2. Two Way Studies (Fluoxetine vs. Placebo)

Study No. 19

Title: A controlled study of the treatment of major depressive disorders with fluoxetine HCl (LY110140) [An evaluation of efficacy and safety of fluoxetine in outpatients with major depressive disorder comparing fluoxetine with placebo].

Investigator: Louis F. Fabre, Jr., M.D., Ph.D. This was a single investigator trial.

Design: This was a double blind, randomized, parallel group comparison of the safety and effectiveness of fluoxetine and placebo in outpatients who were diagnosed as major depressive disorder. The entry criteria and the patient characteristics are described below. The total duration of the trial was six weeks. The trial began with a one week, single blind, placebo phase to eliminate placebo responders. At the end of the week, patients were reevaluated and if they continued to meet the depression severity criteria (a decrease of less than 20% in the total HAM-D or a total HAM-D score greater than 20), they were entered into a five week, double blind treatment phase. Patients failing to meet these criteria were dropped from the trial.

Subjects: Subjects were selected who met the following entry criteria:

1. Adult, male or female outpatients suffering from major depressive disorder that did not respond to placebo.
2. Hamilton Psychiatric Rating Scale for Depression (HAMD) score of at least 20.
3. Raskin Depression Scale score which exceeded the Covi Anxiety Scale score.
4. An educational level and appropriate comprehension such that they were able to communicate intelligently with the doctor and nurse, read, understand and complete the patient rating scales (Zung and Patient's Global Impressions).
5. Expected to comply with treatment and comply with appointments at weekly intervals.
6. Diagnostic Criteria. Research Diagnostic Criteria were used. All patients satisfied the criteria for major depressive disorder and were further classified if possible, as:

    a. Primary Major Depressive Disorder
    b. Recurrent Unipolar Major Depressive Disorder
    c. Psychotic Major Depressive Disorder
    d. Incapacitating Major Depressive Disorder
    e. Endogenous Major, Depressive Disorder
    f. Agitated major Depressive Disorder
    g. Retarded Major Depressive Disorder

Exclusion Criteria: The exclusions were as follows (taken directly from the sponsor's submission):

1. Women of childbearing potential who are not using medically accepted means of contraception
2. Serious suicidal risk
3. Cardiovascular disease, especially patients with conduction defects and hypertensive patients being treated with guanethidine, clonidine, or methyldopa
4. Significant other medical illnesses including hepatic, renal, respiratory, or hematological disease
5. Organic brain disease or history of seizures
6. History of severe allergies or multiple adverse drug reactions
7. History of drug abuse including alcohol
8. Concurrent administration of other psychoactive drugs including lithium
9. History of use of monoamine oxidase inhibitors within two weeks of starting active drug
10. Improvement during placebo treatment, i.e., Hamilton Depression score decrease of more than 20 percent or a score of less than 20
11. Family history of "Failure to Thrive" or phospholipidoses

For the purpose of evaluating the results, the sponsor further categorized patients and visits as evaluable or non-evaluable. This categorization was not included in the protocol. The criteria (taken directly from sponsor's volume 1.30 p. 029-030) for these categories were as follows:

1. Cases were unevaluable for efficacy if any of the following occurred:

   a. Break in therapy

      1. Patient omitted study drug for more than two consecutive days during the first two weeks of active medication
      2. Patient omitted study drug on two occasions for more than one day during the first two weeks of active medication

   b. Insufficient therapy

      1. Patient omitted one or more morning and/or bedtime doses on three or more days during the first two weeks of active medication

   c. Patient missed more than two office visits

d. Protocol Exclusion Criteria

1. The HAMD was less than 20 at admission
2. The HAMD dropped more than 20% or below 20 during the placebo period
3. The Raskin score was less than 8 at admission
4. The Raskin score was lower than the Covi score
5. The patient did not meet the critera for major depressive disorder (RDC) at admission

2. An individual visit was unevaluable for efficacy if any of the following occurred:

a. The interval between office visits was less than five days or more than 9 days
b. Patient omitted study drug for more than two consecutive days during the 3rd, 4th, or 5th week of medication
c. Patient omitted study drug on two occasions for more than one day during one week of therapy during the 3rd, 4th, or 5th week of medication
d. Patient omitted one or more morning and/or bedtime doses on three of more days during one week of therapy during the 3rd, 4th, or 5th week of medication
e. Patient took psychotropic drugs other than benzodiazepines or chloral hydrate

3. Patients who were discontnued prematurely from the study were evaluable for efficacy if they completed at least two weeks of active drug therapy.

Dosage: During the baseline period, one placebo capsule was administered in the morning. During the double blind phase, the capsules contained either 20 mg of fluoxetine or identical placebo.

The treatment regimen was as follows:

	No. of Capsules		Daily Dosage Range (mg)
	AM	Noon	Fluoxetine
Day 1	1		20
Day 2, 3	1	1	40
Day 4 - 7	2	1	60
Day 8 - 14	2	0-2	40-80
Week 3, 4, 5	2	0-2	40-80

Dosage administration was flexible but investigators were encouraged to maintain the dose established during week 3 for the trial duration.

Concomitant Medications: According to the protocol, the only allowable concomitant medications was chloral hydrate for sleep and benzodiazepines (not further specified) for agitation.

Assessment Procedures:

1. Efficacy Assessments

The following scales were rated at entry, at the end of the placebo baseline and weekly during the double blind treatment phase. The variables which were analyzed are given for each scale.

a. Hamilton Rating Scale for Depression (HAM-D)
21-items, and total score, (0 = symptom absent)
4 factors:
1. anxiety/somatization
2. cognitive disturbance
3. retardation
4. sleep

b. Raskin Depression Scale
total score - range 3 to 15

c. Symptoms, signs and illness form

d. Covi Anxiety Scale
total score - range 3 to 15

e. Clinical Global Impression (CGI)
severity, change from baseline and therapeutic index

f. Patient Global Impression
improvement since: (a) start of study, (b) previous visit

g. Zung Self Rating Depression Scale (Patient Rated)
total score

2. Safety Assessments

The following comprised the safety assessment battery:

Test	Schedule
Physical Examination, Chest x-ray Opthalmological examination	pretrial and during the final week of treatment
ECG	pretrial, midtrial and final week of treatment
Blood pressure, pulse, weight,	weekly
Laboratory tests (hematology, urinalysis, blood chemistry [SMA-12/60])	weekly
Adverse experiences	weekly

A table depicting the schedule of efficacy and safety assessment procedures follows:

SCHEDULE OF EVENTS

Visit No.	1	2	3	4	5	6	7
Therapy Wk.	-1	0	1	2	3	4	5
Efficacy Assessments							
Hamilton Psychiatric Rating Scale for Depression	X	X	X	X	X	X	X
Raskin Depression Scale	X	X	X	X	X	X	X
Covi Anxiety Scale	X	X	X	X	X	X	X
Clinical Global Impressions Scale	X	X	X	X	X	X	X
Patient's Global Impressions Scale		X	X	X	X	X	X
Zung Self Rating Depression Scale	X	X	X	X	X	X	X
Safety Assessments							
Blood pressure, pulse rate, weight	X	X	X	X	X	X	X
Physical examination	X						X
ECG	X			X			X
Chest X-ray	X						X
Ophthalmological Examination	X						X
Study Drug Dosage Record Since Last Visit		X	X	X	X	X	X
Therapy for Conditions other than Depression	X	X	X	X	X	X	X
Intercurrent illnesses or adverse clinical experiences since last visit		X	X	X	X	X	X
Hematology (CBC including differential, platelet and reticulocyte count)	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X
Blood Chemistry (SMA 12/60)	X			X			X

Data Analysis:

The efficacy and safety variables which were analyzed are described above. The conditions for categorizing efficacy subjects or visits as evaluable or not evaluable are also described above. The statistical analyses were performed on evaluable subjects and on the total population.

In the following, I will present a summary of the efficacy evaluations including the type of analyses employed and the time periods evaluated. A comprehensive evaluation of the statistical procedures is provided in the report by the Division of Biostatistics.

1. Baseline:

The sponsor compared the demographic variables (sex, age, length of treatment for previous mental illness, onset of symptoms of the present episode and percent of patients evaluable) and baseline scores for all efficacy variables for the three treatment groups. For categorical data, for example, sex, the chi-square test was used and for continuous variables such as age, the ANOVA was used. All efficacy variables were evaluated with the Kruskal-Wallis test and pairwise comparisons by means of a two-tailed Wilcoxon Rank Sum Test. If there were any significant between group differences, this variable was used as a covariate in the efficacy analyses described below.

2. Termination Analysis:

The frequencies and percentages for reasons terminated (lack of efficacy, adverse experiences, and completed trial) were compared among the treatment groups to determine if there were a differential effect among the treatments.

3. Within Group Changes:

The sponsor looked at changes within each treatment using a Wilcoxon Signed-Rank Test. In general, we do not use the results of these analyses in our evaluation of evidence for efficacy.

4. Efficacy Analysis:

The change scores between baseline and each visit and between baseline and the endpoint visit were compared among treatment groups. The basic analysis was the Kruskal-Wallis on the change scores although analyses of covariance were also used (the covariate was any baseline variable which was different among the treatment groups). On any tests which were significant, pairwise comparisons were conducted using a Wilcoxon Rank-Sum Test. The Global scores were evaluated using a categorical chi-square analysis. One-tailed significance levels were used for comparisons with placebo and two-tailed, at baseline and in drug-drug comparisons.

Study Results:

a. Demographic Data

Dr. Fabre entered a total of 47 patients with a primary diagnosis of major depressive disorder. Twenty-two patients were randomized to fluoxetine and 25 to placebo. Of these, ten were classified as unevaluable for efficacy leaving 37 patients. There were 16 evaluable fluoxetine and 21 placebo patients. The demographic characteristics of the 37 patients are given in Tables 1-A and 1-B, pages 11 and 12. Approximately half of the original treatment groups completed five weeks with a higher proportion of evaluable patients completing the trial. The patient flow including reasons for non-evaluability etc. and dropouts, are given in Table 18 taken directly from the sponsor's submission.

b. Baseline Comparisons

Statistical comparisons between treatment groups of demographic variables indicated that the groups of evaluable patients did not differ on any variable. Similarly, there were no significant differences among the treatment groups on any of the efficacy variables at baseline.

c. Efficacy Data

1. Endpoint Analysis

Seventy percent (26) of the 37 evaluable patients completed the final 5 week visit. (Of the total group of patients who entered the double blind phase, fifty-three percent completed the trial). All 37 evaluable patients, however, were included in the endpoint analyses. The number of patients in the weekly analyses included only those patients who actually attended the visit.

The results of the efficacy analyses are given in Table 19. Fluoxetine produced significantly greater improvement than placebo on most major variables (e.g. HAM-D factors and total score, the CGI severity and global improvement variables, the Covi, but not the Zung or Raskin).

2. Weekly Analysis

The results for the weekly analyses were quite similar to endpoint analyses. For example, on the HAM-D total, the CGI severity and improvement items, fluoxetine produced significantly greater improvement than placebo at all time points. Other variables produced trends.

Table 18

Patient Population:

		Fluoxetine	Placebo
A.	No. enrolled in study	22 (M=9,F=13)	25(M=13,F=12)
	1. Completed 5 weeks	11	14
	2. Terminated prior to 5 weeks	11	11
	a. 2° to Adv. Exp.	2	0
	b. Lack of Efficacy	1	6 NS
	c. Lost to Follow-up	7	4 NS
	d. Other	1	1
B.	Unevaluable for efficacy	6	4
	a. Break in Therapy	4	1
	b. Insufficient Therapy	0	2
	c. Concomitant Meds.	2	1
C.	Total evaluable for efficacy	16	21
	a. Mean age	34.1	32.0
	b. Usual Maintenance dose	80 mg	

ADVERSE EXPERIENCES CAUSING DISCONTINUATION

Adverse Experience	Fluoxetine n = 22 # of Pts. (Total Pts=2)	% of Pts.	Placebo n = 25 # of Pts. (Total Pts=1)	% of Pts.
Drowsiness	1	5%	-	-
Nervousness	1	5%	-	-
Headache, sinus	-	-	1	4%

Three of the four placebo controlled trials (Protocols 19, 27 and 62) provide evidence of effectiveness. The remaining placebo controlled study (Protocol 25) found no difference between the treatments. Two active control studies (Protocol 20, Bremner; Protocol 23, Feighner) that found fluoxetine superior to the active control will also be discussed. Although the remaining active control studies do not provide evidence of effectiveness, their results are not inconsistent with the results of the positive placebo controlled studies, i.e., they did not demonstrate a difference between fluoxetine and the active control drugs.

There were other uncontrolled studies of fluoxetine in depression and studies in other patient populations in the NDA, but since they do not have a direct bearing on efficacy in depression, they will not be discussed here.

B. Double Blind Studies With a Placebo Control:

The four placebo controlled studies include Protocol 19 (Fabre), Protocol 25 (Rickels), Protocol 27 (a three-way, six center study) and Protocol 62, a fixed dosage, ten center study. The three protocols which provide evidence of efficacy will be described first.

Protocol 19: Louis F. Fabre, M.D. was the sole investigator in this trial.

Design:

This was a five week, double blind, parallel group comparison of fluoxetine and placebo in depressed outpatients. Patients were required to 1) meet RDC criteria for major depressive disorder, 2) have a baseline total score of at least 20 on the Hamilton Rating Scale for Depression (HAM-D), 3) have a Raskin Depression Scale score of at least 8, which was required to equal or exceed that of the Covi Anxiety Scale score, and 4) have a decrease of less than 20% in the HAM-D total score during the baseline placebo period (while still meeting the requirement of a total score of 20). Exclusion criteria also included significant physical illness, concurrent use of other psychotropic medication, serious suicide risk, and MAOI use within two weeks of entry.

Patients were randomly assigned to fluoxetine or placebo. After a one week, single blind, placebo baseline (to eliminate placebo responders), patients were to be titrated to up to 60mg (3 capsules) by the end of the first week and were then to remain on a dose of 40 to 80 mg (2 - 4 capsules) for the duration of the trial. Placebo patients were titrated similarly, receiving up to four capsules of placebo daily. Treatments were administered on a b.i.d. schedule (morning and noon dosing), for a treatment period of five weeks. Efficacy assessments (completed at baseline and weekly) included the HAM-D (21 item), the Raskin Depression Scale, the Covi Anxiety Scale, physician and patient Clinical Global Impression (CGI), and the Zung Self Rating Depression Scale. Safety assessments (done at baseline and periodically during the trial) included physical exams, chest X-rays, ophthalmological exams, ECGs, vital signs, clinical labs, and ADRs. Concomitant psychotropic medications were to be prohibited.

Conduct and Execution:

A total of 47 patients was entered into the trial. Twenty-two patients were randomized to fluoxetine and 25 to placebo. Twenty-three patients dropped out before completion (50% of fluoxetine patients and 46% of placebo patients). The primary reason for discontinuation of placebo patients was "lack of efficacy," followed by "lost to follow up." The primary reason for active drug patients was "lost to follow up." The dropouts occurred at approximately the same time for both treatments, i.e., there were 73% of fluoxetine patients and 64% of placebo patients still in the trial at the end of week 3, while 55 and 56% respectively remained at the end of week 4.

Statistical analyses were conducted for an intent-to-treat sample (including all patients randomized who had a baseline and at least one on treatment rating) and for a subset who met the sponsor's criteria for evaluability. (In general, results for the two samples were similar.) For the intent-to-treat sample, last observation carried forward (LOCF) analyses and weekly analyses (observed cases at each of the 5 weeks) were conducted.

Dosage:

The usual maintenance dose for fluoxetine during the final four weeks of the trial was 80 mg. Placebo patients usually received four capsules during this time.

Results:

Patients were comparable across treatment groups at baseline with respect to demographic variables and rating scale severity measures. The results favored fluoxetine over placebo for all critical variables for all 5 treatment weeks in the LOCF analyses of the intent-to-treat sample, and the observed cases analyses were generally consistent with the LOCF analyses. The following are the results of the LOCF analyses for the intent-to-treat sample at 5 weeks, for four critical efficacy variables:

Efficacy Measure	Drug	N	Baseline Mean	Mean Change	2-sided significance
HAM-D					
Dep.Item	F	22	3.4	- 1.9	.057
	P	25	3.4	- 1.2	
Ret. Factor	F	22	9.0	- 4.3	.030
	P	25	9.0	- 2.6	
Total Score	F	22	28.6	-12.5	.007
	P	24	28.2	- 5.5	
CGI (Physician)					
Severity	F	22	4.4	- 1.6	.010
	P	25	4.3	- 0.7	

Legend: F = Fluoxetine
P = Placebo

Table 19
Protocol 19
Efficacy Analysis
Significant Treatment Effects and Mean Scores for Key Variables

	Significance	Means			
		Fluoxetine		Placebo	
HAM-D	F v P	Baseline	Endpoint	Baseline	Endpoin
Anx/Somatization	.003	8.1	4.6	7.6	5.2
Cognitive	NS	-	-	-	-
Retardation	.032	9.0	4.5	8.8	5.9
Sleep	.009	4.6	1.9	3.9	3.1
TOTAL	.011	28.9	15.6	27.4	20.9
		4 ? 13.3			6.?
Raskin Depression					
TOTAL	NS	-	-	-	-
Covi Anxiety					
TOTAL	.015	2.4	1.9	2.3	2.1
CGI					
Severity	.012	4.4	2.7	4.2	1.7
Change	.024	4.0	2.1	3.9	2.8
Ther. effect	.034	-	-	-	-
Side effect	NS	-	-	-	-
Ratio	NS	-	-	-	-
Patient CGI					
Change	NS	-	-	-	-
Zung Self Rating					
Depression Scale	NS	-	-	-	-

F - Fluoxetine
P - Placebo

d. Safety Data

1. Adverse effects

(All adverse experiences whether believed to be drug related or not are included in the following discussion.)

A listing of the adverse experiences for each treatment which led to patients being dropped from the study are given in Table 18(taken directly from the sponsor's submission). The number of patients dropped for adverse effects were two for fluoxetine and one for placebo. The difference in incidence among the treatments is not significant.

During the double blind treatment phase, 73% of fluoxetine patients and 36% of placebo patients reported one or more adverse effects.

The most frequent adverse experiences for fluoxetine were insomnia (23%), nervousness (14%), anorexia (14%) and drowsiness (14%).

Placebo produced sinus headache (12%). One patient had a seizure on placebo and the family physician felt the seizure was probably related to Darvocet.

2. Vital Signs

Because the number of subjects in the study was relatively small and because only a small proportion of subjects changed, a discussion of the results would not be meaningful.

Summary and Critique:

This five week study compared fluoxetine and placebo in 47 depressed adult outpatients, 37 of whom were classified as evaluable. There were no differences between the treatment groups at baseline in demographic or efficacy variables. One quarter of the patients received allowed concomitant psychotropic medications and they were equally frequent in the two treatment groups. Approximately half of the total patient group completed the trial.

The results of the statistical analyses indicated that, for the evaluable patients, fluoxetine produced significantly more improvement than placebo on most of the key efficacy variables at endpoint.

Conclusion:

The design and execution of this study were adequate and there did not appear to be any features which might invalidate the study. The results indicated fluoxetine produced more improvement than placebo on most variables.

Table 2
Distribution of Last Evaluable Weeks for Evaluable Patients and Unevaluable Patients
(Protocol #19: Fabre)

Evaluability	Treatment	Week 0	1	2	3	4	5	Margin Total
Yes	Fluoxetine			2	3	2	9	16
	Placebo		1	3	2	5	9	21
No	Fluoxetine		2	2	1	1		6
	Placebo		1	3				4

Table 3
Weekly Comparisons Between Fluoxetine and Placebo
Based on Evaluable Patients Only
(Protocol #19: Fabre)

Week	Approximate Sample sizes* Fluoxetine	Placebo	HAMD Total	HAMD Retardation	Raskin Depression	Severity of Depression	Global Improvement
1	16	20	0.01	0.05	0.08	0.02	0.01
2	16	19	0.01	0.05	0.06	0.06	0.04
3	11	16	0.01	0.06	0.06	0.02	0.06
4	11	14	0.02	0.09	0.02	<0.01	0.03
5	8	9	0.07	0.28	0.14	0.05	0.09

*Sample sizes may vary from one efficacy measure to another. These sample sizes are for HAMD Total.

Study No. 25

Title: A co[illegible]led study of the treatment of major depressive disorders with fluoxetine [illegible]LY110140) [An evaluation of efficacy and safety of fluoxetine in outpatie[illegible] with major depressive disorder comparing fluoxetine with placebo].

Investigator: Karl Rickels, M.D. This was a single investigator trial.

Design: This was a double blind, randomized, parallel group comparison of the safety and effectiveness of fluoxetine and placebo in outpatients who were diagnosed as major depressive disorder. The entry criteria and the patient characteristics are described below. The total duration of the trial was six weeks. The trial began with a one week, single blind, placebo phase to eliminate placebo responders. At the end of the week, patients were reevaluated and if they continued to meet the depression severity criteria (a decrease of less than 20% in the total HAM-D or a total HAM-D score greater than 20), they were entered into a five week, double blind treatment phase. Patients failing to meet these criteria were dropped from the trial.

Subjects: Subjects were selected who met the following entry criteria:

1. Adult, male or female outpatients suffering from major depressive disorder that did not respond to placebo.
2. Hamilton Psychiatric Rating Scale for Depression (HAMD) score of at least 20.
3. Raskin Depression Scale score of 8 or greater and which exceeded the Covi Anxiety Scale score.
4. An educational level and appropriate comprehension such that they were able to communicate intelligently with the doctor and nurse, read, understand and complete the patient rating scales (Zung and Patient's Global Impressions).
5. Expected to comply with treatment and comply with appointments at weekly intervals.
6. Diagnostic Criteria. Research Diagnostic Criteria were used. All patients satisfied the criteria for major depressive disorder and were further classified if possible, as:

   a. Primary Major Depressive Disorder
   b. Recurrent Unipolar Major Depressive Disorder
   c. Psychotic Major Depressive Disorder
   d. Incapacitating Major Depressive Disorder
   e. Endogenous Major Depressive Disorder
   f. Agitated major Depressive Disorder
   g. Retarded Major Depressive Disorder.

Exclusion Criteria: The exclusions were as follows (taken directly from the sponsor's submission):

1. Women of childbearing potential who are not using medically accepted means of contraception
2. Serious suicidal risk
3. Cardiovascular disease, especially patients with conduction defects and hypertensive patients being treated with guanethidine, clonidine, or methyldopa
4. Significant other medical illnesses including hepatic, renal, respiratory, or hematological disease
5. Organic brain disease or history of seizures
6. History of severe allergies or multiple adverse drug reactions
7. History of drug abuse including alcohol
8. Concurrent administration of other psychoactive drugs including lithium
9. History of use of monoamine oxidase inhibitors within two weeks of starting active drug
10. Improvement during placebo treatment, i.e., Hamilton Depression score decrease of more than 20 percent or a score of less than 20
11. Family history of "Failure to Thrive" or phospholipidoses.

For the purpose of evaluating the results, the sponsor further categorized patients and visits as evaluable or non-evaluable. This categorization was not included in the protocol. The criteria (taken directly from sponsor's volume 1.30 p. 029-030) for these categories were as follows:

1. Cases were unevaluable for efficacy if any of the following occurred:

   a. Break in therapy

      1. Patient omitted study drug for more than two consecutive days during the first two weeks of active medication
      2. Patient omitted study drug on two occasions for more than one day during the first two weeks of active medication

   b. Insufficient therapy

      Patient omitted one or more morning and/or bedtime doses on three or more days during the first two weeks of active medication

   c. Patient missed more than two office visits.

d. Protocol Exclusion Criteria

1. The HAMD was less than 20 at admission
2. The HAMD dropped more than 20% or below 20 during the placebo period
3. The Raskin score was less than 8 at admission.
4. The Raskin score was lower than the Covi score
5. The patient did not meet the critera for major depressive disorder (RDC) at admission

2. An individual visit was unevaluable for efficacy if any of the following occurred:

a. The interval between office visits was less than five days or more than 9 days
b. Patient omitted study drug for more than two consecutive days during the 3rd, 4th, or 5th week of medication
c. Patient omitted study drug on two occasions for more than one day during one week of therapy during the 3rd, 4th, or 5th week of medication
d. Patient omitted one or more morning and/or bedtime doses on three of more days during one week of therapy during the 3rd, 4th, or 5th week of medication
e. Patient took psychotropic drugs other than benzodiazepines or chloral hydrate

3. Patients who were discontnued prematurely from the study were evaluable for efficacy if they completed at least two weeks of active drug therapy.

Data Analysis:

The statistical analyses were the same as in the previous protocol (No. 19 - Fabre).

Study Results:

a. Demographic Data

Dr. Rickels enrolled a total of 48 patients with a primary diagnosis of major depressive disorder into this trial. Three patients who were screened never returned leaving 45 patients (21 were randomized to fluoxetine and 24 to placebo). Of these, three fluoxetine patients did not return for an on-drug evaluation and four additional patients (3 fluoxetine and 1 placebo) were unevaluable for efficacy primarily because of insufficient therapy. The demographic characteristics of the 38 evaluable patients (15 fluoxetine and 23 placebo) are given in Tables 1-A and 1-B. Approximately two-thirds of the patients completed 5 weeks of treatment. The patient flow including reasons for non-evaluability etc., are given in Table 20 taken directly from the sponsor's submission. The numbers of dropouts and reasons are given in Table 3.

b. Baseline Comparisons

There were no differences between the two treatment groups on the demographic variables or on the baseline efficacy variables.

c. Efficacy Data

1. Endpoint Analysis

Approximately 63% (24) of the 38 evaluable patients completed the final 5 week visit. All 38 evaluable patients, however, were included in the endpoint-analyses. The number of patients in the weekly analyses included only patients who actually attended the visit.

The results of the statistical analyses and the means are given in Table 21. There was no difference between fluoxetine and placebo on any efficacy variable at endpoint.

2. Weekly Analysis

The results for the weekly analysis were inconsistent. For some variables, fluoxetine was significantly better than placebo for some variables towards the latter weeks while placebo was occasionally nonsignificantly better than at the earlier weeks.

In conclusion, the efficacy data in this study cannot be said to provide evidence for an antidepressant effect of fluoxetine.

Table 20

Patient Population:

	Fluoxetine	Placebo
A. No. enrolled in study	18 (M=5,F=13)	24 (M=4,F=20)
1. Completed 5 weeks	10	14 $p>.1$
2. Terminated prior to 5 weeks	8	10
a. 2° to Adv. Exp.	1	1 $p>.5$
b. Lack of Efficacy	4	5 $p>.1$
c. Lost to Follow-up	1	3
d. Other	2	1
B. Unevaluable for efficacy	3	1
a. Insufficient Therapy	2	1
b. Protocol Deviation	1	0
C. Total evaluable for efficacy	15	23
a. Mean age	49.4	45.7
b. Usual Maintenance dose	40 mg or 60 mg	

Adv. Exp. Causing Discontinuation	Fluoxetine n = 18		Placebo n = 24	
	No. of Pts. (Total Pts.= 1)	% of Pts.	No. of Pts. (Total Pts.= 2)	% of Pts.
Diarrhea	-	-	1	4
Nausea	-	-	2	8
Headache	-	-	2	8
Insomnia	1	6	-	-
Nervousness	1	6	-	-

Table 21
Protocol 25
Efficacy Analysis
Significant Treatment Effects and Mean Scores for Key Variables

	Significance	Means			
		Fluoxetine		Placebo	
HAM-D	F v P	Baseline	Endpoint	Baseline	Endpoint
Anx/Somatization	NS	-	-	-	-
Cognitive	NS	-	-	-	-
Retardation	NS	7.4	4.4	24	4.8
Sleep	NS	-	-	-	-
TOTAL	NS	25.2	16.3	25.8	17.0
		-8.9		-8.8	
[illegible] Depression					
TOTAL	NS	-	-	-	-
Covi Anxiety					
TOTAL	NS	-	-	-	-
CGI					
Severity	NS	4.67	3.33	4.74	3.43
Change	NS	4.20	2.73	4.09	2.87
Ther. effect	NS	-	-	-	-
Side effect	NS	-	-	-	-
Ratio	NS	-	-	-	-
Patient CGI					
Change	NS	-	-	-	-
Zung Self Rating Depression Scale	NS	-	-	-	-

F - Fluoxetine
P - Placebo

d. Safety Data

1. Adverse effects

(All adverse experiences whether believed to be drug related or not are included in the following discussion.)

A listing of the adverse experiences for each treatment which led to patients being dropped from the study are given in Table 20 (taken directly from the sponsor's submission). One fluoxetine and two placebo patients were dropped for adverse effects. The fluoxetine patient was dropped for insomnia and nervousness while the placebo patients were dropped for nausea, headache and diarrhea.

During the double blind treatment phase, 14 (78%) of fluoxetine and 13 (54%) of placebo patients reported adverse effects.

The most frequent adverse experiences for fluoxetine were:

nausea (22%)
insomnia (22%)
upper respiratory infection (22%)
dry mouth (17%)
nervousness (17%).

The most frequent effects for placebo patients were headache (25%) and nausea (12.5%).

2. Vital Signs

The only vital sign which changed with either treatment was systolic blood pressure which decreased with placebo.

Summary and Critique:

This five week study compared fluoxetine and placebo in 45 depressed adult outpatients, 38 of whom were classified as evaluable. There were no differences between the treatment groups at baseline on the demographic or efficacy variables. A small proportion of patients received allowed concomitant psychotropic medications. They were distributed equally between the two treatments.

The results of the statistical analyses indicated that, for the evaluable patients, there was no difference between fluoxetine and placebo on any variables at endpoint. There were significant differences on a few variables at some weeks but consistent differences among the treatments were not apparent.

Conclusion:

The design and execution of this study were adequate and there did not appear to be any features which might invalidate the study. The results did not show fluoxetine to be different than placebo.

3. Summary of Placebo Controlled Studies

A summary of the outcomes (significant endpoint analyses) of each of the placebo controlled studies is given in Table 22. Inspection of the table would suggest that fluoxetine produced significantly more improvement than placebo on the major efficacy variables in the revised pooling of Protocol 27 and in two studies (Cohn and Fabre). This finding received support in a third study (Bremner). Imipramine, on the other hand, was shown to be more effective than placebo in six out of the seven studies where it was included.

There are at least two issues which affect these conclusions. The first is that of dropouts. As is described extensively in a subsequent section, the protocols allowed investigators to drop patients from the trial at different times depending on whether the patient was doing well or poorly. That is, patients who were doing poorly (presumably based on efficacy evaluations or efficacy and side effect results) could be dropped after two weeks of treatment. Their code would be broken and if they were not on fluoxetine, they could be crossed over to fluoxetine for up to 6 months. Patients who were doing well, on the other hand, could only be dropped at the end of the trial (that is, six weeks). Their code would be broken and if they were on fluoxetine or the standard comparison, they could be continued on an open basis for up to 6 months.

Breaking the codes on an individual basis before the conclusion of the trial can be hypothesized to affect the investigator's behavior and hence, evaluations of subsequent patients. That is, it can create a "problem solving" approach (what drug is the patient on, for example) which can lead to focusing on subtle clues to solve the "problem". The sponsor was told that we were concerned over this and we recommended they not break the code. This was not accepted by the sponsor.

The particular procedure used in these studies, however, caused a more problematic result than the simple breaking of the codes. That is, the successes could be dropped at the trial conclusion (week 6) while the failures could be dropped anytime after week two. Since patients could be entered into the long-term extensions following the breaking of the blind, this might have increased the incentive to drop patients very early in the trial (possibly even before a drug effect might be expected) interfering with the conduct of the trial. In addition, depending on the use made of this option by the investigators, the endpoint analysis could end up comparing two weeks on placebo and standard drug with six weeks of fluoxetine treatment, in effect, invalidating the end point analysis.

Table 22

Summary Table of Placebo Studies
End Point Analyses - Placebo Comparisons

	Fluoxetine	Imipramine	Imipramine vs Fluox.
Protocol 27			
John P. Feighner	+	+++	I > F
Jay B. Cohn	+++	+++	F > I
James D. Bremner	++	+++	0
David L. Dunner	+	+++	I > F
Bernard I. Grosser	+	+++	0
F.S. Abuzzahab	+	+	0
Pooled	+	+++	0
Pooled (New)	+++	+++	I > F
Protocol 19			
Louis Fabre	+++	NA	
Protocol 25			
Karl Rickels	0	NA	

Legend:

+++ significant on all key variables
++ significant on at least 3 key variables
+ significant on scattered variables
0 not significant on any variable
NA not applicable
> better than

Key Variables:
HAM-D - retardation, total
Raskin - total
CGI - severity, change
Hopkins - depressive factor

In Table 23, the last visit fre encies for each week for each drug for each of the placebo controlled stu is given. The basic part of the table was constructed by the sponsor for evaluable patients. I have included a row for the number of unevaluable ents and I have created two columns, one showing the percent of all patient valuable and unevaluable) for whom the visit is the last and secondly, a mn of the cumulative percent of patioents dropped following each t. That is, each successive number in the cumulative all column is the lative number of patients that are not in the trial following that week's tion.

In this table, it can be see the Cohn study lost a high proportion of imipramine and placebo patients at end of week two while at the same time, the fluoxetine patients tended to plete the trial. This differential dropout makes it difficult to dra clusions from this study.

A second possible problem wit studies was the use of concomitant CNS medications. Psychotropic medicat were either allowed by the protocol (benzodiazepines and chloral hyd or were disallowed (any other psychotropic medication). Patien disallowed psychotropics were excluded from the statistical analysis. The oled analysis for Protocol 27 (the major efficacy protocol) excluded all pa nts on either allowed or disallowed psychotropics. (The fluoxetine - p ebo comparisons in this analysis were not consistently statistically signifi t.) In addition, however, there were other drugs administered which do have a psychotropic effect but which do have a CNS effect or which interac th psychotropic agents, which were not originally identified by the spons Such compounds include propranolol, climetidine, Fiorinal, meperidine, phenhydramine, phenylpropanolamine HCl, phenylpropanolamine and caffeine. e sponsor prepared a complete compilation by study of the use of allowed, d lowed and other CNS effect drugs. Counts of the numbers of patients using e drugs for each treatment in the placebo controlled studies indicated that proportion was similar for each treatment in each trial. Hence, it ould appear that concomitant medication use is not a problem in this NDA.

