Specifications (Release)
	T0 N=6	6mts N=6	9mts N=6	12mts N=6	
1	2.2 +/- 0.6	1.6 +/- 1.3	2.5 +/- 0.8	3.8 +/- 1.5	
2	15.6 +/- 1.8	14.3 +/- 5.4	12.6 +/- 1.9	14.2 +/- 6.9	
4	42.5 +/- 3.3	39.1 +/- 2.6	37.5 +/- 0.7	40.3 +/-3.0	
6	53.8 +/- 5.8	51.8 +/- 6.1	48.2 +/- 2.4	52.1 +/- 6.2	
8	**73.8 +/- 7.0**	**62.7 +/- 7.0**	**54.7 +/- 3.0**	**63.3 +/- 6.4**	
10	90.7 +/- 5.1	77.9 +/- 3.7	70.5 +/- 3.5	78.8 +/- 5.9	
12	97.9 +/- 3.8	86.2 +/- 3.5	82.3 +/- 2.0	86.1 +/- 4.1	

Bold indicates data will not meet the proposed release specifications



MEAN PLOT - CROSSOVER DATA



Log-transformed Pharmacokinetic Parameters Geometric Mean (n=22 subjects)

Summary Pharmacokinetic Parameters

Parameter	Treatment A -	Treatment B - Count Bottles	MDD (%) +, -	Power
Cmax (ng/ml)	21.79	17.70*	31.2, 23.8	0.63
90% CI		69 – 95		
AUClast (ng/ml.h)	542.10	538.73	15.5, 13.4	0.99
90% CI		91 – 108		
AUCall (ng/ml.h)	554.16	553.55	15.3, 13.3	0.99
90% CI		92 – 108		
AUCinf (ng/ml.h)	565.10	565.64	15.3, 13.3	0.99
90% CI		92 – 108		

* P = 0.03, statistically significant difference between the two treatments

DISCUSSION AND OVERALL CONCLUSIONS

Statistical analysis of the log-transformed parameters demonstrated that the 90% confidence intervals comparing the capsules packaged in bottles were within 80-125% in terms of AUC but not in terms of Cmax. The fluvoxamine capsules packaged in bottles showed a lower mean Cmax compared to . No differences were observed between the capsules packaged in bottles in terms of the untransformed parameters, tmax and t½.

To summarise, the pharmacokinetics of fluvoxamine capsules packaged in ——bottles and stored at 25°C/60% RH for at least 9 months were equivalent in terms of extent of absorption, but displayed a slower rate of absorption compared to fluvoxamine capsules packaged in —— s and stored at 25°C/60% RH for the same period. This study therefore shows that there is an in-vivo impact of the slowing of the dissolution of the —— packaged product over time and does not justify a wider shelf-life dissolution specification for this product than the currently proposed release specification.

Study-S1141109- Single Dose Bioequivalence of Two Fluvoxamine Maleate 100 mg CR Capsules Slow Release vs Fast Release

A Pharmacokinetic Study to Investigate the Single Dose Bioequivalence of Two Fluvoxamine Maleate 100 mg CR Capsules in Healthy Male Subjects

STUDY RATIONALE

The present study was conducted to demonstrate the *in-vivo* bioequivalence between two batches of fluvoxamine maleate CR with distinct *in vitro* dissolution performances (the so-called "side batch" approach). "Side batches" are batches representing the intended upper and lower *in vitro* release specification derived from the defined manufacturing process by setting process parameters within the range of maximum variability expected. The findings of this bioequivalence study will enable the manufacturing processing tolerance limits to be clearly defined.

STUDY OBJECTIVES

The objective of this study was to assess the *in-vivo* bioequivalence of two 100 mg capsule formulations of fluvoxamine maleate CR, following a single 100 mg dose, administered in the fasted state.

OVERALL STUDY DESIGN AND PLAN – DESCRIPTION

This study was to have an open-label, randomized, single-dose, two-sequence, two-period, crossover design. Subjects were to be in the fasted state having had a 10-hour overnight fast. There was to be a 7-day washout interval between the 2 dose administrations. The subjects were to be confined to the clinic during each study period. During the study, the subjects were to remain in an upright position (sitting or standing) for 4 hours after the treatment was administered. Water was to be restricted 1 hour predose and 1 hour postdose, and food was to be

restricted 10 hours predose until 4 hours postdose. During the study, the subjects were not to be allowed to engage in any strenuous activity.

PHARMACOKINETIC SAMPLING TIMES

For pharmacokinetic purposes, 5 mL blood samples were to be collected during each study period at Hour 0 (predose), and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours postdose.

TREATMENTS ADMINISTERED

Treatment A: Fluvoxamine maleate 100 mg CR capsules formulation 1 (Fast Batch, formulated with the intended upper *in vitro* release specification)
Treatment B: Fluvoxamine maleate 100 mg CR capsules formulation 2 (Slow Batch, formulated with the intended lower *in vitro* release specification)

Identity of Investigational Products

A: Drug: Fluvoxamine maleate 100 mg CR capsule
Manufactured by Elan Pharmaceuticals, Ltd.
Lot No: 0000031959
Expiration date: 15 JUN 2004
Subjects randomized to Treatment A were to receive a single oral dose of one fluvoxamine maleate 100 mg CR capsule taken with 240 mL of water.
B: Drug: Fluvoxamine maleate 100 mg CR capsule
Manufactured by Elan Pharmaceuticals, Ltd.
Lot No: 0000031960
Expiration date: 15 JUN 2004
Subjects randomized to Treatment B were to receive a single oral dose of one fluvoxamine maleate 100 mg CR capsule taken with 240 mL of water.

DEMOGRAPHIC DATA

Summary of Demographics

Trait		Overall
Gender	Male	36
Race	Asian	2
	Caucasian	34
Frame Size	Small	18
	Medium	18
Age	Mean	25
	SD	6
	Minimum	19
	Maximum	42
	N	36
Weight (kg)	Mean	73.5
	SD	6.0
	Minimum	60.6
	Maximum	82.9
	N	36.0
Height (cm)	Mean	178
	SD	7
	Minimum	162
	Maximum	193
	N	36

PHARMACOKINETIC DATA ANALYSIS

The primary parameters for the assessment of bioequivalence were to be AUC and Cmax.

STATISTICAL DATA ANALYSIS

The maximum plasma concentration (Cmax) and its corresponding time (tmax) were recorded from the observed plasma concentration-time profiles. Individual subject data were inspected and the last three to five non-zero plasma concentrations were selected to determine the elimination-rate constant (λz). Using those plasma concentrations selected, individual λz values were determined by linear regression of the respective natural logarithm of fluvoxamine plasma concentration versus time curve. The terminal half-life (t1/2) were calculated by $t1/2 = \ln 2/\lambda z$. The area under the concentration versus time curve, AUClast up to the time point (t) of the last concentration above the lower limit of quantification (Ct) were calculated by the linear trapezoidal rule. Extrapolation of AUClast to time infinity, AUC was achieved by dividing the observed Ct by the elimination rate constant (λz) and adding the resulting residual area to AUClast.

For calculation of the PK characteristics the following rules were applied:

- At time points in the lag-time between time zero and the first concentration equal or above LLOQ, concentrations below LLOQ were calculated as zero.
- Concentrations below LLOQ between two concentrations equal or above LLOQ, were calculated with half the LLOQ.
- Trailing concentrations below LLOQ were not used in calculations.

After log (ln) transformation of the AUC and Cmax the test treatment was to be tested against the reference treatment by mixed model analysis of variance (ANOVA) with fixed effects:

Sequence, Period, and Treatment and Subject within Sequence as random effect.

After antilogarithmic transformation the resultant ratio of geometric means and 90% confidence intervals (CIs) was to be calculated. The test treatment was to be considered bioequivalent to the reference treatment if the 90% CIs for the ratio of mean AUC and Cmax were contained within a range of 0.80-1.25.

ANALYTICAL

Study-S1141109

Clinical study began:August 5, 2003
Sample analysis completed: September 19, 2003
Longest Possible Storage-45 days

Parameter	Fluvoxamine
Method	LC-MS/MS
Sensitivity/LOQ	0.5 ng/mL

Linearity (Standard curve samples)	0.5-200 ng/ml
Quality Control (QC) Samples	4, 120, & 600 ng/mL
Precision of Standards (%CV)	1.2%@0.5 ng/ml 3.3%@ 1000 ng/ml
Precision of QC Samples (%CV)	7%@4 ng/ml 3%@120 ng/ml 4%@ 600 ng/ml
Accuracy of Standards (%)	99%@0.5 ng/ml 97%@ 1000 ng/ml
Accuracy of QC Samples (%)	97%@4 ng/ml 100%@120 ng/ml 96%@ 600 ng/ml

RESULTS

Figure 1. Geometric Mean Concentration-Time Course of Fluvoxamine for Treatments A and B

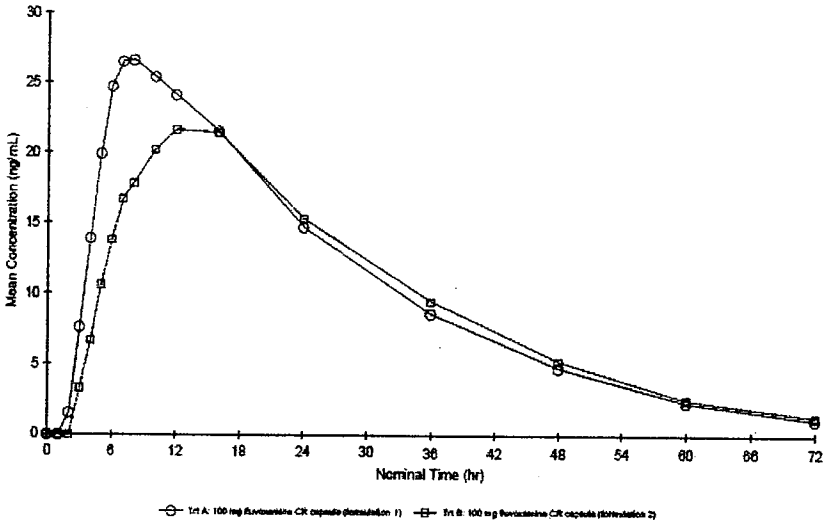


Table 2 Summary Results of the Primary and Secondary Model-Independent
Fluvoxamine Pharmacokinetic Characteristics

Treatment	Dose mg	N	t_{max} h	C_{max} ng/mL	AUC_{last} h*ng/mL	AUC h*ng/mL	$t_{1/2}$ h
A	100	36	8.56	30.3	768	815	13.7
B	100	36	11.9	25.1	721	770	13.3

For t_{max} and $t_{1/2}$, the arithmetic means are given. For the C_{max}, AUC_{last}, and AUC, the geometric mean is presented

Table 3 Point Estimates (Ratios A * 100/B), 90% Confidence Intervals, and ANOVA
CVs for the Primary Target Parameter Cmax as Well as for AUClast and AUC

Parameter	Point estimate A* 100/B [%]	90% Confidence Interval [%]	Intrasubject coefficient of variation [%]
AUC	105.88	100.1-112.0	14.0
AUC_{last}	106.38	100.9-112.2	13.3
C_{max}	121.10	114.7-127.8	13.4

Pharmacokinetic Conclusions

In conclusion, bioequivalence was not demonstrated between the two fluvoxamine CR treatments with distinct *in vitro* performances.

The relative bioavailability of the test treatment (Treatment A 100 mg fluvoxamine maleate CR [Fast Batch]) as determined by AUC extrapolated to infinity was 106% that of the reference treatment (Treatment B 100 mg fluvoxamine maleate CR [Slow Batch]). The test treatment has comparable extent of absorption (as determined by AUC) but an increase rate of absorption (as determined by Cmax: 121%) compared to that of the reference treatment. The median time to reach peak concentration was reduced for the test treatment compared to that of the reference treatment; however, the half lives of the two treatments were comparable. The 90% confidence intervals based on log-transformed data were 100.1-112.0% for AUC and 114.7-127.8% for Cmax.

PHARMACOMETRICS REVIEW

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW
DRUG:Fluvoxamine CR PRIMARY REVIEWER: Andre Jackson
NDA: 22033 TYPE: NDA
FORMULATION: STRENGTHS: 100 mg and 150 mg
APPLICANT: Submission Dates: April 28, 2006

INDICATIONS:
Generic Name:

PHARMACOMETRICS REVIEW

LABEL

There was no claim for labeling from the firm related to the analysis presented in this pop pk study.