Table 23

PROTOCOL 27

Feighner — LAST VISIT FREQUENCIES FOR EVALUABLE PATIENTS

Last Visit	Week	Fluoxetine	Imipramine	Placebo	Total(percent) Evaluable	ALL Pts.	Cum. Pct.
4	2	7	2	6	15(10%)	8%	10
5	3	9	7	9	25(17%)	14%	40
6	4	4	5	9	18(12%)	10%	50
7	5	2	3	3	8(5%)	4%	54
8	6	29	29	21	79(54%)	43%	100
Total		51	46	48	145	178	
Unevaluable		10	12	11	33		18%

Cohn

Last Visit	Week	Fluoxetine	Imipramine	Placebo	Total(percent)		Cum. Pct.
4	2	2	12	22	36(26%)	22%	16%
5	3	4	6	5	15(11%)	9	39
6	4	1	3	8	12(9%)	7	47
7	5	2	1	3	6(4%)	4	54
8	6	33	20	18	71(51%)	43	100
Total		46	42	52	140	166	
Unevaluable		6	13	6	26		16

Stenmler

Last Visit	Week	Fluoxetine	Imipramine	Placebo	Total(percent)		Cum. Pct.
4	2	0	2	0	2(3%)	3%	15%
5	3	2	2	2	6(10%)	9%	24
6	4	0	0	2	2(3%)	3%	32
7	5	1	0	0	1(2%)	1%	33
8	6	21	20	8	49(82%)	67%	100
Total		24	24	12	60	73	
Unevaluable		5	6	2	13		15%

Dimmer

Last Visit	Week	Fluoxetine	Imipramine	Placebo	Total(percent)		Cum. Pct.
4	2	1	2	4	7(9%)	7%	20%
5	3	4	3	1	8(10%)	8%	37
6	4	2	3	3	8(10%)	8%	43
7	5	0	3	3	6(8%)	6%	49
8	6	16	18	17	51(64%)	57%	100
Total		23	29	28	80	100	
Unevaluable		9	5	6	20		20%

Clicker

Last Visit	Week	Fluoxetine	Imipramine	Placebo	Total(percent)		Cum. Pct.
4	2	0	1	1	2(2%)	2%	14%
5	3	4	3	6	13(15%)	13%	29
6	4	5	1	1	7(8%)	7%	36
7	5	1	2	1	6(7%)	6%	42
8	6	18	20	18	56(67%)	57%	100
Total		30	27	27	84	99	
Unevaluable		3	1	4	15		14%

Hamilton

Last Visit	Week	Fluoxetine	Imipramine	Placebo	Total(percent)		Cum. Pct.
4	2	9	6	15	30(42%)	33%	20%
5	3	1	1	1	3(4%)	3%	53
6	4	0	3	1	4(6%)	4%	56
7	5	0	0	0	0(0%)	0%	66
8	6	13	13	9	35(49%)	39%	100
Total		23	23	26	72	91	
Unevaluable		7	5	3	15		20%

Table 23

(Cont'd)

FABRE #19

LAST VISIT FREQUENCIES

Last Visit	Week	Fluoxetine	Placebo	Total(percent)
4	2	2	4	6(16%)
5	3	2	2	4(11%)
6	4	0	1	1(3%)
7	5	12	14	26(70%)
Total		16	21	37 49
Unevaluable		6	6	12

RICKELS #25

LAST VISIT FREQUENCIES

Last Visit	Week	Fluoxetine	Placebo	Total(Percent)
4	2	2	2	4(11%)
5	3	3	3	6(16%)
6	4	0	5	5(13%)
7	5	10	13	23(61%)
Total		15	23	38 42
Unevaluable		3	1	4

SMITH #35

LAST VISIT FREQUENCIES FOR EVALUABLE PATIENTS

Last Visit	Week	Fluoxetine Q.D.	Fluoxetine B.I.D.	Total (percent)
4	2	2	3	5(7%)
5	3	2	4	6(8%)
6	4	4	2	6(8%)
7	5	1	1	2(3%)
8	6	30	24	54(74%)
Total		39	34	73

B. Active Drug Controlled Studies

Fluoxetine was compared to imipramine in three studies, to amitriptyline in three studies and to doxepin in four studies. None of these studies included a parallel placebo condition. Each study is described in the following; a summary of the study designs and outcomes are given at the end of the section.

1. Imipramine Studies

The following set of studies compared fluoxetine and imipramine in outpatients (Study 20, Dr. Bremner) and inpatients (Study 29, Dr. Feighner and Dr. Davis). None of the studies included placebo. It should be noted that imipramine was also included as a standard treatment condition in a set of studies with placebo described above.

Protocol 20

Title: A controlled study of the treatment of major depressive disorders with fluoxetine HCL (LY 110140).

Investigator: Dr. James D. Bremner

Protocol: The protocol was identical to Study 19 above (Dr. Fabre) except that:

(1) imipramine replaced placebo as the comparison agent

(2) the exclusions included the contraindications for imipramine in addition to the basic exclusions and

(3) drug administration: the imipramine dosage range was 75 to 300 mg daily. Patients were given two bottles of medication, one for the daytime doses and one for the H.S. dose. The daytime bottles contained 20 mg of fluoxetine or 25 mg of imipramine. The bedtime bottles contained placebo for the fluoxetine patients and 50 mg capsules of imipramine for the imipramine patients. All capsules were identical.

Omitted non-placebo co-treated

F. Summary of NDA

1. Efficacy.

The double blind trials comparing fluoxetine with standard drugs and/or placebo have been reviewed. A study by Dr. Fabre (Protocol 19) showed fluoxetine to produce more improvement than placebo in outpatients with a diagnosis of major depressive disorder. (A standard drug treatment condition was not included in the trial.) This can be said to constitute an adequate and well controlled trial. A revised pooling of Protocol 27 was submitted at the request of Dr. Chi, the FDA statistician. This pooling excluded Dr. Cohn because of interactions and replaced patients who received allowed psychotropics (chloral hydrate and flurazepam). The analysis of this pooling showed fluoxetine to produce more improvement than placebo on key efficacy variables. At the same time, imipramine produced more improvement than fluoxetine. This pooling does not have the problems of other studies described above and hence, can be said to constitute a positive adequate and well controlled trial.

A study by Dr. J.B. Cohn (excluded from the revised Protocol 27 pooling) compared fluoxetine, imipramine and placebo in a similar population. The sponsor reported fluoxetine produced significantly more improvement than either imipramine or placebo. This was based primarily on the end point or "last observation carried forward" analyses. However, the end point analysis comprised comparisons of six weeks of treatment with fluoxetine with what were essentially week two scores for the placebo treatment group (approximately 40% of the placebo patients were dropped after their week two evaluation) and with the week two and three scores for the imipramine treatment group (approximately 42 percent of the imipramine patients were dropped by the end of week three). This comparison does not evaluate equivalent treatment periods and hence, is not interpretable. At the same time, the analysis of the completers was only mildly supportive of the sponsor's conclusion. That is, only alternate weeks showed a significant difference between treatments.

The remaining studies with placebo did not show a strong effect for fluoxetine. However, almost all the studies showed imipramine to produce significantly more improvement than placebo providing some evidence that the studies were adequately designed and the patient population were probably representative of the population of major depressive disorder.

There were also two studies comparing fluoxetine with a standard agent (without a placebo condition) where fluoxetine appeared to exceed the standard agent in the amount of improvement produced. In one study (J.P. Feighner, Protocol 23), fluoxetine produced more improvement than amitriptyline in the total group analysis (evaluable and non-evaluable patients combined) but not in the evaluable group end point analysis. The reason for the significant finding was that a high proportion of amitriptyline patients dropped out for side effects before completing week two (unevaluable patients) resulting in a comparison similar to that described above. That is, six weeks of fluoxetine were compared with less than two weeks of amitriptyline. Once again the longer treatment produced more improvement. The sponsor recognized this was not a valid comparison because of the differential lengths of treatment and because it included unevaluable patients.

In the second study where fluoxetine produced more improvement than the standard treatment, namely, imipramine (Protocol 20, Bremner), the patients appeared to differ from those in other studies. That is, a high proportion in both treatment groups were described as psychotic but without supporting symptomatology in their rating scales. In addition, a number of patients had scores of zero on the HAM-D total at the end of the study which is also quite uncommon. These two features of the study suggest the patients may not have been representative and make it difficult to interpret.

2. Adverse Effects.

A complete listing of side effects for both the regular trials and the extensions is provided in the review. In addition, a list of adverse events resulting in discontinuation is provided for each study.

The adverse effects differed from those produced by the tricyclic antidepressants used in the comparative trials. The most frequent effects with fluoxetine (1173 patients) were nausea 25%, nervousness 21%, headache 18%, insomnia 17%, dry mouth 15%, anxiety 15%, drowsiness 15%, tremors 15%, excessive sweating 12% , diarrhea 11% and dizziness 10%.

In the profile of side effects for imipramine in the placebo controlled trials, dry mouth was the most frequent (70%) followed by dizziness (28%), constipation (22%), drowsiness (22%), sweating, (21%), headache and tremor (both 17%) and nausea (16%). Thus, the profile of effects differed and there were more effects with imipramine but apart from the incidence of dry mouth, there was not a great deal of difference in the frequencies of effects. A comprehensive review of the safety findings is provided in the separate safety review.

Conclusion. The sponsor has provided substantial evidence of efficacy based on the study by Dr. Fabre and the revised pooling of Protocol 27.

Recommendation. Approval of the NDA for efficacy.

J. Hillary Lee, Ph.D. (HFN-120)

cc:
Orig:NDA 18-936
HFN-120
HFN-120/HLee/2/13/85/4/12/85
8/1/85
fd/mb/2/14/85/fd/mb/4/12/85
DOC 0492C
DOC2421C

Table 15
A Comparison of the Distributions of Last Visit Weeks
Between Fluoxetine and Amitriptyline Patients
(Protocol #23: Feighner)

Week of Last Visit	Fluoxetine #Evaluable	Fluoxetine #Not Evaluable	Amitriptyline #Evaluable	Amitriptyline #Not Evaluable
1		1		6
2	1		1	4
3		1		1
4	3			
5	16		8	2
Total	20	2	9	13

$p<0.02$*

*Comparing fluoxetine to amitriptyline based on all patients data

Table 16
Comparisons of Mean Reduction from Baseline in HAMD Total Scores Between Imipramine, Fluoxetine and Placebo
(Protocol #27)
(Endpoint Analysis on Evaluable Patients Only)

Investigators	Imipramine	Fluoxetine	Placebo	Two-sided Significance Level I Vs P	I vs F	F vs P
Bremner	21.2	18.1	13.5	0.02	NS	0.13
Feighner	10.2	8.2	6.2	0.04	NS	0.30
Dunner	13.6	8.7	9.2	0.05	0.05	NS
Grosser	12.3	10.0	7.6	0.04	NS	0.20
Abuzzahab	17.3	17.0	12.9	0.26	NS	0.22
Cohn	10.2	15.7	4.0	0.001	0.002	0.001

The following are the results of the LOCF analyses of the intent-to-treat sample at 6 weeks, for four key efficacy variables:

Efficacy Measure	Drug	N	Baseline Mean	Mean Change	2-sided P (vs. Pbo)
HAM-D					
Dep. Item	F-20	99	2.68	-1.16	0.010
	F-40	101	2.62	-1.11	0.025
	F-60	104	2.66	-1.01	0.096
	Pbo	48	2.69	-0.65	
Ret. Factor	F-20	97	7.49	-2.80	0.095
	F-40	97	7.44	-2.72	0.167
	F-60	103	7.43	-2.56	0.329
	Pbo	48	7.58	-2.00	
Total Score	F-20	97	24.72	-9.78	0.007
	F-40	97	24.09	-9.58	0.010
	F-60	103	24.20	-7.20	0.338
	Pbo	48	24.25	-5.69	
CGI (Physician) Severity	F-20	99	4.24	-1.17	0.052
	F-40	101	4.22	-1.14	0.080
	F-60	104	4.24	-1.12	0.105
	Pbo	48	4.19	-0.75	

Overall, the results were persuasive only for fluoxetine 20 mg, and even for this group, the results are not as strong as in studies 19 and 27. The higher rate of dropouts for adverse events in both the 40 and 60 mg groups, along with the higher rate of dropouts early for the 60 mg group, would tend to bias the LOCF analyses against these groups. However, there was a suggestion from the observed cases analyses that, for the patients continuing on therapy for 6 weeks, the 60 mg dose may actually have been superior to the lower doses. Thus, it is not possible to interpret the results for the 40 and 60 mg groups. While these data do provide support for the antidepressant efficacy of fluoxetine at a 20 mg dose, they do not provide a clear basis for dosing recommendations.

Protocol 25: Karl Rickels, M.D., was the sole investigator in this study.

Design:

This was a five week, double blind, parallel group comparison of fluoxetine and placebo in depressed outpatients. The entry and exclusion criteria, the doses, the assessment procedures and the overall design were similar to Protocol 27 described above.

Conduct and Execution:

A total of 48 patients was enrolled in the study. Three patients who were screened never returned for drug assignment. In addition, no on drug ratings were obtained on three fluoxetine patients. This left a total of 42 patients who received treatment and had at least one on-drug rating (18 fluoxetine and 24 placebo patients). These patients were comparable at baseline regarding demographic variables and baseline rating scale severity measures. The usual maintenance dosage for fluoxetine was 40 or 60mg.

Results:

Efficacy Measure	Drug	N	Baseline Mean	Mean Change	2-sided Significance
HAM-D					
Dep.Item	F	18	3.3	- 1.3	0.50
	P	24	3.3	- 1.5	
Ret. Factor	F	18	7.4	- 2.5	0.50
	P	24	7.3	- 2.7	
Total Score	F	18	26.2	- 7.2	0.50
	P	24	25.8	- 8.8	
CGI (Physician)					
Severity	F	18	4.8	- 1.1	0.50
	P	24	4.8	- 1.3	

Thus, there was no difference in the amount of improvement associated with either fluoxetine or placebo on any of the key items for depression.

C. Double Blind Studies with a Standard Treatment Control

Ten studies compared fluoxetine with a tricyclic antidepressant (TCA), and eight found no difference between fluoxetine and the active control drug. In two studies, fluoxetine was found to be more effective than the comparison TCA. In Feighner's study (Protocol 23) comparing fluoxetine and amitriptyline, fluoxetine was superior to amitriptyline in the LOCF analysis. However, a high proportion of amitriptyline patients dropped out early because of side effects, and consequently, these scores were carried forward and compared to scores of patients treated for longer periods with fluoxetine. The observed cases analyses demonstrated no difference between the treatments. In Bremner's study (Protocol 20) comparing fluoxetine and imipramine, fluoxetine was also generally superior to imipramine.

Protocol 27. This was a multicenter (six investigator) study, including J. P. Feighner, J. B. Cohn, J. D. Bremner, D. L. Dunner, B. I. Grosser and fluoxetine. S. Abuzzahab.

Design:

This was a six week, double blind, parallel group comparison of fluoxetine, imipramine and placebo in depressed outpatients. Patients were required to 1) meet DSM III criteria for major depressive disorder, with the additional requirement that the duration of the episode be at least four weeks, 2) have a baseline HAM-D total score of 20 or greater, 3) have a Raskin Depression Scale score of at least 8, which was also required to equal or exceed that of the Covi Anxiety Scale score, and 4) have a decrease of less than 20% in HAM-D total score during the baseline placebo period (while still meeting the requirement of a total score of 20). Exclusion criteria generally included significant physical illness, significant psychiatric disorder other than depression, concurrent use of other psychotropic medication, serious suicide risk, and use of MAOI within two weeks of entry.

Patients were randomly assigned to fluoxetine, imipramine, or placebo. After a one week, single blind, placebo baseline (to eliminate placebo responders), patients receiving fluoxetine were to be titrated to up to 60mg by the end of the first week and were to be maintained at a dose of 40 to 80 mg for the remaining five weeks. For patients on imipramine, the maximum dose during the first week was to be 125mg daily with a subsequent range of 150 to 300mg daily for the trial duration. Placebo patients were titrated similarly, receiving up to 8 capsules daily. Capsules were administered on a TID basis, but patients in the fluoxetine group were administered active drug only in the morning and at noon, with placebo at bedtime. Imipramine and placebo were administered on a TID schedule. Efficacy assessments (completed at baseline and weekly) included the HAM-D (21 item), the Raskin Depression Scale, the Covi Anxiety Scale, physician and patient Clinical Global Impression (CGI), and the Symptom Check List (SCL-58). Safety assessments (done at baseline and periodically during the trial) included physical exams, chest X-rays, ophthalmological exams, ECG's, vital signs, clinical labs, and ADRs. Concomitant psychotropic medications were to be prohibited.

Conduct and Execution:

A total of 804 patients entered the trial. Two hundred seventy-one patients were randomized to fluoxetine, 275 to imipramine and 258 to placebo. As described below, the data for one investigator (Dr. Cohn, 202 patients) were excluded from the pooled analysis, leaving 602 patients who began the baseline period, of whom 537 (fluoxetine, 185; imipramine, 184; and placebo, 168) entered the double blind phase and had a baseline assessment.

Overall, 54 percent of the patients in the pooled sample completed the trial (fluoxetine-56%, imipramine-59%, placebo-47%). The primary reason for discontinuation was "lack of efficacy," which occurred most frequently in the placebo group, followed by the fluoxetine group. The second most frequent reason for discontinuation was "side effects," which occurred most frequently in the imipramine group, followed by the fluoxetine group. Discontinuations for other reasons occurred infrequently and did not appear to be associated with any specific treatment. There did not appear to be any substantial differences in the proportion of dropouts among the treatment groups at any time point.

Statistical analyses were conducted for an intent-to-treat sample (including all patients randomized who had a baseline rating and at least one evaluation on therapy) and for a subset who met the sponsor's criteria for evaluability. (In general, results for the two samples were similar.) For the intent-to-treat sample, last observation carried forward (LOCF) analyses (to the end of each of the 6 weeks of the study) and weekly analyses (observed cases at each of the 6 weeks) were conducted.

Dose:

The usual maintenance dose for fluoxetine during the final five weeks of the study was 80 mg. The corresponding dose for imipramine was between 150 and 250 mg, and the number of capsules for placebo was 6-8.

Results:

Patients were comparable across treatment groups at baseline with respect to demographic variables and rating scale severity measures. While the pooled analysis for all six centers strongly favored fluoxetine over placebo, there was a treatment-by-center interaction with a markedly greater treatment effect in the Cohn center compared to the remaining five centers. Therefore, the Cohn data were analyzed separately.

For the 5 center analysis, beginning with week 4, the results favored fluoxetine over placebo for all critical variables in the LOCF analyses of the intent-to-treat sample. This superiority for fluoxetine over placebo persisted in the week 5 and 6 LOCF analyses, and was also apparent in the observed cases analyses at weeks 4 through 6. Imipramine was also superior to placebo, with the effect generally being apparent one week earlier, i.e., at week 3.

The following are the results of the LOCF analyses for the intent-to-treat sample (excluding Cohn) at 6 weeks, for four critical efficacy variables:

Efficacy Measure	Drug	N	Baseline Mean	Mean Change	2-sided Significance FvsP	IvsP	FvsI
HAM-D							
Dep.Item	F	184	2.8	-1.3	.001	.001	n.s.
	I	184	2.8	-1.3			
	P	167	2.9	-0.8			
Ret. Factor	F	181	7.9	-3.2	.009	.002	n.s.
	I	181	8.1	-3.5			
	P	163	8.3	-2.3			
Total Score	F	181	27.5	-11.0	.012	.001	n.s.
	I	181	28.2	-12.0			
	P	163	28.2	- 8.4			
CGI (Physician)							
Severity	F	185	4.6	- 1.2	.004	.001	n.s.
	I	184	4.5	- 1.3			
	P	168	4.5	- 0.8			

Legend: F = Fluoxetine
I = Imipramine
P = Placebo

The data from the Cohn center were analyzed separately, but because of a differential dropout rate (placebo patients dropped out early and active treatment patients continued in the trial), it is not possible to interpret the results of an LOCF analysis of these data. Thus, although the analysis favors fluoxetine, the LOCF analysis in effect compares the scores after two weeks with placebo and six weeks with fluoxetine. In a condition with spontaneous improvement, there is a substantial bias favoring the group whose patients remain longer in the study. The results of the analyses of patients who actually participated at various weeks (observed cases analyses) did not, for the most part, show significant differences between fluoxetine and placebo. Thus, it is not possible to interpret the data from the Cohn study.

Protocol 62. This was a fixed dose, multicenter study conducted in mildly and moderately depressed outpatients. Ten investigators contributed patients to each level of severity. The results were pooled and analyzed separately for each level of severity.

Design:

This was a six week, double blind, parallel group comparison of fixed doses of fluoxetine (20mg, 40mg, and 60mg) with placebo in 746 depressed outpatients. The protocol was the same as Study 27 described above, with two exceptions. First, the study consisted of two independent samples,

Table 4
Weekly Comparison Between Fluoxetine and Placebo
Based on Evaluable Patients Only
(Protocol #27: Cohn)

Week	Approximate Sample Sizes* Fluoxetine	Placebo	HAMD Total	HAMD Retardation	Raskin Depression	Severity of Depression	Global Improvement
0	46	52					
1	46	50	NS**	NS+	NS+	NS	NS
2	44(96%)	51(98%)	0.01	0.05	0.01	0.02	0.07
3	41(89%)	30(58%)	NS	NS	NS	NS	NS
4	40(87%)	24(46%)	0.06	0.13	0.05	0.02	NS
5	36(78%)	16(31%)	NS	NS	NS	NS	NS
6	30(65%)	15(29%)	0.10	NS+	NS	0.12	0.16

*Sample sizes may vary from one efficacy measure to another. These sample sizes are for HAMD total.

**NS means that $p>0.20$

+Placebo is numerically greater than fluoxetine.

Table 5
Classification of Number of Patients by Evaluability
(Protocol #27: Cohn)

	Fluoxetine	Imipramine	Placebo
1. Total no. of patients	54	54	58
2. Total no. of patients terminated before 6 weeks	13	34	42
3. Total no. of unevaluable patients	8	12	6
4. Total no. of evaluable patients (item 1-item 3)	46	42	52
5. Total no. of evaluable patients completed 6 weeks	35	20	16
6. Total no. of evaluable patients terminated before 6 weeks	11(24%)*	22(52%)*	36(69%)*

*As % of line 4.

Table 6
Comparisons of the Distributions of Evaluable Patients by Last Week of Evaluable Visits Between Fluoxetine, Imipramine and Placebo (Protocol #27: Cohn)

Last Week of Evaluable Visit	Frequencies Fluoxetine	Imipramine	Placebo
0 (Baseline)	46	42	52
1	0	2	1
2	4(9%)*	12(29%)*	21(40%)*
3	2	4	5
4	4	5	6
5	6	0	4
6	30(65%)*	19(45%)*	15(29%)
Comparison of Distributions	F vs P $p<0.005$	F vs I $p=0.01$	

*As % of total number of evaluable patients (Week 0)

Table 7
A Summary of Sponsor's Endpoint Analyses
Based on Evaluable Patients Who Were Pooled from
the Five Investigators Excluding Cohn
(Protocol #27)

Efficacy Measure	Mean Reduction from Baseline Imipramine (147)*	Fluoxetine (149)*	Placebo (136)*	significance level I>F	F>P	95% Confidence Interval (F-P)
HAMD Total	14.1	11.6	8.9	0.03	0.03	(0.5,4.9
HAMD Retardation	3.9	3.4	2.4	0.13	0.01	(0.3,1.6
Raskin Depression	1.2	1.1	0.7	0.12	0.004	(0.1,0.6
Severity of Depression	1.5	1.3	0.8	0.16	0.002	(0.2,0.8
Global Improvement	1.8	1.5	1.0	0.04	<0.001	(0.2,0.8

*Total Sample Sizes

Table 8
Weekly Comparisons Between Fluoxetine and Placebo
Based on Evaluable Patients Only From Pooled Data Excluding Cohn
(Protocol #27)

Week	Approximate Sample Sizes* Fluoxetine	Placebo	HAMD Total	HAMD Retardation	Raskin Depression	Severity of Depression	Global Improvemen
0	128	108					
3	121(95%)	101(94%)	NS	NS	NS	NS	NS
4	100(78%)	87(81%)	0.02	0.05	0.05	0.003	<0.001
6	82(64%)	61(56%)	<0.001	0.002	0.001	<0.001	<0.001

*Sample sizes may vary from one efficacy measure to another. These sample sizes are for HAMD total.

**NS means that p>0.20

+Placebo is numerically greater than fluoxetine.

Table 9
Comparisons of the Distributions of Evaluable Patients by Last Week of Evaluable Visits Between Fluoxetine, Imipramine and Placebo From Pooled Data Excluding Cohn (Protocol #27)

Last Week of Evaluable Visit	Frequencies Fluoxetine	Imipramine	Placebo
0 (Baseline)	149	147	136
1	0	0	0
2	17(11%)*	13(9%)*	24(18%)*
3	19(13%)	16(11%)	18(14%)
4	12(8%)	10(7%)	15(11%)
5	6(4%)	8(5%)	7(5%)
6	95(64%)*	100(68%)*	72(53%)*
Comparison of Distributions	F vs P not significant	F vs I not signficant	

*As % of total number of evaluable patients (Week 0)

Table 10
A Summary of Sponsor's Endpoint Analyses
Based on Evaluable Patients Who Were Pooled from
the Five Investigators Excluding Cohn and Who
Were Not under Concomitant Psychotropic Medication
(Protocol #27)

Efficacy Measure	Mean Reduction from Baseline Imipramine (113)*	Fluoxetine (109)*	Placebo (105)*	I>F	F>P
HAMD Total	14.3	11.5	9.5	0.06	0.15
HAMD Retardation	4.0	3.5	2.8	0.19	0.12
Raskin Depression	1.3	1.1	0.8	0.12	0.03
Severity of Depression	1.5	1.4	0.9	0.17	0.02
Global Improvement	1.8	1.5	1.1	0.04	0.02

*Total Sample Sizes

Placebo Controlled Studies

1. Three Way Studies (Fluoxetine vs ...ipramine vs Placebo)

Study No. 27 Feighner

Title: An evaluation of efficacy and s...fety of fluoxetine in outpat...ts with major depressive disorder comparing fl...etine with imipramine and placebo.

This was a multicenter trial with six ...estigators following a common protocol. In the following, the protoc... will be described and the efficacy results will be presented separately f... each investigator. The section will conclude with the results obtained whe... the investigators were pooled.

An analysis of the safety findings for ...l studies combined will be provided in another review. In the individual ...dy reviews, I will present a brief description of selected safety finding...ith an emphasis on any frequent, serious or unusual adverse experiences.

Design: This was a double blind, ran...ized, parallel group trial comparing the safety and effectiveness of fluox...ne, imipramine and placebo in ... outpatients with a diagnosis of major ...pressive disorder. The entry criteria and the patient characteristics are ...ribed below. The trial lasted seven weeks. All patients received placebo ...ingle blind) for approximately one week (not less than four days nor mo...than 14 days) to identify placebo responders. At the end of the week, ...ients were reevaluated and if they continued to meet the depression seve...y criteria (a decrease of less than 20% in the total HAM-D or a total HA... score greater than 20), they were entered into the six week, double bl... treatment phase. Patients failing to meet these criteria were dropped fro...e trial.

Subjects: Subjects were selected w... at the following entry criteria:

1. ...ult, male or female outp...nts suffering from major depressive ...isorder that did not resp...o placebo
2. ...amilton Psychiatric Rati...le for Depression (HAMD) score of at least 20
3. Raskin Depression Scale s... of at least 3 which equaled ... exclusion the Covi Anxiety Scale sc...
4. An educational level and ...chension such that they were able to communicate intelligently ... the doctor and nurse, read, understand and complete the patient ...g scales (SCL-90 and Patient's Global Impressions)
5. ...xpected to comply with ...ons and comply with appointments at weekly intervals
6. The sponsor indicates th... III criteria (were) used. ... Full patients satisfied the ...a for major depressive disorder (except duration of illness whi... at least one month). They were unipolar depressed patien... with either a single or a recurrent episode. They were furt... classified according to one or more of the following subtypes (... 32, p. 35):

a. Primary major depres.. e disorder
b. Single episode unipo.. major depressive disorder
c. Recurrent unipolar ma.. or depressive disorder
d. Endogenous major depr.. sive disorder
e. Agitated major depres.. ive disorder
f. Retarded major depres.. ive disorder."

Comment: Major depressive dis.. er is an RDC not a DSM III diagnosis. The DSM III equivalent is Major .. pressive Episode. The required duration of symptoms for the DSM III di.. osis is two weeks while the present protocol called for a four week .. ation.

Inspection of the case report f.. as indicated that the investigator was required only to indicate the p.. ient's diagnosis, not the symptoms which were present. That is, the cas.. report forms did not include a detailed check list of symptoms.

Exclusion Criteria: The exclusions .. ased primarily on Imipramine labeling) were as follows (taken directly fro.. the sponsor's submission):

1. Pregnant women; women of c.. dbearing potential who are not using medically accepted means o.. ontraception
2. Serious suicidal risk
3. Glaucoma
4. Chronic urinary retention
5. Serious cardiovascular dis.. e especially patients with conduction defects
6. Hypertensive patients bein.. reated with guanethidine, reserpine, clonidine or methyldopa
7. Serious illness including .. tic, renal, respiratory, endocrinologic, neurologic .. hematologic disease that is not stabilized
8. Organic brain disease or h.. ry of seizures
9. Schizophenia and other psy.. ic states likely to be aggravated by Imipramine
10. Active thyroid disease
11. History of severe allergi.. multiple adverse drug reactions
12. Recent history (less than .. r) of drug abuse including alcohol abuse
13. Current use of other psycho.. rugs including lithium
14. History of use of monamin.. ase inhibitors within two weeks of.. starting active drug
15. Improvement during placebo .. od. i.e., a decrease in Hamilton depression score of 20% per .. or more, or below 20
16. Family history of "failure .. thrive" or phospholipidoses.

For the purpose of evaluating the r.. s, the sponsor further categorized .. patients as evaluable or .. evaluable. This categorization was .. carried out. The .. ria (taken directly from sponsor's .. submission) were as follows:

a. Primary major depressive disorder
b. Single episode unipolar major depressive disorder
c. Recurrent unipolar major depressive disorder
d. Endogenous major depressive disorder
e. Agitated major depressive disorder
f. Retarded major depressive disorder."

Comment: Major depressive disorder is an RDC not a DSM III diagnosis. The DSM III equivalent is Major Depressive Episode. The required duration of symptoms for the DSM III diagnosis is two weeks while the present protocol called for a four week duration.

Inspection of the case report forms indicated that the investigator was required only to indicate the patient's diagnosis, not the symptoms which were present. That is, the case report forms did not include a detailed check list of symptoms.

Exclusion Criteria: The exclusions (based primarily on imipramine labeling) were as follows (taken directly from the sponsor's submission):

1. Pregnant women; women of childbearing potential who are not using medically accepted means of contraception
2. Serious suicidal risk
3. Glaucoma
4. Chronic urinary retention
5. Serious cardiovascular disease especially patients with conduction defects
6. Hypertensive patients being treated with guanethidine, reserpine, clonidine or methyldopa
7. Serious illness including hepatic, renal, respiratory, endocrinologic, neurologic, or hematologic disease that is not stabilized
8. Organic brain disease or history of seizures
9. Schizophenia and other psychotic states likely to be aggravated by imipramine
10. Active thyroid disease
11. History of severe allergies or multiple adverse drug reactions
12. Recent history (less than one year) of drug abuse including alcohol abuse
13. Regular use of other psychotropic drugs including lithium
14. History of use of monamine oxidase inhibitors within two weeks of starting active drug
15. Improvement during placebo period, i.e., a decrease in Hamilton Depression score of 20 percent or more, or below 20
16. Family history of "Failure to Thrive" or phospholipidoses.

For the purpose of evaluating the results, the sponsor further categorized patients and visits as evaluable or non-evaluable. This categorization was not included in the protocol. The criteria (taken directly from sponsor's volume 1.32 p. 028-029) for these categories were as follows:

1. Cases were unevaluable for efficacy if any of the following occurred:

   a. Break in therapy

      1. Patient omitted study drug for more than two consecutive days during the first two weeks of active medication
      2. Patient omitted study drug on two occasions for more than one day during the first two weeks of active medication

   b. Insufficient therapy

      Patient omitted one or more morning and/or bedtime doses on three or more days during the first two weeks of active medication

   c. Patient missed more than two office visits

   d. Protocol Exclusion Criteria

      1. The HAMD was less than 20 at admission
      2. The HAMD dropped more than 20% or below 20 during the placebo period
      3. The Raskin score was less than 3 at admission and lower than the Covi score
      4. The Raskin score was lower than the Covi score
      5. The patient did not meet the critera for major depressive disorder (DSM III) at admission

2. An individual visit was unevaluable for efficacy if any of the following occurred:

   a. The interval between office visits was less than five days or more than 9 days
   b. Patient omitted study drug for more than two consecutive days during the 3rd, 4th, 5th or 6th week of medication
   c. Patient omitted study drug on two occasions for more than one day during one week of therapy during the 3rd, 4th, 5th or 6th week of medication
   d. Patient omitted one or more morning and/or bedtime doses on three of more days during one week of therapy during the 3rd, 4th, 5th or 6th week of medication
   e. Patient took psychotropic drugs other than benzodiazepines or chloral hydrate

3. Patients who were discontinued prematurely from the study were evaluable for efficacy if they completed at least two weeks of active drug therapy.

Dosage: During the baseline perio[d] one placebo capsule was administered in the morning and at bedtime. During the double blind phase, patients were given two packages, one labeled "Daytime Doses" and another labeled "Bedtime Doses". Patients were instructed to take the morning and noon doses from the package marked "Daytime Doses" and the last dose of the day from the package labeled "Bedtime Doses".

For the fluoxetine group, the "Daytime Doses" contained 20 mg fluoxetine capsules. The "Bedtime Doses" contained identical placebo.

For the imipramine group, the "Daytime Doses" contained 25 mg imipramine capsules. The "Bedtime Doses" contained identical 50 mg imipramine capsules.

The treatment regimen was as follows:

	No. of Capsules			Daily Dosage Range (mg)	
	AM	Noon	H.S.	Fluoxetine	Imipramine
Day 1	1		1	20	75
Day 2, 3	1	1	1	40	100
Day 4 - 7	2	1	1	60	125
Day 8 - 11	2	0-2	1	40-80	100-150
Day 12 - 14	2	0-2	2	40-80	150-200
Week 3, 4, 5, 6	2	0-2	2-4	40-80	150-300

Dosage administration was flexible but investigators were encouraged to maintain the dose established during week 3 for the trial duration.

Concomitant Medications: According to the protocol, the only allowable concomitant medications were chloral hydrate or flurazepam for sleep.

Assessment Procedures:

1. Efficacy Assessments

The following scales were rated at entry, at the end of the placebo baseline and weekly during the double blind treatment phase. The variables which were analyzed are given for each scale.

a. Hamilton Rating Scale for Depression (HAM-D)
21-items, and total score (0 = symptom absent)
4 factors:
1. anxiety/somatization
2. cognitive disturbance
3. retardation
4. sleep

b. Raskin Depression Scale
total score - range 3 to 15

c. Covi Anxiety Scale
total score - range 3 to 15

d. Clinical Global Impression (CGI)
severity, change from baseline and therapeutic index

e. Patient Global Impression
improvement since: (a) start of study, (b) previous visit

f. SCL-58 Patient Rated
total score
6 factors: 1. somatization
2. obsessive-compulsive
3. interpersonal sensitivity
4. depression
5. anxiety
6. total score

2. Safety Assessments

The following comprised the safety assessment battery:

Test	Schedule
Physical Examination, ECG Chest x-ray Opthalmological examination	pretrial and during the final week of treatment
Blood pressure, pulse, weight	weekly
Laboratory tests (hematology, urinalysis, blood chemistry [SMA-12/60])	weekly
Adverse experiences	weekly

A table depicting the schedule of efficacy and safety assessment procedures follows:

SCHEDULE OF EVENTS

Visit No.	1	2	3	4	5	6	7	8
Therapy Wk.	-1	0	1	2	3	4	5	6
Efficacy Assessments								
Hamilton Psychiatric Rating Scale for Depression	X	X	X	X	X	X	X	X
Raskin Depression Scale	X	X	X	X	X	X	X	X
Covi Anxiety Scale	X	X	X	X	X	X	X	X
Clinical Global Impressions Scale	X	X	X	X	X	X	X	X
Patient's Global Impressions Scale		X	X	X	X	X	X	X
SCL-58	X	X	X	X	X	X	X	X
Safety Assessments								
Blood pressure, pulse rate, weight	X	X	X	X	X	X	X	X
Physical examination	X							X
ECG	X							X
Chest X-ray	X							X
Ophthalmological Examination	X							X
Study Drug Dosage Record Since Last Visit		X	X	X	X	X	X	X
Therapy for Conditions other than Depression	X	X	X	X	X	X	X	X
Intercurrent illnesses or adverse clinical experiences since last visit		X	X	X	X	X	X	X
Hematology (CBC including differential, platelet and RBC count)	X			X		X		X
Urinalysis	X			X		X		X
Blood Chemistry (SMA 12/60)	X			X		X		X

Data Analysis:

The efficacy and safety variables ...ich were analyzed are described above. The conditions for categorizing aff...acy subjects or visits as evaluable or not evaluable are also described ab...e. The statistical analyses were performed on evaluable subjects and ...n the total population.

In the following, I will present a ...mary of the efficacy evaluations including the type of analyses empl...ed and the time periods evaluated. A comprehensive evaluation of the sta...istical procedures is provided in the report by the Division of Biostatis...cs.

1. Baseline:

The sponsor compared the demog...hic variables (sex, age, length of treatment for previous mental ...ness, onset of symptoms of the present episode and percent of patients ...valuable) and baseline scores for all efficacy variables for the thre... treatment groups. For categorical data, for example, sex, the chi-squar... test was used and for continuous variables such as age, the ANO... was used. All efficacy variables were evaluated with the Kruskal-Wall... test and pairwise comparisons by means of a two-tailed Wilcoxon Rank ... Test. If there were any significant between group differences, thi...ariable was used as a covariate in the efficacy analyses described bel...