Clinical Report No.:	S1143103.01
Clinical Report Date:	28 July 2000
Protocol No.:	S1143103
Protocol Title:	Population Pharmacokinetics of Fluvoxamine CR in Outpatients with Obsessive Compulsive Disorder

INTRODUCTION

The primary objective of this study was to establish the efficacy and safety of fluvoxamine CR (100 mg to 300 mg/day) compared to placebo for a 12-week period in adults with OCD meeting DSM-IV criteria (300.3). The secondary objective of this study was to establish the tolerance of fluvoxamine CR and to evaluate the population pharmacokinetic parameters for fluvoxamine CR.

The primary objective of this analysis is to characterize the pharmacokinetics of fluvoxamine CR in outpatients with OCD and to determine whether a concentration-effect relationship exists between fluvoxamine plasma concentrations and change from Baseline Y-BOCS scores and adverse events.

STUDY DESIGN

The trial consisted of a one-week screening period followed by 12 weeks of treatment with either fluvoxamine CR (100 to 300 mg/day) or placebo. Subjects randomized to fluvoxamine CR were titrated in 50 mg increments per week between 100 and 300 mg/day at bedtime over the first six weeks of treatment. Thereafter, the dose was to remain constant for the duration of the double blind period. Clinic visits occurred at screening, Baseline (Day 1), weekly for the first two weeks (Weeks 1 and 2), and every two weeks for the remainder of the study (Weeks 4, 6, 8, 10 and 12). Safety visits were made at Weeks 3 and 5. During the safety visit, the subjects were to visit the clinic, be evaluated for adverse events and concomitant medications and receive the appropriate blister package of study medication. Subjects had the option to enter a 40 week double blind extension protocol after completion of this study.

Efficacy assessments consisted of the Y-BOCS, and Clinical Global Impression – Severity (CGI-S) Scale and Clinical Global Impression – Improvement (CGI-I) Scale. The Y-BOCS and CGI-S scales were performed at screening, Baseline, the end of Weeks 2, 4, 6, 8, 10 and 12; the CGI-I was done at the end of Weeks 2, 4, 6, 8, 10 and 12.

KEY INCLUSION CRITERIA

1. Male or female. All females were required to have a negative serum pregnancy test (β-hCG) at the Screening visit. Females of childbearing potential, including females less than two years post-menopausal, must have been using a medically acceptable method of birth control as listed below and not planning a pregnancy:
    - A stable dose of oral contraceptive for at least three months prior to Day 1 (Baseline)
    - Intrauterine device (IUD) for at least two months prior to Day 1 (Baseline)
    - Various barrier methods (diaphragm or combination condom-spermicide)
2. Aged 18 years or older; there was no upper age limit
3. Have a Diagnostic and Statistical Manual 4th edition (DSM-IV) diagnosis of OCD (300.3)
4. Score at least 21 on the Y-BOCS at the Screening and Baseline visits
5. Score ≤16 on the 17-item Hamilton Depression Scale (HamD) at the Screening visit

KEY EXCLUSION CRITERAI

1. Lifetime or current DSM-IV diagnoses of the following disorders were exclusionary:

    - Schizophrenia and Other Psychotic Disorders
    - Bipolar Disorders
    - Pervasive Developmental Disorders: Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Disorder, Pervasive Developmental Disorder Not Otherwise Specified (NOS)
    - Tic Disorders: Tourette's Disorder, Chronic Motor or Vocal Tic Disorder, Transient Tic Disorder, or Tic Disorder NOS
    - Dementia
    - Alcohol or Substance Abuse or Dependence, unless the Alcohol or Substance Abuse or Dependence has been in Full Remission for at least six months prior to Day 1 (Baseline). (Caffeine-related disorders and nicotine-related disorders were an exception to this exclusion and were allowed)
    - The following Paraphilias: Exhibitionism, Pedophilia, Voyeurism, Genderual Masochism, Genderual Sadism

2. A DSM-IV diagnosis within the past six months, treatment for these disorders within the past six months, or a current DSM-IV diagnosis of the following disorders was exclusionary:

    - MDD subjects with secondary depression (defined as Depression NOS or Dysthymia and a HamD 17 item total score <16 at the Baseline visit) were permitted in the study
    - Panic Disorder Without Agoraphobia, Panic Disorder With Agoraphobia, Agoraphobia Without History of Panic Disorder, Social Phobia, Posttraumatic Stress Disorder, Generalized Anxiety Disorder
    - Attention-Deficit/Hyperactivity Disorder
    - Factitious Disorders and Dissociative Disorders

METHODS

Table 1 Demographics

Continuous Covariates	Age (yr.)	Height (in.)	Weight (lb.)	BSA (m^2)	BMI (kg/m^2)
n	100	100	100	100	100
mean	37.8	66.5	179.0	1.956	28.5
standard deviation	12.1	3.7	52.4	0.302	8.0
minimum	19.1	58.0	100	1.420	17.6
maximum	70.9	74.0	397	3.056	55.5

Categorical Covariates	
Race	85 Whites/3 Blacks/3 Oriental/1 Native American/4 Hispanic/4 Other
Gender	39 Males/61 Females
Alcohol	91 ≤4 drinks per week/9 > 4 drinks per week
Smoker	98 non-smokers/2 smokers
On Concomitant Medications at time of blood sample*	126 yes/ 53 no
Dose*	
100 mg	n = 8
150 mg	n = 14
200 mg	n = 16
250 mg	n = 17
300 mg	n = 117
350 mg	n = 1
500 mg	n = 1
600 mg	n = 5

* Subjects may be counted twice due to multiple sampling events.

Supporting Data:
Appendix 11.9.2 Demographic Analysis and NONMEM Datafile Preparation (LISTING)

GENERAL APPROACH TO PK ANALYSIS

The complete data set was randomly split into two groups. One group consisted of ~80% of the data and was used for model development and building. The other group of ~20% was used for validation. The general modeling approach taken followed the guidelines set forth in Ette and Ludden[5] and Bruno et al.[6] Model selection was based on physiological and pharmacological rationale and the principle of parsimony – simpler models were chosen over more complex model's when statistically justified.[7] First, exploratory data analysis (EDA) was undertaken to examine the basic structure of the concentration-time data and to identify any outliers. Second, population pharmacokinetic models were developed without covariates. Using conditional estimation methods, individual pharmacokinetic parameter estimates were obtained. Third, individual covariates were screened to determine if there was any relationship between individual pharmacokinetic parameter estimates and individual covariates. Fourth, any significant covariates identified previously were entered into the population model to identify the population model that best described the data. Fifth, appropriate methods were used to evaluate the performance of the model. Lastly, once the final covariate model was identified, individual pharmacokinetic parameter estimates were again estimated and summarized by descriptive statistics.

BASE MODEL DEVELOPMENT

Fluvoxamine concentration-time data was analyzed by nonlinear mixed-effects modeling using NONMEM, Version V to develop a base structural population pharmacokinetic model. The base model was identified by comparing different structural pharmacokinetic models, e.g. a one-compartment model with oral absorption. The general approach is to identify the structural model and then refine the model by adding or removing random effects from the model. Random effects (between-subject variability on the pharmacokinetic parameters) were assumed to follow a log-normal distribution

$$P_j = \theta * \exp(\eta_j) \qquad (3)$$

where P is the parameter of interest, j is the jth subject, θ is the estimate of the population mean and η_j is the deviation from the population mean for the jth subject under the assumption that $\eta \sim N(0, \omega^2)$.[8],[9],[10] For a 1-compartment model, random effects were initially modeled on clearance. For a 2-compartment model, random effects were initially modeled on clearance and volume of the central compartment. Additional random effects were then added or removed from the model sequentially. The basis for addition or removal of model terms was based on whether the models were nested or non-nested, all other things being equal, e.g., precise standard error of the parameter estimates, unbiasedness of residual plots, and precise estimation of the variability associated with the random effects. If multiple random effects were

included in the model, a diagonal covariance matrix for the random effects was used. Also, residual error was modeled as a combination of additive and proportional error

$$Y_{ij} = C_{ij}\left(1+\varepsilon_{1ij}\right)+\varepsilon_{2ij}. \quad (4)$$

The significance of the additional off-diagonal covariance terms was evaluated using the nested model selection criteria with a significance level of 0.05. Note that the NONMEM objective function value (OFV) is equivalent to –2 times the log-likelihood function.

Three possible residual variance models were examined:

- Additive and proportional error model (APEM) $Y_{ij} = C_{ij}\left(1+\varepsilon_{1ij}\right)+\varepsilon_{2ij}$ (5)
- Proportional error model $Y_{ij} = C_{ij}\left(1+\varepsilon_{ij}\right)$ (6)
- Additive error model $Y_{ij} = C_{ij}+\varepsilon_{ij}$ (7)

where Y is the observed concentration for the ith subject's jth concentration, C is the predicted concentration, and ε are the residual errors under the assumption that $\varepsilon \sim N\left(0,\sigma_{\varepsilon}^2\right)$. Additive alone and proportional random error models (reduced models) were compared to the APEM (full model) for improvement in the goodness of fit as follows:

1. The APEM (full) model was compared to a proportional error (reduced) model.
2. If the difference in the NONMEM OFVs (reduced - full) in Step 1 was less than the critical value from a chi-squared distribution with 1 degree of freedom at 0.05, the proportional error model was considered the superior model.
3. If in Step 2, the proportional error model was the superior model, the residual variance estimate was compared to the residual variance estimate from the additive error only model. The model with the smallest residual variance estimate was considered the final residual variance model.
4. If in Step 2, the APEM was the superior model, the APEM (full) was compared to the additive error (reduced) model.
5. If the difference in the NONMEM OFVs (reduced - full) in Step 4 was less than the critical value from a chi-squared distribution with 1 degree of freedom at

0.05, the additive error model was considered the superior model. Otherwise, the final variance model was the APEM.

Model selection was dependent on whether models were nested or non-nested. For nested models, the following selection rationale and criteria was used. It has been shown that if two models are nested and the full model having p model parameters is compared to a reduced model with q model parameters, such that $q < p$ and the set of parameters in q is a subset of the parameters in p, then difference in the NONMEM OFVs between the two models (reduced – full) has a chi-squared distribution with p-q degrees of freedom under the null hypothesis that the additional model parameters in the full model are zero.[11],[12] Thus, for this analysis if the difference between the OFVs for two nested models (reduced – full) was greater than the critical value based on a Chi-square test with p-value 0.05, assuming both OFVs were obtained using the same estimation method, the full model was considered the superior model.

The Akaike Information Criterion (AIC) can be computed from the NONMEM OFV as

$$AIC = OFV + 2p \tag{8}$$

where p is the number of estimable parameters in the model. In comparing two non-nested models, M1 and M2, the difference in the AICs was computed as

$$\Delta AIC = OFV_{M1} - OFV_{M2} + 2(p_{M1} - p_{M2}). \tag{9}$$

If $p_{M1} = p_{M2}$, the model with the smallest AIC was chosen, all other things being equal. If $p_{M1} \neq p_{M2}$ and $\Delta AIC < 0$, model M1 was chosen; otherwise, model M2 was chosen as the superior model.

Once the base model was identified, individual subject pharmacokinetic parameters for which random effects were included in the model were calculated by the posterior conditional estimation technique using the POSTHOC step with first order conditional estimation (FOCE) in NONMEM.

Once Bayesian Post-Hoc estimates for the random effects were determined, the data set was examined for outliers by examining weighted residuals. Data points with weighted residuals greater than ±4 were considered outliers. Outliers were documented and removed from the model. The model was re-fit and the individual subject pharmacokinetic characteristics recalculated. At this point, no further outlier removal was done.

COVARIATE SCREENING

For covariates that were continuous in nature, pharmacokinetic parameters were regressed against the covariate using quadratic linear regression to identify covariates of significance. The F-test testing the overall "significance" of the model was used as the criteria for covariate significance. Covariates having an F-test p-

value of less than 0.05 were considered statistically significant. Also, scatter plots of plasma concentrations vs. covariate overlaid with a nonparametric locally weighted scatter plot smoother (LOESS) were used to help identify functional relationships.[13]

For covariates that were categorical in nature, analysis of variance was used to test for differences in the rank-transformed pharmacokinetic parameters between groups. The variable DOSE was analyzed by three different analyses: as a categorical variable, as a continuous variable, and as a dichotomous variable with subjects assigned to group 1 (less than 300 mg) or group 2 (300 mg). When dose was treated as a categorical variable, orthogonal polynomials were used to assess the trend between dose and pharmacokinetic response.[14] Also, box and whisker plots of pharmacokinetic parameters for each of the groups were used to identify differences between groups.

The covariates to be screened were selected *a priori* following International Conference on Harmonization (ICH) Guidelines.[15] The potential covariates examined were defined by the sponsor prior to initiation of the modeling process. Specifically, the following covariates that were screened include: age, height, weight, dose, body surface area, body mass index, race, gender, smoker (current cigarette use), alcohol use (Y or N), and concomitant medication (Y or N within 3 days of blood sample collection). No specific concomitant medications were examined. If both BSA and BMI were statistically significant, the one with the largest coefficient of determination to the pharmacokinetic parameter of interest was to be tested in the covariate model.