2. Termination Analysis:

The frequencies and percentage...for reasons terminated (lack of efficacy, adverse experiences, and compl...d trial) were compared among the treatment groups to determine ...there were a differential effect among the treatments.

3. Within Group Changes:

The sponsor looked at changes ...hin each treatment using a Wilcoxon Signed-Rank Test. In general, ... do not use the results of these analyses ... in our evaluation of evidence ... efficacy.

4. Efficacy Analysis:

The change scores between bas...e and each visit and between baseline and the endpoint visit were compa...among treatment groups. The basic analysis was the Kruskal-Walli...n the change scores although analyses of covariance were also used (th...variate was any baseline variable which was different among the treat...t groups). On any tests which were significant, pairwise comparis... were conducted using a Wilcoxon Rank-sum Test. The Global scores were ...luated using a categorical chi-square analysis. One-tailed signifi...ce levels were used for comparisons with placebo and two-tailed, at ba...ine and in drug-drug comparisons.

Individual and Pooled Study Results

In the following I have focused pr..rily on the analysis for the evaluable patients. Similar assessments wer.. performed for the total group (evaluable and non-evaluable patients with at ..ast one on treatment rating) and these are mentioned when the results diff..ed from that found for the evaluable group. I have provided a complete ..sting of the patient flow including the number of and reason for categoriz.. patients as unevaluable.

1. Investigator No. 1 - John P. F.. ..hner, M.D.

a. Demographic Data

Dr. Feighner enrolled, at .. ur sites, a total of 198 patients with a primary diagnosis of majo.. epressive disorder. Sixty-six patients were randomized to fluoxa..e, 66 to imipramine and 66 to placebo. Of these, 20 failed to reach the double blind phase and a further 33 were classified as unevalu..ble for efficacy leaving 145 patients. The demographic character..tics of the 145 patients are given in Tables 1-A and 1-B. The n..bers of "evaluable" patients were 51, 46, and 48 for the fluoxetine, imipramine and placebo groups respectively. Approximat.. half of each treatment group completed six weeks. The patient fl.. including reasons for non-evaluability etc., are given in Table ..ken directly from the sponsor's submission. The number a..nd reasons for dropouts are given in Table 3.

b. Baseline Comparisons

Statistical comparisons, b..ween treatment groups, of demographic variables indicated that .. groups of evaluable patients differed only in the number with (..hout) prior treatment for mental illness. The percents w..ut prior treatment were 27, 22, and 8 for fluoxetine, imipramine a.. placebo respectively. Consequently, this became a control variabl.. covariate) in the subsequent parametric analyses. It should be ..d that the age variable was significant for the total groups alt..h the means were virtually identical to the (nonsignificant) eval..le groups, viz. 40, 45, and 42 years for the fluoxetine, imipramin..nd placebo groups, respectively. At baseline there were no si..ficant differences among the treatment groups on any of the effi..variables.

Table 4
Protocol 27
Efficacy Analysis
Mean Scores for Key Variables
Evaluable Patients

		HAM-D Total Base	HAM-D Total End	HAM-D Retardation Base	HAM-D Retardation End	Raskin Total/3 Base	Raskin Total/3 End	CGI Severity Base	CGI Severity End	CGI Change Endpoint	SCL 58 Depression Base	SCL 58 Depression End	Patient Global Change Endpoint
Feighner	F	26.0	17.8	8.3	5.6	3.37	2.56	4.65	3.61	2.92	2.31	2.14	3.04
	I	26.0	15.8	8.3	4.7	3.38	2.44	4.66	3.28	2.52	2.32	2.01	2.63
	P	26.3	20.1	8.6	6.5	3.39	2.83	4.58	3.92	3.35	2.38	2.16	3.40
Cohn	F	26.8	18.1	7.3	3.9	3.32	1.86	4.20	1.78	1.33	2.16	1.59	1.78
								4.12	3.48	3.17	2.10	1.95	3.37
Brewerton 28.5	F	28.0	18.2	7.4	2.3	4.04	1.97	4.79	2.42	1.67	2.25	1.71	1.71
	I	30.0	9.1	7.5	2.2	4.08	1.93	4.79	2.54	1.67	2.27	1.59	1.67
	P	28.5	16.3	6.8	4.1	4.08	2.61	4.67	3.17	2.33	2.05	1.94	2.33
Dunlop	F	21.1	15.5	7.6	5.0	3.45	2.46	4.43	3.13	2.74	2.47	2.07	2.65
	I	23.5	10.5	7.6	3.5	3.51	2.00	4.38	2.48	2.00	2.31	1.58	1.97
	P	23.7	14.5	8.3	5.1	3.51	2.56	4.31	3.08	2.85	2.35	2.05	3.19
Grossman	F	27.4	17.8	7.9	5.1	3.43	2.64	4.90	3.63	2.90	2.81	2.25	3.07
	I	28.1	16.1	8.6	5.4	3.47	2.53	4.78	3.37	2.63	2.64	2.22	2.89
	P	27.9	20.2	8.3	6.5	3.48	3.04	4.78	4.19	3.19	2.56	2.39	3.33
Abouzahra	F	31.9	13.9	9.9	3.6	3.01	2.03	4.17	3.22	2.48	2.36	2.12	2.48
	I	37.0	19.0	8.5	4.7	3.07	2.20	4.35	3.35	2.61	2.66	2.43	2.61
	P	36.1	28.2	8.8	5.7	3.09	2.49	4.42	3.81	3.23	2.62	2.52	3.23

...eline Base = Baseline
...eline End = Endpoint

Table -A
Protocol 27
Efficacy Analysis
Significant Treatment Effects*
Evaluable Patients

	Feighner Endpoint			Cohn Endpoint			Bremner Endpoint		
	O	F v P	I v P	O	F v P	I v P	O	F v P	I v P
atization	NS	-	-	S	.001	.001	S	-	.021
ive Dist.	NS	-	-	S	.001	.005	NS	-	-
ation	NS	-	.011	S	.001	.055	NS	.025	.009
	NS	-	.003	S	.001	NS	NS	-	-
	NS	-	.018	S	.001	.002	S	-	.008
ression									
	NS	-	.013	S	.001	.017	NS	.025	.013
			.016	S	.001	.005	NS	.015	.016
y	NS	-	.023	S	.001	.004	NS	.039	.04
	NS	.019	.001	S	.001	.003	S	.013	.015
tic effect	S	.05	.001	S	.001	.001	NS	.027	.03
fect	S	.003	.001	S	.001	.003	S	-	.009
	NS	-	-	S	.001	.001	NS	-	NS
	S	-	.007	S	.001	.001	S	.006	.016
Esrt)									
ial)									
tion	NS	-	-	S	.001	.017	NS	-	.045
oup	NS	-	-	S	.001	.042	S	.045	.003
sonal	NS	-	-	S	.001	.015	S	.006	.001
n	NS	-	-	S	.001	.001	S	.028	.005
	NS	-	-	NS	.01	-	NS	-	-
	NS	-	-	S	.001	.002	S	.027	.03

Fluoxetine
Imipramine
Placebo

O = Overall analysis
NS = Nonsignificant
S = Significant

* The numbers indicate p levels.

Table ..-8
Protocol 27
Efficacy Analysis
Significant Treatment Effects*
Evaluable Patients

		Hamilton Endpoint			Grosser Endpoint			Abuzzahab Endpoint		
		O	F v P	I v P	O	F v P	I v P	O	F v P	I v P
ization		NS	-	-	NS	-	-	NS	.04	-
			-	.001	NS	.04	.03	S	.007	.011
n			-	-	NS	-	.02	NS	.04	-
		NS	-	-	NS	-	-	NS	-	-
		NS	-	.027	NS	-	.019	NS	-	-
sion										
		NS	-	.014	NS	-	.011	NS	.04	-
		S	-	.020	NS	-	.04	NS	-	-
			-	.023	NS	.013	.02	NS	-	.04
			-	.005	NS	.038	.02	NS	-	.02
ic effect			-	.003	NS	.03	.007	NS	-	-
		S	.036	.001	S	.04	.001	S	.04	.001
		NS	-	-	NS	-	-	NS	-	-
		S	.05	.001	NS	-	.05	NS	.05	.02
n		NS	-	-	NS	-	-	NS	-	-
		S	-	.002	NS	.04	.03	NS	-	-
nal		S	.001	.001	S	.01	.01	NS	-	-
		S	-	.001	S	.01	.02	NS	-	-
		NS	-	-	NS	-	-	NS	-	-
		S	-	.001	NS	.03	.02	NS	-	-

xetine
ipramine
ebo

O - Overall analysis
NS - Nonsignificant
S - Significant

* The numbers indicate p levels.

Table 6

ADVERSE EXPERIENCES CAUSING DISCONTINUATION

Adverse Experience	Fluoxetine n=61 No. of Pts. (Total	% of Pts. Pts.=12)	Imipramine n=58 No. of Pts. (Total	% of Pts. Pts.=19)	Placebo n=59 No. of Pts. (Total	% of Pts. Pts.=7)
Asthenia	1	2	3	5	-	-
Chills	-	-	1	2	-	-
Herpes Zoster	1	2	-	-	-	-
Injury (NOS)	-	-	1	2	-	-
Malaise	-	-	2	3	-	-
Pain, Chest	1	2	-	-	-	-
Aneurysm (NOS)	-	-	-	-	1	2
Hot Flushes	-	-	1	2	-	-
Constipation	2	3	4	7	-	-
Dyspepsia	2	3	1	2	-	-
Mouth Dryness	1	2	8	14	-	-
Nausea	2	3	3	5	2	3
Stools, Dark	-	-	1	2	-	-
Taste Change	-	-	1	2	-	-
Vomiting	-	-	1	2	-	-
Thirst	-	-	1	2	-	-
Joint Repair	-	-	-	-	1	2
Pain, Joint	-	-	1	2	1	2
Alcoholism, Chronic	-	-	1	2	-	-
Anxiety	-	-	3	5	-	-
Burning or Prickling Sensation	-	-	1	2	-	-
Concentration Decrd.	-	-	1	2	-	-
Confusion	-	-	1	2	-	-
Convulsions	-	-	-	-	1	2
Dizziness	4	7	6	10	-	-
Drowsiness	3	5	3	5	-	-
Headache	4	7	2	3	-	-
Hypersomnia	1	2	2	3	-	-
Hypomania	1	2	-	-	-	-
Irritability	-	-	-	-	1	2
Nervousness	1	2	3	5	1	2
Sedated	-	-	1	2	-	-
Sensation Dist.	-	-	1	2	-	-
Tremor	1	2	2	3	1	2
Upper Respiratory Infection	-	-	1	2	-	-
Pruritis	1	2	-	-	-	-
Rash	1	2	2	3	-	-
Sweating, Excessive	-	-	2	3	-	-
Urticaria	-	-	1	2	-	-
Eye Pressure	-	-	1	2	-	-
Vision Disturbance	1	2	3	5	-	-
Frequency of Micturition	1	2	-	-	-	-
Sexual Dysfunction	-	-	1	2	-	-
Swelling, Male Genitalia	-	-	1	2	-	-
Urinary Retention	-	-	2	3	1	2

Summary and Critique:

This six week study compared fluoxetine, imipramine and placebo in 175 depressed adult outpatients. 145 of whom were classified as evaluable. There was only one difference among the treatment groups of evaluable patients at baseline and that was in the proportion of patients with no previous treatment (lowest in the placebo group). Age was significantly different among treatment groups in the total patient group but not in the evaluable patient group. There were also 2 out of 60 significant baseline comparisons with the efficacy variables. Because of the small number, the sponsor felt that the treatment groups were probably similar at baseline.

Large numbers of patients received concomitant psychotropic medications (one third of the total population) most of which were "allowed" by the protocol. They were slightly more frequent among the imipramine treatment group. There was also a fairly high proportion of patients with concurrent physical diagnoses with slightly fewer in the placebo group as compared with the other treatments. Also, more imipramine than placebo patients were dropped for adverse effects and more placebo than imipramine patients were dropped for lack of efficacy during the trial. (Fluoxetine was mid-point in the comparisons.

The results of the statistical analyses indicated that, for the evaluable patients, imipramine produced significantly more improvement than placebo on almost all the efficacy variables at end point. Fluoxetine was significantly better than placebo on only one variable (physician global) at the same time period. No significant differences were noted between the two active treatments. For the total group, there were fewer significant outcomes at endpoint for the imipramine-placebo comparison than in the evaluable analysis and slightly more significant outcomes for the fluoxetine-placebo comparison although still fewer than the number of significant imipramine outcomes. As with the evaluable patient analyses, there were no significant differences at end point between the two active treatments.

Conclusion:

The design and execution of this study were adequate. There were some baseline differences and differential dropout rates for several variables but it is unlikely they would invalidate the study. Imipramine produced significantly more improvement than placebo on all variables. Fluoxetine was not shown to be consistently different than placebo.

2. Investigator No. 2 - Jay S. Cohn, M.D.

a. Demographic Data

Dr. Cohn enrolled a total of 202 patients with a primary diagnosis of major depressive disorder into this trial. Sixty-seven patients were randomized to fluoxetine, 68 to imipramine and 67 to placebo. Of these, 36 failed to reach the double blind phase and a further 26 were unevaluable for efficacy primarily because of insufficient therapy. The demographic characteristics of the 140 evaluable patients are given in Tables 1-A and 1-B. The numbers of evaluable patients were 46, 42 and 52 for the fluoxetine, imipramine and placebo groups respectively. Less than half of the imipramine and placebo treatment groups completed six weeks of treatment although more than half the fluoxetine patients did so. The patient flow including reasons for non-evaluability etc., are given in Table 7 taken directly from the sponsor's submission. The numbers of dropouts and reasons are given in Table 3.

b. Baseline Comparisons

There was a significant effect of sex in the evaluable group (females comprised 74%, 52% and 46%) of the fluoxetine, imipramine and placebo groups respectively which was also the case in the total group. The treatment groups did not differ on the remaining demographic variables. On the baseline efficacy parameters, the HAM-D retardation factor and Covi anxiety total were significant. For both variables, the imipramine scores were significantly higher (more pathology) than placebo and fluoxetine. A number of pairwise comparisons were significant again usually reflecting a greater severity of illness for imipramine over placebo.

c. Efficacy Data

1. Endpoint Analysis

Approximately 50% (71) of the 140 evaluable patients completed the final 6 week visit. There was a difference among the treatments in percentage completing. All 140 evaluable patients, however, were included in the endpoint analyses. The number of patients in the weekly analyses included only patients who actually attended the visit.

The results of the efficacy analyses are given in Table 4 (means) and Table 5 (statistical outcomes). Fluoxetine was significantly more effective than placebo on every efficacy variable at endpoint. The effect of imipramine also exceeded that of placebo for most of the variables. In addition, fluoxetine's effect exceeded that of imipramine on all variables except the HAM-D retardation and sleep factor and the SCL58 anxiety factor.

Table 7

Patient Population:

	Fluoxetine	Imipramine	Placebo
A. No. enrolled in study	54 (M=15, F=39)	54 (M=23, F=31)	58 (M=30, F=28)
1. Completed 6 weeks	35	20	16 $P < .001$
2. Terminated prior to 6 weeks	19	34	42
a. 2° to Adv. Exp.	8	24	1 $P < .001$
b. Lack of efficacy	0	4	34 $P < .001$
c. Lost to follow-up	9	3	3
d. Patient decision	1	3	4
e. Suicide attempt	1	0	0
B. Unevaluable for efficacy	8	12	6
1. Insufficient Therapy	7	12	5
2. Other	1	0	1
C. Total evaluable for efficacy	46	42	52
a. Mean age	39.4	42.3	41.9
b. Usual Maintenance dose	80 mg	300 mg	

2. Weekly Analyses

The weekly visits analyses for the key variables indicated there was no difference between fluoxetine and imipramine on HAM-D total, global improvement or SCL58 total. Fluoxetine was significantly better than placebo on HAM-D total at weeks 2, 4, and 6 and on global improvement at week 2. Imipramine was significantly better than placebo only on the HAM-D total at week 2. There were other differences between the treatments on the numerous other efficacy variables which are detailed in the submission and which were generally similar to the above effect.

d. Safety Data

1. Adverse effects

(All adverse experiences whether believed to be drug related or not are included in the following discussion.)

A listing of adverse experiences for each treatment which led to patients being dropped from the study are given in Table 8 (taken directly from the sponsor's submission). The number of patients dropped for adverse effects were 10, 30, and 1 for fluoxetine, imipramine, and placebo, respectively. The difference in incidence among the treatments is significant.

During the double blind phase, 89% of the fluoxetine patients, 93% of the imipramine and 57% of the placebo patients reported one or more adverse effects.

The most frequent adverse experiences for fluoxetine were:

drowsiness (33%)
excessive sweating (28%)
nausea (28%)
dry mouth (26%)
tremor (22%)
insomnia (20%)
nervousness (19%)
headache (17%)
asthenia (13%)
visual disturbance (13%)
dyspepsia (11%)
anxiety (11%).

Table 8

ADVERSE EXPERIENCES CAUSING DISCONTINUATION

Adverse Experience	Fluoxetine n=54 No. of Pts. (Total	% of Pts. Pts.=10)	Imipramine n=54 No. of Pts. (Total	% of Pts. Pts.=30)	Placebo n=58 No. of Pts. (Total	% of Pts. Pts.=1)
Asthenia	2	4	4	7	-	-
Chills	-	-	1	2	-	-
Fever	-	-	1	2	-	-
Influenza	-	-	1	2	-	-
ECG Changes	-	-	1	2	-	-
Hot Flushes	-	-	1	2	-	-
Palpitation	-	-	1	2	-	-
Tachycardia	1	2	1	2	-	-
Anorexia	1	2	1	2	-	-
Constipation	-	-	3	6	-	-
Diarrhea	-	-	1	2	-	-
Dyspepsia	1	2	3	6	-	-
Flatulence	-	-	1	2	-	-
Mouth dryness	-	-	20	37	-	-
Nausea	1	2	6	11	-	-
Pain, abdominal	1	2	1	2	-	-
Thirst	-	-	1	2	-	-
Pain, muscle	-	-	1	2	-	-
Anxiety	2	4	2	4	-	-
Concentration dec.	2	4	2	4	-	-
Confusion	-	-	2	4	-	-
Disorientation	-	-	1	2	-	-
Dizziness	2	4	12	22	-	-
Drowsiness	3	6	4	7	1	2
Headache	1	2	6	11	-	-
Hypersomnia	-	-	1	2	-	-
Insomnia	4	7	1	2	-	-
Libido, decreased	-	-	2	4	-	-
Lightheadedness	-	-	3	6	-	-
Nervousness	3	6	2	4	-	-
Neurosis, hysterical	-	-	1	2	-	-
Sedated	-	-	4	7	1	2
Sensation disturbance	1	2	4	7	-	-
Tremor	1	2	5	9	-	-
Dyspnea	-	-	2	4	-	-
Upper Resp. Infec.	-	-	1	2	-	-
Eczema	1	2	-	-	-	-
Pruritus	-	-	1	2	-	-
Rash	2	4	-	-	-	-
Skin Diseases(Nos)	1	2	-	-	-	-
Sweating, excessive	1	2	11	20	-	-
Vision Disturbance	1	2	3	6	-	-
Cervical Erosion and Ulceration	1	2	-	-	-	-
Impotence, sexual	-	-	1	2	-	-
Neop.B., vulva	1	2	-	-	-	-
Pelvic Inflam. Dis.	1	2	-	-	-	-
Sexual Dysfunction	-	-	1	2	-	-

The most frequent adverse experiences for imipramine were:
dry mouth (7[illegible]%)
dizziness (4[illegible]%)
excessive sweating (41%)
tremor (26%)
drowsiness (24%)
nausea (22%)
headache (22%)
constipation (19%)
sensation disturbance (19%)
lightheadedness (15%)
vision disturbance (15%)

The most frequent adverse experiences for placebo were:
dry mouth (17%)
headache (14%)
drowsiness (12%)

2. Vital Signs
Fluoxetine decreased pulse rate and systolic blood pressure and increased diastolic blood pressure while imipramine increased pulse rate and decreased systolic blood pressure.

Summary and Critique:

This six week study compared fluoxetine, imipramine and placebo in 166 depressed adult outpatients, 140 of whom were classified as evaluable. There was only one difference on demographic variables among the treatment groups at baseline and that was in the proportion of females to males (fewer females in the placebo group). There were a number of significant differences (6 out of 60 comparisons) between treatment groups at baseline on efficacy variables. A small number of patients received concomitant psychotropic medications most of which were allowed by the protocol. Their use was equally frequent among the three treatment groups. In contrast, a high proportion of patients (almost 100%) had a concurrent physical diagnosis. This appeared to reflect either an overly zealous questioner or the use of a check list approach, as most diagnoses were of minor significance.

This study also had a very high dropout rate particularly in the imipramine and placebo groups where approximately two thirds of the patients failed to complete six weeks. In fact, there was a differential dropout rate with approximately 40% of the placebo patients dropping out following the week two evaluation (primarily for lack of efficacy), while approximately 25% of the imipramine patients dropped out at the same time point (for adverse effects) and almost none of the fluoxetine patients dropped out until the trial's completion.

The results of the statistical analyses indicated that, for the evaluable patients, fluoxetine produced significantly more improvement than placebo on all the efficacy variables at end point. Imipramine was also significantly better than placebo on most variables at the same time period. Fluoxetine exceeded imipramine in the degree of improvement for all but three variables. Results in the weekly analyses were not so overwhelmingly positive.

The sponsor indicated the end point results probably provided a more accurate reflection of the study because so many patients dropped in the imipramine and placebo groups making weekly analyses difficult to interpret. In fact, the large number of dropouts for the placebo and imipramine groups following the week two evaluation (particularly in comparison with fluoxetine where most patients completed the trial) probably means the end point analyses are also uninterpretable. That is, the end point analyses are essentially a comparison between placebo patients who received only two weeks of treatment and fluoxetine patients with six weeks of treatment.

Conclusion:

The design of this study was adequate. There were, however, some differences between the treatment groups at baseline (primarily reflecting greater pathology in the imipramine group) which may have influenced the outcomes despite correction by statistical means.

The statistical results for the end point comparisons provided by the sponsor indicated that fluoxetine produced significantly more improvement than placebo on all variables and more improvement than imipramine, although the imipramine scores were slightly higher than both groups at baseline. Imipramine was also shown to produce more improvement than placebo.

Despite these seemingly overwhelmingly positive results, the investigator made use of the option in the protocol which allowed for a different dropout time depending on how the patient was doing. This meant that the end point analysis was in fact a comparison of a six week fluoxetine trial with a two week placebo trial and with a two week imipramine trial. This differential dropout rate in fact invalidates the end point analysis. At the same time, the weekly analyses were not overwhelmingly positive. Hence, this study can, at best, be said to be supportive.

3. Investigator No. 3 - James D. Bremner, M.D.

a. Demographic Data

Dr. Bremner enrolled a total of 77 patients with a primary diagnosis of major depressive disorder. Thirty patients were randomized to fluoxetine, 32 to imipramine and 15 to placebo. (This study was randomized to have one-half the number of placebo patients as the number of active treatment patients.) Of these, 4 failed to reach the double blind phase and a further 13 were classified as unevaluable for efficacy leaving 60 patients. The demographic characteristics of the 60 patients are given in Tables 1-A and 1-B. The numbers of "evaluable" patients were 24, 24, and 12 for fluoxetine, imipramine and placebo groups respectively. Approximately two thirds of each treatment group completed six weeks. The patient flow including reasons for non-evaluability etc., are given in Table 9 taken directly from the sponsor's submission. The number of and reasons for dropouts are given in Table 3.

Table 9

Patient Population:

	Fluoxetine	Imipramine	Placebo*
A. No. enrolled in study	29 (M=8, F=21)	30 (M=8, F=22)	14 (M=6, F=8)
1. Completed 6 weeks	22	22	8 p=.42
2. Terminated prior to 6 weeks	7	8	6
a. 2° to Adv. Exp.	4	8	0 p=.075
b. Lack of efficacy	2	0	5 p=.001
c. Lost to follow-up	0	0	1
d. Patient decision	0	0	0
e. Protocol violated	1	0	0
B. Unevaluable for efficacy	5	6	2
1. Insufficient therapy	3	4	2
2. Protocol deviation	2	1	0
3. Concomitant medication	0	1	0
C. Total evaluable for efficacy	24	24	12
a. Mean age	38.5	42.3	36.9
b. Usual Maintenance dose	60 mg	175 mg	

*This study was randomized to have one-half the number of placebo patients as the number of active study drug patients.

b. Baseline Comparisons

Statistical comparisons, between treatment groups, of demographic variables indicated that the groups of evaluable patients differed only in the "length of previous treatment for mental illness." The percents without prior treatment were 29, 21, and 75 for fluoxetine, imipramine and placebo respectively. Consequently, this became a control variable (covariate) in the subsequent parametric analyses. At baseline there were a few "marginally" significant differences among the treatment groups: SCL-58 somatization ($p = .072$ overall) and several other SCL-58 factors.

c. Efficacy Data

1. Endpoint Analysis

Eighty-one percent (52) of the 60 evaluable patients completed the final 6 week visit. All 60 evaluable patients, however, were included in the endpoint analyses. The number of patients in the weekly analyses included only those patients who actually attended the visit.

The results of the efficacy analyses are given in Table 4 (means) and Table 5 (statistical outcomes). Imipramine was significantly superior to placebo on all major variables while fluoxetine exceeded placebo on most variables. There were no significant differences between fluoxetine and imipramine on any efficacy variables. (The CGI side effect variable favored fluoxetine over imipramine.)

2. Weekly Analysis

The results for the weekly analyses were similar to the endpoint analyses. That is, fluoxetine was significantly better than placebo on a number of variables at some time points. Imipramine and placebo were significantly different on a number of variables at later time periods; imipramine and fluoxetine were generally not significantly different although there were comparisons marginally in favor of imipramine.

d. Safety Data

1. Adverse effects

(All adverse experiences whether believed to be drug related or not are included in the following discussion.)

A listing of the adverse experiences for each treatment which led to patients being dropped from the study are given in Table 10 (taken directly from the sponsor's submission). The number of patients dropped for adverse experiences were 4, 7, and 0 for fluoxetine, imipramine and placebo, respectively. The difference in incidence among the treatments approaches significance.

During the double blind phase, 45% of fluoxetine patients, 83% of imipramine patients and 21% of placebo patients reported adverse effects.

The most frequent adverse experiences for fluoxetine were drowsiness (10%), nervousness (10%) and sweating (10%). The most frequent effects for imipramine were dry mouth (47%), drowsiness (30%), nervousness (17%) and there were no frequent effects for placebo. No unexpected or serious effects were noted in the study.

2. Vital Signs

Fluoxetine produced a decrease in pulse rate and systolic blood pressure while imipramine produced an increase in pulse rate and a decrease in systolic blood pressure. Diastolic blood pressure, weight and temperature were generally not changed with treatment.

Summary and Critique:

This six week study compared fluoxetine, imipramine and placebo in 73 depressed adult outpatients, 60 of whom were classified as evaluable. There was only one difference among the treatment groups at baseline and that was in the proportion of patients with no previous treatment (highest in the placebo group). Approximately one third of patients received allowable concomitant psychotropic medications. They were equally frequent among the three treatment groups. A high proportion of patients completed the trial. There were differences in the proportion of patients dropped for adverse effects with placebo having the smallest incidence.

The results of the statistical analyses indicated that, for the evaluable patients, imipramine produced significantly more improvement than placebo on all the efficacy variables at end point. Fluoxetine was significantly better than placebo on most variables at the same time period. There were no significant differences between fluoxetine and imipramine in these analyses.

For the total group endpoint analyses, there were fewer significant outcomes at endpoint for the imipramine-placebo comparison than in the evaluable analysis and slightly more significant outcomes for the fluoxetine-placebo comparison. As with the evaluable analysis, there were no significant differences at endpoint between the two active treatments.

Conclusion:

The design and execution of this study were adequate and there did not appear to be any features which might invalidate the study. The results for the evaluable patients indicated fluoxetine produced more improvement than placebo on most efficacy variables while imipramine exceeded placebo on all efficacy variables, with no differences between the active treatments.

4. Investigator No. 4 - David L. Dunner, M.D.

a. Demographic Data

Dr. Dunner enrolled a total of 119 patients with a primary diagnosis of major depressive disorder into this trial. Forty patients were randomized to fluoxetine, 39 to imipramine and 40 to placebo. Of these, 15 failed to reach the double blind phase, 4 were lost to follow up (no on-drug evaluation), and a further 20 were classified as unevaluable for efficacy primarily because of insufficient therapy. The demographic characteristics of the 80 evaluable patients are given in Tables 1-A and 1-B. The numbers of "evaluable" patients were 23, 29, and 28 for the fluoxetine, imipramine and placebo groups respectively. Over half of the patients completed six weeks. The patient flow including reasons for non-evaluability etc., are given in Table 11 taken directly from the sponsor's submission. The number of and reasons for dropouts are given in Table 3.

b. Baseline Comparisons

There were no significant differences between the treatment groups on any of the demographic variables. The treatment groups did differ on several baseline efficacy parameters, namely, the HAM-D retardation factor (Kruskal Wallis p = 0.77) and the SCL-58 interpersonal sensitivity factor (Kruskal Wallis p = .047). A number of pairwise comparisons were also significant at baseline: HAM-D retardation fluoxetine less than placebo; imipramine less than placebo; SCL-58 interpersonal sensitivity imipramine less than fluoxetine.

c. Efficacy Data

1. Endpoint Analysis

Approximately 60% (56) of the 90 evaluable patients completed the final 6 week visit. All 80 evaluable patients, however, were included in the endpoint analyses. The number of patients in the weekly analyses included only those patients who actually attended the visit.

The results of the efficacy analyses are given in Table 4 (means) and Table 5 (statistical outcomes). There was essentially no difference in efficacy between fluoxetine and placebo. However, imipramine was significantly more effective than placebo on every efficacy variable at endpoint. The effect of imipramine also exceeded that of fluoxetine for most of the variables.

2. Weekly Analysis

The results for the weekly analyses were similar to the endpoint analyses. That is, there is generally no significantly difference between fluoxetine and imipramine. Also both fluoxetine and imipramine were significant in comparison with placebo on a number of variables at several time points.

d. Safety Data

1. Adverse Effects

(All adverse experiences whether believed to be drug related or not are included in the following discussion.)

A listing of the adverse experiences for each treatment which led to patients being dropped from the study are given in Table 12 (taken directly from the sponsor's submission). The number of patients dropped for adverse effects were 10, 11, and 1 for fluoxetine, imipramine and placebo, respectively. The difference in incidence among the treatments is significant.

During the double blind phase, 97% of both fluoxetine and imipramine patients and 76% of placebo patients reported side effects.

The most frequent adverse experiences for fluoxetine were:

nausea (47%)
headache (31%)
tremor (31%)
nervousness (22%)
decreased concentration (19%)
drowsiness (19%)
dizziness (12%)
insomnia (12%)
dry mouth (12%)

The most frequent adverse effects for imipramine were:

dry mouth (88%)
drowsiness (44%)
excessive sweating (35%)
headache (32%)
dizziness (32%)
nausea (27%)
tremor (27%)
constipation (23%)

The most frequent adverse effects for placebo were:

headache (32%)
nausea (18%)

2. Vital Signs

With fluoxetine and placebo there was a tendency for decreases to occur in pulse rate, and systolic and diastolic blood pressure, whereas with imipramine, increases occurred in pulse rate and decreases in both blood pressure figures.

Summary and Critique:

This six week study compared fluoxetine, imipramine and placebo in 100 depressed adult outpatients, 80 of whom were classified as evaluable. There were no differences among the treatment groups at baseline on the demographic variables. There were small differences in three efficacy baseline variables but no treatment was favored consistently. Concomitant psychotropic medications were not a problem in this study. Slightly over 50% of patients in each treatment group completed the six week trial. Sixty-four percent of evaluable patients completed six weeks and dropouts were evenly distributed among the treatment groups.

The results of the statistical analyses indicated that, for the evaluable patients, imipramine produced significantly more improvement than placebo on almost all the efficacy variables at endpoint. Fluoxetine was significantly better than placebo on only one variable (SCL-58 interpersonal sensitivity) at the same time period. Imipramine also produced significantly more improvement than fluoxetine on key efficacy variables.

Inclusion of the unevaluable patients affected the outcomes only slightly eliminating several formerly significant imipramine-fluoxetine comparisons.

Conclusion:

The design and execution of this study were adequate and there did not appear to be any features which might invalidate the study. The results, however, did not show fluoxetine to be consistently different than placebo.

5. Investigator No. 5 - Bernard I. Grosser, M.D.

a. Demographic Data

Dr. Grosser enrolled a total of 104 patients with a primary diagnosis of major depressive disorder. Thirty-four patients were randomized to fluoxetine, 35 to imipramine and 35 to placebo. Of these, 6 failed to reach the double blind phase, and a further 14 were classified as unevaluable for efficacy leaving 84 patients. The demographic characteristics of the 84 evaluable patients are given in Tables 1-A and 1-B. The numbers of "evaluable" patients were 30, 27, and 27 for the fluoxetine, imipramine and placebo groups respectively. Approximately 70% of the patients completed six weeks. The patient flow including reasons for non-evaluability etc., are given in Table 13 taken directly from the sponsor's submission. The number of and reasons for dropouts are given in Table 3.

b. Baseline Comparisons

Statistical comparisons between treatment groups at baseline indicated that the groups of evaluable patients did not differ on the demographic variables. At baseline there were no significant differences among the treatment groups on any of the efficacy variables (Kruskal Wallis, p less than .05). There were some differences on the SCL-58 with pairwise comparisons reflecting more pathology in the fluoxetine than the placebo group at baseline.

c. Efficacy Data

1. Endpoint Analysis

Sixty-six percent (56) of the 84 evaluable patients completed the final 6 week visit. All 84 evaluable patients, however, were included in the endpoint analyses. The number of patients in the weekly analyses included only those patients who actually attended the visit.

The results of the efficacy analyses are given in Table 4 (means) and Table 5 (statistical outcomes). In general, imipramine was significantly superior to placebo on all major variables. Fluoxetine, on the other hand, was associated with significant superiority on only four or five variables (namely CGI severity and therapeutic ratio, SCL-58 factors for depression and anxiety with trends on the Raskin and Covi). Statistically, however, there was no difference between fluoxetine and imipramine.

Table 13

Patient Population:

	Fluoxetine	Imipramine	Placebo
A. No. enrolled in study	33 (M=8,F=25)	34 (M=12,F=22)	31 (M=12,F=19)
1. Completed 6 weeks	20[a]	24[b]	19[c]
2. Terminated prior to 6 weeks	13	10	12
a. 2° to Adv. Exp.	2	5	1
b. Lack of efficacy and adverse experience	2	-	-
c. Lack of efficacy	7	5	8
d. Lost to follow-up	-	-	1
e. Patient decision	1	-	2
f. Protocol violation	1	-	-
B. Unevaluable for efficacy	3	7	4
1. Insufficient Therapy	1	1	1
2. Protocol deviation	1	2	-
3. Placebo responder	1	3	3
4. Concomitant medication	-	1	-
C. Total evaluable for efficacy	30	27	27
a. Mean age	39.33	40.63	37.33
b. Usual Maintenance dose	80 mg	200 mg	

[a] Of these 20 patients, 3 completed six weeks of therapy but terminated for other reasons: lack of efficacy, patient decision, and adverse experience study drug related.

[b] Of these 24 patients, 3 completed six weeks of therapy but terminated for other reasons: two for lack of efficacy and one for study drug related adverse experiences.

[c] Of these 19 patients, one completed six weeks of therapy but terminated for lack of efficacy.

2. Weekly Analyses

The results for the weekly analyses were similar to the endpoint analyses. That is, imipramine was frequently significantly better than placebo (e.g. HAM-D total at each week) whereas fluoxetine was less frequently significantly better than placebo (e.g. HAM-D total week 6 only). Imipramine was occasionally better than fluoxetine (e.g. HAM-D total at week 1) and fluoxetine produced more improvement than IMI on the SCL-58 total at week 6.

d. Safety Data

1. Adverse Effects

(All adverse experiences whether believed to be drug related or not are included in the following discussion.)