COVARIATE SUBMODELS

Once significant covariates were identified, they were then added to the base model incrementally and tested by NONMEM to determine if they were indeed statistically significant. The covariate with the highest correlation was entered first into the model. Covariates were then entered into the model based on rank-order coefficient of determination. By default, covariates that were continuous in nature were entered into the model in a covariate-normalized linear manner

$$P_j = \theta_0 + \theta_{1j} * \left[X_{1j} - M(X_{1j}) \right], \qquad (10)$$

where P_j is the jth parameter, θ_0 is the intercept, θ_{1j} is the slope relating the covariate, X_{1j}, to the pharmacokinetic parameter, and M(X) is the median of X_{1j}. Centering of covariates has a number of advantages including: reduced numerical instability in the parameter estimates when there are high correlations among the parameters, the extended least squares algorithm is least likely to terminate with rounding errors, and more meaningful estimates in that the θ_0 represents the population mean parameter estimate at the mean of X_{1j}, while θ_1 represents the rate of change in the parameter per unit change in X_1.[16] If the scatter plot between the

covariate and the pharmacokinetic parameter indicated a log-linear relationship, a multiplicative model was used

$$P_j = \left[\theta_0 - M(X_{ij})\right] * X_{ij}^{\theta_1} . \quad (11)$$

Combinatory linear and log-linear models were developed as needed.

Categorical covariates were entered into the model using dummy variables (0 or 1) using a fractional change model. For the linear model with a dichotomous covariate

$$P_j = \theta_0 (1 + \theta_{1j} X_1), \quad (12)$$

where $1+\theta_{1j}$ is the fractional multiplier for X_{1j}. Thus when $X_1 = 1$, $P_j = \theta_0(1 + \theta_1)$. When $X_1 = 0$, $P_j = \theta_0$. For a multiplicative model

$$P_j = \theta_0^{\theta_1 X_1} . \quad (13)$$

Thus when $X_{1j} = 1$, $P_j = \theta_0^{\theta_1}$. When $X_{1j} = 0$, $P_j = \theta_0$. The level of significance for inclusion into the model was 0.05.

In addition, pharmacokinetic parameters were summarized statistically by stratification. The following stratification break-downs were used:

1. Race
2. Gender
3. Age (<30, 30-40, 40-50, 50-60, 60-70, 70+)
4. Age (<30, 30-40, 40-50, 50-60, 60-70, 70+) by Gender
5. Smoker vs. non-smoker
6. Body mass index (≤19, 20 to 24, 25 to 29, ≥ 30)
7. Concomitant medications (yes or no)
8. Dose (mg)

Box and whisker plots were used to graphically summarize the distribution of the pharmacokinetic parameters by stratification. Descriptive statistics, including mean, median, n, standard deviation, minimum, and maximum, were used to summarize the pharmacokinetic parameters by stratification.

PHARMACODYNAMIC ANALYSIS

For each subject, the average steady state plasma fluvoxamine concentration was computed from the POSTHOC parameter estimates under the final NONMEM model. Correlation analysis of pharmacokinetic estimates against the primary efficacy measure, Y-BOCS, was used to assess whether any pharmacokinetic-pharmacodynamic correlation existed. The dependent variable of interest was Y-BOCS score at end-study minus Y-BOCS score at Baseline. Also, subjects were classified into responders and non-responders. Responders were defined as having a decrease of 8 points or greater in their Y-BOCS score at Week 6, Week 12, or end-study. Average steady-state plasma concentrations were then compared between responders and non-responders.

The top five adverse events on Weeks 6 and 12 were identified as follows. On Weeks 6 and 12, subjects were queried on occurrence of any adverse events. If they reported an adverse event, that event was coded on the Case Report Form. After completion of the study, all subjects (active and placebo) were then re-coded to 0 or 1 about the absence or presence of a particular adverse event. The total number of subjects reporting a particular adverse event at that week or in previous weeks was then tabulated. The five adverse events with the greatest frequency were then identified and carried into the pharmacodynamic analysis. Logistic regression was used to determine whether a difference in average steady-state fluvoxamine plasma concentrations existed between subjects experiencing the adverse event and those that did not. Appropriate transformations were used, if needed, to meet the assumptions of the statistical test.

The nature of the relationship between total number of adverse events and fluvoxamine plasma concentrations over time was examined. The total number of adverse events reported by a subject on Days 43 and 85 was counted. By definition, the total counts on Day 85 should be equal to or greater than Day 43. Since the dependent variable in this case is not continuous, but rather count data, Poisson regression was used.[17] The dependent variable was total number of adverse events, while the independent variables (both continuous) were visit number and fluvoxamine plasma concentration. The model deviance residuals were examined for normality. If the residuals were not normally distributed, various transformations were to be examined to ensure residual normality.

PARAMETER STABILITY

The stability of the parameter estimates in the covariate model was compared to the stability of the parameter estimates in the base model. The condition number, computed as the ratio of the largest eigenvalue to the smallest eigenvalue of the variance-covariance matrix, for the covariate model was compared to the condition number for the base model. A condition number less than 20 indicates good stability in the parameter estimates.[18]

A nonparametric estimate of the standard error of the parameter estimates was estimated using the delete-1 jackknife.[19] The jackknife is a computer-intensive, non-parametric method in the sense that it does not assume a normal error distribution or even homoscedasticity, whereby the standard error of a test statistic can be calculated. Briefly, for the nonlinear case define θ and $\hat{\theta}_{(i)}$ as the vector of parameter estimates with and without the ith observation deleted, respectively. Then define the ith pseudo-value as

$$P_i = n\hat{\theta} - (n-1)\cdot\hat{\theta}_{(i)} \tag{14}$$

The average of all pseudo-values,

$$\bar{P} = \frac{\sum_{i=1}^{n} P_i}{n} \tag{15}$$

is called the jackknife estimate of θ with variance-covariance matrix

$$\Sigma = \frac{1}{n(n-1)}\sum_{i=1}^{n}(P_i - \bar{P})(P_i - \bar{P})^T \tag{16}$$

The square root of Σ is the jackknife standard error of the estimate. The jackknife standard errors were compared to the parametric standard errors. A 95% asymptotic confidence interval was calculated for each parameter as

$$\theta_L, \theta_U = \hat{\theta} \pm Z_{0.995} * SE(\hat{\theta}) \tag{17}$$

where:

θ_L and θ_U are the lower and upper confidence interval estimates, respectively;
$\hat{\theta}$ is the parameter estimate;
$Z_{0.995}$ is the inverse cumulative distribution from a Z-distribution with 0.995 probability or 2.576; and
$SE(\hat{\theta})$ is the standard error of the parameter estimate based on parametric theory.