A listing of the adverse experiences for each treatment which led to patients being dropped from the study are given in Table 14 (taken directly from the sponsor's submission). The number of patients dropped for adverse effects were 6, 5, and 1 for fluoxetine, imipramine, and placebo, respectively. The difference in incidence among the treatments is not significant.

During the double blind phase, the percentage of patient reporting adverse effects were 91%, 100% and 90% for fluoxetine, imipramine and placebo respectively.

The most frequent adverse experiences for fluoxetine were:

nervousness (2[illegible]%)
dry mouth (24%)
nausea (21%)
tremor (21%)
vision disturbances (21%)
anorexia (15%)
insomnia (15%)
excessive sweating (15%)

The most frequent adverse experiences for imipramine were:

dry mouth (73%)
constipation ([illegible]2%)
headache (23%)
tremor (23%)
asthenia (21%)
sensation disturbance (18%)

The most frequent adverse experiences for placebo were:

headache (29%)
dry mouth (19%)
influenza (16%)
diarrhea (16%)
nausea (16%)

2. Vital Signs

With fluoxetine, both pulse rate and systolic blood pressure decreased whereas with imipramine, pulse rate increased while systolic blood pressure decreased. There were no consistent changes in the other variables.

Summary and Critique:

This six week study compared fluoxetine, imipramine and placebo in 98 depressed adult outpatients. Eighty-four of whom were classified as evaluable. There were no differences among the treatment groups at baseline on the demographic variables or on the mean efficacy variables (except for several SLC-58 variables where fluoxetine patients showed more pathology than placebo). Approximately one third of the patients received allowed concomitant psychotropic medications with a slightly higher proportion in the fluoxetine group. There were more dropouts in the placebo group (51%) than in the active treatments (30-40%).

The results of the statistical analyses indicated that, for the evaluable patients, imipramine produced significantly more improvement than placebo on all major efficacy variables at endpoint. Fluoxetine was significantly better than placebo on only four variables at the same time period. No significant differences were noted between the two active treatments.

The inclusion of the unevaluable patients in the analyses did not markedly change the imipramine-placebo comparison. The number of significant fluoxetine-placebo comparisons increased however and there was one significant fluoxetine-imipramine comparison.

Conclusion:

The design and execution of this study were adequate and there did not appear to be any features which might invalidate the study. Fluoxetine was not shown to be consistently different than placebo.

6. Investigator No. 6 - F.S. Abuzzahab, Sr., M.D., Ph.D.

a. Demographic Data

Dr. Abuzzahab enrolled a total of 104 patients with a primary diagnosis of major depressive disorder. Thirty-four patients were randomized to fluoxetine, 35 to imipramine and 35 to placebo. Of these, 13 failed to reach the double blind phase, and a further 19 were unevaluable for efficacy because of insufficient therapy because of adverse experiences. The demographic characteristics of the 72 evaluable patients are given in Tables 1-A and 1-B. The numbers of "evaluable" patients were 23, 23, and 26 for the fluoxetine, imipramine and placebo groups respectively. Approximately 50% of the patients in each treatment group completed the six week trial. The patient flow including reasons for non-evaluability etc., are given in Table 15 taken directly from the sponsor's submission. The number of and reasons for dropouts are given in Table 3.

b. Baseline Comparisons

There were no significant differences between the treatment groups on any demographic variables. The treatment groups did differ on several efficacy variables at baseline on the Kruskal-Wallis test: HAM-D total $p = .01$; HAM-D anxiety/somatization $p = .02$; HAM-D retardation $p = .07$ and SCL-90 somatization $p = .06$. There were also pairwise differences, primarily with the same variables. The rank of the severities of the treatment groups (from greatest to least) was imipramine, placebo, and fluoxetine.

c. Efficacy Data

1. Endpoint Analysis

Approximately 50% (35) of the 72 evaluable patients completed the final 6 week visit. All 72 evaluable patients, however, were included in the endpoint analyses. The number of patients in the weekly analyses included only those patients who actually attended the visit.

Table 15

Patient Population:

	Fluoxetine	Imipramine	Placebo
A. No. enrolled in study	30 (M=14, F=16)	30 (M=11, F=19)	31 (M=13, F=18
1. Completed 6 weeks	14	14*	10 P>.5
2. Terminated prior to 6 weeks	16	16	21 P=.049
a. 2° to Adv. Exp.	2	3	-
b. Lack of efficacy	9	11	18 P=.087
c. Adverse exp. and lack of efficacy	-	1	-
d. Lost to follow-up	-	-	2
e. Patient decision	4	1	1
f. Suicide attempt	1	-	-
B. Unevaluable for efficacy	7	7	5
1. Insufficient Therapy	4	5	4
2. Protocol deviation	1	2	1
3. Placebo responder	1	-	-
4. Concomitant Medication	1	-	-
C. Total evaluable for efficacy	23	23	26
a. Mean age	37.1	35.4	41.3
b. Usual Maintenance dose	80 mg	300 mg	

*Of these 14 patients who completed the study, two terminated for other reasons: one for lack of efficacy and one for adverse experiences study drug related.

The results of the efficacy analyses are given in Table 4 (means) and Table 5 (statistical outcomes). Both fluoxetine and imipramine were significantly more effective than placebo on a number of the efficacy variables at endpoint. Fluoxetine's effect exceeded that of placebo on the overall analysis for the HAM-D cognitive factor and the CGI side effect variables. There were also significant pairwise comparisons. Imipramine exceeded placebo on aproximately the same number of items including the two mentioned above. There were no differences between fluoxetine and imipramine.

2. Weekly Analyses

The weekly visits analyses for the key variables indicated there was no difference between fluoxetine and imipramine on HAM-D total, global improvement or SCL-58 total. Fluoxetine was significantly better than placebo on HAM-D total weeks 2, 4 and 6 and on global improvement at week 2. Imipramine was significantly better than placebo only on the HAM-D total at week 2. There were other differences between the treatments on the numerous other efficacy variables which are detailed in the submission and which were generally similar to the above effect.

d. Safety Data

1. Adverse Effects

(All adverse experiences whether believed to be drug related or not are included in the following discussion.)

A listing of the adverse experiences for each treatment which led to patients being dropped from the study are given in Table 16 (taken directly from the sponsor's submission). The number of patients dropped for adverse effects were 3, 8, and 0 for fluoxetine, imipramine, and placebo, respectively. The difference in incidence among the treatments is significant.

During the double blind treatment, 77%, 87% and 55% of fluoxetine, imipramine and placebo patients, respectively reported adverse effects.

The most frequent adverse experiences for fluoxetine were:

nausea (20%)
insomnia (17%)

The most frequent adverse effects for imipramine were:

dry mouth (77%)
insomnia (33%)
dizziness (20%)
excessive sweating (20%)

The most frequent adverse effects for placebo were:

insomnia (15%)
dry mouth (13%)

No unexpected or serious effects were noted in the study.

2. Vital Signs

Fluoxetine tended to produce a decrease in diastolic blood pressure; placebo and imipramine produced a decrease in systolic blood pressure.

Summary and Critique:

This six week study compared fluoxetine, imipramine and placebo in 91 depressed adult outpatients, 72 of whom were classified as evaluable. There were no differences among the treatment groups at baseline on the demographic variables. Several efficacy variables were significant reflecting greatest initial severity with imipramine and least with fluoxetine. Almost half of the patients received allowed concomitant psychotropic medications but they were equally frequent among the treatments. A high proportion of patients dropped out before six weeks (greater than 50%).

The results of the statistical analyses indicated that, for the evaluable patients, both fluoxetine and imipramine produced significantly more improvement than placebo on some scattered efficacy variables (e.g. not the HAM-D total, not the SCL-58) at endpoint. No significant differences were noted between the two active treatments.

For the total group endpoint analyses, there were fewer significant outcomes at endpoint for all comparisons than in the evaluable analysis.

Conclusion:

The design and execution of this study were adequate and there did not appear to be any features which might invalidate the study. The results showed fluoxetine produced more improvement than placebo on a few variables. The differences, however, were not consistent and included only some key variables.

7. Pooled Study

(The following is taken directly from the sponsor's submission.)

Title: Statistical Evaluation of Efficacy: A comparison of fluoxetine, imipramine, and placebo in the treatment of Major Depressive Disorder, for patients who did not receive concomitant psychotropic drugs while on Protocol 27.

Investigators: J.P. Feighner, M.D. J.B. Cohn, M.D.
J.D. Bremner, M.D. D.L. Dunner, M.D.
B.I. Grosser, M.D. F.S. Abuzzahab, M.D., Ph.D.

Study Design: Protocol 27 provided for a double-blind, randomized, parallel study; one week on placebo was followed by 6 weeks of fluoxetine (20 mg to 80 mg), or imipramine (75 mg to 300 mg), or placebo. Individual investigator summaries are presented elsewhere in the NDA. This protocol permitted the concurrent use of flurazepam and/or chloral hydrate. For purposes of examining the pooled efficacy data in this presentation, patients were excluded if the following concomitant psychotropic drugs were taken:

amphetamine	chloral hydrate	chlordiazepoxide
clonazepam	clorazepate	diazepam
*doxepin	*fluoxetine	flurazepam
*imipramine	perphenazine	phenobarbital
prazepam	prochlorperazine	temazepam

* drugs erroneously prescribed or dispensed

Patient Population:

A. Patients Enrolled on Protocol 27:

Inv. No.	Investigator	Total Patients Enrolled	Pts Excl. for Psycho Drugs	Pts Incld	Uneval Pts	Total
001	J. Feighner, M.D.	178	58	120	25	95
002	J. Cohn, M.D.	166	7	159	25	134
003	J. Bremner, M.D.	73	25	48	9	39
004	D. Dunner, M.D.	100	8	92	17	75
005	B. Grosser, M.D.	98	18	80	11	69
006	F. Abuzzahab, M.D.	91	26	65	15	50
	Total:	706	- 142	= 564	- 102	= 462

B. Patients Who Did Not Receive Psychotropic Drugs:

Inv. No.	Investigator	Evaluable Patients			All Patients		
		Fluox	Imi	Plac	Fluox	Imi	Plac
001	J. Feighner, M.D.	34	29	32	44	36	40
002	J. Cohn, M.D.	43	40	51	51	51	57
003	J. Bremner, M.D.	15	17	7	19	21	8
004	D. Dunner, M.D.	19	29	27	27	33	32
005	B. Grosser, M.D.	24	24	21	26	30	24
006	F. Abuzzahab, M.D.	17	14	19	22	20	23
	Total:	152	153	157	189	191	184

Results:

Efficacy: This pooling of data excluded the data of J.B. Cohn from the comparison of fluoxetine vs. imipramine and fluoxetine vs. placebo because in his study fluoxetine was significantly better than imipramine and placebo for the majority of the variables. This resulted in significant investigator-by-treatment interactions in the comparisons involving fluoxetine. However, the imipramine-placebo comparisons did include Cohn's data.

	p-value	p-value	p-value
HAM-D Total	F < I (.039)	F > P (.125)	I > P ($p < .001$)
Raskin Depression	F < I (.203)	F > P (.032)	I > P ($p < .001$)
Covi Anxiety	F < I (.058)	F > P (.184)	I > P ($p < .001$)
Severity of Depression	F < I (.304)	F > P (.018)	I > P ($p < .001$)
Global Improvement	F < I (.045)	F > P (.013)	I > P ($p < .001$)

A complete listing of the statistical analysis is given in Table 17 (taken directly from the sponsor's submission).

The section taken from the sponsor's submission ends here.

Critique and Summary:

In the pooled analysis, imipramine was clearly more effective than placebo whereas fluoxetine was less consistently better than placebo. Similarly, imipramine produced somewhat more improvement than fluoxetine on half of the key variables. This study is supportive but not strongly positive in demonstrating fluoxetine's role in the treatment of depression. [Dr. Chi, our statistician has asked for additional analyses and these will be included when the results are available. That is, the pooling excluded all patients who received any concomitant medication including those allowed by the protocol. This constitutes a post hoc exclusion and he has asked for analyses with the excluded patient replaced in the analysis.

Table 17

ENDPOINT ANALYSIS OF PATIENTS WHO DID NOT RECEIVE CONCOMITANT PSYCHOTROPIC DRUGS: SUMMARY OF RESULTS, STUDY 27, Investigators 001-006

Variable	Mean Difference Fluox.	Mean Difference Imipr.**	Mean Difference Plac.**	Pairwise p-value F vs. I	Pairwise p-value F vs. P*	Pairwise p-value I vs. P*
Efficacy Index--Therapeutic Effect	-1.41	-1.67 (-1.71)	-0.99 (-0.97)	.121	.007	<.001
Efficacy Index--Side Effect	-0.59	-0.96 (-1.11)	-0.22 (-0.24)	<.001	<.001	<.001
Efficacy Index--Ratio	-0.75	-0.61 (-0.56)	-0.71 (-0.70)	.357	>.5	>.5
HAMD--Total	11.61	14.29 (13.17)	9.54 (7.70)	.039	.125	<.001
HAMD--Anxiety/Somatization	3.00	3.94 (3.29)	2.67 (1.94)	.041	.209	<.001
HAMD--Cognitive Disturbance	3.08	3.50 (3.42)	2.01 (1.72)	.177	.020	<.001
HAMD--Retardation	3.47	4.02 (3.80)	2.78 (2.38)	.173	.076	<.001
HAMD--Sleep Disturbance	1.29	2.02 (1.92)	1.38 (1.08)	.008	>.5	<.001
Raskin Depression	1.08	1.27 (1.19)	0.76 (0.64)	.203	.032	<.001
Covi Anxiety	0.52	0.63 (0.61)	0.33 (0.24)	.058	.184	<.001
Severity of Depression	1.38	1.58 (1.59)	0.90 (0.82)	.304	.018	<.001
Global Improvement	1.47	1.78 (1.76)	1.06 (0.98)	.045	.013	<.001
Patient: How felt since start	1.45	1.70 (1.53)	0.94 (0.83)	.133	.005	<.001
Patient: How felt since last visit	0.45	0.50 (0.44)	0.13 (0.07)	.398	.050	.001
SCL58--Overall Average	0.25	0.36 (0.35)	0.18 (0.18)	.120	.263	<.001
SCL58--Somatization	0.08	0.17 (0.15)	0.16 (0.14)	.078	>.5	.362
SCL58--Obsessive/Compulsive	0.33	0.45 (0.44)	0.18 (0.19)	.303	.071	<.001
SCL58--Interpersonal Sensitivity	0.50	0.53 (0.53)	0.13 (0.15)	>.5	<.001	<.001
SCL58--Depression	0.37	0.54 (0.54)	0.25 (0.21)	.047	.079	<.001
SCL58--Anxiety	0.07	0.23 (0.24)	0.17 (0.16)	.102	>.5	.410

*One-tailed test (ANOVA p-value divided by 2)
**The mean in parentheses includes investigator 002, and is used in the comparison of imipramine to placebo.
Note: P-values for the fluoxetine comparisons are obtained from Tables 2A and 2B. The imipramine-placebo p-values are from Table 1C.

B. Revised Pooling

The FDA statistician (Dr. George Chi) asked Eli Lilly to develop a more appropriate pooling. That is, he asked them to replace patients excluded for receiving concomitant medications allowed by the protocol. After replacing the patients, he requested that them examine any investigator by treatment interactions and if necessary, exclude the investigator(s) responsible.

Lilly determined that Dr. J. B. Cohn was contributing the interaction and hence, excluded him from their revised pooled analysis. The results of the revised pooled analysis are as follows (taken from Dr. Chi's review):

A Summary of Sponsor's Endpoint Analyses
Based on Evaluable Patients who were Pooled from
the Five Investigators excluding Cohn

Efficacy Measure	Mean Reduction from Baseline: Imipramine (147)*	Fluoxetine (149)*	Placebo (136)*	significance level: I>F	F>P	95% Confidence Interval (F-P)
HAMD Total	14.1	11.6	8.9	0.03	0.03	(0.5,4.0)
Retardation	3.9	3.4	2.4	0.13	0.01	(0.3,1.6)
Raskin Depression	1.2	1.1	0.7	0.12	0.004	(0.1,0.6)
Severity of Depression	1.5	1.3	0.8	0.16	0.002	(0.2,0.8)
Global Improvement	1.8	1.5	1.0	0.04	<0.001	(0.2,0.8)

*Total Sample Sizes

As can be seen in the table, fluoxetine produced significantly more improvement than placebo on the major efficacy variables. For this reason, the revised pooling of Protocol 27 can be said to contribute to the judgment of substantial evidence of efficacy.

149
+ 147
+ 136
---
437 = 5 centers, included excluded

706 enrolled
- 134 Cohn

572
77 - unevaluable
495 = Evaluable

? 135 "Total sample"
58 "Evaluable" pts

NOV 19 1986 (3)

NOV 16 1986

Statistical Review and Evaluation

NDA #: 18-936/Drug Class: 4C

Date : November 17, 1986

Sponsor : Eli Lilly Research Laboratories

Drug Name : Prozac (fluoxetine hydrochloride)

Indication : Anti-depression

Documents Reviewed : Volumes 7.1-7.10 dated December 17, 1985, a supplementary requested by this reviewer dated February 23, 1986, and the fluoxetine statistical review dated July 31, 1985, (P-62)

The content of this review has been discussed with Richard Kapit, M.D. of HFN-120 and he agreed with my conclusion.

This review pertains mainly the efficacy aspect of two parallel, placebo-controlled, dose ranging studies of fluoxetine 20, 40 and 60 mg in patients with major depressive disorder of mild severity and moderate severity. The safety aspect has been relegated primarily to the medical review.

I. A Description of the Two Studies

These two studies were identical in design. They were both randomized, double-blind, multicenter, parallel study of depressed patients. Patients were entered into the study if they were adult male or female outpatients between the age of 18 and 65 years suffering from major depressive disorder diagnosed by the DSM III criterion. They were unipolar depressed patients with either a single or recurrent episode. All patients received placebo for approximately a week to eliminate placebo responders from the studies. Patients whose Hamilton Depression Scale scores had a drop of 20% or more, or a drop below 14 were considered as placebo responders and were excluded from the studies. A patient's Raskin Depression Scale score must also exceed their COVI Anxiety Scale score at visit 1 and visit 2 to be included. At the end of the placebo washout period, patients who had a Hamilton Depression Scale score of at least 20 were considered as moderately depressed, and patients who scored between 14 and 19 inclusive were considered as mildly depressed patients.

Patients were randomized to fluoxetine 20, 40, 60 mg and placebo separately in the mildly and moderately depressed groups for the 6 weeks double-blind treatment period. Patients were scheduled weekly visits during which efficacy parameters and safety parameters were measured and recorded. Efficacy parameters included

HAMD Total score, Raskin Depression score, COVI Anxiety score, Clinical Global Impression scale, Patient Global Impression scale and Symptom Check List. Safety parameters included vital signs, study drug dosage record, concomitant therapy, intercurrent illness etc. Physical examinations, blood chemistry, urinalysis, hematology were done only at visit 1 and visit 8 (the end of the double-blind treatment period).

Safety analyses were performed on all patients. The relative frequencies of adverse events were compared among treatment groups on a pairwise basis using the Chi-square tests. Efficacy analyses were performed on all patients, evaluable patients, all completers and evaluable completers. Two types of analyses were done : the endpoint analysis and the weekly analysis. In the endpoint analysis, a patient's last available visit value was used; this analysis is also called the last value carried forward analysis. In the weekly analysis, only patients still active up to that week would be included in the analysis. A patient was considered to be unevaluable for efficacy if he dropped out prior to completing one week of active drug therapy. Standard nonparametric methods (Wilcoxon Rank-sum test for two way comparison and ANOVA on ranks) were used in all of these analyses. The least significance difference procedure was used in multiple treatment comparisons. Two-sided significance levels were used for all comparisons.

The objectives of these studies were to demonstrate the efficacy and safety of fluoxetine and the dose-response relationship of fluoxetine at 20, 40 and 60 mg.

In this review, we shall focus on the endpoint analysis of all patients data and the week 5 and week 8 analyses of all patients who were still under active treatment up to the respective week for the following efficacy parameters : HAMD Total, HAMD-Item 1, HAMD-Retardation, CGI-Severity of Depression, CGI-Global Improvement, Raskin Depression. The results based on the evaluable patients and all completers were similar and did not provide additional information not already known and hence will not be discussed below.

II. Sponsor's Results of the Studies

A total of 910 patients were enrolled in the study with a primary diagnosis of major depressive disorder. One hundred sixty-four patients were not assigned a randomization number and thus did not enter the active phase of the study. The remaining 746 patients were stratified into either the mildly depressed group (HAMD Total score between 14 and 19) or the moderately depressed group (HAMD Total score exceeded 19). Three hundred eighty-one patients were stratified to the mildly depressed group. These patients were assigned at random to the four treatments : Fluoxetine 20, 40, 60 mg and placebo. Nine of these patients never returned for visit 3 and were subsequently excluded from both the efficacy and safety analyses. On the other hand, 365 patients were stratified to the moderately depressed group. These patients were assigned to the four treatments at random. Nine of these patients did not return for visit 3 and were also excluded from the efficacy and safety analyses.

There were no significant differences between the treatment groups in the various demographic characteristics for both the mildly and moderately depressed groups. However, for the mildly depressed group, there were significant baseline differences between the treatment groups in the following efficacy parameters : HAMD Total, HAMD-Cognitive Disturbance and HAMD-Retardation. The sponsor performed analysis of covariance for these parameters based on the all patients data and all completers.

Since the covariance analysis provides similar results, they will not be discussed further.

For both the mildly depressed and moderately depressed groups (see Table 1 and Table 2), there were significantly greater number of dropouts in the fluoxetine 40 and 60 mg treated groups than in the placebo group. In fact, a greater proportion of the fluoxetine patients were terminated due to adverse experiences and were terminated earlier than the placebo patients (see Table 3 and Table 4). Such differential dropout rates will tend to bias against the treatment groups in an endpoint analysis. Recall that the differential dropout rates in the previous study, Protocol#27, were biased against the placebo because in that study, Dr. Cohn had a significantly greater number of patients dropped out early due to lack of efficacy in the placebo group than in the fluoxetine group. The situation here is just the reverse.

In both the mildly depressed and moderately depressed groups, there were no significant treatment by investigator (there were 10 investigators) interactions in both the endpoint analysis and the weekly analyses. The analyses were quite straight forward. For the mildly depressed group, the endpoint analyses (Tables 5-10) showed that there were no differences between the four treatment groups except for Severity of Depression between fluoxetine 40 mg and placebo ($p=0.04$). The results improved somwhat in the 8 weeks analyses (see Tables 11-16). Fluoxetine 40 and 60 mg showed significant superiority over placebo in Severity of Depression ($p=0.01$ and $p=0.004$ respectively) and fluoxetine 20 and 60 mg showed significant superiority over placebo in HAMD-Retardation ($p=0.01$ and $p=0.005$ respectively). One may also note that there were dose-response relationships among the fluoxetine doses relative to almost all efficacy parameters at 8 weeks.

For the moderately depressed group, the endpoint analyses (see Tables 17-22) generally showed that fluoxetine 20 and 40 mg were significantly superior to placebo but that fluoxetine 60 mg was not significantly better than placebo. The results of the 8 weeks analyses (see Tables 23-28) showed that all three fluoxetine treatments were superior to placebo except for fluoxetine 20 and 40 mg relative to Severity of Depression and HAMD-Retardation. However, a dose-response relationship among the fluoxetine doses was not discernable relative to any of the efficacy measures at week 8.

For both the mildly and moderately depressed groups, neither efficacy nor dose-response relationship were observed at the 5 weeks analyses (see Tables 11-16,23-28).

Based on the sponsor's safety analyses, there were significant dose-related adverse effects observed in both the mildly and moderately depressed groups. These side effects were principally anorexia, nausea, anxiety, diarrhea and weight loss (see Tables 29-30).

III. Reviewer's Conclusions

Due to the higher early termination rates observed among the fluoxetine 40 and 60 mg treated patients, a bias is introduced in the endpoint analyses against these two dose groups because patients who had dropped out early would have their early visit values carried forward in the analyses. Therefore, for both the mildly and moderately depressed groups, the results of the endpoint analyses should not be taken at their face values.

For the mildly depressed group, both the endpoint analyses and the 5 weeks analyses showed no differences among the treatment groups. For the 8 weeks analyses, fluoxetine 40 and 60 mg showed some significant and marginally significant superiority to placebo in HAMD-Item 1, Severity of Depression, and HAMD-Retardation. One can also observe a weak dose-response relationship among the fluoxetine doses relative to almost all efficacy measures.

For the moderately depressed group, the endpoint analyses showed that fluoxetine 20 and 40 mg were significantly more effective than placebo relative to all efficacy measures except HAMD-Retardation. Although, fluoxetine 60 mg was numerically superior to placebo, it achieved marginal significance only in HAMD-Item 1 and Raskin Depression. On the other hand, fluoxetine 20 and 40 mg were generally shown to be numerically superior to fluoxetine 60 mg but only achieved statistical significance in HAMD-Total.

No treatment effects were detected in the 5 weeks analyses. In the 8 weeks analyses, all three doses of fluoxetine demonstrated significant superiority to placebo relative to all efficacy measures except for Severity of Depression and HAMD-Retardation (fluoxetine 60 mg only). Unlike in the mildly depressed group, a dose-response relationship was not discernable among the fluoxetine doses.

In view of the bias present in the endpoint analyses, this reviewer suggests that the appropriate analyses to be considered in this case be the 8 weeks analyses (which is the same as the all completers analyses for this week). However, as a reassurance that the results based on the 8 weeks analyses are reasonable, a table summarizing the HAMD-Total scores from other controlled trials involving fluoxetine (mainly 80mg) is presented in Tables 31 and 32. The tables show that the baseline mean HAMD-Total scores for the moderately depressed patients in the 8 weeks analyses are slightly lower than the mean baseline HAMD-Total scores observed for the patients in these studies, while the mean reductions in HAMD-Total scores generally fall within the observed range.

From the reported adverse experiences for mildly and moderately depressed patients, there were obvious dose-related side effects in anorexia, nausea, diarrhea, anxiety, drowsiness, tremor, dizziness, excessive sweating, asthenia and weight loss. In particular, patients treated with fluoxetine 40 and 60 mg had significantly higher frequencies of nausea, anorexia and weight loss than the placebo patients.

In summary, fluoxetine 20, 40 and 60 mg were effective in treating moderately depressed patients. For the treatment to be effective, the duration of treatment should be at least 5-6 weeks. Fluoxetine at these doses were not effective for treating the mildly depressed patients. In view of the significant side effects in anorexia, weight loss and nausea which were apparently dose-related, and the corresponding lack of a dose-response relationship relative to the efficacy measures (in the moderately depressed patients), this reviewer concludes that fluoxetine 20 mg should be the recommended dose for treating moderately depressed patients..

George [illegible], Ph.D.
Mathematical Statistician

cc:

Orig. NDA 18-936
HFN-120
HFN-120/Dr. Leber
HFN-120/Dr.Kapit
HFN-120/Dr.Lee
HFN-344/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Chi
Chron.
File: DRU 1.3.2 NDA
Dr.Chi/x34594/gyhc/11/17/86

Concur: Dr. Dubey 11-18-86

Table 1

Frequencies of Patient Dropouts by Weeks

(Protocol # 62 - Mild Depression)

Treatment	N	Week 1	2	3	4	5	6	Total
60 mg	104	19 (9)*	10 (7)	12 (4)	8 (2)	2 (2)	0 (0)	51 (49%) (24) (23%)
40 mg	105	8 (7)	9 (5)	12 (3)	7 (2)	6 (3)	1 (1)	43 (41%) (21) (20%)
20 mg	107	7 (2)	10 (2)	8 (3)	7 (1)	4 (0)	1 (0)	37 (35%) (8) (7%)
Placebo	56	4 (2)	4 (2)	2 (0)	3 (0)	6 (1)	0 (0)	19 (34%) (5) (9%)

* Number of patients who dropped out due to adverse reactions.

Table 2

Frequencies of Patient Dropouts by Weeks

(Protocol # 62 - Moderate Depression)

Treatment	N	Week 1	2	3	4	5	6	Total
60 mg	105	17 (12)*	11 (6)	10 (4)	13 (6)	5 (1)	2 (1)	58 (55%) (30) (29%)
40 mg	103	8 (5)	12 (2)	9 (1)	8 (2)	3 (1)	1 (0)	41 (40%) (11) (11%)
20 mg	100	4 (2)	10 (2)	14 (3)	5 (0)	5 (1)	0 (0)	38 (38%) 8 (8%)
Placebo	48	2 (0)	7 (2)	6 (2)	5 (1)	1 (1)	0 (0)	21 (44%) (6) (13%)

* Number of patients who dropped out due to adverse reactions.

Table 3

Frequencies of Early Terminations by Reasons

(Protocol # 62 - Mild Depression)

	Treatment			
	60 mg	40 mg	20 mg	Placebo
# Completed 6 Weeks	53	62	70	37
# Terminated Prior to 6 Weeks	51 (49%)	43 (41%)	37 (35%)	19 (34%)
1. Due to Adverse Experience	24* (23%)	21** (20%)	7 (7%)	5 (9%)
2. Lack of Efficacy	9	12	9	7
3. Both (1) and (2)	0	0	1	0
4. Lost to Follow-up	7	6	4	1
5. Patient Decision	8	3	9	3
6. Other Reasons	3	1	7	3
Total Number of Patients	104	105	107	56

* Significantly different from placebo (p=0.027)
**Marginally significantly different from placebo (p=0.069)

Table 4

Frequencies of Early Terminations by Reasons

(Protocol # 62 - Moderate Depression)

	Treatment			
	60 mg	40 mg	20 mg	Placebo
# Completed 6 Weeks	47	62	62	27
# Terminated Prior to 6 Weeks	58 (55%)	41 (40%)	38 (38%)	21 (44%)
1. Due to Adverse Experience	27* (26%)	11 (11%)	8 (8%)	4 (8%)
2. Lack of Efficacy	12	16	20	10
3. Both (1) and (2)	3	1	0	2
4. Lost to Follow-up	8	4	1	2
5. Patient Decision	6	9	6	1
6. Other Reasons	2	3	0	2
Total Number of Patients	105	103	100	48

* Singificantly different from placebo (p=0.03)

Table 5

Mean Reduction from Baseline in

HAMD Total Score

for Mildly Depressed Patients

(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison — Two-sided Significance Level 40mg	20mg	Placebo
60mg	97	17.20	-5.39	0.36	0.29	0.50
40mg	99	16.83	-6.04		0.50	0.50
20mg	103	16.99	-6.23			0.43
Placebo	56	17.41	-5.82			

Table 6

Mean Reduction from Baseline in

HAMD - Item 1

for Mildly Depressed Patients

(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
60mg	✓ 100	2.11	-0.90 ✓	0.33	0.50	0.38
40mg	✓ 103	2.02	-0.99 ✓		0.50	0.09
20mg	✓ 105	2.15	-0.97 ✓			0.17
Placebo	✓ 56	2.23	-0.75 ✓			

✓

Table 7

Mean Reduction from Baseline in

HAMD - Retardation

for Mildly Depressed Patients

(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
60mg	97	6.04	-2.31	0.50	0.50	0.14
40mg	99	5.32	-2.01		0.30	0.30
20mg	103	6.07	-2.56			0.06
Placebo	56	5.84	-1.73			

Table 8

Mean Reduction from Baseline in
Raskin Depression
for Mildly Depressed Patients
(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
60mg	100	2.64	-0.63	0.33	0.42	0.50
40mg	103	2.63	-0.71		0.50	0.28
20mg	105	2.61	-0.71			0.32
Placebo	56	2.68	-0.61			

Table 9

Mean Reduction from Baseline in
Severity of Depression
for Mildly Depressed Patients
(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
60mg	√ 100	3.22	-0.75 √	0.50	0.50	0.11
40mg	√ 103	3.17	-0.81 √		0.50	0.04
20mg	√ 105	3.12	-0.72 √			0.08
Placebo	√ 56	3.11	-0.46 √			

√

Table 10

Mean Reduction from Baseline in

Global Improvement

for Mildly Depressed Patients

(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
60mg	100	3.92	-1.19	0.34	0.48	0.50
40mg	103	3.90	-1.38		0.50	0.34
20mg	105	3.90	-1.33			0.46
Placebo	56	4.00	-1.21			

Table 11

Mean Reduction from Baseline in
HAMD Total Score
for Mildly Depressed Patients
(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	71	17.17	-5.28	0.50	0.24	0.50
	40mg	85	16.81	-5.53		0.40	0.50
	20mg	83	16.70	-6.41			0.50
	Placebo	44	17.32	-6.39			
6	60mg	✓50	17.20	-9.24 ✓	0.50	0.50	0.13
	40mg	✓60	16.55	-8.82 ✓		0.50	0.26
	20mg	✓68	16.76	-8.46 ✓			0.21
	Placebo	✓36	17.36	-7.97 ✓			

Table 11

Mean Reduction from Baseline in
HAMD Total Score
for Mildly Depressed Patients
(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	71	17.17	-5.28	0.50	0.24	0.50
	40mg	85	16.81	-5.53		0.40	0.50
	20mg	83	16.70	-6.41			0.50
	Placebo	44	17.32	-6.39			
6	60mg	✓50	17.20	-9.24 ✓	0.50	0.50	0.13
	40mg	✓60	16.55	-8.82 ✓		0.50	0.26
	20mg	✓68	16.76	-8.46 ✓			0.21
	Placebo	✓36	17.36	-7.97 ✓			

Table 12

Mean Reduction from Baseline in

HAMD - Item 1

for Mildly Depressed Patients

(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	73	2.07	-0.99	0.50	0.50	0.11
	40mg	88	2.05	-0.90		0.50	0.21
	20mg	88	2.14	-1.00			0.08
	Placebo	46	2.15	-0.72			
6	60mg	✓ 53	2.08	-1.42✓	0.50	0.50	0.11
	40mg	✓ 63	2.03	-1.38✓		0.50	0.08
	20mg	✓ 71	2.15	-1.32✓			0.17
	Placebo	✓ 37	2.14	-1.05✓			

Table 13

Mean Reduction from Baseline in

HAMD - Retardation

for Mildly Depressed Patients

(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	71	6.10	-2.35	0.10	0.50	0.11
	40mg	85	5.29	-1.74		0.06	0.50
	20mg	83	6.10	-2.45			0.08
	Placebo	44	5.64	-1.75			
6	60mg	50	6.04	-3.60	0.09	0.50	0.005
	40mg	60	5.08	-2.80		0.19	0.17
	20mg	68	6.15	-3.47			0.01
	Placebo	36	5.64	-2.33			

Table 14

Mean Reduction from Baseline in

Raskin Depression

for Mildly Depressed Patients

(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	73	2.63	-0.57	0.13	0.30	0.36
	40mg	88	2.63	-0.68		0.50	0.50
	20mg	88	2.57	-0.66			0.50
	Placebo	46	2.68	-0.69			
6	60mg	53	2.67	-1.06	0.50	0.19	0.16
	40mg	63	2.60	-1.02		0.38	0.29
	20mg	71	2.56	-0.93			0.5
	Placebo	37	2.71	-0.88			

Table 14

Mean Reduction from Baseline in

Raskin Depression

for Mildly Depressed Patients

(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	73	2.63	-0.57	0.13	0.30	0.36
	40mg	88	2.63	-0.68		0.50	0.50
	20mg	88	2.57	-0.66			0.50
	Placebo	46	2.68	-0.69			
6	60mg	53	2.67	-1.06	0.50	0.19	0.16
	40mg	63	2.60	-1.02		0.38	0.29
	20mg	71	2.56	-0.93			0.5
	Placebo	37	2.71	-0.88			

Table 15

Mean Reduction from Baseline in Severity of Depression for Mildly Depressed Patients (Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	73	3.26	-0.62	0.50	0.50	0.50
	40mg	88	3.17	-0.68		0.44	0.31
	20mg	88	3.09	-0.57			0.50
	Placebo	46	3.13	-0.54			
6	60mg ✓	53	3.30	-1.45 ✓	0.50	0.03	0.004
	40mg ✓	63	3.16	-1.30 ✓		0.12	0.01
	20mg ✓	71	3.11	-1.01 ✓			0.22
	Placebo ✓	37	3.14	-0.84 ✓			