MODEL PREDICTABILITY

At the time of creation of the NONMEM data file, approximately 20% of the data was randomly removed and saved for model performance assessment. The predictive validity of the model was examined by comparing the model predicted plasma concentration for a typical subject (setting all eta's equal to zero). For each subject, the relative error for each observation was calculated

$$RE_{ij}(\%) = \frac{Ln(\hat{Y}_{ij}) - Ln(Y_{ij})}{Ln(Y_{ij})} \times 100\%, \qquad (18)$$

where:

Y_{ij} is the ith observed concentration for the jth subject; and

$\hat{Y}_{ij}$ is the corresponding predicted concentration.

Relative errors were summarized by descriptive statistics.

ANALYTICAL

A total of 189 plasma samples from 106 human subjects was analyzed for fluvoxamine by Elan Corporation PLC. During the study, the back calculated calibration standards had coefficients of variation ranging from 1.80 to 9.82% with an accuracy of 97.57 to 104.63%. The quality control samples had coefficients of

variation ranging from 2.93 to 11.32% with an accuracy of 94.25 to 104.54%. Samples were received in two lots on 13 January 2000 and 10 March 2000.

Test and Reference Substance Stability:

1. The drug is stable in plasma over 4 freeze-thaw cycles.
2. Samples containing Fluvoxamine are stable stored at -20°C for up to 12 weeks.
3. Samples containing Fluvoxamine are stable stored at -80°C for up to 15 weeks.
4. Extracts containing drug are stable in the fridge for three days (72 hours) prior to injection.
5. Extracts containing drug are stable on the autosampler tray for three days (72 hours) prior to injection.
6. Extracts may be re-injected on day two after initial injection on day one.
7. Drug is stable in plasma on the benchtop for up to 4 hours at room temperature.
8. Reference standard aliquots are stable for up to 7 months at fridge temperature.

MODELLING RESULTS

Figure 1 presents a histogram of blood sample collection times. Most samples were collected between 10 to 20 h post dose, although two samples were collected more than 144 h post-dose. Figure 2 presents a scatter plot of observed fluvoxamine plasma concentrations from the time of most recent dose. Figure 3 presents Figure 2 from 0 to 48 h post-dose. The data indicate that all information related to the absorption phase was not captured with the blood sampling design and that at most, elimination kinetics can be characterized.

Figure 1 Histogram of Sample Distribution Times

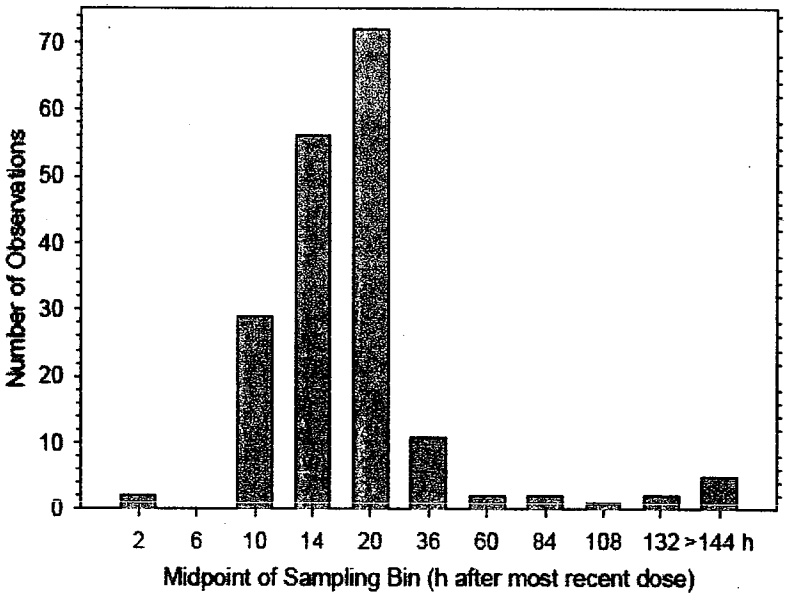


Figure 2 Scatter plot of fluvoxamine plasma concentrations vs. time from most recent dose (linear scale)