Table 16

Mean Reduction from Baseline in
Global Improvement
for Mildly Depressed Patients
(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	73	3.92	-1.26	0.50	0.50	0.50
	40mg	88	3.91	-1.23		0.50	0.50
	20mg	88	3.88	-1.33			0.50
	Placebo	46	4.00	-1.39			
6	60mg	53	3.89	-2.11	0.50	0.12	0.11
	40mg	63	3.87	-2.03		0.22	0.18
	20mg	71	3.87	-1.76			0.50
	Placebo	37	4.00	-1.76			

Table 17

Mean Reduction from Baseline in

HAMD Total Score

for Moderately Depressed Patients

(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
60mg	103	24.20	-7.20	0.04	0.03	0.34
40mg	97	24.19	-9.58		0.50	0.01
20mg	97	24.72	-9.78			0.007
Placebo	48	24.25	-5.69			

Table 18

Mean Reduction from Baseline in

HAMD-Item 1

for Moderately Depressed Patients

(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
60mg	104	2.66	-1.01	0.45	0.23	0.10
40mg	101	2.62	-1.11		0.50	0.03
20mg	99	2.68	-1.16			0.01
Placebo	48	2.69	-0.65			

Table 19

Mean Reduction from Baseline in

HAMD - Retardation

for Moderately Depressed Patients

(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
60mg	103	7.43	-2.56	0.50	0.38	0.33
40mg	97	7.44	-2.72		0.50	0.17
20mg	97	7.49	-2.80			0.10
Placebo	48	7.58	-2.00			

Table 20

Mean Reduction from Baseline in
Raskin Depression
for Moderately Depressed Patients
(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
60mg	104	3.33	-0.88	0.50	0.50	0.07
40mg	101	3.28	-0.95		0.50	0.02
20mg	99	3.31	-0.94			0.02
Placebo	48	3.25	-0.60			

Table 21

Mean Reduction from Baseline in

Severity of Depression

for Moderately Depressed Patients

(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
60mg	104	4.24	-1.12	0.50	0.50	0.11
40mg	101	4.22	-1.14		0.50	0.08
20mg	99	4.24	-1.17			0.05
Placebo	48	4.19	-0.75			

Table 22

Mean Reduction from Baseline in
Global Improvement
for Moderately Depressed Patients
(Protocol # 62 - All Patients Endpoint Analysis)

Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
60mg	104	4.09	-1.10	0.19	0.08	0.14
40mg	101	4.08	-1.40		0.50	0.01
20mg	99	4.11	-1.43			0.005
Placebo	48	3.94	-0.73			

Table 23

Mean Reduction from Baseline in

HAMD Total Score

for Moderately Depressed Patients

(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	71	24.10	-7.87	0.15	0.18	0.50
	40mg	78	24.00	-9.64		0.50	0.12
	20mg	83	24.41	-9.16			0.14
	Placebo	34	24.15	-7.26			
6	60mg	✓ 46	24.20	-13.11 ✓	0.50	0.50	0.02
	40mg	✓ 61	23.87	-12.57 ✓		0.39	0.04
	20mg	✓ 62	24.24	-13.47 ✓			0.008
	Placebo	✓ 27	23.59	- 9.19 ✓			

Table 24

Mean Reduction from Baseline in

HAMD - Item 1

for Moderately Depressed Patients

(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison, Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	73	2.71	-1.14	0.50	0.50	0.19
	40mg	82	2.62	-1.18		0.50	0.10
	20mg	85	2.72	-1.09			0.20
	Placebo	35	2.63	-0.86			
6	60mg	✓47	2.79	-1.79✓	0.17	0.38	0.001
	40mg	✓ 62	2.60	-1.50✓		0.50	0.01
	20mg	✓ 62	2.73	-1.65✓			0.003
	Placebo	✓ 27	2.52	-0.89✓			

Table 25

Mean Reduction from Baseline in

HAMD - Retardation

for Moderately Depressed Patients

(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	71	7.48	-2.73	0.50	0.50	0.46
	40mg	78	7.26	-2.56		0.50	0.32
	20mg	83	7.55	-2.81			0.31
	Placebo	34	7.71	-2.47			
6	60mg	46	7.65	-4.48	0.09	0.20	0.013
	40mg	61	7.28	-3.67		0.50	0.23
	20mg	62	7.40	-3.82			0.11
	Placebo	27	7.41	-3.00			

Table 26

Mean Reduction from Baseline in

Raskin Depression

for Moderately Depressed Patients

(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	103	3.33	-0.94	0.50	0.50	0.34
	40mg	100	3.24	-0.94		0.50	0.28
	20mg	99	3.30	-0.93			0.25
	Placebo	47	3.17	-0.78			
6	60mg	47	3.29	-1.41	0.42	0.50	0.002
	40mg	62	3.23	-1.28		0.50	0.009
	20mg	62	3.30	-1.37			0.003
	Placebo	27	3.08	-0.82			

Table 27

Mean Reduction from Baseline in
Severity of Depression
for Moderately Depressed Patients
(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	73	4.27	-1.01	0.48	0.50	0.50
	40mg	82	4.20	-1.09		0.50	0.31
	20mg	85	4.20	-1.06			0.45
	Placebo	27	4.11	-1.33			
6	60mg	✓ 41	4.26	-1.87 ✓	0.29	0.50	0.05
	40mg	✓ 62	4.21	-1.65 ✓		0.50	0.23
	20mg	✓ 62	4.21	-1.74 ✓			0.11
	Placebo	✓ 27	4.11	-1.33 ✓			

Table 28

Mean Reduction from Baseline in

Global Improvement

for Moderately Depressed Patients

(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	73	4.15	-1.30	0.41	0.33	0.23
	40mg	82	4.02	-1.49		0.50	0.06
	20mg	85	4.08	-1.41			0.05
	Placebo	35	3.89	-1.00			
6	60mg	47	4.13	-2.09	0.24	0.50	0.002
	40mg	62	4.00	-1.90		0.20	0.02
	20mg	62	4.10	-2.11			0.001
	Placebo	27	3.81	-1.26			

Table 28

Mean Reduction from Baseline in

Global Improvement

for Moderately Depressed Patients

(Protocol # 62 - Weekly Analyses)

Weeks of Treatment	Treatment	N	Baseline	Mean Reduction	Treatment Comparison Two-sided Significance Level 40mg	20mg	Placebo
3	60mg	73	4.15	-1.30	0.41	0.33	0.23
	40mg	82	4.02	-1.49		0.50	0.06
	20mg	85	4.08	-1.41			0.05
	Placebo	35	3.89	-1.00			
6	60mg	47	4.13	-2.09	0.24	0.50	0.002
	40mg	62	4.00	-1.90		0.20	0.02
	20mg	62	4.10	-2.11			0.001
	Placebo	27	3.81	-1.26			

Table 29

Frequencies of Selected Adverse Effects

(Protocol # 62 - Mild Depression)

Adverse Effect	Treatment 60mg (N=104)	40mg (N=105)	20mg (N=107)	Placebo (N=56)
Anorexia	21** (20%)	16** (15%)	14* (13%)	5 (9%)
Nausea	33** (32%)	37** (35%)	19 (18%)	7 (13%)
Diarrhea	17 (16%)	19* (18%)	20* (19%)	4 (7%)
Anxiety	19 (18%)	24 (23%)	19 (18%)	7 (13%)
Insomnia	30* (29%)	23 (22%)	14 (13%)	6 (11%)
Nervousness	25* (24%)	23 (22%)	7 (7%)	5 (9%)
Drowsiness	11 (11%)	13 (12%)	7 (7%)	2 (4%)
Tremor	10 (10%)	12 (11%)	3 (3%)	1 (2%)
Weight Loss (lbs)	-2.4**	-2.7***	-1.4	-0.04

* Significantly higher than placebo at p=0.05.

** Significantly higher than palcebo at p=0.01.

*** Significantly higher than placebo at p=0.001.

Table 30

Frequencies of Selected Adverse Effects

(Protocol # 62 - Moderate Depression)

Adverse Effect	Treatment 60mg (N=105)	40mg (N=103)	20mg (N=100)	Placebo (N=48)
Anorexia	19* (18%)	15 (14%)	7 (7%)	1 (2%)
Nausea	46** (44%)	27 (26%)	31* (31%)	7 (15%)
Diarrhea	19 (18%)	20 (19%)	9 (9%)	5 (10%)
Anxiety	24 (22%)	11 (10%)	10 (10%)	6 (12%)
Drowsiness	11 (11%)	14 (14%)	5 (5%)	1 (2%)
Tremor	14 (13%)	11 (11%)	6 (6%)	3 (6%)
Dizziness	16 (15%)	4 (4%)	9 (9%)	2 (4%)
Excessive Sweating	11 (11%)	13 (13%)	6 (6%)	3 (6%)
Asthenia	7 (7%)	2 (2%)	0	0
Weight Loss(lbs)	-3.8***	-3.0***	-0.6	-0.06

* Significantly higher than placebo at p=0.05.

** Significantly higher than placebo at p=0.01.

*** Significantly higher than placebo at p=0.001.

The following are the results of the LOCF analyses for the intent-to-treat sample (excluding Cohn) at 6 weeks, for four critical efficacy variables:

Efficacy Measure	Drug	N	Baseline Mean	Mean Change	2-sided Significance FvsP	IvsP	FvsI
HAM-D							
Dep.Item	F	184	2.8	-1.3	.001	.001	n.s.
	I	184	2.8	-1.3			
	P	167	2.9	-0.8			
Ret. Factor	F	181	7.9	-3.2	.009	.002	n.s.
	I	181	8.1	-3.5			
	P	163	8.3	-2.3			
Total Score	F	181	27.5	-11.0	.012	.001	n.s.
	I	181	28.2	-12.0			
	P	163	28.2	- 8.4			
CGI (Physician)							
Severity	F	185	4.6	- 1.2	.004	.001	n.s.
	I	184	4.5	- 1.3			
	P	168	4.5	- 0.8			

Legend: F = Fluoxetine
I = Imipramine
P = Placebo

The data from the Cohn center were analyzed separately, but because of a differential dropout rate (placebo patients dropped out early and active treatment patients continued in the trial), it is not possible to interpret the results of an LOCF analysis of these data. Thus, although the analysis favors fluoxetine, the LOCF analysis in effect compares the scores after two weeks with placebo and six weeks with fluoxetine. In a condition with spontaneous improvement, there is a substantial bias favoring the group whose patients remain longer in the study. The results of the analyses of patients who actually participated at various weeks (observed cases analyses) did not, for the most part, show significant differences between fluoxetine and placebo. Thus, it is not possible to interpret the data from the Cohn study.

Protocol 62. This was a fixed dose, multicenter study conducted in mildly and moderately depressed outpatients. Ten investigators contributed patients to each level of severity. The results were pooled and analyzed separately for each level of severity.

Design:

This was a six week, double blind, parallel group comparison of fixed doses of fluoxetine (20mg, 40mg, and 60mg) with placebo in 746 depressed outpatients. The protocol was the same as Study 27 described above, with two exceptions. First, the study consisted of two independent samples,

based on the severity of the disorder. Patients with mild depression were required to have a baseline HAM-D total score between 14 and 19 inclusive. Patients with moderate depression were required to have a total score of 20 or greater. Second, the dose was fixed for each treatment group, rather than titrated, and the total daily dose was administered once daily in the morning.

Conduct and Execution:

There were no differences in outcome among the four treatment groups in the mildly depressed sample; the efficacy data for this sample will therefore not be presented.

A total of 365 patients from the moderately depressed sample was randomized to double blind treatment and 13 did not return for the first drug evaluation. Thus, 352 patients (20mg - 99; 40mg - 101; 60mg - 104; placebo - 48) were included in the intent-to-treat sample.

Overall, 56 percent of patients completed the trial (20mg - 62%, 40mg - 60%, 60mg - 45%; and placebo - 56%). There was a difference among treatment groups in the timing of dropouts, i.e., more patients in the 60 mg group dropped out early, compared to the other groups. There were also differences in the reasons for dropout, with more patients dropping out for adverse effects in the 40 and 60 mg groups, especially the latter, compared to the 20 mg and placebo groups.

Analyses were conducted on an intent-to-treat sample (the total patient population randomized that had a baseline rating and at least one rating on treatment) and on a subset of patients who met the sponsor's criteria for evaluability. The results for the intent-to-treat and evaluable samples were similar. For the intent-to-treat sample, last observation carried forward (LOCF) analyses (at the end of each of the 6 weeks of the study) and weekly observed case analyses were conducted.

Results:

Patients were comparable at baseline with respect to demographic variables and rating scale severity measures. For the moderately depressed group, there were no significant treatment-by-center interactions for the LOCF or the observed cases analyses.

Beginning with week 4, and persisting through weeks 5 and 6, the results generally favored fluoxetine 20 mg over placebo in the LOCF analyses of the intent-to-treat sample. This superiority for fluoxetine 20 mg over placebo was also apparent in the observed cases analyses beginning at week 4, but was less consistently demonstrated in these analyses.

For fluoxetine 40 mg, there was a trend favoring fluoxetine over placebo at weeks 4 and 5, but not a clear superiority until week 6 of the LOCF analyses, and there was no evidence for the superiority of fluoxetine 60 mg over placebo in the LOCF analyses. However, there was strong evidence of superiority for fluoxetine 60 mg over placebo in the 6 weeks observed cases analyses.

The following are the results of the LOCF analyses of the intent-to-treat sample at 6 weeks, for four key efficacy variables:

Efficacy Measure	Drug	N	Baseline Mean	Mean Change	2-sided P (vs. Pbo)
HAM-D					
Dep. Item	F-20	99	2.68	-1.16	0.010
	F-40	101	2.62	-1.11	0.025
	F-60	104	2.66	-1.01	0.096
	Pbo	48	2.69	-0.65	
Ret. Factor	F-20	97	7.49	-2.80	0.095
	F-40	97	7.44	-2.72	0.167
	F-60	103	7.43	-2.56	0.329
	Pbo	48	7.58	-2.00	
Total Score	F-20	97	24.72	-9.78	0.007
	F-40	97	24.09	-9.58	0.010
	F-60	103	24.20	-7.20	0.338
	Pbo	48	24.25	-5.69	
CGI (Physician) Severity	F-20	99	4.24	-1.17	0.052
	F-40	101	4.22	-1.14	0.080
	F-60	104	4.24	-1.12	0.105
	Pbo	48	4.19	-0.75	

Overall, the results were persuasive only for fluoxetine 20 mg, and even for this group, the results are not as strong as in studies 19 and 27. The higher rate of dropouts for adverse events in both the 40 and 60 mg groups, along with the higher rate of dropouts early for the 60 mg group, would tend to bias the LOCF analyses against these groups. However, there was a suggestion from the observed cases analyses that, for the patients continuing on therapy for 6 weeks, the 60 mg dose may actually have been superior to the lower doses. Thus, it is not possible to interpret the results for the 40 and 60 mg groups. While these data do provide support for the antidepressant efficacy of fluoxetine at a 20 mg dose, they do not provide a clear basis for dosing recommendations.

Protocol 25: Karl Rickels, M.D., was the sole investigator in this study.

Design:

This was a five week, double blind, parallel group comparison of fluoxetine and placebo in depressed outpatients. The entry and exclusion criteria, the doses, the assessment procedures and the overall design were similar to Protocol 27 described above.

Prot 62

DEC 30 [redacted]

F5

(1)

REVIEW AND EVALUATION OF CLINICAL DATA
AMENDMENT

NDA 18-936

Amendment to (2)

Sponsor: Lilly Research Laboratories

Drug: fluoxetine (Prozac™)

Category: Antidepressant

Date of Submission: December 17, 1985

Date of Review: December 30, 1985

Contents of Submission:

The submission contains the report of a ten investigator, multicenter study comparing fixed dosages of fluoxetine (20, 40, 60 mg) with placebo in approximately 900 patients who were stratified either to the mild depression or to the moderate depression segment of the protocol. According to the sponsor's analysis, the lower dosages were more effective than the higher, particularly in the patients with moderate depression.

Review of Report:

The investigators together with the number of subjects they contributed to each stratification were as follows:

	Mild				Moderate			
	1	2	3	4*	1	2	3	4*
Roland J. Branconnier, Ph.D., Eric Dessain, M.D.	4	6	4	3	6	6	6	3
Jay B. Cohn, M.D., Ph.D.	12	12	12	6	11	12	12	6
M. Lynn Crismon, Pharm.D., Allen Childs, M.D.	2	2	2	1	2	2	2	1
David L. Dunner, M.D.	8	8	8	4	8	10	10	4
Louis F. Fabre, Jr., M.D., Ph.D.	10	11	11	6	12	14	14	6
John P. Feighner, M.D.	19	18	18	10	16	16	15	7
Roland R. Fieve, M.D.	10	10	10	5	10	10	10	5
Joseph Mendels, M.D.	28	22	27	14	14	15	16	6
Ram K. Shrivastava, M.D.	7	8	7	4	10	9	10	5
Ward T. Smith, M.D.	7	8	5	3	10	9	10	5

* 1-20mg Fluox., 2-40mg Fluox., 3-60mg Fluox., 4-Placebo

The study was coordinated by a contract research group, International Clinical Research Corporation.

Since the two segments were the same in all respects except for the inclusion criteria (mild vs moderate depression), the description of the protocol will be combined for the two depression severities. However, the results will be described separately for the two depression groups

I. Protocol Summary:

The study followed a double-blind, parallel group design which compared fixed doses of fluoxetine (20, 40 or 60 mg) and placebo in 381 outpatients with major depressive episode (mild severity) and in 365 outpatients with major depressive episode (moderate severity). (A total of 910 patients were enrolled although 164 were not randomized to treatment).

The study began with a one week, placebo baseline (washout) followed by a six week, double-blind "treatment" trial. Patients entered the double-blind phase only if they continued to meet the criteria for entry (Dx of major depressive disorder, HAM-D total of 14 for mild severity and 20 for moderate severity) and had shown a decrease of HAM-D total of less than 20% during the baseline.

Patients were seen weekly throughout; efficacy scales included the HAM-D, Raskin, Covi, CGI, Patient Global Impression and SCL-58. Safety assessments included a physical exam and history pre and final week, an EKG pre, vital signs weekly lab tests pre and final.

Dosage - Fluoxetine: 20, 40 and 60 mg or placebo which the patient was instructed to take in a single dose in the morning. (There was no initial titration).

The inclusion and exclusion criteria and the evaluability criteria (taken directly from the sponsor's submission) are provided in Appendix A. There is a lack of concordance between the evaluability criteria and actual practice: psychotropic drugs other than chloral hydrate were to be excluded although in the results, benzodiazepines were not classed as reasons for exclusion. In addition, according to the protocol, a patient was to be considered evaluable if they had a week 1 visit. A week 1 visit was also required for the all patient analysis.(Usually, the duration for evaluability is longer than that for the all patient analysis.)

II. Efficacy Results:

A. Mild Depression Stratification:

1. Patient Flow. A total of 381 patients were randomized to double blind treatment and 9 patients did not return for the first on-drug evaluation. (Five of the fluoxetine 40mg patients and three of the fluoxetine 60mg patients were lost to follow up. One fluoxetine 60mg patient was dropped for insufficient screening period.)

The following table (taken from the sponsor's submission) details the patient flow through the study (excluding the above):

Patient Population	Fluoxetine 20 mg	Fluoxetine 40 mg	Fluoxetine 60 mg	Placebo
A. No. enrolled in study	107 (M=41,F=66)	105 (M=46,F=59)	104 (M=43,F=61)	56 (M=28,F=28)
1. Completed 6 weeks	70	62	53	37
2. Terminated prior to 6 weeks	37	43	51	19
a. 2° to Adv. Exp.	7	21	24	5
b. Lack of efficacy	9	12	9	7
c. Both a. and b.	1	0	0	0
d. Lost to follow-up	4	6	7	4
e. Patient decision	9	3	8	3
f. Poor compliance	2	1	1	2
g. Protocol violation	4	0	2	1
h. Physician decision	1	0	0	0
3. Mean age	39.97	39.80	38.31	38.96
Minimum - Maximum	(18-70)	(20-64)	(20-64)	(22-65)
4. Unevaluable for effic.	5	5	10	0

The number of patients who terminated at each week are shown in the following table:

Mild Depression
Terminations

	Week 1	2	3	4	5	6
Placebo						
Patient Decision	-	1	-	-	2	-
Lost to Follow-up	1	-	-	-	-	-
Lack of Efficacy	1	-	1	3	2	-
Poor Compliance	-	1	1	-	-	-
Protocol Violation	-	-	-	-	1	-
Adverse Experience	2	2	-	-	1	-
Total	4	4	2	3	6	(37 Complete)
Fluoxetine (20 mg)						
Patient Decision	1	1	2	4	1	-
Physician Decision	1	-	-	-	-	-
Lost to Follow-up	1	1	1	-	1	-
Lack of Efficacy	1	4	1	2	1	-
Poor Compliance	-	-	1	-	-	1
Protocol Violation	1	2	-	-	-	-
Adverse Experience	2	2	3	1	-	-
Total	7	10	8	7	4	(70 Complete)
Fluoxetine (40 mg)						
Patient Decision	1	1	1	-	-	-
Lost to Follow-up	-	2	-	2	2	-
Lack of Efficacy	-	1	7	3	1	-
Poor Compliance	-	-	1	-	-	-
Adverse Experience	7	5	3	2	3	1
	8	9	12	7	6	(62 Complete)
Fluoxetine (60 mg)						
Patient Decision	3	1	3	1	-	-
Lost to Follow-up	6	1	-	-	-	-
Lack of Efficacy	-	1	4	4	-	-
Poor Compliance	-	-	1	-	-	-
Protocol Violation	1	-	-	1	-	-
Adverse Experience	9	7	4	2	2	-
Total	19	10	12	8	2	(53 Complete)

This table and the table of patient flow show a greater dropout rate for the fluoxetine 60 mg group than for the other fluoxetine groups and placebo. Only 50% of the patients in this group completed the trial whereas between 60 and 70 percent of patients in the other groups completed. The termination table shows that the higher incidence of dropouts in the 60mg group is attributable to more patients 'lost to follow up' and to adverse reactions, both of which occurred more frequently early in the trial.

2. Statistical Results

The statistical procedures were essentially the same as in the NDA submission, that is, non-parametric analyses of change scores and analyses of covariance on scores when treatment group differences at baseline were significant. Four different patient groups were analyzed: (1) all patients (randomized to treatment and at least one on-drug evaluation), (2) all evaluable patients, (3) all evaluable patients who completed the trial, and (4) all trial completers. Last Observation Carried Forward (LOCF) analyses were used for groups 1 and 2 to yield weekly and endpoint results (with an emphasis on the latter). Weekly analyses were carried on on groups 3 and 4 again with an emphasis on the final (week six) rating. In addition, weekly analyses of the completers for each week (that is, all patients in the trial at that rating) were carried out.

The sponsor also developed and analyzed a treatment response measure: the number of patients who had at least three weeks of treatment and whose HAM-D total score was reduced by 50%.

The number of patients in each of the analyses were as follows:

Mild Depression
Number of Subjects in Analyses

	Fluoxetine 20 mg	Fluoxetine 40 mg	Fluoxetine 60 mg	Placebo
Total Patients Stratified	107	110	108	56
No Wk.1 visit		5	4	
Theoretical All Patient	107	105	104	56
Ham-D All Patient Analysis	103	99	97	56
Unevaluable	5	5	10	0
Theoretical Evaluable	102	100	94	56
Ham-D Evaluable	98	95	88	55
Theoretical All Completers	70	62	53	37
Ham-D All Completers	68	61	51	37
Ham-D Evaluable Completers	66	60	51	36
No. at Week 1	101	96	95	54
Week 2	93	95	81	49
Week 3	83	85	71	44
Week 4	79	73	58	45
Week 5	71	65	48	42
Week 6	68	60	50	36

The all patient analysis includes all patients who received drug and had at least one rating on drug. The "No. at Week 1 etc." are the number of patients who were in the trial for that week's rating and had a HAM-D evaluation.

The statistical analyses were carried out for the following efficacy variables:

HAM-D Total 21 item
Anxiety/Somatization Factor
Cognitive Disturbance Factor
Retardation Factor
Sleep Disturbance Factor
Raskin Depression Scale
Covi Anxiety Scale
Clinical Global Impression Scale - 2 item
Patient Global Impressions
SCL-58 Total Score

The analyses were done for the five different populations described above.

a. All Patient End Point Analysis

The results of the all patient, endpoint analyses for the above 11 variables are shown in the following table (taken directly from the sponsor's submission)

Endpoint Analysis: Summary of Results for All Patients with Mild Depression

	Mean Change From Baseline to Last Visit			
		Fluoxetine		
Measure	Placebo	20 mg	40 mg	60 mg
HAMD-Total	-5.82	-6.23	-6.04	-5.39
HAMD-Anxiety/Somatization	-1.79	-1.50	-1.58	-1.30
HAMD-Cognitive Disturbance	-1.05	-0.91	-1.39	-0.79
HAMD-Retardation	-1.73	-2.56	-2.01	-2.31
HAMD-Sleep Disturbance	-0.77	-0.86	-0.52	-0.54
Raskin Depression	-0.61	-0.71	-0.71	-0.63
Covi Anxiety	-0.26	-0.19	-0.07	-0.07
CGI: Severity of Depression	-0.46	-0.72	-0.81	-0.75
CGI: Global Improvement	-1.21	-1.33	-1.38	-1.19
Patient's Global Impressions	-0.62	-0.97	-0.66	-0.55
SCL-58	-0.23	-0.28	-0.26	-0.19
Weight	-0.04	-1.41*	-2.70***	-2.39**
Heat Rate	-0.25	-0.85	0.25	-0.92
Systolic Blood Pressure	3.77	-0.60	-0.32	0.02
Diastolic Blood Pressure	-0.77	-1.06	-0.68	0.20

*Fluoxetine 20 mg significantly different from placebo ($p \leq .05$).
**Fluoxetine 60 mg significantly different from placebo ($p < .001$).
***Fluoxetine 40 mg significantly different from placebo ($p < .001$) and fluoxetine 20 mg ($p \leq .05$).

None of the efficacy analyses using the all patient group (modified intent-to-treat) showed a significant treatment effect. Numerically, fluox. 20 mg demonstrated the greatest improvement in 7 of the 11 efficacy variables. Fluoxetine 60mg produced the least improvement of the four groups on 7 of the 11 variables. Placebo produced the most improvement in 2/11 items, namely, the anxiety measures (HAM-D anxiety factor and the Covi anxiety scale). This latter presumably resulted because of an increase in anxiety and nervousness with fluoxetine, one of the most frequent adverse effects.

b. Response Rate Measure

The sponsor also computed a response measure comprising the number of patients whose Ham-D Total score decreased by at least 50%. This analysis was carried out on patients who completed at least three weeks of treatment, with dropout scores for later weeks carried forward. That is, it is an end point analysis including only those patients who had at least three weeks of treatment. This analysis, shown below, indicated that 60 mg fluoxetine is more effective than placebo in this population.

	Number and Percentage of Patients Responding to Treatment			
		Fluoxetine		
Analysis Group	Placebo	20 mg	40 mg	60 mg
All Patients (on drug 3 weeks)	45 35.6%	79 53.2%	75 50.7%	61 59.0%*

Pairwise Comparisons: *Significantly different from placebo ($p<.05$).

B. Moderate Depression

1. Patient Flow. A total of 365 patients were randomized to double blind treatment and 9 patients did not return for the first on-drug evaluation (8 patients were lost to follow up and one patient terminated at his own request.)

A table describing the patient flow (taken directly from the sponsor's submission) is given below:

Patient Population

	Fluoxetine 20 mg	Fluoxetine 40 mg	Fluoxetine 60 mg	Placebo
A. No. enrolled in study	100 (M=40,F=60)	103 (M=45,F=58)	105 (M=44,F=61)	48 (M=24,F=24)
1. Completed 6 weeks	62	62	47	27
2. Terminated prior to 6 weeks	38	41	58	21
a. 2° to Adv. Exp.	8	11	27	4
b. Lack of efficacy	20	16	12	10
c. Both a. & b.	0	1	3	2
d. Lost to follow-up	1	4	8	2
e. Patient decision	6	9	6	1
f. Protocol violation	2	0	1	0
g. Administration error	1	0	0	0
h. Poor compliance	0	0	0	2
i. Suicide attempt	0	0	1	0
3. Mean Age (Minimum-Maximum)	39.40 (21-64)	41.15 (19-65)	39.93 (19-65)	38.56 (26-54)

The number of terminations by treatment by week is given in the following table:

Moderate Depression
Terminations

	Week 1	2	3	4	5	6
Placebo						
Patient Decision	-	-	1	-	-	-
Lost to Follow-up	1	-	1	-	-	-
Lack of Efficacy	1	4	1	4	-	-
Poor Compliance	-	1	1	-	-	-
Adverse Experience	-	2	2	1	1	-
	2	7	6	5	1	(27 Complete)
Fluoxetine (20 mg)						
Patient Decision	1	1	-	1	3	-
Lost to Follow-up	-	-	-	-	1	-
Lack of Efficacy	-	7	9	4	-	-
Protocol Violation	1	-	1	-	-	-
Adverse Experience	2	2	3	-	1	-
Administrative Error	-	-	1	-	-	-
Total	4	10	14	5	5	(62 complete)
Fluoxetine (40 mg)						
Patient Decision	1	3	2	2	1	
Lost to Followup	-	1	-	2	1	-
Lack of Efficacy	2	6	6	2	-	-
Adverse Experience	5	2	1	2	1	1
Total	8	12	9	8	3	(62 Complete)
Fluoxetine (60 mg)						
Patient Decision	-	2	1	-	2	1
Lost to Followup	3	-	2	3	-	-
Lack of Efficacy	-	3	3	4	2	-
Protocol Violation	1	-	-	-	-	-
Adverse Experience	12	6	4	6	1	1
Suicide Attempt	1	-	-	-	-	-
Total	17	11	10	13	5	(47 Complete)

These tables show the same effect that was seen in the mild depression section, namely, a greater dropout rate for the 60mg group with more of the dropouts occurring early in the trial primarily for adverse experiences.

2. Statistical Results. A brief description of the statistical procedures are described under the mild depression segment above.

The number of patients in each of the analyses was as follows:

Moderate Depression
Number of Patients in Each Analysis

	Fluoxetine 20 mg	40 mg	60 mg	Placebo
Total Patients Stratified	103	105	106	51
Did not return Wk.1	3	2	1	3
Theoretical All Patient	100	103	105	48
Ham-D All Patients Analysis	97	97	103	48
Unevaluable Patients	4	6	10	0
Theoretical Evaluable Patients	96	97	95	48
Ham-D Evaluable Patient	94	93	94	48
Theoretical Completers	62	62	47	27
Ham-D Completers	62	61	47	27
Evaluable Completers	62	62	46	27
No. at Week 1	94	96	101	47
Week 2	90	90	80	45
Week 3	83	78	72	34
Week 4	68	70	63	33
Week 5	64	65	51	26
Week 6	62	61	46	27

The all patient analysis includes all patients who received drug and had at least one rating on drug. The "No. at Week 1 etc." are the number of patients who were in the trial for that week's rating and had a HAM-D evaluation.

Of the nine patients who were randomized to treatment and never appeared for the week one evaluation, eight patients (F-20:2, F-40:2, F-60:1, PL-3) were last to follow up. One F-20 patient terminated at his own request.

a. All Patient End Point Analysis

A summary table of the endpoint analyses of all patients (taken directly from the sponsor's submission) is shown below:

Endpoint Analysis: Summary of Results
(All Patients with Moderate Depression)

	Mean Change From Baseline to Last Visit			
		Fluoxetine		
Measure	Placebo	20 mg	40 mg	60 mg
HAMD-Total	-5.69	-9.78**+	-9.58**+	-7.20
HAMD-Anxiety/Somatization	-1.13	-2.43**++	-2.39**++	-1.40
HAMD-Cognitive Disturbance	-1.19	-2.35**	-2.56**+	-1.73
HAMD-Retardation	-2.00	-2.80	-2.72	-2.56
HAMD-Sleep Disturbance	-1.23	-1.51	-1.38	-1.05
Raskin Depression	-0.60	-0.94	-0.95	-0.88
Covi Anxiety	-0.11	-0.38**++	-0.29*	-0.15
CGI: Severity of Depression	-0.75	-1.17	-1.14	-1.12
CGI: Global Improvement	-0.73	-1.43**	-1.40*	-1.10
Patient's Global Impressions	-0.13	-0.92**	-0.82*	-0.66*
SCL-58	-0.11	-0.33*	-0.37***+	-0.25
Weight	-0.06	-0.56	-2.97***#	-3.76***#
Heart Rate	-0.04	-1.41	-1.07	-0.75
Systolic Blood Pressure	1.25	0.82	-1.21	0.024
Diastolic Blood Pressure	-0.10	-0.75	-0.82	0.96

*Significantly different from placebo ($p \leq .05$).
**Significantly different from placebo ($p < .01$).
***Significantly different from placebo ($p < .001$).
+Significantly different from fluoxetine, 60 mg ($p \leq .05$).
++Significantly different from fluoxetine, 60 mg ($p \leq .01$).
#Significantly different from fluoxetine, 20 mg ($p < .001$).

The fluoxetine 20 and 40 mg groups produced significantly more improvement than placebo on 7/11 items. Fluoxetine 60 mg significantly exceeded placebo on one item (patients global). The fluoxetine 20 mg group produced more improvement than fluoxetine 60 mg on 3 items and the fluoxetine 40 mg produced more improvement than 60 mg on 4 items. Numerically, fluoxetine 20 mg exceeded fluoxetine 40 mg on 8/11 items and fluoxetine 60 mg on 11/11.

b. Response Rate Measure

As was described above, the sponsor also developed a categorical analysis using as the measure, the number of patients showing a 50% response rate in their HAM-D total score. This analysis, shown below, indicated that all three fluoxetine groups were significantly different from placebo. The 40mg group showed the greatest difference from placebo.

III. Safety Evaluations;

The safety assessments included were described above. The results will be discussed in detail when the safety update is submitted and reviewed.

At this time, it can be noted that no new, unusual or serious adverse effects or physiological changes occured in this sample of 900 patients. The frequent adverse effects were nausea, insomnia, nervousness, anorexia, anxiety and diarrheo (all above 15%).

The frequency of adverse effects and number of terminations is as follows (taken directly from the sponsor's submission).

Mild Depression

Drug	No.of Patients	No. Reporting Adverse Effect	Disc. for Adverse Effect
Placebo	56	40	5
Fluoxetine-20	107	77	8
Fluoxetine-40	105	91	22
Fluoxetine-60	104	95	26

Moderate Depression

Drug	No.of Patients	No. Reporting Adverse Effect	Disc. for Adverse Effect
Placebo	48	33	7
Fluoxetine-20	100	73	8
Fluoxetine-40	103	84	14
Fluoxetine-60	105	95	31

Discussion:

1. The study design was seriously flawed by not allowing dose titration in the early days of the trial. This led to high dropout rates early in the trial in the 60mg group primarily for adverse reactions. This in turn led to a confounding of the statistical analyses because the high scores of large numbers of early dropouts in the one group were carried forward and compared at end point with smaller numbers of early dropouts carried forward in the lower dosage groups.

2. Both the evaluable patient and the all patient analyses included and carried forward the scores of the first week dropouts. This means that the problem of the differential dropout rate for the 60mg group occurs with both sets of analyses. (It is more usual in antidepressant trials to declare a patient evaluable if they have at least two on drug ratings, i.e., two weeks of treatment.)

3. When one examines the completer analyses, there is some evidence that the study outcome as described by the sponsor (low dosages more effective than high) may not be the appropriate conclusion. That is, numerically at least, in the completer analyses, the 60 mg group appears to produce more improvement than placebo and is at least similar to the 20mg and 40mg group outcomes. See Appendix B for tables and graphs showing the outcome for completers with particular emphasis on the final weeks of the trials. (It should be noted that the comparisons described as significant in the graphs were based on pairwise comparisons and did not depend on a significant overall F test.

4. The criterion measure (HAM-D total score reduction of 50%) which only includes patients who had at least 3 weeks of treatment shows the 60mg group to produce more improvement than placebo in both the mild and moderate depression groups. However, no rationale is given for the choice of three weeks and it is possible that the usual 'post hoc' criticism applies to this.

Summary:

According to the sponsor, this six week, parallel group, fixed dose comparison of fluoxetine 20 mg, 40 mg, 60 mg vs placebo in 381 patients with mild depression found no statistically significant difference in efficacy among the four treatments when all patient end point analyses were used. [Numerically, 20 mg daily produced the most improvement in 6/11 variables followed by 40 mg in 4/11 and placebo in 2/11 (one tie). 60 mg produced the least improvement in 7/11 variables.]

The sponsor made a similar conclusion concerning the same study in 365 patients with moderate depression. That is, the results of their all patient analysis tended to favor 40 mg daily although there was essentially no difference between 20 mg and 40 mg. Both were significantly better than 60 mg per day which was numerically superior to placebo.

My conclusion would be somewhat different. It is likely that the lack of dose titration affected the 60mg group more than the lower dosages. That is, there were larger numbers of early dropouts for side effects in this group and thus, there was a larger number of high scores carried forward in the all patient analysis and in the evaluable patient analysis . This differential early dropout rate would argue against using the all patient analysis as the most important analysis or as the best reflection of the study outcome.

Because of the flawed design and the differential early dropout rate for the 60mg group, I would argue that the completer analysis and the criterion analysis should carry more weight. These analyses would suggest that 60 mg is at least as effective as the lower dosages and, in the moderate depression group, is numerically superior on many important variables to the lower dosages. [Appendix B]

In summary, the study does not necessarily present totally contradictory results to the NDA submission where 80mg, usually the most frequent dosage, was found to be significantly better than placebo. However, because of the flaws in the design of the fixed dose study, it is not possible to arrive at a single, unequivocal interpretation of the results.

J. Hillary Lee, Ph.D.
Psychologist

cc:
Orig:NDA 18-936
HFN-120
HFN 120/TLaughren
HFN-120/HLee/1/6/86
rd/mb/1/7/86/1/13/86
ft/mb/1/14/86
DOC 0285h

12-22-86

I agree that this study is difficult to interpret for the 60 mg dose, since the intent-to-treat and completer analyses are not in agreement. However, these analyses are positive and essentially in agreement for the 20 and 40 mg doses, and I think, therefore, that this study does provide additional evidence of the antidepressant efficacy of fluoxetine (in moderate depression). However, I also agree that it is difficult to interpret how well patients do with 60 mg relative to 40 and 20 mg because of the design flaw, and the dosing recommendation for this drug will need to address this uncertainty, especially since the other supportive studies utilized doses of approximately 80 mg/day.

Thomas P. Laughren, MD
Group Leader, DPAP

FDA SSRI Studies

Study#	Authors	Drug	HAM-D vs Placebo p	Pub
P-19 1985	Fabre	fluoxetine	Wk 4: 0.02 Wk 5 : 0.07 re-analysis: .007	1987
P-25	Rickels Reviewer: ns	fluoxetine	0.81 re-analysis: 0.50	1985 1990
P-27	Feighner Cohn Bremmer Dunner Grosser Abuzzahab Reviewer: P-19 & P-27 fluox > placebo	fluoxetine	0.31 FDA: p>.20/ Pub: p=0.10 0.13 0.99 0.20 0.22 re-analysis: .012	1989 1985 1989 1984 1998 1988
P-62	Branconnier & Dessain Cohn Crimson & Childs Dunner et al	fluoxetine	20m ns 40m ns 60m ns 20m ns 40m ns 60m ns reviewer: uninterpretable re-analysis: 20m 0.007 40m 0.010 60m 0.338	

recovery dogs. In rats there was an equivocal increase in mineralization at HD in the 1 year (but not in the 2 year) study but no effects were seen in recovery animals. In mice, focal hypospermatogenesis (irreversible) was seen at HD (30 mg/kg) in the 3 month study but not in the 2 year studies (HD = 12 mg/kg). Fluoxetine produced no adverse effects on fertility in Segment I studies in rats. Testicular degeneration has been produced by other antidepressants, including imipramine, in chronic animal studies.

8. Nisoxetine is a close structural analog of fluoxetine that has produced leukopenia in man. In a 2 week monkey study with fluoxetine, both doses (10 and 25 mg/kg) caused decreases in WBC, RBC, Hb, and Hct; however, no control group was used. In a follow-up monkey study (which used a 10 mg/kg dose and a control group), WBCs were clearly decreased in 1 (and equivocally in another) of 4 monkeys but this normalized after a 2 week recovery period. Decreased WBCs were also seen in a 3 month combination study of F/carbidopa/5-HTP in rats, in HD males only. In 1 of 2 two-year mouse studies, WBC was decreased in HD males but was increased in HD females.

9. Various degenerative changes in kidney were seen in the 3 HD females (20 mg/kg) that died in the 1 year dog toxicity study which were not seen in other dogs; however, the causal relationships to drug treatment is not clear. In the 3 month dog study there was an equivocal increase in nephrocalcinosis. There were no clearly drug-related findings in kidney in rats and mice.

V. Clinical:

This section provides 1) a brief overview, 2) a description of the adequate and well controlled trials which provided evidence of efficacy, 3) a brief review of other adequate and well controlled trials which, because of their design, did not contribute to the efficacy claim, 4) a summary of safety data, and 5) a summary of clinical biopharmaceutic studies.

A. General:

All clinical trials to evaluate the efficacy of fluoxetine were carried out in adult outpatients with diagnoses of major depressive disorder (RDC or DSM III).

In the NDA, there were fourteen controlled trials submitted in support of the efficacy of fluoxetine in major depressive disorder. One study compared fluoxetine with imipramine and placebo (a six investigator, multicenter study). Another, a fixed dosage study, compared fluoxetine 20mg, 40mg, and 60mg with placebo (a ten investigator, multicenter study). Two studies compared fluoxetine and placebo. Ten studies compared fluoxetine with an active control agent (three were comparisons with imipramine, three with amitriptyline and four with doxepin). Because active control studies cannot generally provide clear evidence of effectiveness, the placebo controlled studies provide the most pertinent data on effectiveness.

Three of the four placebo controlled trials (Protocols 19, 27 and 62) provide evidence of effectiveness. The remaining placebo controlled study (Protocol 25) found no difference between the treatments. Two active control studies (Protocol 20, Bremner; Protocol 23, Feighner) that found fluoxetine superior to the active control will also be discussed. Although the remaining active control studies do not provide evidence of effectiveness, their results are not inconsistent with the results of the positive placebo controlled studies, i.e., they did not demonstrate a difference between fluoxetine and the active control drugs.

There were other uncontrolled studies of fluoxetine in depression and studies in other patient populations in the NDA, but since they do not have a direct bearing on efficacy in depression, they will not be discussed here.

B. Double Blind Studies With a Placebo Control:

The four placebo controlled studies include Protocol 19 (Fabre), Protocol 25 (Rickels), Protocol 27 (a three-way, six center study) and Protocol 62, a fixed dosage, ten center study. The three protocols which provide evidence of efficacy will be described first.

Protocol 19: Louis F. Fabre, M.D. was the sole investigator in this trial.

Design:

This was a five week, double blind, parallel group comparison of fluoxetine and placebo in depressed outpatients. Patients were required to 1) meet RDC criteria for major depressive disorder, 2) have a baseline total score of at least 20 on the Hamilton Rating Scale for Depression (HAM-D), 3) have a Raskin Depression Scale score of at least 8, which was required to equal or exceed that of the Covi Anxiety Scale score, and 4) have a decrease of less than 20% in the HAM-D total score during the baseline placebo period (while still meeting the requirement of a total score of 20). Exclusion criteria also included significant physical illness, concurrent use of other psychotropic medication, serious suicide risk, and MAOI use within two weeks of entry.

Patients were randomly assigned to fluoxetine or placebo. After a one week, single blind, placebo baseline (to eliminate placebo responders), patients were to be titrated to up to 60mg (3 capsules) by the end of the first week and were then to remain on a dose of 40 to 80 mg (2 - 4 capsules) for the duration of the trial. Placebo patients were titrated similarly, receiving up to four capsules of placebo daily. Treatments were administered on a b.i.d. schedule (morning and noon dosing), for a treatment period of five weeks. Efficacy assessments (completed at baseline and weekly) included the HAM-D (21 item), the Raskin Depression Scale, the Covi Anxiety Scale, physician and patient Clinical Global Impression (CGI), and the Zung Self Rating Depression Scale. Safety assessments (done at baseline and periodically during the trial) included physical exams, chest X-rays, ophthalmological exams, ECGs, vital signs, clinical labs, and ADRs. Concomitant psychotropic medications were to be prohibited.

NDA file

MAR 28 85

cite ERR

REVIEW AND EVALUATION OF EFFICACY DATA

NDA 18-936

PROZAC TM
(FLUOXETINE HYDROCHLORIDE)

Sponsor: Eli Lilly

Submissions: September 6 1983
September 7, 1984
October 10, 1984
October 23, 1984
December 17, 1984
April 25, 1985

TABLE OF CONTENTS

A diagnosis of major depression is based upon the presence of a prominent and persistent dysphoric or depressed mood plus at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, loss of energy or ability to think or concentrate, and suicidal ideation or attempts.

The effectiveness of (Trademark) in long term use, i.e., up to one year, has been shown in extensions of the controlled clinical studies; these included 218 patients evaluated for at least six months, with 71 continuing for over one year. The physician should periodically reevaluate the usefulness of the drug for the individual patient.

IV. Dosage Form: pulvule

V. Route of Administration: oral

VI. Related Drugs: experimental antidepressants: nisoxetine (withdrawn)
Zimelidine (withdrawn)

VII. Pharmacology:

Fluoxetine is a straight chain phenyl propylamine which inhibits the uptake of serotonin into neurons. It does not affect noradrenergic or dopaminergic neurons.

VIII. Foreign Studies:

There were 31 investigators who participated in the clinical section of the NDA. Thirty of them were American and one was Canadian. The Canadian, Dr. G. Chouinard, participated in two studies, one of which was a double blind comparison with amitriptyline and the other, for compassionate use. Neither trial was involved in the decision regarding efficacy.

XIX. Clinical Studies:

The sponsor identified three protocols (two single investigator trials comparing fluoxetine with placebo and one six investigator multicenter trial where fluoxetine was compared both with imipramine and placebo) as adequate and well controlled clinical trials and as the basis for their demonstration of efficacy. The NDA also contains three clinical trials where fluoxetine was compared with imipramine, three where fluoxetine was compared with amitriptyline and four, with doxepin. Two of the latter trials vs doxepin were carried out in geriatric patients. None of these trials latter trials included a placebo group.

In the following, the placebo controlled trials will be described first and will be followed by the standard drug trials.

Table 1-A
Demographic Data - Evaluable Patients

Investigator	No. of Evaluable			Sex						Mean Age			Concom. Meds[1]									Modal Maintenance Dosage		
				F		I		P					F			I			P					
Protocol 27	F	I	P	M	F	M	F	M	F	F	I	P	A	D	O	A	D	O	A	D	O	F	I	P[2]
. J.P. Feighner	51	46	48	16	35	11	35	9	39	41	45	40	15	2	7	23	0	8	18	1	8	60	100-200	6-8
. Jay D. Cohn	46	42	52	12	34	20	22	28	24	39	42	42	3	1	2	2	0	3	0	0	5	60	300	8
. J.B. Dremmer	24	24	12	6	18	5	19	6	6	38	42	37	9	0	2	8	1	3	6	0	0	60	150-200	6
. D.L. Dunner	23	29	28	8	15	8	21	11	17	40	42	43	3	0	1	1	0	2	1	3	0	80	250+	8
. G.I. Grosser	30	27	27	7	23	11	16	11	16	39	41	37	7	0	2	3	1	1	5	1	2	60	150-200	6-8
[illegible]	[illegible]	[illegible]	26	[illegible]	[illegible]	[illegible]	15	11	15	37	36	41	7	1	3	11	0	2	8	0	1	80	250+	8
Protocol 19	151	[illegible]	141 (5)																					
. L. Fabre	16	-	21	4	12	-	-	11	10	34	-	32	4	1	1				4	1	0	80	-	4
Protocol 25																								
. K. Rickels	15	-	23	4	11	-	-	4	19	49	-	46	7	0	2				4	1	1	40/60	-	4

- F - Fluoxetine
- I - Imipramine
- P - Placebo

M - Male
F - Female

[1] Concomitant medications
Number with:
A - allowed psychotropics
D - disallowed psychotropics
O - other CNS effect

[2] No. of capsules:
Protocol 27: range 2-8 daily
Protocol 19: " 2-4 daily
Protocol 25: " 0-4 daily

Table 1-8
Demographic Data - Evaluable Patients

Investigator				Diagnosis F							Diagnosis I					Diagnosis P					No. w/Concomitant Physical Diagnosis		
Clinic No.	Sex	Race	Total	sing	rec	end	ag	ret	sing	rec	end	ag	ret	sing	rec	end	ag	ret	F	I	P
1. Feighner	18	[illegible]	59	13	32	9	49	55	11	25	7	52	59	11	32				34	30	23
2. Cohn	22	32	54	1	0	25	29	53	1	0	30	28	57	4	4				39	45	44
3. Dresser	9	19	27	11	13	7	23	30	16	11	9	5	13	10	4				13	16	5
4. Gunner	11	21	31	7	15	13	21	29	6	15	12	22	32	5	19				9	8	9
5. Grosser	10	23	33	10	11	4	30	33	13	5	6	25	30	7	6				7	8	9
6. Shuckit	2	28	30	-	-	2	28	30	1	-	1	36	37	2	1				[illegible]	[illegible]	[illegible]
7. Pub.	5	19	22	0	6	-	-	-	-	-	11	10	25	0	0				5	-	6
Protocol 25																							
1. Rickels	6	10	17	6	3	-	-	-	-	-	8	16	22	7	11				15	-	20

F - Fluoxetine
I - Imipramine
P - Placebo

sing - single episode
rec - recurrent
end - endogenous
ag - agitated
ret - retarded

Table 2

Patient Population:

		Fluoxetine	Imipramine	Placebo
A.	No. enrolled in study	61 (M=19,F=42)	58 (M=16,F=42)	39 (M=13,F=46)
	1. Completed 6 weeks	31[a]	31[b]	22[c]
	2. Terminated prior to 6 w[illegible]	30	27	17
	a. 2° to Adv. Exp.	12	17	5
	b. Lack of efficacy an[illegible] adverse experienc[illegible]	-	1	-
	c. Lack of efficacy	13	6	12
	d. Lost to follow-up	1	-	-
	e. Patient decision	3	1	3
	f. Protocol violation	1	-	-
	g. Poor compliance	-	1	1
	h. Physician decision	-	1	1
B.	Unevaluable for efficacy	10	12	11
	1. Insufficient Therapy	8	8	7
	2. Break in therapy	1	-	-
	3. Protocol deviation	1	1	2
	4. Concomitant med.	-	-	1
	5. Poor compliance	-	-	1
	6. Placebo responder	-	3	-
C.	Total evaluable for efficacy	51	46	28
	a. Mean age	40.9	45.1	39.6
	b. Usual Maintenance do[illegible]	80 mg	150 mg 200 mg	

[a] Of these 31 patients who [illegible]leted the study, one terminated [illegible] of adverse experience not [illegible]y drug related.

[b] Of these 31 patients who [illegible]leted the study, one terminated [illegible] lack of efficacy.

[c] Of these 22 patients who [illegible]eted the study, three [illegible] other reasons: one for la[illegible] efficacy and two by [illegible]

3
Dropouts
(Prior to 6 weeks)

	Feighner			Cohn			Bressler			Danner			Grosser			Abuzzahab		
	F	I	P	F	I	P	F	I	P	F	I	P	F	I	P	F	I	P
Total Trial	66	66	66	67	68	67	30	32	15	40	39	40	34	35	35	34	35	35
Dropped (Total)																		
Never entered double blind	3	8	7	11	12	7	1	2	1	6	4	5	1	1	4	2	4	2**
Lost to follow up	2	-	-	2	2	2	-	-	-	2	1	1	-	-	-	2	1	2
Entered double blind	61	58	59	54	54	58	29	30	14	32	34	34	33	34	31	30	30	31
Completed 6 weeks = Number	31	31	22	35	20	16*	22	22	8	17	19	20	20	24	19	14	14	10
Percent (of entered D.B.)	51	53	37	64	37	27	76	73	57	53	56	58	60	71	49	47	47	32
Dropped	30	27	37	19	34	42	7	8	0	15	15	14	13	10	12	16	16	21
Dropped efficacy [illegible]	7	14	3*	5	21	0*	2	6	0	6	9	2*	2	5	0	2	3	0*
)																		
					5	5**	2	0	5**	3	3	9	9	5	8	9	12	10
Withdrawn at patient's request	3	1	5	1	3	4	0	0	0	1	0	0	1	0	2	4	1	1
Terminated for protocol violation	1	0	0	0	0	0	1	0	0	1	0	0	1	0	0	0	0	0
Lost to follow up	1	0	0	9	3	3	0	0	1	1	1	3	0	0	1	0	0	2
Withdrawn for poor compliance	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Terminated for physician's decision	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Suicide attempt	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Administrative error	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Started D.B. but terminated	1	1	3	0	0	0	0	0	0	2	0	0	3	3	1	0	2	0
Usable for efficacy	10	12	11	8	12	6	5	6	2	9	5	6	3	7	4	7	7	5
Evaluable for Efficacy	51	46	48	46	42	52	24	24	12	23	29	28	30	27	27	23	23	26

Fluoxetine
Imipramine
Placebo

* p less than .05 (probabilities can range to less than .001)
** one is a suicide
*** known or unknown relationship

The "dropped prior to efficacy" category partially overlaps with the "dropped" category. A breakdown of the former is given in the patient population tables.

c. Efficacy Data

1. Endpoint Analysis

Fifty-four percent (79) [illegible] the 145 evaluable patients completed the final 6 week visit. [illegible] 145 evaluable patients, however, were included in the end[illegible]nt analyses. The number of patients in the weekly analyses [illegible]luded only those patients who actually attended the visit.

The results of the eff[illegible] analyses are given in Table 4 (means) and Table 5 (s[illegible]tical outcomes). In general, imipramine was signific[illegible]y superior to placebo on all major variables (e.g. HAM-D D[illegible]dation, HAM-D total score, all CGI variables, Raskin and Co[illegible] if the requirement for a significant overall test is ignored. Fluoxetine, on the other hand, was associated with signific[illegible]t superiority on only one or two variables namely, CGI [illegible]ge, CGI "therapeutic effect" and "side effects". Statistically[illegible] however, imipramine was not more effective than fluoxeti[illegible]

The sponsor provided a[illegible]ewhat elaborate analysis of the therapeutic ratio item [illegible]n the CGI. This variable takes into account the effect of [illegible]se events on global efficacy. However, the sponsor a[illegible]zed each segment separately and as a ratio (outcome divided [illegible]side effect) yielding three scores and it appeared they consi[illegible]d each aspect equally valid. The global therapeutic eff[illegible] segment is similar to the global improvement item on th[illegible]I except that it contains fewer categories and thus m[illegible] less sensitive than the CGI improvement item. [illegible]since the two components were not intended to be analyze[illegible]arately, I have reported the results with this scale but h[illegible]ot elaborated extensively on their significance.

2. [illegible]ekly Analyses

The results for the [illegible] analysis were similar to the endpoint analyses. That is, [illegible] was significantly better [illegible] placebo for some vari[illegible]s but not all times. Fluoxetine was [illegible]tatistically and only [illegible]ignificant (p less than .10 two-tailed) on [illegible] of four occasions and [illegible] was significantly (p less than .05) better than fluoxetine.

(15)

Statistical Review and Evaluation

Date: JUL 31 1985

NDA #: 18-936/Drug Class: 4C

Applicant: Eli Lilly and Company

Name of Drug: Fluoxetine Hydrochloride

Indication: Anti-depression

Documents Reviewed: Volumes 1.1, 1.24, 1.24A, 1.30-1.54, 1.62, 1.64-1.65 and 1.72-1.76 of the "Biostatistical Package" dated September 6, 1983, and additional analysis requested by this reviewer dated April 23, 1985.

This NDA contains three placebo-controlled studies: Protocol #19 (Fabre), Protocol #25 (Rickels), and Protocol #27 (Feighner, Cohn, Bremner, Dunner, Grosser and Abuzzahab) and ten active control studies (Protocols #20, 22, 23, 26, 29, 31 and 33; Protocols #29, 31 and 33 were used by 2 investigators each.). As a result of our preliminary review which revealed some problems in these studies, additional analyses were requested of the sponsor. This review will focus on the effects these problems have on the efficacy question. As suggested by the clinical reviewer, Dr. Hillary Lee/HFN-120, only the following five efficacy measures will be looked at in this review: HAMD Total, HAMD Retardation, Raskin Depression, Severity of Depression and Global Improvement. The emphasis of the following discussion will be placed mainly on the four studies: Protocol #19 (Fabre), Protocol #27, Protocol #20 (Bremner) and Protocol #23 (Feighner). The content of this review has been discussed with Dr. Lee and Dr. Kapit (safety aspects) who basically agree with this reviewer's conclusion.

Standard non-parametric methods (Kruskal-Wallis test and Wilcoxon Rank-sum test for two-way comparison and ANOVA on ranks) were employed in all of these studies. Weekly analyses and endpoint analyses were done. In an endpoint analysis, generally a patient's last available visit value was used. However, in some studies, a substantial number of patients also had unevaluable visits (due to e.g. insufficient therapy, protocol violation, missing value, etc.). Consequently, in the sponsor's endpoint analyses, it was not clear what were the actual visits used. In response to this reviewer's inquiry, the sponsor made the following clarification. In an endpoint analysis based on evaluable patients, the last evaluable visits were used. However, in an endpoint analysis based on all patients data, the last visits were used regardless of evaluability.

In the treatment comparisons with placebo, the sponsor presented one-sided significance levels. Throughout this review two-sided p-values are used.

Placebo-Controlled Studies

Overview

There are three randomized, parallel, placebo-controlled studies, namely Protocol #19 (Fabre), Protocol #25 (Rickels) and the multicenter study Protocol #27 which also contains an imipramine arm. As Table 1 indicates, Fabre's study showed that except for HAMD Retardation and Raskin Depression scores based on evaluable patients fluoxetine was significantly favored over placebo. On the other hand, in the Rickels study the results for the fluoxetine and placebo groups were very similar across all five efficacy measures. For Protocol #27, Cohn's patients exhibited an unusually strong positive indication for fluoxetine ($p<0.001$) across all efficacy measures. Some marginally positive results were also achieved by Feighner and Bremner. Protocol #27 was a multicenter study, and therefore data from all 6 investigators should be analyzed together. Due to the presence of significant investigator by treatment interaction (largely due to the differential treatment effects observed between the data of Cohn and the data from the other 5 investigators), the sponsor presented separate analyses for each of the six investigators. It would also have been more appropriate for the sponsor to pool the data from the five investigators and analyze it separately from Cohn. This was later requested of the sponsor. The sponsor also analyzed a subset of this pooled data, namely those patients who did not receive any concomitant psychotropic drugs excluding unevaluable visits and patients.

Protocol #19 (Fabre)

The endpoint analysis based on evaluable patients from Fabre's study (see Table 1) showed that fluoxetine is significantly better than placebo in HAMD Total ($p=0.02$), Severity of Depression ($p=0.02$) and Global Improvement ($p=0.05$). A comparison of the frequency distributions of last evaluable visits (weeks) between fluoxetine and placebo patients reveals no significant difference ($p>0.5$, see Table 2). Furthermore, despite the presence of these early terminations, Table 3 shows that fluoxetine appears to maintain its superiority to placebo at each week from Week 1 through Week 5.

The corresponding results based on all patients data put fluoxetine in even a more favorable light (see Table 1). This can be explained by the observation that the inclusion of the 6 unevaluable fluoxetine patients in the analysis contributed a net reduction over baseline of 48 points in the HAMD Total score, whereas the inclusion of the 4 unevaluable placebo patients added a net reduction of 0 point. Similar observations may be made with respect to the other efficacy measures.

The results of this study appear to demonstrate the superiority of fluoxetine to placebo.

Protocol #27

As mentioned earlier, Protocol #27 was a multicenter study. In view of the significantly different treatment effects observed between investigator Cohn and the other five investigators, the data from Cohn was analyzed separately.

The data from the remaining 5 investigators (Feighner, Bremner, Dunner, Grosser and Abuzzahab) were pooled together and analyzed. The sponsor also reported an analysis based on a subset of this pooled data, namely the subset of all evaluable patients who were not taking concomitant psychotropic drugs. The main focus here will be on Cohn's portion of the study which showed an unusually strong indication in favor of fluoxetine. A separate discussion will be given to the results obtained based on the pooled data.

Cohn

The endpoint analysis performed on this study gives the impression that fluoxetine is significantly superior to placebo with a two-sided $p<0.001$ for all five efficacy measures (see Table 1). However, the weekly comparisons between fluoxetine and placebo (see Table 4) reveal only scattered significance mainly in Weeks 2 and 4. How does one account for such discrepancy? The explanation lies in the differential early termination rates observed among the evaluable patients between fluoxetine and both the placebo and imipramine groups (see line 6 in Table 5). A further breakdown of the evaluable patients by their last evaluable visit weeks (Table 6) shows that there were significantly more placebo and imipramine patients than fluoxetine patients who were terminated early ($p<0.001$ for fluoxetine vs. placebo and $p=0.01$ for fluoxetine vs. imipramine). The differences came mainly after the second week. This difference may bias the endpoint analysis in favor of fluoxetine. Since about 40% of the evaluable placebo patients were terminated after 2 weeks, any analysis past 2 weeks would not be very meaningful. On the other hand, analysis based on just the first 2 weeks of the trial is also of questionable validity, because the patients may not have received the full benefit of the treatments. The preceding discussion is also applicable to the endpoint analysis based on all patient data. It is difficult to interpret the result of this study.

Pooled Data (Feighner, Bremner, Dunner, Grosser and Abuzzahab)

The endpoint analysis based on evaluable patients (see Table 7) shows that fluoxetine was significantly better than placebo relative to all five efficacy measures considered (significance levels range from 0.03 to <0.001). There was no apparent difference in time and frequency of early termination ($p>0.25$, see Table 9) as observed in the Cohn study. The weekly comparisons (see Table 8) show that fluoxetine was also significantly superior to placebo after Week 3 relative to all five efficacy measures. Similar results were obtained based on all patients data and on the subset of the pooled data consisting only of patients who took no other concomitant psychotropic drugs (Table 10).

The results of the various analyses based on the pooled data were consistent and were supportive of the efficacy of fluoxetine.

Active Control Studies

Overview

There were ten separate active control studies. In three studies, Bremner [20], Feighner[29] and Davis [29], the control was imipramine. In

three other studies, Masco[22], Feighner[23] and Chouinard[26], the control was amitriptyline, and in the remaining 4 studies, Kiev[31], Masco[31], Feighner[33] and Cohn[33], the control was doxepin. Generally, the sponsor's analyses (see Table 11) showed no significant differences between fluoxetine and the active controls. There were some marginal indications that imipramine was superior to fluoxetine (Feighner[29] and Davis[29]). Bremner's [20] study showed that for most efficacy measures fluoxetine was significantly better than imipramine based on both evaluable and all patients data. Feighner's[23] study showed that for some efficacy measures fluoxetine was significantly better than amitriptyline based on all patients data. These two studies will be examined in more detail below.

Bremner's Study (Protocol #20)

The results of the sponsor's endpoint analysis for evaluable patients are summarized in Table 12. The results for all patients data were marginally favoring fluoxetine and are not discussed here (see Table 11). As Table 12 indicates, fluoxetine was superior to imipramine across all efficacy measures except Global Improvement. A comparison between the two treatment groups with respect to their distributions of last evaluable visit weeks did not reveal any substantial difference. However, the week by week analysis (Table 13) shows no significant treatment difference until the last week (week 5). In order to better understand what happened during Week 5, a listing of patients' HAMD Total scores at baseline, Week 4 and Week 5 is given in Table 14. One observes that these two groups of patients were severely depressed and had high HAMD Total baseline scores. What was unusual is the fact that 38% of the fluoxetine patients and 58% of the imipramine patients ($p=0.23$) also had a secondary psychotic diagnosis. Of the 16 evaluable fluoxetine patients, 14 had a reduction in Week 5 from the preceding week and 2 had no change in their HAMD Total scores. Most of them had a reduction of at least 5 points and 3 patients even achieved a score of 0 at Week 5. In contrast, ten of the 17 imipramine patients had an increase from Week 4 in their Week 5 HAMD Total scores, 6 had only modest reduction and 1 had no change in score. Therefore, the significant treatment difference at Week 5 was essentially due to a large reduction in the HAMD Total scores observed in the fluoxetine patients and a simultaneous increase in the scores for the imipramine patients. Similar observation can be made with regard to the other efficacy measures. This reviewer cannot offer any plausible explanation for this sudden difference observed at week 5. Genuine treatment difference ought to be observable over time as seen in Tables 3 and 8.

Feighner's Study (Protocol #23)

The significant treatment difference observed in this study based on all patients data (see Table 11) was primarily due to the presence of a disproportionately large number of nonevaluable amitriptyline patients (46% vs. 5%) and the fact that most of these patients were terminated prior to Week 4. A comparison of the frequency distributions by week of last visit between fluoxetine and amitriptyline (See Table 15) shows that there were significantly more ($p<0.02$) amitriptyline patients than fluoxetine patients who were terminated early. Consequently, the endpoint analyses applied to the all patients data may bias in favor of fluoxetine as observed. Therefore, based on this study, one cannot conclude that fluoxetine is significantly better that amitriptyline.

Overall Safety Evaluation

For purpose of safety analysis, the sponsor defined six data pools:

Pool I - all placebo controlled studies, double-blind portion only

Pool II - all controlled studies, double-blind portion only

Pool III - all patients who completed a double-blind study and elected to continue on the previously assigned study drug, i.e., either fluoxetine, imipramine, doxepin or amitriptyline.

Pool IV - all patients who crossed over from their original double-blind study drug (imipramine, amitriptyline, doxepin or placebo) to fluoextine in an open label study.

Pool V - all fluoxetine patients in all efficacy studies

Pool VI - all imipramine patients in all efficacy studies

Frequencies of adverse experiences were tabulated by treatment for all six pools. Vital signs (pulse rate, weight, blood pressures) were analyzed for pools I, II, and for the individual investigator data from these pools; Wilcoxon rank sum tests were performed for treatment comparisons with respect to change from endpoint to baseline and from week 1 to baseline; comparison between fluoxetine and imipramine was also made for the 6-month data from pool V and pool VI. For each clinical laboratory parameter, a normal range was defined (for neutrophils and lymphocytes, normal ranges specified by each laboratory were used) and a clinically significant increment or decrement from baseline was also specified; for example, the normal range for hemoglobin is (13.5-18.0) g/dl for males and (12.0-16.0) g/dl for females and an increment/decrement of 1.5 is considered clinically significant. The sponsor also provided rules for defining clinically significant changes as persistent or repeated for each parameter (except neutrophils, etc); percent of patients with persistent or repeated clinically significant changes were tabulated for pools I-VI; the distributions of patients with respect to their classifications as high, normal or low were given both at baseline and at double-blind phase for pools I, II and V. A summary description of some special tests (ECG, Chest X-ray, Opthalmological examination, and EEG) were given by the sponsor for pools II and IV.

In this review, a brief discussion of these safety results will be given mainly for pool II. Results from the other pools, whenever comparable, were generally similar.

Table 18 presents the frequencies of a selected list of adverse experiences by treatments. These adverse experiences were mainly associated with the central nervous system and the digestive system. For most of these ADR's, the fluoxetine patients reported significantly higher ($p<0.05$) incidences than the placebo patients. Fluoxetine patients had fewer incidences of dry mouth, dizziness, drowsiness, excessive sweating and vision disturbances than either imipramine, amitriptyline, or doxepin. On the other hand, fluoxetine patients

reported significantly higher incidences of anorexia, nausea, anxiety, insomnia and nervousness than all of the other treatments. It should be noted that among all 1173 fluoxetine treated patients in Pool II, there were two reported cases (0.2%) of leukopenia. The association of their occurrences to fluoxetine was unknown.

With respect to vital signs, there were no significant changes observed in blood pressures either over the double-blind or the open label studies. Sponsor's analysis based on both pool II (see Table 19) and data from individual investigators suggests that fluoxetine patients experienced significant weight loss in the short term. This may be related to incidences of anorexia experienced by some of these patients; however, this weight loss was not observed in the open label study (pool V). It is of interest to note in contrast that weight gain appeared to be associated with all the other active treatments.

The original tabulation of the clinical parameter data suggested that perhaps there were significant changes from baseline in hemoglobin, neutrophils and serum calcium when compared to placebo. However, no statistical test could be performed due to the lack of tables cross-classifying measurements at baseline by measurements at double-blind phase for these patients. The sponsor was requested to submit cross-classification tables for these three clinical parameters based on Pool I and Pool II data. Of the three parameters, only serum calcium showed a significant reduction from baseline when compared to placebo ($p<0.03$ for Pool I and $p<0.01$ for Pool II). More specifically, based on Pool I (see Table 21), 18.8% of fluoxetine patients vs. 11.8% of placebo patients ($p<0.03$) had at least one (or more) serum calcium measurements during the double-blind phase that was in a category lower than its baseline category. Similar result may be observed for Pool II (see Table 22)

Overall Conclusion and Recommendation

1. Of the three placebo-controlled studies, Fabre's study (Protocol(#19) exhibited clear indications that fluoxetine was significantly more effective than placebo (For example, based on evaluable patients, $p<0.02$ for HAMD Total and Severity of Depression, and $p=0.05$ for Global Improvement; based on all patients data, $p<0.05$ for all efficacy measures).

On the other hand, Rickel's study (Protocol #25) showed no detectable difference between fluoxetine and placebo.

For the multicenter study (Protocol #27), Cohn's study was significantly in favor of fluoxetine ($p<0.001$ for all efficacy measures). However, his results may be biased by the presence of a disproportionately large number of placebo patients who were terminated prior to the 3rd week of the trial (42% for placebo, 33% for imipramine and only 9% for fluoxetine, see Table 6). The weekly analyses (see Table 4) also did not provide any valid evidence beyond week 2 due to the fact that less than half of the placebo patients had completed 4 weeks (87% for fluoxetine and 46% for placebo), and only 58% had completed 3 weeks of the trial.

Because of the presence of significant differential treatment effects due to the unusual nature of Cohn's results, the sponsor was asked to pool and analyze the data from the other five investigators. The results of the sponsor's analysis demonstrated that based on either the evaluable patients data or the all patients data, the endpoint analysis showed that fluoxetine was superior to placebo relative to all five efficacy measures, and the weekly analysis showed that fluoxetine was superior to placebo after Week 3 relative to all five efficacy measures. There was no apparent difference in time and frequency of early terminations. Therefore, the results of the analysis based on the pooled data supports the efficacy of fluoxetine.

2. Bremner's study (Protocol #20) was the only active-control study showing significant superiority of fluoxetine (over imipramine in this case). However, the patient population in this study was highly unusual in that they all had been diagnosed as having major depressive disorder, and 38% of the fluoxetine and 58% of the imipramine patients also had a secondary psychotic diagnosis. Futhermore, the weekly analyses indicated no treatment differences in the first four weeks, but during the fifth (and last week), almost all of the fluoxetine patients had experienced sizable improvement over the preceding week while half of the imipramine patients had worsened. Given the fact that most of these patients were diagnosed to have major depressive disorder, it is surprising to find that 63% of the fluoxetine patients and only 1% (1) of the imipramine patients had practically become normal (i.e., HAMD Total score ≤ 5) at the end of 5 weeks.

On the remaining nine active-control studies, a failure to detect significant treatment differences does not necessarily imply that fluoxetine was equally effective. There are in fact indications to the contrary. For example, consider the multicenter study Protocol #27 excluding Cohn. It is apparent from Table 16 that with respect to mean reduction from baseline in HAMD Total score, imipramine was numerically greater than fluoxetine which in turn was greater than placebo (except in Dunner's study). Except for Dunner, no significant difference between fluoxetine and imipramine was detected. However, imipramine was significantly superior to placebo in all 5 studies except Abuzzahab, while no statistically significant difference was detected between fluoxetine and placebo in each of these five studies.