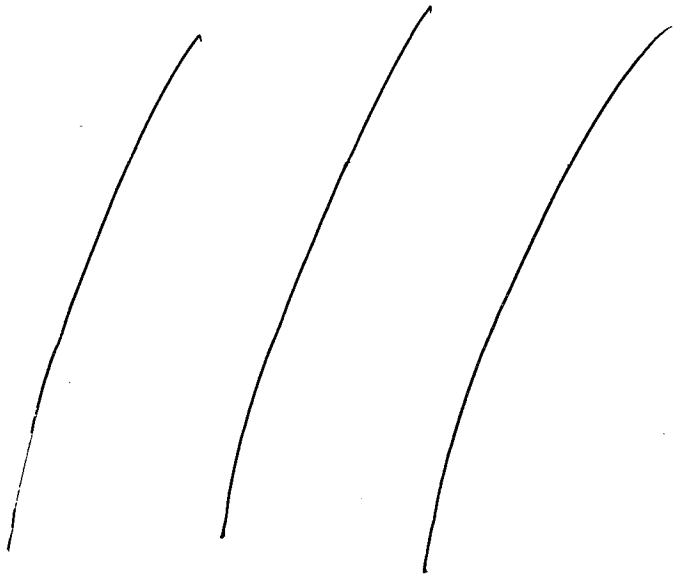
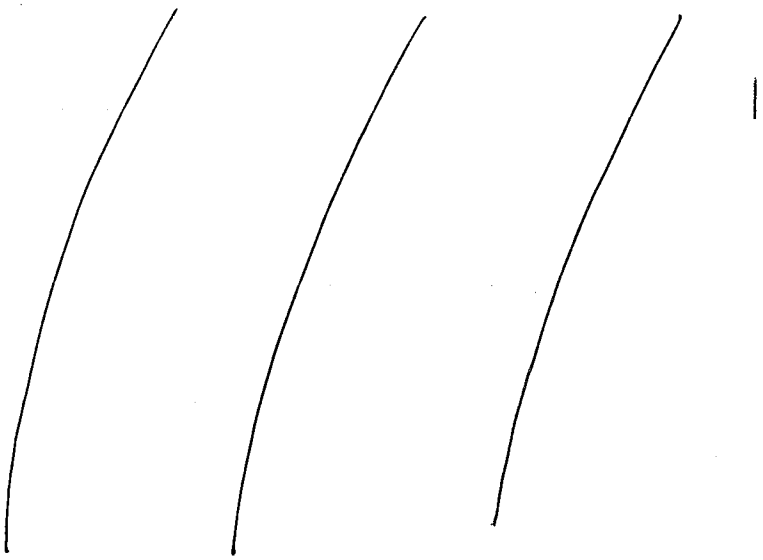
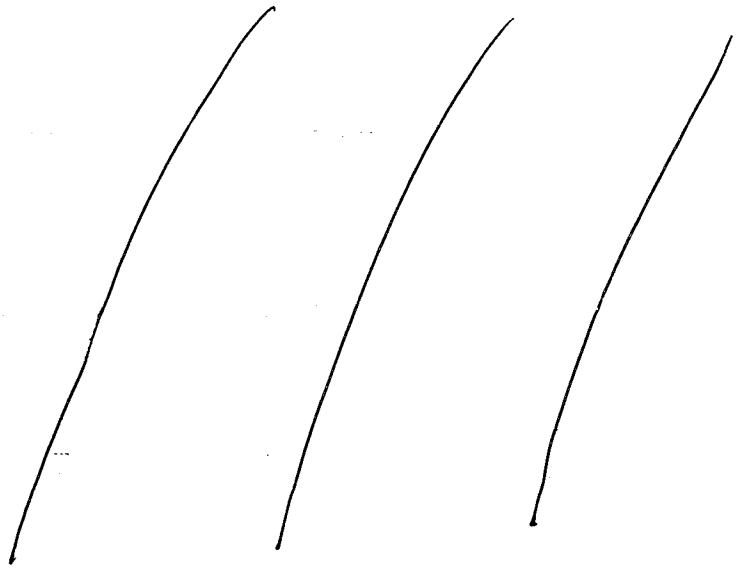


Figure 3 **Scatter plot of fluvoxamine plasma concentrations vs. time from most recent dose up to 48 h**



The best fit model was the 1-compartment model with intravenous administration (model M1B.NMN). This model was re-fit using first order conditional estimation, a more precise estimation algorithm within NONMEM (model M1BFO.NMN). The resulting OFV decreased by 35.7 points, a value that was highly significant ($p<0.01$). This model was then deemed the base model. Figure 4 presents the predicted (PRED) vs. observed plasma concentrations under the base model. Predicted plasma concentrations in this plot assume that each subject has the typical values in the population for clearance (90.5 L/h) and volume of distribution (5540L).

Figure 4 **Predicted vs. observed concentrations under base model (1-compartment with intravenous administration, model M1BFO.NMN)**



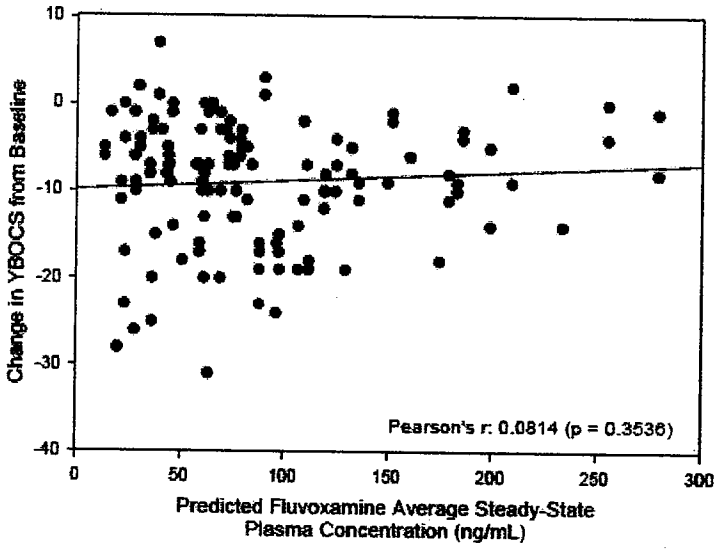
PHARMACODYNAMIC RESULTS

CORRELATION BETWEEN FLUVOXAMINE PLASMA CONCENTRATIONS AND EFFICACY

Figure 34 and Figure 35 present a scatter plot of change from Baseline in Y-BOCS scores against predicted steady-state plasma concentrations and observed plasma concentrations at the time of measurement, respectively. There was no correlation between either predicted or observed plasma concentrations and change from Baseline in Y-BOCS scores.

Subjects were categorized into responders or non-responders at the time of measurement. A responder was a subject that had a change from Baseline Y-BOCS score of at least 8 points or greater. Figure 36 presents a box and whisker plot of predicted average-steady state plasma concentrations, observed plasma concentrations, and apparent oral clearance for responders vs. non-responders. There was no difference between groups in any variable. Appendix 11.11.4 presents the results from this analysis.

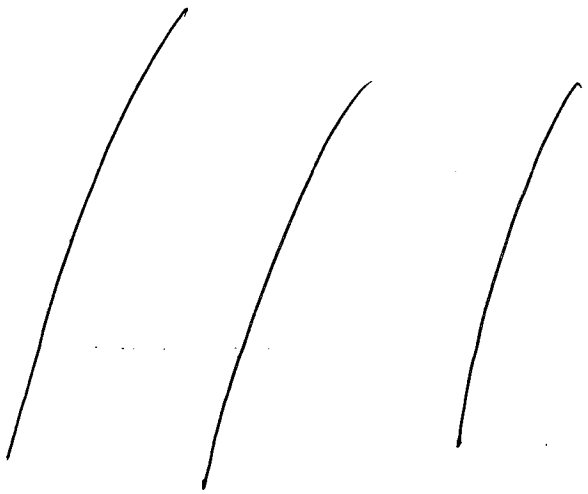
Figure 34 **Scatter plot of change from Baseline in Y-BOCS scores against predicted fluvoxamine plasma concentrations**



Note: Solid line is least-squares fit to the data. Subjects may be counted twice on different visits.

APPEARS THIS WAY
ON ORIGINAL

Figure 35 Scatter plot of change from Baseline in Y-BOCS scores against observed fluvoxamine plasma concentrations at time of measurement



Observed Fluvoxamine Plasma Concentration at Time of Measurement (ng/mL)

Note: Solid line is least-squares fit to the data. Subjects may be counted twice on different visits.