3. Fluoxetine patients reported significantly higher incidences of a few adverse reactions than did placebo patients (see Table 18). Furthermore, incidences of anorexia, nausea, anxiety, insomnia and nervousness were significantly higher than those reported for the other active treatment groups. There were two reported cases of leukopenia (0.2%).

Significant weight loss was experienced by fluoxetine patients. This may be related to the higher incidence of anorexia reported by these patients. It is of interest to note that weight gain was observed for imipramine, doxepin and amitriptyline patients.

The clinical significance of the reduction observed in serum calcium needs to be assessed.

In summary, among the three placebo-controlled studies, Protocol #19 (Fabre) and Protocol #27 (Pooled data excluding Cohn) indicate that fluoxetine was

superior to placebo while Protocol #25 (Rickels) shows no difference between fluoxetine and placebo. Although, generally no significant differences were observed between fluoxetine and the other active drugs, this is not indicative of the fact that these drugs were equally effective. With respect to safety, fluoxetine patients reported significantly higher incidences of anorexia, nausea, anxiety, drowsiness, insomnia and nervousness than placebo patients. When compared to imipramine, amitriptyline and doxepin, fluoxetrine was associated less frequently with constipation, drymouth, dizziness, drowsiness and tremor, but more frequently with anorexia, nausea, anxiety, insomnia and nervousness. Furthermore, fluoxetine was associated with weight loss (probably related to anorexia) while the other active drugs were associated with weight gain. The clinical significance of the reduction in serum calcium needs to be assessed. Two cases of leukopenia were reported among the fluoxetine patients. However, their association with fluoxetine was unknown.

There are no comments to be conveyed to the sponsor.

George Chi, Ph.D.
Mathematical Statistician

cc: Orig. NDA 18-936
HFN-120
HFN-120/Dr. H. Lee
HFN-120/Dr. R. Kapit
HFN-344/Dr. Lisook
HFN-713/Dr. Dubey
HFN-713/Dr. Chi
Chron.
File: DRU 1.3.2 NDA
GYHChi/njs/plt/07/22/85/34594/#0182n

Concur: Dr. Pledger 7/25/85

Dr. Dubey 7/31/85

Table 1
Two-sided Significance Levels for the Comparison of Fluoxetine
to Placebo over the Improvement from Baseline of Five Efficacy Measures
(Based on Endpoint Analysis)

Type of Data	Efficacy Measure	Fabre [19]+ (46)#	Rickels [25] (42)	Cohn [27] (160)	Feighner [27] (178)	Bremner [27] (33)	Dunner [27] (97)	Grosser [27] (98)	Abuzzahab [27] (91)
Evaluable Patients	HAMD Total	0.02	0.81	<0.001	0.30	0.13	0.99*	0.20	0.22
	HAMD Retardation	0.06	0.54	<0.001	0.30	0.05	0.99*	0.19	0.08
	Raskin Depression	0.16	0.72	<0.001	0.20	0.05	0.86	0.19	0.08
	Severity of Depression	0.02	0.90	<0.001	0.20	0.08	0.78	0.04	0.18
	Global Improvement	0.05	0.60	<0.001	0.04	0.03	0.50	0.17	0.11
All Patients	HAMD Total	0.01	0.99*	<0.001	0.08	0.19	0.60	0.11	0.54
	HAMD Retardation	0.03	0.99*	<0.001	0.08	0.07	0.99*	0.21	0.30
	Raskin Depression	0.02	0.99*	<0.001	0.02	0.08	0.70	0.17	0.30
	Severity of Depression	0.01	0.99*	<0.001	0.14	0.13	0.98	0.03	0.48
	Global Improvement	0.01	0.82*	<0.001	0.02	0.06	0.44	0.08	0.64
Direction of Numerical Comparison		F>P	F>P**	F>P	F>P	F>P	F>P**	F>P	F>P

+ Protocol number

Total number of patients in the study.

* An "*" indicates that the direction of numerical comparison is reversed.

Table 11
Two-sided Significance Levels for the Comparison of Fluoxetine to Active Controls over the Improvement from Baseline of Five Efficacy Measures
(Based on Endpoint Analysis)

Type of Data	Efficacy Measure	Breemer [20]+ (35)#	Feighner [29] (30)	Davis [29] (36)	Masco [22] (30)	Feighner [23] (29)	Chouinard [26] (44)	Kiev [31] (39)	Masco [31] (49)	Feighner [33] (37)	Cohn [33] (58)
Evaluable Patients	HAMD Total	<0.01	NS**	0.17	NS	NS*	NS	NS	NS	NS	NS
	HAMD Retardation	0.04	0.06*	0.19	0.07	NS*	NS*	NS	NS	NS	NS
	Raskin Depression	<0.001	NS	NS	NS	NS*	NS	NS*	0.17	NS	NS
	Severity of Depression	<0.01	NS	NS	NS	NS*	NS	NS*	NS	NS	NS
	Global Improvement	0.07	NS*	NS*	0.12	NS*	NS	NS	0.17	NS	NS
All Patients	HAMD Total	0.05	0.06	0.13	NS	0.09	0.19	0.19	NS	NS	NS
	HAMD Retardation	0.16	NS	NS	0.14	0.03	NS	0.07	NS	0.19	NS
	Raskin Depression	0.02	NS	NS	NS	0.15	NS	NS*	0.15	NS	NS
	Severity of Depression	0.04	0.08	NS	NS	0.04	NS	NS	NS	NS	NS
	Global Improvement	NS	0.12	NS*	0.11	0.02	NS	NS	0.17	NS	NS
Direction of Numerical Comparison		F>I	I>F**	I>F**	F>A	F>A**	A>F**	F>O**	O>F	F>O	F>O

+ Protocol Number
# Total number of patients
* An ** indicates that the direction of numerical comparison is reversed.
** NS means that p>0.20

The following table summarizes the designs and outcomes of these active control studies:

Protocol Number	Investigator	Control Drug	Duration of Trial (weeks)	In/Out Patient	Number of Pts. F	Number of Pts. C	Usual Dosage F	Usual Dosage C	Intent to Treat
20	Bremner	IMI	5	Out	20	20	60	175	F > C
29a	Feighner	IMI	6	In	18	23	80	200	F = C
29b	Davis	IMI	6	In	21	22	80	200	F = C
22	Masco	AMI	5	Out	20	21	80	300	F = C
23	Feighner	AMI	5	Out	22	22	40	150	F > C
26	Chouinard	AMI	5	Out	23	28	80	200	F = C
31a	Kiev	DXP	6	Out	27	26	80	200	F = C
31b	Masco	DXP	6	Out	28	28	80	300	F = C
33a	Feighner	DXP	6	Out	24	23	80	125	F = C
33b	Cohn	DXP	6	Out	42	41	80	200	F = C

Legend:
IMI = imipramine; AMI = amitriptyline; DXP = doxepin
F = fluoxetine; C = control

D. Safety:

1. Population Exposed:

As of July 31, 1987, approximately 7920 subjects had been exposed to fluoxetine in premarketing studies, including 6070 in US studies and 1850 in foreign studies. For the latter, only drug experience reports, rather than detailed analyses of event rates, were available. The larger data base is relevant to detection of rare events, but the primary safety data were obtained from the US subjects.

2. Extent of Exposure:

Of the US patients receiving fluoxetine, approximately 86% were treated for three months or less, while approximately 6% received treatment for greater than one year (including 63 on fluoxetine for greater than two years). Of the patients receiving fluoxetine in phase II and later studies, the percentages receiving various daily maintenance doses were as follows: 20 mg (23%), 40 mg (21%), 60 mg (25%), 80 mg (24%). Less than 1% of patients received maintenance doses of 100 mg/day or greater.

SEDATED	1	0%	1	0%
SENSATION DISTURBANCE	2	1%	1	0%
TREMOR	9	3%	4	1%
TWITCH	15	5%	1	0%
VERTIGO	59	18%	8	2%
	4	1%	0	0%
	1	0%	0	0%

16

MAR 12 1987

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 18-936

Sponsor: Eli Lilly

Drug: Fluoxetine

Category: Antidepressant

Date of Submission: February 20, 1987

Date of Review: February 27, 1987

Re-analyses of P-19, 27, 62, 25

While preparing the SBA for fluoxetine, we determined that several additional statistical analyses were required to complete our documentation of the efficacy of fluoxetine. We had also noted a discrepancy in the number of patients used in two sets of analyses for protocol 62 and this needed clarification. We sent a letter to the sponsor (Feb. 17, 1987) in which we detailed our requests. The present submission was in response to our letter.

1. FDA request:

We wished to examine for each week the statistical results together with the percent of patients available in each treatment group so that we could evaluate the outcomes at a time point when approximately 70 percent of patients remained in the study. We requested that analyses be carried out for the three positive studies (Protocol 19, 27 and 62) and for four key variables (HAM-D Total, HAM-D Depression Item, HAM-D Retardation Factor and CGI Severity). We asked for two sets of analyses for each study and variable, viz, LOCF analyses including all patients (an intent to treat analysis) for each week and a weekly observed cases analysis. [It should be noted that the observed cases analyses had been done for most studies and while the LOCF analyses had been done for the final week in two studies and for each week in one, we requested that they be done for each week in all three studies.]

2. Sponsor's Results:

There was a high degree of similarity in the studies concerning the week at which there were at least 70% of patients remaining in all treatment groups. Generally, this criterion occurred at the end of the third week in the three protocols. However, the percent of placebo subjects remaining was significantly lower than 70% (67% in Protocol 19 and in Protocol 62). There was also an exception for the 60 mg group in Protocol 62 where the percent was also 67%. An examination of the percent remaining in the fourth week analysis indicated that, except for Protocol 19, the decrease in percent from the third week was not large. Protocol 19 was an exception in that the decrease in percent was larger. However, this may have occurred because the number of subjects in the study was small and a dropout of 2 to 4 patients made a larger difference in percent.

OCT 3 1988

Summary Basis of Approval

NDA 18-936

Applicant:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Drug Generic Name:
fluoxetine hydrochloride

Drug Trade Name:
Prozac

I. Indications for Use:

Prozac is indicated for the treatment of depression. The efficacy of Prozac was established in five and six week trials with depressed outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder.

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least two weeks); it should include at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of Prozac in hospitalized depressed patients has not been demonstrated.

The effectiveness of Prozac in long term use, that is, for more than five to six weeks, has not been demonstrated in controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

II. Dosage Form, Route of Administration and Recommended Dosage:

Prozac is available in a capsule containing fluoxetine hydrochloride equivalent to 20 mg fluoxetine base, and is for oral administration.

The antidepressant efficacy of fluoxetine was demonstrated in three placebo controlled studies (See Section V, Clinical). In two of these studies [Fabre (19) and a multicenter study (27)], patients were administered fluoxetine on a divided schedule (morning and noon), and were titrated up to 60 mg/day by the end of the first week and up to 80 mg/day for the remainder of these trials. In both studies, a majority of patients were dosed at 80 mg/day for most of their treatment.

The manufacturing processes for both the empty, hard, gelatin capsules and the dosage form, fluoxetine hydrochloride capsule, 20 mg, are fully described. The analytical specifications and methods for the finished dosage form are adequate to establish and maintain its identity, strength, quality, purity and dissolution characteristics.

B. Stability Studies:

Data derived from stability studies, and the labeled storage conditions proposed for the drug product packaged in amber glass bottles, high density polyethylene (HDPE) bottles and vinyl blister packages, are adequate to support the 24 month expiration dating requested. An adequate stability commitment has also been made.

C. Methods Validation:

Analytical methods for fluoxetine HCl, new drug substance and the finished capsules have been validated by two FDA laboratories. They have been found satisfactory for control and regulatory purposes.

D. Labeling:

Draft copies of immediate container labels and carton labels for capsules in bottles and blister packages are in compliance with the technical requirements pertaining to the following: proprietary name, generic name, ingredient statement, net contents, control number, expiration dating, storage conditions, prescription "Caution" statement, and applicant's name and address.

The information in the "Description", "Dosage and Administration" and "How Supplied" sections relating to chemistry and manufacturing controls is satisfactory. The trade name, PROZAC™, is not in conflict with the name of any other marketed drug.

E. Establishment Inspection:

Manufacturing Review Branch (HFN-325), Division of Drug Quality Compliance, found operations at the facilities responsible for manufacturing, controls, packaging and labeling the finished drug product to be in compliance with the CGMP regulations.

F. Environmental Impact Analysis Assessment:

An environment impact statement has been provided in accordance with 21 CFR Part 25.21. This statement has been reviewed and found to be acceptable. Further environmental assessment is not necessary.

IV. PHARMACOLOGY:

A. Pharmacology:

Fluoxetine is structurally dissimilar from currently marketed antidepressants. It is a member of a group of investigational antidepressants, including zimeldine and nisoxetine, characterized by the presence of (1) 2 aryl or aryloxy groups connected by a 1 or 2 atom bridge and (2) a basic side chain. (Van Dijk, et al., Progress in Medicinal Chemistry 15:262, 1978).

Fluoxetine blocked the uptake of 5-HT (5-hydroxytryptamine or serotonin), NE (norepinephrine), and DA (dopamine), into rat brain synaptosomes in vitro with potencies in the range of those of the reference antidepressants used. Fluoxetine was more potent in blocking the uptake of 5-HT than that of NE, placing it in the category of "5-HT specific" uptake inhibitors such as zimelidine, fluvoxamine, and clomipramine. The demethylated metabolite of fluoxetine (DMF) was approximately equipotent with fluoxetine in blocking amine uptake in vitro and showed a similar selectivity for 5-HT. Fluoxetine given in vivo resulted in a blockade of 5-HT (but not NE or DA) uptake into synaptosomes which was quite long-lasting, e.g., 10 mg/kg i.p. in rats caused blockade for at least 24 hr. Numerous other studies (using various models indicative of amine uptake) were performed, primarily in rats and mice, showing similar results. For example, fluoxetine antagonized the para-chloroamphetamine-induced depletion of rat brain 5-HT with an i.p. ED 50 of 3.5 mg/kg, with some activity still demonstrable at 1 week post-dosing. (fluoxetine was about one third as potent when given p.o. in this study). DMF was also active in this test with a potency similar to that of fluoxetine. In mice, fluoxetine was active in this test with an ED 50 of 0.4 and 1-2 mg/kg i.p and p.o., respectively; however, the duration of action was not as long as in rats. Other studies showed that, in general, fluoxetine or DMF did not block the uptake of NE and/or DA in vivo. This in vivo selectivity differentiates fluoxetine from certain other antidepressants, e.g., clomipramine, which show 5-HT selectivity in vitro but not in vivo. The reason may be that the desmethyl metabolites of some of these drugs are not selective for 5-HT, whereas that of fluoxetine is selective. The conversion of fluoxetine to an equipotent and selective 5-HT uptake inhibitor (as well as the long T 1/2 of both fluoxetine and DMF) may also explain the long duration of action of fluoxetine.

Fluoxetine was also shown to block the uptake of 5-HT into platelets, both in vitro and in vivo, in rat and man. Since uptake is the only way that platelets can obtain 5-HT, fluoxetine administration results in a large decrease in blood 5-HT content. For example, dogs receiving 5-20 mg/kg/day p.o. for 3 months had blood 5-HT levels 5-15% of controls, and humans receiving 20-30 mg/day p.o. for 1 month had platelet 5-HT levels 20% of controls (with levels still 35% of controls after 7 days off drug).

Numerous effects of 5-hydroxytryptophan (5-HTP) were potentiated by fluoxetine (and vice-versa), which would be expected based on the ability of fluoxetine to block 5-HT uptake. Another effect of fluoxetine believed to be secondary to 5-HT uptake blockade was a decrease in brain 5-HT turnover and in brain serotonergic neuron firing rate, which are presumed to occur as compensatory mechanisms to an increased amount of 5-HT at postsynaptic receptors. Another postulated compensatory mechanism is a decrease in brain 5-HT postsynaptic receptor density; in one study fluoxetine given to rats for 2-6 weeks caused such a decrease although several published studies showed no effects.

In contrast to these effects on serotonergic systems, fluoxetine was not active in potentiating the blood pressure response to NE and in antagonizing the blood pressure response to tyramine in man, effects which are thought to reflect NE uptake blockade. Fluoxetine antagonized reserpine-induced hypothermia in mice (also thought to be due to noradrenergic effects) when given after the reserpine, but did not have a preventative effect when given before the reserpine. No decrease in rat brain receptors for alpha and B adrenergic ligands, DA, or opiates was seen after 10 days treatment with fluoxetine. Fluoxetine was not a potent inhibitor (in vivo or in vitro) of rat brain MAO, using 5-HT as a substrate, although no positive controls were used. (Some, but not all studies, showed a slight increase in endogenous brain 5-HT). Fluoxetine also did not appear to potently cause release of amines from brain synaptosomes at the concentrations used (up to 10 uM), although no positive controls were used.

Receptor binding studies showed that fluoxetine bound weakly to various rat or bovine brain receptors compared to the reference antidepressant drugs (except for fluvoxamine and zimelidine, which also bound weakly). In contrast, fluoxetine showed potent binding to a site which had the characteristics of a presynaptic binding site involved in 5-HT uptake. Various pharmacological studies showed that fluoxetine caused weak or no antagonism of peripheral receptors for Ach, histamine, 5-HT, and B adrenergic agonists; however, no positive controls were used to test for the sensitivity of the preparations used.

Fluoxetine had no effect on exploratory locomotor activity in mice at 0.3-40 mg/kg p.o. Fluoxetine had a slight hypothermic effect in mice. In cats, 2.5 mg/kg p.o. caused almost complete supression of REM sleep for 24 hr.; tolerance developed to this after 2-3 weeks daily dosing. In rats, fluoxetine at 5-10 but not 2.5 mg/kg p.o. decreased REM sleep. Fluoxetine caused a dose-related increase in serum corticosterone in rats at 2.5-20 mg/kg i.p.; no effects were seen with the reference antidepressants used. This effect of fluoxetine was potentiated by 5-HTP. Most studies showed no effect of fluoxetine on serum prolactin in rats, although the 5-HTP-induced increase was potentiated. In human studies fluoxetine given to males at 30 mg p.o./day for 7 days produced no changes in serum cortisol, ACTH, prolactin, LH, or GH. (Lemberger et al., Clin. Pharm. Therap. 23:421, 1978); fluoxetine in combination with 5-HTP did not alter serum prolactin in males (IND 12,274, submission of March 1, 1979). Fluoxetine at 10 mg/kg i.p. caused a 3-fold increase in plasma B endorphin in rats.

Fluoxetine was shown to potentiate the actions of several drugs (tranylcypromine, morphine, chlordiazepoxide, phenytoin, phenobarbital, hexobarbital, theophylline, 5-HTP). These potentiations were likely due in some cases to inhibition of drug metabolism and/or potentiation of serotonergic transmission. In humans, the sponsor reported that fluoxetine (30 mg as a single or 7-8 daily doses) had no effect on the pharmacokinetics of single doses of secobarbital, warfarin, chlorothiazide, or tolbutamide.

A cardiovascular study was performed in anesthetized dogs, in which fluoxetine, its N-demethylated metabolite (DMF), or amitriptyline was infused i.v. at 0.1 mg/kg/min for 50 min. Fluoxetine and DMF produced little or no effect on blood pressure, cardiac contractility, or cardiac conduction. Cardiac output fell 15-20% during fluoxetine infusion due to nonsignificant decreases in heart rate (10%) and stroke volume (5-10%). In contrast, amitriptyline decreased blood pressure, increased heart rate, and produced changes suggestive of impaired cardiac conduction and decreased cardiac contractility. (The doses of fluoxetine, DMF, and amitriptyline used were approximately "equi-effective" in that all produced similar, large decreases in platelet serotonin uptake, but it was not shown where these doses lay on the dose-response curves for this effect.) In another study in anesthetized dogs, 5 mg/kg i.v. (given over 5 min.) caused a slight decrease in h.r. without change in b.p. or response to bilateral carotid occlusion, although in combination with 5-HTP (at a dose having no effect alone) a large decrease in b.p. and in responses to bilateral carotid occlusion was seen. In anesthetized cats, 1-2 mg/kg i.v. caused no consistent effects on h.r. or b.p.; slight decreases were seen at 4-8 mg/kg i.v. (given over 1 min.). It was stated that 4 mg/kg i.v. produced no EKG changes in these cats, although no data were shown. Fluoxetine produced no significant decreases in b.p. in DOCA/salt- or spontaneously-hypertensive rats (10 mg/kg i.p. or s.c., resp.), although decreased blood pressure was seen when these doses of fluoxetine were combined with doses of 5-HTP which produced no effects alone. In the 1 year oral dog toxicity study, EKG was taken prior to the daily dose on several days. A dose-related decrease in h.r. was seen at 4.5 and 10/20 mg/kg but not at 1 mg/kg; no effect on conduction was noted. No EKG effects (measured 2 hr. post-dosing on days 1 and 9) in a 2 week dog toxicity study were seen (daily dose = 25 and 50 mg /kg p.o.).

B. ADME: Pharmacokinetics:

1. Absorption and Excretion:

In dogs, comparison of AUCs after acute p.o. or i.v. doses of 1 mg/kg unlabelled fluoxetine showed 72% absolute bioavailability by the oral route. (Since labelled drug was not used, it cannot be determined whether the remaining 28% was unabsorbed or subjected to first pass metabolism.) Absorption or bioavailability in other species were not systematically examined. An excretion study in rats after an oral dose of labeled fluoxetine showed that 66% and 21% of the dose was excreted in feces and urine, respectively; thus a minimum of 21% of the dose was absorbed. Relative routes of excretion were not systematically studied in other species.

2. Tissue and Plasma Levels:

In mice and dogs receiving fluoxetine p.o., peak plasma levels of fluoxetine were reached by 0.5 and 1 hr., respectively (first time point measured). Levels of the demethylated metabolite (DMF) peaked somewhat later, after which levels of DMF were greater than those of fluoxetine. Similar results were seen in rats dosed i.p. Data on plasma T 1/2 of fluoxetine in animals showed a long T 1/2 for both fluoxetine and DMF. In rats dosed i.p. with unlabelled fluoxetine, T 1/2 for fluoxetine and DMF was approximately 25 hr., and in rats dosed p.o. with labelled fluoxetine, T 1/2 for total label was approximately 40 hr. In dogs given 1 mg/kg unlabelled fluoxetine p.o. or i.v., plasma T 1/2 for fluoxetine and DMF was 3.2 and 2.4 days, respectively. In a 15 day oral dog study (5-20 mg/kg), T 1/2 calculated from the decline in plasma levels after the last dose was approximately 1 day and 2-5 days for fluoxetine and DMF, respectively. In man, the plasma T 1/2 of fluoxetine and especially DMF appear still greater, approximately 3 and 7 days, respectively.

In rats dosed with unlabelled fluoxetine i.p., levels of fluoxetine and DMF in tissues were 200-1000x those in plasma; highest levels were in lung followed by liver, kidney, and spleen. (In a 2 year dietary study in rats, levels were highest in lung followed by liver, brain, and plasma; no other tissues were assayed). Tissue distribution in dogs showed interstudy variability, making determination of relative distribution difficult; it appears that greatest levels are in liver, lung, and adrenal, with lowest levels in plasma. In a 3 month p.o. study in mice, levels of fluoxetine and DMF in lung were 2-10x those in heart, which in turn were 10-20x those in plasma; no other tissues were studied. In a study in which rats were dosed p.o. with labelled fluoxetine, total label declined in liver and brain faster than in blood (T 1/2 = 9.6, 9.5, and 39.4 hours, respectively).

In subacute/chronic studies in rat, mouse, and dog, plasma and tissue levels of fluoxetine and DMF increased much greater than in proportion to dose (except for DMF in dog). Also, except for the HD in mice, plasma and tissue levels of DMF were several fold greater than those of fluoxetine; this effect was inversely proportional to dose. In the 2 year rat study, females had levels of fluoxetine in plasma and tissues which were several times greater than those in males; DMF was greater in females in tissues but not in plasma.

Plasma protein binding of fluoxetine was studied in humans and was found to be about 95% at concentrations of 0.2-8 ug/ml; binding was independent of drug concentration. In addition, DMF at 0.2-1 ug/ml did not alter the binding of fluoxetine at 0.2 ug/ml.

3. Metabolism:

The primary metabolic conversions of fluoxetine involve demethylation to form the pharmacologically active DMF, and O-dealkylation to form para-trifluoromethylphenol. The products of these reactions undergo further changes which were not clearly defined. Species differences in the various reaction rates (as measured in vitro) were noted. As discussed above, demethylation of fluoxetine to DMF appeared to be extensive in all animal species studied.

Fluoxetine was found to inhibit the metabolism of several drugs in animals, including hexobarbital and amphetamine. On the other hand, in man, fluoxetine (30 mg as a single or 7-8 daily doses) had no effect on the pharmacokinetics of single doses of secobarbital, warfarin, chlorothiazide, or tolbutamide.

C. Acute Toxicity:

Seven day p.o. LD 50 was approximately 250 mg/kg in mouse (done in females only) and 450 mg/kg in rat. I.V. LD 50s were approximately 1/5 and 1/20 of the respective p.o. values in mouse and rat, respectively. Toxic signs after oral dosing included hyperirritability, salivation, leg weakness, loss of righting reflex, dyspnea, tremors, and convulsions; hyperactivity was seen in mice but hypoactivity was reported in rats. Deaths continued to occur for several days after p.o. dosing. Immediate convulsions occurred after i.v. dosing. Acute oral toxicity studies in cat, dog, and monkey showed no deaths at the doses used (25-50, 25-100, and 25-50 mg/kg, respectively); the actual doses were likely reduced due to emesis. The acute toxicity of the demethylated metabolite of fluoxetine (DMF) was studied in female mice (i.v. and p.o.) and in female rats (i.v.); results were generally quantitatively and qualitatively similar to those obtained with the parent compound.

D. Subacute/Chronic Toxicity:

1. The following studies were performed (daily oral doses in parentheses):

a. Mice (dietary administration):

1) 2 week (20, 65, 200 mg/kg).

2) 3 month (2, 7, 30 mg/kg) (5/sex/group kept for 1 month recovery period.)

3) 2 year (2 separate studies) (1, 5, 12 mg/kg)

b. Rats (dietary administration):

1) 2 week (40, 80, 160 mg/kg)

2) 3 month (10, 25, 70 mg/kg)

3) 1 year (0.5, 2, 10 mg/kg) (5/sex/group kept for 2 month recovery period).

4) 2 year (0.5, 2, 10 mg/kg)

c. Dogs (capsules):

1) 2 week

a) (25, 50 mg/kg)
b) (5, 10, 20 mg/kg)

2) 3 month (5, 10, 20 mg/kg)

3) 1 year (1, 4.5, 20 decreased to 10 mg/kg) (selected animals kept for 2 month recovery period).

d. Monkeys:

1) 2 week (10, 25 mg/kg)

2) 2 week hematology (10 mg/kg)

e. Special studies to further characterize the onset, nature, and reversibility of fluoxetine-induced phospholipidosis:

1) Rats: 2-4 weeks dosing at 40 mg/kg followed by recovery periods of 1-6 weeks.

2) Dogs: 11 months dosing at 50 mg/kg (3 doses per week).

f. 3 month combination studies (fluoxetine/carbidopa/5-HTP):

1) Rats (dietary administration)

LD 3/4/18 mg/kg
MD 5/7/36 mg/kg
HD 11/14/72 mg/kg

2) Dogs (capsules)

LD 1.25/1.0/2.5 mg/kg
MD 2.5/2.0/5.0 mg/kg
HD 5.0/4.0/10.0 mg/kg

2. Results:

a. Mice:

Hyperactivity and clonic convulsions upon handling were seen at all doses (1-12mg/kg) in one of the 2 year studies. Hyperactivity and clonic convulsions were also seen at the higher doses used in the shorter term studies. In the 2 week study 65 and 200mg/kg were lethal (3/10 and 10/10 deaths, respectively) and a few deaths were associated with the 30mg/kg dose in the 3 month study. In the 2 year studies overall mortality was slightly increased at HD (12mg/kg). Bodyweight loss was seen at 65 mg/kg +; 12-30mg/kg caused a very slightly decreased weight gain, in males only.

The principal pathology findings in the mouse studies are as follows:

1) Heart:

In the 2 week study a D-R multifocal myocardial degeneration and necrosis was seen in 3/10 at 65 mg/kg and in 8/10 at 200 mg/kg. This lesion, as seen with the light microscope, was generally associated with mice that died, however, EM exam showed cardiac changes at all doses (20-200 mg/kg), including mice which survived. In the 3 month study no effects on heart were seen at the doses used (2-30 mg/kg), either by light microscopy or (in 2/sex/group) by EM exam. No changes were seen in the 2 year studies (HD = 12 mg/kg).

2) Phospholipidosis:

Pulmonary phospholipidosis was seen in the 2 wk. study at HD (200 mg/kg) but not at lower doses (20-65 mg/kg, although vacuolation of circulating lymphocytes was seen at 65 mg/kg, which may be indicative of phospholipidosis); it was not seen in the 3 month study by light microscopy although it was detectable by EM (i.e., presence of multilamellated inclusions in alveolar macrophages and/or type I cells) at HD (30 mg/kg). Phospholipidosis was not seen in the 2 year studies (HD = 12 mg/kg).

3) Testes:

Bilateral focal hypospermatogenesis was increased in HD M (30 mg/kg) in the 3 month study (not reversible after 1 month off drug) but not in the 2 year studies (HD = 12 mg/kg).

4) Liver:

Minimal hepatocytic degeneration (centrilobular glycogen infiltration and/or fatty change) was seen at HD (30 mg/kg) in the 3 month study; this was not seen in the 1 month recovery animals. The elevations in SAP (and SGPT in a few mice) at HD may be related to these liver changes. Hepatic changes were also seen in the 2 year studies; these included degenerative changes, occasionally progressing to necrosis of individual hepatocytes, hepatocellular hypertrophy and cytomegaly, and increased hepatocytic fat. These were generally seen at MD (5mg/kg) and HD (12mg/mg). In one of the 2 year studies SGPT was elevated in MD and HD males; AP was increased in HD females to a lesser degree.

5) Tumor Incidences:

There were no drug induced increases in the incidence of total benign or malignant tumors, or in the incidence of any specific tumor type.

b. Rats:

No toxic signs were reported in the 1 and 2 year studies at LD and MD (0.5 and 2 mg/kg). At HD (10 mg/kg) in these studies an "unusual" behavior (after handling, animals walked on toes with feet extended and backs arched) was seen almost exclusively in females. (Histological exam of spinal cord showed no drug effects which could explain this behavior; it was not seen after 2 weeks off drug in the 1 year study). These HD females also showed thinness, poor grooming, and chromodacryorrhea. Height gain and food consumption were decreased at HD (10 mg/kg) in both sexes. There was no drug-related mortality in the 1 year study; in the 2 year study there was a slight excess of deaths in HD females during the final month only. At the higher doses used in the 2 week and 3 month studies, hyperirritability to touch was seen at 25 mg/kg +, ataxia and piloerection were seen at 160 mg/kg, weight loss and/or decreased weight gain and decreased food consumption were seen above 10 mg/kg, and lethality was seen at 70 mg/kg +.

Several slight lab value changes were seen in the various rat studies but their toxicological significance is unclear. Urinalyses were not performed. The following are the principal pathology findings in the 1 and 2 year studies (Reversibility determined in 1 year study only, after a 2 month recovery period. Aside from phospholipidosis, discussed below, there was no clearly drug-related histopathology in the 3 month study; histopathology was not performed in the 2 week study):

1) Phospholipidosis:

Pulmonary phospholipidosis was seen primarily at HD (10 mg/kg), although a few rats at the lower doses (0.5-2 mg/kg) were also affected. (Phospholipidosis was also seen in the 3 month study at all doses, i.e. 10-70mg/kg. In a special study it was shown to occur as early as the first day of dietary dosing with 40mg/kg). Manifestations included gross lung lesions, microscopic lesions (alveolar macrophages with foamy cytoplasm), EM findings (lamellar inclusions), and an elevated phospholipid phosphorous content of lung. The changes tended to be reversible upon drug discontinuation. Evidence of phospholipidosis was also seen in other organs, primarily at HD: slightly increased phospholipid phosphorous in liver, and (by EM exam) lamellar inclusions in liver, adrenal cortex, and retina.

2) Liver:

a) Fat deposition (fatty change) was increased at all doses (dose -related) in the 1 year study, in males only, with a trend toward reversibility. It was not seen in the main 2 year study, but was seen at all doses (almost always in males) in a special supplementary 2 year study.

b) Minimal lymphoid/reticuloendothelial cell hyperplasia was seen at all doses, D-R; reversibility was equivocal.

c) "Phagocytosis" (intracytoplasmic phagocytic vacuoles containing cholesterol-like clefts and golden brown hemosiderin pigment in Kupffer cells) was seen in all groups but LD F, D-R, in the 2 year study only.

d) Minimal focal granuloma (consisting primarily of macrophages with a few lymphocytes) was increased at HD in the 1 year study only; reversibility was equivocal.

3) Lymph Node:

Minimal reticuloendothelial hyperplasia was increased at HD in both studies, with a suggestion of reversibility during the recovery period.

4) Testes:

There was an equivocal increase in unilateral mineralization at HD in the 1 year study only; no effects after recovery period.

5) Uterus:

A slight and equivocal increase in polyps was seen at all doses in the 2 year study.

6) Tumor Incidences:

There were no drug-induced increases in the incidence of benign or malignant tumors (total or any specific type). In the 2 year study the incidence of total benign tumors was decreased in HD females, primarily due to a decrease in mammary and pituitary tumors.

c. Dogs:

Anorexia and decreased weight gain and/or weight loss were seen at 5 mg/kg and higher. (No effect on weight gain was seen at 4.5 mg/kg in the 1 year study). In the 1 year study tremors and slow and/or incomplete pupillary responses were seen at all doses (1-20 mg/kg); in addition mydriasis, aggressive behavior, hypoactivity, ataxia, and emesis were seen at HD (10-20 mg/kg). Convulsions were seen in 1 dog each at 1 and 20 mg/kg in the 1 year study and in 1 dog at 50 mg/kg in the 2 week study. Three of 5 HD females (20 mg/kg) died in the 1 year study; no deaths occurred in the other studies. Ophthalmoscopic exams showed no effects aside from transient nystagmus at 10-20 mg/kg. EKG, measured on various days in the 1 year study prior to the daily dose showed a moderate dose-related decrease in heart rate at MD and HD (4.5-20 mg/kg); no adverse effects on conduction were noted. Several equivocal lab value changes occurred which were generally slight and transient and of unclear significance. (Slight increases in platelets were seen in all 3 studies, at 5 mg/kg and higher; the sponsor suggests this may be related to the 5-HT-depleting effects of fluoxetine. However, in an auxiliary study, 50 mg/kg 3x/wk. for 11 months did not affect platelet count despite a large decrease in blood 5-HT.) There was no clearly drug-related pathology in the 3 month study; nephrocalcinosis was seen in 1/4 MD (10 mg/kg) and 3/4 HD (20 mg/kg) but was considered incidental. The primary pathological finding in the 1 year study was phospholipidosis involving several organs, primarily lung, lymph node, spleen, and G.I. tract. All groups were affected (1-20 mg/kg) in a dose-related fashion. It was not seen in the 2 month recovery animals. EM exam also showed evidence of phospholipidosis (lamellar inclusions) in lymphocytes at all doses, in lung and adrenal cortex at MD and HD, and in retina (inclusions in inner plexiform layer) at HD only. Recovery animals showed no inclusions (although HD females were not examined). (In an auxilary 11 month study, 50 mg/kg 3x/wk. also produced EM evidence of phospholipidosis in liver and cerebellar cortex). Phospholipid phosphorous levels of lung, liver, and adrenal were elevated at HD. Other, more equivocal drug effects in the 1 year study included the following: (1) testes -decreased weight at HD, and various lesions seen only among treated dogs (at all doses), including lipid accumulation or vacuolated cytoplasm in germinal epithelium of seminiferous tubules, seminiferous tubules containing sloughed cells and nuclear debris, and minimal hypospermatogensis; some of these were also seen in recovery dogs. (2) Kidney - various degenerative changes seen in the 3 HD females that died-which were not seen in other dogs.

d. Monkeys:

In the first 2 week study, both doses (10 and 25 mg/kg) produced anorexia and weight loss. Twenty five mg/kg produced convulsions. Hematology showed progressive decreases in RBC, Hb, and Hct at both doses. WBC was also decreased. Blood chemistry showed increased SGOT and LDH at 25 mg/kg. These changes were difficult to evaluate without concurrent controls. In the second study (which used a 10 mg/kg dose and a control group), WBC was clearly decreased in only 1 of 4 treated monkeys; no effect was seen after a 2 week recovery period; other hematological parameters were not clearly affected.

e. Special Phospholipidosis Studies:

1) Rats:

Studies were performed to characterize further the drug-induced phospholipidosis that had been seen in rats. Rats were fed fluoxetine in diet at approximately 40mg/kg/day and sacrificed (5/group) after 1, 2, 4, 6, 8, 10, and 14 days of treatment. Light microscopic evidence of phospholipidosis (increased alveolar macrophages) was seen from the first day of treatment, and the magnitude of this effect increased over the 14 day treatment period. The phospholipid content of lung increased gradually after an initial decrease seen at day 1. In another study, rats were treated with fluoxetine (0.05% in diet) or chlorphentermine at an equimolar dose for 30 days, and evidence of phospholipidosis (light microscopic and EM exam, and phospholipid content of lung) was looked for over a 6 week drug withdrawal period. Fluoxetine and chlorphentermine produced similar changes in these parameters. All changes returned to normal by the end of the 6 week recovery period, although the chlorphentermine-treated rats tended to recover more rapidly, possibly due to the more rapid disappearance of chlorphentermine from tissues. The sponsor suggests that the desmethyl metabolite of fluoxetine was responsible for the observed effects, but the results do not rule out involvement of the parent compound.