DISCUSSION

These results indicate that the fluvoxamine plasma concentration-time data were best modeled using a 1-compartment model with intravenous absorption. Clearly, this model is not the best model to characterize the pharmacokinetics of fluvoxamine CR, which is an oral sustained release formulation. A better model would be one where zero-order absorption kinetics are used. However, since fluvoxamine CR is to be administered in the evening prior to bedtime, collection of the blood samples necessary to characterize the absorption phase is difficult to impossible. Most subjects returned the next morning or afternoon for blood sampling. Hence, the majority of blood samples were collected between 10 and 20 h post-dose. At this time, absorption and distribution of the drug was complete. As such, the only phase that could be characterized was the elimination phase. Nevertheless, theoretical studies that have shown that even if the absorption phase model is misspecified, or missing as in this case, apparent oral clearance can be estimated with a small degree of underprediction. Similarly, if no absorption data are present, apparent volume of distribution will also be estimated with no bias.[23] For this study, even though the structural pharmacokinetic model was misspecified to account for the lack of absorption phase, it is expected that the apparent oral clearance and volume estimates will be unbiased and reflective of the true population values.

COMMENTS

1. The formulation developed by the firm is a CR formulation for which the Tmax is reported to be 7 hrs with a 13 hr half-life.
2. A previous study S1141106 which investigated multiple doses from 100-300 mg QD indicated that following multiple dosing nonlinearity is reflected in the dose-normalized (DN) AUC(0-24h) and Cmax values. This was not supported by the current pop pk analysis by the firm.
3. It is very likely that the data modeled at 10 hrs contains absorption information while that at 20 hrs may be elimination which makes any predicted steady-state levels based on the model to be questionable.
4. The firm could have supported their position by doing a qualification not only based upon the single dose post-hoc predictions but also by comparing their predicted steady-state data with the data previously obtained from study S1141106.
5. The POP PK/PD analysis presented by the firm is inconclusive so there may be a relationship found between PK and PD if better quality data were analyzed.
6. Due to the poor quality of the data OCP did not replicate the firm's base and final model analysis.

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/s/

Andre Jackson
2/8/2007 11:04:17 AM
BIOPHARMACEUTICS

Atul Bhattaram
2/8/2007 02:07:40 PM
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Raman Baweja
2/8/2007 03:52:04 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-033	Brand Name	Luvox
OCP Division (I, II, III)	DIV I	Generic Name	Fluvoxamine Maleate
Medical Division	Psychiatry	Drug Class	Serotonin(SSRI)
OCPB Reviewer	Andre Jackson	Indication(s)	SAD and OCD
OCPB Team Leader	Raman Baweja	Dosage Form	Capsules
		Dosing Regimen	Once-a-day
Date of Submission	April 28, 2006	Route of Administration	Oral
Estimated Due Date of OCP Review	January 11, 2007	Sponsor	Solvay Pharmaceuticals
PDUFA Due Date	March 1, 2007	Priority Classification	1S
Division Due Date	January 28, 2007		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x	[redacted]		
HPK Summary	X			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	NA			
Isozyme characterization:	NA			
Blood/plasma ratio:	NA			
Plasma protein binding:	NA			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	x	2		1. Biostudy 1098001-(fluvoxamine CR capsule prototype C vs Luvox) 2. Study 1098002--(fluvoxamine CR capsule prototype D vs Luvox)
Patients-				
single dose:	NA			
multiple dose:	NA			
Dose proportionality -				
fasting / non-fasting single dose:	NA			
fasting / non-fasting multiple dose:	x	1		Study S1141106- 100mg, 200mg and 300 mg once daily dosing
Drug-drug interaction studies -				
In-vivo effects on primary drug:	NA			
In-vivo effects of primary drug:	NA			
In-vitro:				
Subpopulation studies -				
ethnicity:	NA			
gender:	NA			
pediatrics:	NA			
geriatrics:	NA			
renal impairment:	NA			
hepatic impairment:	NA			
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:	x	1		Study S1143103 (POP PK study to determine if a concentration-effect relationship exists between plasma concentration, adverse events and change from baseline Yale-Brown OCS scores)
Population Analyses -				
Data rich:	x	1		Study CR S1143104 (Evaluate the POP PK for fluvoxamine)
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	**NA**			
Relative bioavailability -	[redacted]			
solution as reference:				
alternate formulation as reference:		3		**1.Study 0398002 (4 Elan CR formulations vs Luvox 100 mg)** **2.Study 0798005 (effect of food on BA of fluvoxamine CR)** **3.Study 0698001(4 Elan CR formulations vs Luvox 100 mg)**
Bioequivalence studies -				
traditional design; single / multi dose:	x	2		1. Study 0300002 (BE 100 mg fluvoxamine CR capsule in bottles vs ——) 2. Study S1141109 (BE of two fluvoxamine 100 mg CR capsules)
replicate design; single / multi dose:				
Food-drug interaction studies:	**x**	**1**		Study S1141107 (100 mg Luvox fasting vs CR 100 mg capsule fasting and fed)
Dissolution:	**x**			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]			
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**11**		

Filability and QBR comments				
	"X" if yes	**Comments**		
Application fileable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		1.The organization of the analytical data is not clear. The firm has included the same validation data in several locations. 2.For study reports 0300002 and S1141109 there was no specific analytical data for these studies (i.e., calibrators and QC samples). 3.For study S1141106 the analytical report could not be located. 4.For several studies only summary data was provided for QC there was no data for calibrators. 5.The firm should audit the analytical data for all of their studies and provide the location of summary calibration and QC data.		
QBR questions (key issues to be considered)	**1.What is the BA of the CR product relative to IR Luvox.** **2. Does the fluvoxamine CR product exhibit linear kinetics** **3. Is the CR product BE to IR Luvox** **4. Is there any evidence of dose dumping for the CR product** **5. Is there a relationship between fluvoxamine CR plasma levels and** adverse events and change from baseline Yale-Brown OCS scores			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA HFD-850 (Electronic Entry or Lee), HFD-130 (CSO), HFD-860 (Jackson, Mehta, Baweja), CDR (Biopharm-CDR)

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

/s/

Andre Jackson
6/20/2006 08:04:23 AM
BIOPHARMACEUTICS

Raman Baweja
7/5/2006 01:35:11 PM
BIOPHARMACEUTICS
Memo to File -- OCP NDA Filing and Review Form