2) Dogs:

Dogs received 50 mg/kg p.o., 3x/week, for 11 months. Results were similar to those obtained in the 1 year toxicity study, discussed above.

f. Combination Studies (fluoxetine/carbidopa/5-HTP):

1) Rats:

The principal findings were: decreased weight gain and food consumption at MD (5/7/36 mg/kg) and HD (11/14/72 mg/kg), decreased WBC in HD males (due primarily to very low values in 3 of 12 rats), slightly decreased activated partial thromboplastin time in all male groups, slightly increased SAP in HD females, minimal-slight fat deposition in all male groups, and minimal reticuloendothelial hyperplasia in lymph node in HD females. Aside from the decreases in WBC in HD males, no findings were seen that had not been seen in studies with fluoxetine alone at similar doses.

2) Dogs:

Aside from a slight and transient initial weight loss at MD and HD, the only drug-related toxicity seen in this study was observed signs, which included vascular congestion of conjunctiva, peripheral vasodilation, anorexia, hypoactivity, tremors, and slow pupillary response. These signs were described as minimal. The latter 4 signs were seen in studies of fluoxetine alone at similar doses; the first 2 may be due to serotonergic stimulation caused by the combination. (Potentiation of various pharmacological effects of 5-HTP by fluoxetine have been seen in numerous studies; see Pharmacology Section). (In pilot studies of this combination, doses approximately 2x those used here produced "severe" toxicity, including severe hyperalgesia, rigidity, hypoactivity, fine tremors, and 1 death. Such severe reactions were not seen with these doses [5-10 mg/kg] of fluoxetine alone. This suggests a potential for a toxic interaction between these compounds, although it was not ruled out that 5-HTP and/or carbidopa may have caused these effects by themselves.)

E. Mutagenicity:

Several studies were performed, including the Ames test, *in vitro* induction of DNA repair synthesis in rat hepatocytes, *in vivo* induction of SCE in hamsters, and *in vitro* induction of mutations in mouse lymphoma cells. Both fluoxetine and DMF were studied in these tests. Neither compound was positive in any test at the concentrations and doses used.

F. Reproduction:

1. Segment I:

Two studies were performed in rats: (1) a standard Segment I study (with some females being treated through lactation period) with females only treated by gavage at daily oral doses of 2, 5, or 12.5 mg/kg, and (2) a two generation study in which both males and females were treated by dietary administration at approximate daily doses of 1.4, 3.5, and 8.6 mg/kg, respectively, except that doses were higher in females during lactation: 2, 5.5, and 14 mg/kg. Dam weight gain was decreased at the HD in both studies during the premating period. Dam food consumption was decreased in HD in both studies - in the first, throughout the treatment period; in the second, during the premating period only. There were no drug effects on fertility. Pup survival was decreased at HD (12.5 mg/kg) in the first study and at MD and HD (3-6 and 8-14 mg/kg, resp.) in the second study. Pup weight was decreased at HD in both studies. External, visceral, and skeletal exams of fetuses were done in the second study and no drug effects were seen. There were no drug effects on various developmental tests or on reproductive performance in the F_1 generation.

2. Segment II:

Segment II studies were performed in rats and rabbits; daily oral (gavage) doses were 2, 5, and 12.5 mg/kg in rats and 2.5, 7.5, and 15 mg/kg in rabbits. In rats, no teratological effects were found. Dam bodyweight gain and food consumption were decreased at HD. In rabbits, slight decreases in fetal weight were seen at all doses, but no teratological effects were seen. The incidence of 13 ribs was slightly increased in all drug groups but was less than the historical control incidence. Doe food consumption was substantially decreased at all doses; bodyweight gain was also decreased at all doses. Two HD does died and 3 aborted. Postimplantation loss at HD was twice that of controls; this was due to an increase in early resorptions.

3. Segment III:

No Segment III studies were submitted *per se*, however the Segment I and two-generation studies performed were adequate to characterize the effects of fluoxetine on this phase of reproduction.

G. Overall Evaluation:

The pharmacology and toxicology of fluoxetine have been adequately characterized in animals. The following findings are of potential relevance to man:

1. Drug Interactions

a. Fluoxetine produced a toxic interaction with tranylcypromine. Toxic interactions between MAO inhibitors and other antidepressant drugs are well known.

b. Fluoxetine and 5-HTP potentiated each other's actions in a variety of studies.

c. Fluoxetine was highly (95%) bound to human plasma proteins, suggesting a potential for interaction with other drugs which also bind.

2. ADME and Pharmacokinetics

a. Fluoxetine is converted to an active metabolite (desmethylfluoxetine). Both fluoxetine and this metabolite have long half-lives, especially in man.

b. In rats, females had much higher plasma and tissue levels of fluoxetine than did males.

3. Convulsions were produced by fluoxetine in animals, although primarily at the higher doses (with the exception of handling-induced convulsions which were seen at all doses in a 2 year mouse study [LD = 1mg/kg]).

4. In the 1 year dog study a moderate decrease in heart rate was seen at MD and HD (4.5 and 10-20 mg/kg, respectively).

5. Fluoxetine produced phospholipidosis in several organs in mice, rats, and dogs (Histopathology was not performed in the monkey studies). This occurred primarily at the highest doses used in mice and rats, but at all doses in dogs (LD =1 mg/kg/day). It was shown to be reversible upon drug discontinuation. Phospholipidosis is produced by numerous drugs, including several antidepressants, but its human significance is unknown. No adverse effects attributable to phospholipidosis have been produced in man by other antidepressants.

6. Various liver changes (degeneration, fatty change, glycogen infiltration, hypertrophy, etc.) were seen in the rat and mouse studies. In rats, this was seen at all doses (LD = 0.5 mg/kg); in mice it was seen at 5 mg/kg + with no effect at 1 mg/kg. At least some of these changes were shown to be reversible after a 1-2 month drug-free period. The significance of these findings is not clear, however; the changes may reflect adaptive responses of the liver or may be related to phospholipidosis. Elevations in serum liver enzymes were seen in some of these studies, but the relationship of these elevations to the histological findings is unclear. No drug-related liver pathology was seen in dogs.

7. Testicular changes were seen in dogs and equivocally in mice and rats. In dogs, various lesions were seen at all doses in the 1 year study (1-20 mg/kg), including lipid accumulation or vacuolated cytoplasm in germinal epithelium of seminiferous tubules, seminiferous tubules containing sloughed cells and nuclear debris, and minimal hypospermatogenesis; some of these were also seen in

recovery dogs. In rats there was an equivocal increase in mineralization at HD in the 1 year (but not in the 2 year) study but no effects were seen in recovery animals. In mice, focal hypospermatogenesis (irreversible) was seen at HD (30 mg/kg) in the 3 month study but not in the 2 year studies (HD = 12 mg/kg). Fluoxetine produced no adverse effects on fertility in Segment I studies in rats. Testicular degeneration has been produced by other antidepressants, including imipramine, in chronic animal studies.

8. Nisoxetine is a close structural analog of fluoxetine that has produced leukopenia in man. In a 2 week monkey study with fluoxetine, both doses (10 and 25 mg/kg) caused decreases in WBC, RBC, Hb, and Hct; however, no control group was used. In a follow-up monkey study (which used a 10 mg/kg dose and a control group), WBCs were clearly decreased in 1 (and equivocally in another) of 4 monkeys but this normalized after a 2 week recovery period. Decreased WBCs were also seen in a 3 month combination study of F/carbidopa/5-HTP in rats, in HD males only. In 1 of 2 two-year mouse studies, WBC was decreased in HD males but was increased in HD females.

9. Various degenerative changes in kidney were seen in the 3 HD females (20 mg/kg) that died in the 1 year dog toxicity study which were not seen in other dogs; however, the causal relationships to drug treatment is not clear. In the 3 month dog study there was an equivocal increase in nephrocalcinosis. There were no clearly drug-related findings in kidney in rats and mice.

V. Clinical:

This section provides 1) a brief overview, 2) a description of the adequate and well controlled trials which provided evidence of efficacy, 3) a brief review of other adequate and well controlled trials which, because of their design, did not contribute to the efficacy claim, 4) a summary of safety data, and 5) a summary of clinical biopharmaceutic studies.

A. General:

All clinical trials to evaluate the efficacy of fluoxetine were carried out in adult outpatients with diagnoses of major depressive disorder (RDC or DSM III).

In the NDA, there were fourteen controlled trials submitted in support of the efficacy of fluoxetine in major depressive disorder. One study compared fluoxetine with imipramine and placebo (a six investigator, multicenter study). Another, a fixed dosage study, compared fluoxetine 20mg, 40mg, and 60mg with placebo (a ten investigator, multicenter study). Two studies compared fluoxetine and placebo. Ten studies compared fluoxetine with an active control agent (three were comparisons with imipramine, three with amitriptyline and four with doxepin). Because active control studies cannot generally provide clear evidence of effectiveness, the placebo controlled studies provide the most pertinent data on effectiveness.

Fluoxetine is demethylated to an active metabolite. After a single 40 mg dose of parent drug, maximum concentrations of norfluoxetine were 4 to 15 ng/ml and occurred about 72 hours after dosing (range 36 to 144 hours). This metabolite also had a large distribution volume (46 +/- 33 L/kg). The pharmacokinetics of norfluoxetine were not affected by the dose of parent drug. The mean half-life of norfluoxetine, 7.7 days, was even longer than that of the parent drug.

The plasma concentration profiles suggest that biliary recirculation occurs.

2. Food Interaction (Study 48):

The effects of food upon the bioavailability of fluoxetine were studied in two parallel groups of six normal volunteers. Each received a total dose of 70 mg (30 mg of a deuterated solution which served as an internal control and then 40 mg given either without food or immediately after a meal).

Single dose coadministration of fluoxetine with food did not alter the extent of drug absorption. The area under the blood concentration time profile did not change significantly. While the peak concentrations were essentially unchanged by the coadministration with food, peak blood levels of fluoxetine were delayed about 25%. The pharmacokinetics of norfluoxetine were unchanged by food.

3. Metabolism and Elimination:

a. Study 58:

Twelve normal volunteers were assigned to receive either 40 mg or 60 mg. First, each was given a single dose followed by a 14 day washout; then each was dosed for 30 days. On the last day of multiple dosing, each subject again received a single dose as a deuterated solution. This allowed a comparison of the disposition of a single dose both before and after steady state as well as total drug disposition at steady state.

This multiple-dose study corroborated the nonlinear pharmacokinetic disposition of fluoxetine. Peak steady state plasma concentrations for the six subjects who received 40 mg were higher than projected from the single dose; they ranged from 137 to 302 ng/ml. Furthermore, the mean terminal half-life after the initial single dose was 2 days whereas after 30 days it increased to 4 days. The mean terminal half-life for the 4 subjects who could tolerate 60 mg/day was 5.1 days. Plasma clearance (dose/ AUC) was reduced and the volume of distribution (V_B) was smaller.

Although the metabolite was not at steady state after 30 days, the half-life, AUC, apparent plasma clearance and volume of distribution for norfluoxetine did not change significantly upon multiple dosing; the mean terminal half-life for the subjects who received 40 mg/day was 9.3 days and 13.2 days for those who received 60 mg/day. The ratio between the AUC of fluoxetine and norfluoxetine increased from a single dose to multiple dosing. As evidenced by a decreased Cmax and delayed Tmax during chronic dosing, the rate of norfluoxetine formation appeared to be slowed.

b. Study 63:

Cmax, AUC, half-life, and clearance were estimated in thirteen patients treated for periods between one and three years with fluoxetine 40 to 80 mg. There appeared to be no continued accumulation or increased clearance compared to measurements made after 30 days of treatment. This suggests a lack of inhibition or self-induction of metabolism. In this study, as in others, fluoxetine disposition appeared nonlinear, while the metabolite appeared to obey linear pharmacokinetics.

Total plasma clearance (dose/AUC_{0-24}) was 126 ml/min (+/- 75 ml/min). Renal clearance of fluoxetine (amount excreted unchanged in urine/AUC_{0-24}) was 3.23% (+/- 2.45%) of total plasma clearance. Urinary recovery of fluoxetine, norfluoxetine, and their respective glucuronides each was about 3% of the total dose.

c. Study 6:

After a single 30 mg dose of radiolabeled fluoxetine, 7.9% of the radioactivity was recovered in the urine in the first 24 hours. When urine collection was exterded for 35 days, 56.1% of the radioactivity, on the average, was recovered. Another 12.9% was recovered in the feces after a ten day collection. Radioactive expired CO_2 was also collected, but the results were not reported. Since excretion was still occurring when sample collections were stopped, not all of the radioactivity was accounted for. The continued fecal elimination supports biliary recirculation.

[The sponsor performed a second radiolabelled disposition study. The results of Study #67 have not yet been submitted.]

4. Special Populations:

a. Elderly Subjects (Study 45):

In this single 40 mg dose study, there was no difference in pharmacokinetic parameters between 11 healthy elderly (greater than 65 years of age) subjects and younger healthy subjects. However, given the long half-lives of fluoxetine and norfluoxetine and the nonlinear disposition of the parent drug, a single dose study may be inadequate to expose potential differences at higher doses or in chronic dosing. Because fluoxetine's elimination is primarily dependent on hepatic metabolism, the elderly may be susceptible to accumulation.

b. Renal Impairment (Study 42):

The single dose (40 mg) pharmacokinetic characteristics of fluoxetine and norfluoxetine were examined in 25 subjects with varying degrees of renal impairment, including anephric patients on hemodialysis. While there was great intersubject variability, the mean half-life of fluoxetine in subjects with chronic renal impairment was 4.8 days versus 3.6 in normal subjects. The mean norfluoxetine half-life, similarly, was increased from 6.1 days in normal subjects to 10.4 days in subjects with impairment. There was little or no correlation between creatinine clearance and half-life. However, with chronic administration, accumulation of fluoxetine or its metabolites (possibly including some not yet identified) may occur in patients with impaired renal function, and caution is advised.

Since pre- and post-dialysis fluoxetine levels are similar, and less than 5% of dose is renally excreted as unchanged fluoxetine, and the drug has a very long half-life, hemodialysis would not be likely to have a significant impact in management of overdoses.

c. Liver Dysfunction (Preliminary Results of Study 65):

Twenty-five subjects were given single doses of either 40 mg or 60 mg; 12 of these subjects had liver dysfunction secondary to alcohol-induced cirrhosis. Interim results (submitted in summary form) indicate that the half-lives of fluoxetine and norfluoxetine are increased and that the rate of formation of norfluoxetine is decreased. In five healthy subjects given 40 mg, the mean half-life was 3.2 days for fluoxetine and 6.9 days for norfluoxetine. Seven cirrhotics given 40 mg had half-lives of 8.6 days and 11.5 days for fluoxetine and norfluoxetine, respectively. Thus, dose reductions should be considered in individuals with impaired liver function.

5. In Vitro Protein Binding:

In an in vitro study, fluoxetine was shown to be highly protein bound (94.5%) over the concentration range from 200 to 1000 ng/ml. There was no evidence of saturation of binding. Lowered levels of plasma proteins or the presence of other highly bound drugs could lead to decreased protein binding with increased free drug levels.

6. In Vitro Dissolution:

All proposed marketing capsule strengths and the lots used in clinical trials show acceptable in vitro dissolution when tested using the USP Apparatus II (Paddle) at 50 rpm in 900 ml water, 37°C. They would meet a dissolution specification of Q = 80% in thirty minutes. FDA recommends the following in vitro dissolution specification: not less than 80% dissolved in thirty minutes when tested using the USP Apparatus II (Paddle) at 50 rpm in 900 ml water, 37°C.

Conclusions:

Summary of the pertinent pharmacokinetic findings:

1. Fluoxetine is bioequivalent to an oral solution.

2. Coadministration with food does not substantially alter the extent of absorption or the peak levels of single, oral 40 mg doses of fluoxetine, but peak levels are delayed about 25%.

3. After a single oral dose of 40 mg, peak blood levels of fluoxetine range from 11 to 42 ng/ml and occur between 6 and 8 hours after dosing.

4. Fluoxetine shows nonlinear pharmacokinetics, suggesting saturation of the conversion of fluoxetine to norfluoxetine. With single doses, the half-life increases with increasing dose. After single doses of 40 mg, the half-life is on the order of 2 days whereas after a 90 mg dose it is about 3 days.

5. Upon multiple dosing at a particular dose, steady state levels are higher than would be predicted from studies of single doses, reflecting the nonlinear kinetics of fluoxetine metabolism. The half-life is also increased, e.g., after multiple dosing with 40 mg for 30 days, the half-life increased from 2 to 4 days.

6. Fluoxetine is demethylated to an active metabolite, norfluoxetine. After single 40 mg doses of parent drug, peak levels of the metabolite are 4 to 16 ng/ml and are late occurring, about 72 hours after the dose. The elimination appears to be non-dose dependent; with single doses, the metabolite has a very long half-life (7.7 days). With chronic dosing of the parent drug, the rate of norfluoxetine formation appears to be slowed; the half-life after 40 mg/day was 9.3 days.

7. There was neither continued accumulation nor increased clearance of drug beyond five weeks of therapy. This suggests that neither enzyme inhibition nor induction occurs.

8. The elimination of a dose of fluoxetine is very slow as evidenced by radiolabel collection. Only 7.9% of a dose is recovered in the urine within the first 24 hours. After 35 days, urinary excretion continues, with a total urinary recovery of 56.1% at that time. A 10 day fecal collection recovered 12.9%.

9. There is evidence of enterohepatic recirculation.

10. Single doses of 40 mg of fluoxetine are eliminated similarly by young and old patients, but the disposition of fluoxetine in the elderly has not been fully studied, in particular the disposition of large doses and disposition in chronic dosing have not been studied.

11. Renal impairment does not have a significant impact on the disposition of fluoxetine after single doses, but norfluoxetine half-life appears to be increased. There are insufficient data to rule out the accumulation of fluoxetine or its metabolites (possibly including some not yet identified) during chronic administration of fluoxetine and dose increases beyond 20 mg should be carried out with particular caution.

12. Liver impairment significantly decreases the clearance of both fluoxetine and norfluoxetine.

13. Fluoxetine is extensively protein bound: 94.5% over a concentration range from 200 to 1000 ng/ml.

VI .Pertinent Advisory Committee Minutes:

Fluoxetine was presented to the Psychopharmacologic Drugs Advisory Committee on October 10, 1985. After presentations of efficacy and safety data by FDA staff and representatives of Eli Lilly and Co., the Committee unanimously, by a 6-0 vote, concurred in the FDA judgement that fluoxetine was an effective antidepressant and, given the data available, that there were no apparent safety issues to preclude approval.

VII.Post Approval:

The sponsor has agreed to submit within the first year of marketing full reports of the two additional efficacy studies they have conducted that may provide a basis for revising the dosing recommendations made in the proposed product labeling. They have also agreed that, should the two studies described above prove inadequate, they will perform additional trials to establish a basis for drafting more precise directions for the use of fluoxetine.

In addition, the sponsor has agreed to explore existing databases to further assess the relationship of agitation and underweight status at baseline to outcome. In particular, they will identify subgroups within the controlled studies upon which the approval is based (i.e., studies 19, 27 and 62) with regard to agitation and weight loss at baseline [e.g., using high scores on items #9 (agitation) and #16 (weight loss) of the HAMD]. The outcomes of these subgroups on these identified variables, as well as their responses on measures of depression (e.g., item #1 of the HAMD), will be compared for the assigned treatments in each of these studies. Such analyses should produce additional useful information on the question of whether or not fluoxetine has any particular risk for such patients.

VIII. Approved Package Insert:

The draft package insert is attached.

The third study demonstrating the efficacy of fluoxetine (Study 62) involved a comparison of placebo and three fixed doses of fluoxetine: 20, 40, and 60 mg/day, with the entire dose being given in the morning. Treatment was initiated with the assigned dose (i.e., no titration) and this may have contributed to the high dropout rate in the 60 mg group.

This study demonstrated the superiority of the 20 and 40 mg fluoxetine doses over placebo, and less clearly showed a response to 60 mg, but did not suggest a dose-response relationship, perhaps because of the greater proportion of dropouts for adverse events in the two higher dose groups. No unequivocal conclusion can be made about the relative efficacy of different fluoxetine doses, but there was no discernable benefit of doses above 20 mg in this study.

Two recent studies suggest that 20 mg/day may be sufficient to obtain a satisfactory antidepressant response.

Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. A dose increase may be considered after several weeks if no clinical improvement is observed. Doses above 20 mg/day should be administered on a b.i.d. schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

As with other antidepressants, the full antidepressant effect may be delayed until 4 weeks of treatment or longer.

As with many other medications, a lower or less frequent dosage should be used in patients with renal and/or hepatic impairment. A lower or less frequent dosage should also be considered for patients, such as the elderly, with concurrent disease or on multiple medications.

There is no body of evidence available to answer the question of how long the patient treated with fluoxetine should remain on it. It is generally agreed among expert psychopharmacologists (circa 1987) that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

III. Chemistry:

A. Manufacturing and Controls:

The new drug substance, fluoxetine hydrochloride, is prepared by a multi-step, organic synthesis. Specifications for the new drug substance and methods to check these specifications are adequate to establish and maintain its identity, strength, quality and purity.

Adequate specifications and test methods are also provided to identify, characterize and control the raw materials used in the synthesis of the bulk, new drug substance, and those used to prepare the finished dosage form.

Table 31

Mean Reduction in HAMD Total Score from Other Placebo-Controoled Studies

Investigator (Protocol #)	Fluoxetine (80mg) N	Baseline	Reduction	Placebo N	Baseline	Reduction	P
Fabre (#19)	16	29	13	20	27	7	0.05
Rickels (#25)	15	25	9	23	26	9	N.S.
Cohn (#27)	46	26	16	52	25	4	0.04
Pooled - Cohn (#27)	149	28	12	136	28	9	0.05

Table 31

Mean Reduction in HAMD Total Score from Other Placebo-Controlled Studies

Investigator (Protocol #)	Fluoxetine (80mg) N	Baseline	Reduction	Placebo N	Baseline	Reduction	P
Fabre (#19)	16	29	13	20	27	7	0.05
Rickels (#25)	15	25	9	23	26	9	N.S.
Cohn (#27)	46	26	15	52	25	4	0.04
Pooled - Cohn (#27)	149	28	12	136	28	9	0.05

Table 32

NO PLACEBO

Mean Reduction in HAMD Total Score from Other Active-Controlled Studies

Investigator (Protocol #)	Fluoxetine (80mg) N	Baseline	Reduction	Control N	Baseline	Reduction
Feighner (#29)	12	26	13	18	30	14
Feighner (#23)	20	28	12	9	27	15
Chouinard (#26)	20	28	12	24	26	15
Kiev (#31)	17	27	14	21	25	13
Feighner (#33)	22	27	12	16	28	12
Rickels (#35)	41	23	10	43	24	10
Smith (#35)	34	29	13	37	28	15
Davis (#29)	19	29	9	17	26	12
Cohn (#33)	32	24	9	28	24	10
More Severely Depressed Patients						
Masco (#22)	18	32	16	18	33	13
Masco (#31)	26	34	13	23	30	17
Bremner (#20)	16	37	31	19	38	24

The following table summarizes the designs and outcomes of these active control studies:

Protocol Number	Investigator	Control Drug	Duration of Trial (weeks)	In/Out Patient	Number of Pts. F	Number of Pts. C	Usual Dosage F	Usual Dosage C	Intent to Treat
20	Bremner	IMI	5	Out	20	20	60	175	F > C
29a	Feighner	IMI	6	In	18	23	80	200	F = C
29b	Davis	IMI	6	In	21	22	80	200	F = C
22	Masco	AMI	5	Out	20	21	80	300	F = C
23	Feighner	AMI	5	Out	22	22	40	150	F > C
26	Chouinard	AMI	5	Out	23	28	80	200	F = C
31a	Kiev	DXP	6	Out	27	26	80	200	F = C
31b	Masco	DXP	6	Out	28	28	80	300	F = C
33a	Feighner	DXP	6	Out	24	23	80	125	F = C
33b	Cohn	DXP	6	Out	42	41	80	200	F = C

Legend:
IMI = imipramine; AMI = amitriptyline; DXP = doxepin
F = fluoxetine; C = control

D. Safety:

1. Population Exposed:

As of July 31, 1987, approximately 7920 subjects had been exposed to fluoxetine in premarketing studies, including 6070 in US studies and 1850 in foreign studies. For the latter, only drug experience reports, rather than detailed analyses of event rates, were available. The larger data base is relevant to detection of rare events, but the primary safety data were obtained from the US subjects.

2. Extent of Exposure:

Of the US patients receiving fluoxetine, approximately 86% were treated for three months or less, while approximately 6% received treatment for greater than one year (including 63 on fluoxetine for greater than two years). Of the patients receiving fluoxetine in phase II and later studies, the percentages receiving various daily maintenance doses were as follows: 20 mg (23%), 40 mg (21%), 60 mg (25%), 80 mg (24%). Less than 1% of patients received maintenance doses of 100 mg/day or greater.

3. Clinical Laboratory Effects:

a. Hematology:

Hematology data were available at two or more visits for approximately 3500 patients treated with multiple doses of fluoxetine in the U.S. program. Platelet counts were available for 2600 of these patients. Control data were available for approximately 750 patients treated with placebo and approximately 600 patients treated with tricyclic antidepressants (TCAs). Discontinuations primarily for hematologic abnormalities in fluoxetine patients included four patients with changes in total WBC.

Of the fluoxetine patients having hematocrit and hemoglobin determinations, 3.78% had hematocrits of less than 35% at one or more visits, compared to 3.37% of TCA patients and 2.04% of placebo patients. For hemoglobin, 2.35% of fluoxetine patients had values less than 11.5 grams/dl, compared to 2.30% of TCA patients and 1.47% of placebo patients. Of the fluoxetine patients identified as having a low hematocrit (less than 35%) or hemoglobin (less than 11.5 gm/dl), only 17 had decreases of hematocrit greater than 6% (relative to baseline) and/or decreases of hemoglobin greater than 2 grams/dl (relative to baseline). Eleven of these cases were either normal or improving at the final visit, and as noted above, none of the cases required discontinuation due to these abnormalities.

Of the fluoxetine patients having total WBCs, 1.36% had WBCs less than 2800/mm^3 or greater than 16,000/mm^3 at one or more visits, compared to 1.07% of TCA patients and 0.57% of placebo patients. Of the fluoxetine patients identified as meeting the above criteria for abnormal WBC, 30 had the abnormality for the first time during treatment compared to baseline (13 decreased, 17 increased). Only one of these patients had an on-drug WBC less than 2000/mm^3, i.e., this patient had an isolated WBC of 1300 (with 52% neutrophils) after 10 months of treatment, which was 5700 six days later, after discontinuation of fluoxetine. Two other fluoxetine patients were discontinued for mild leukopenia of questionable clinical significance. The highest leukocytosis (i.e., 40,000) occurred in a patient subsequently diagnosed as having leukemia. All other patients with leukocytosis had maximum values less than 20,000, and many of these occurred in patients with concurrent rash.

Of the fluoxetine patients having platelet counts, 2.25% had platelet counts less than 125,000/mm^3 or greater than 500,000/mm^3 at one or more visits, compared to 3.37% of TCA patients and 2.15% of placebo patients. Of the fluoxetine patients identified as meeting the above criteria for abnormal platelet count, 50 had abnormalities for the first time during treatment compared to baseline, i.e., 15 had decreases and 35 had increases. None of the changes noted were of clear clinical significance.

b. Chemistry:

Overall, chemistry data were available at two or more visits for approximately 3500 patients treated with multiple doses of fluoxetine in the US program. However, for some of the variables, the numbers of tests available were fewer: SGPT-1800; LDH-1500; creatinine-1800. Control data were available for approximately 750 placebo patients and approximately 600 TCA patients. No patients were discontinued primarily for changes in serum chemistry parameters.

Of the fluoxetine patients having SGOT and SGPT determinations, 0.54% had SGOT values greater than 3 times the upper limit of normal (ULN) at one or more visits, compared to 1.23% of TCA patients and 0.34% of placebo patients. For SGPT, 0.69% of fluoxetine patients had values greater than 3 times ULN, compared to 0.15% of TCA patients and 0.34% of placebo patients. Of the fluoxetine patients meeting the above criteria for elevated SGOT or SGPT, 18 had abnormalities of at least one of these enzymes for the first time during treatment compared to baseline, including 5 with elevations of both SGOT and SGPT. The most prominent elevations were noted for the first time at the final visit for a patient (HCBO-6790) in an open label study: SGOT-2710 U/l; SGPT-4380 U/l; alkaline phosphatase-1160 U/l; bilirubin-11.1 mg/dl. This patient had viral hepatitis (determined to be Type A). The four other cases of combined elevation of SGOT and SGPT (3 of whom were in an alcoholism study) involved modest increases (the highest SGPT was 380 and the highest SGOT was 347), with either normalization or improvement towards normal shortly after the final visit. Of the six cases of SGOT elevation (without SGPT elevation), all were modest increases (less than 220), and were improving at or shortly after the final visit (in the four cases where follow up data were available). This was also the case for the seven patients with SGPT elevations (without SGOT elevations), i.e., 300 or less at the highest elevation, with improvement in the three patients for whom followup values were available. As noted above, no patients were discontinued for changes in SGOT or SGPT.

Of the fluoxetine patients having alkaline phosphatase determinations, 0.20% had values greater within 3 times ULN at one or more visits, compared to 0.15% of TCA patients and 0.23% of placebo patients. Of the fluoxetine patients meeting the above criterion for abnormality, four had abnormalities for the first time during treatment compared to baseline, including the case noted above (HCBO-6790). One of the remaining cases was an isolated increase at the tenth visit (911 U/l), with a normal value at the final visit. The two remaining cases involved moderate increases noted for the first time at the final visit, and no followup was available.

Of the fluoxetine patients having bilirubin determinations, 0.49% had total bilirubins greater than 2.0 mg/dl at one or more visits, compared to 0.46% of TCA patients and 0.23% of placebo patients. Of the fluoxetine patients meeting the above criterion for abnormality, 12 had abnormalities for the first time during treatment compared to baseline, including the case noted above (HC80-6790). Of the remaining 11 cases, 7 were either normal or improving at the final visit, despite continued fluoxetine treatment. The remaining 4 cases were noted for the first time at the final visit, and although no followup was available, all had modest increases.

Of the fluoxetine patients having BUN determinations, 0.69% had BUNs greater than 30 mg/dl at one or more visits, compared to 1.99% of TCA patients and 0.34% of placebo patients. Creatinine determinations were available only in fluoxetine patients, and only three cases met the criterion of being greater than 2.0 mg/dl at one or more visits, and one of these cases was also abnormal at baseline. One of the remaining patients had only a modest increase (2.2), and was normal at the final visit. The other case was noted to have a creatinine of 10.8 at the final visit (without followup), but also had a normal BUN at this visit. Several fluoxetine patients had single, isolated BUN elevations with normal values at preceding and following visits, and no other abnormalities. The remaining cases represented modest elevations (i.e., highest value of 44), with unclear clinical significance.

c. Urinalyses:

Overall, routine urinalysis data were available at two or more visits for approximately 2800 fluoxetine patients treated with multiple doses in the US program. No patients were discontinued primarily for changes in urinalysis parameters. For albumin determinations, 0.89% of fluoxetine patients had increases of at least two units at some follow up visit relative to baseline, compared to 0.77% of TCA patients and 0.23% of placebo patients. Quantitative protein determinations were not done in any of these cases and these findings were of unknown clinical significance. For glucose, 0.84% of fluoxetine patients had increases of at least 2 units at some follow up visit relative to baseline, compared to 1.38% of TCA patients and 0.34% of placebo patients. About half of the identified fluoxetine cases also had increased blood glucose. These findings were of unknown relationship to fluoxetine.

There were also apparently random abnormalities noted for other laboratory parameters in patients taking fluoxetine and control drugs, but none occurred in a pattern suggesting any clear relationship to fluoxetine use. Overall, these findings did not suggest that fluoxetine use is predictably associated with clinically signficant changes in hematology, chemistry or urinalysis parameters.

4. Vital Signs Effects:

Data on blood pressure and pulse rate were available for approximately 2300 fluoxetine patients, and comparative data were available for approximately 700 patients taking placebo and 600 patients taking tricyclic antidepressants (TCA). Outliers were defined as follows: systolic blood pressure (SBP) less than 100 mmHg and a change of -30 (relative to baseline or some earlier on-drug value), or SBP greater than 160 mmHg and a change of +40; diastolic blood pressure (DBP) less than 60 mmHg and a change of -20, or a DBP greater than 100 mmHg and a change of +30; heart rate (HR) less than 60 bpm and a change of -30, or HR greater than 110 bpm and a change of +30. Patients were identified as outliers only if they met one or more of these criteria for at least two on-drug visits.

More fluoxetine patients met the criteria for decreased BP [i.e., for SBP, n=30 (0.74%) and for DBP n=91 (2.25%)] than for increased BP [i.e., for SBP, n=19 (0.47%) and for DBP, n=8 (0.20%)], although orthostatic hypotension was not a common complaint among fluoxetine patients, and no patients were identified as dropping out primarily because of hypotension. The proportions of placebo and TCA patients meeting the criteria for decreased BP were approximately the same as for fluoxetine patients. A greater percentage of fluoxetine patients met the criteria for increased BP (particularly SBP) than for control drugs. Seven fluoxetine patients were identified as being discontinued, either primarily or in part due to increased BP, but only three had objective increases in BP of possible clinical significance. Overall, there was not a pattern suggesting clinically important BP changes in association with fluoxetine use.

More fluoxetine patients met the criteria for decreased HR [i.e., n=27 (0.67%)] than for increased HR [i.e., n=9 (0.22%)]. The proportions of placebo and TCA patients meeting the criteria for increased HR were greater than for fluoxetine patients, while the proportions for these two control groups meeting the criteria for decreased HR were less than for fluoxetine patients. Only one fluoxetine patient had a potentially clinically important decrease in heart rate, i.e., a bradycardia ranging from 44 to 48 bpm on fluoxetine, compared to 88 bpm at baseline. No flouxetine patients were discontinued for decreased HR. While eight fluoxetine patients were identified as being discontinued primarily or in part due to complaints of tachycardia, most had multiple other symptoms suggestive of anxiety and none had any actual increases in heart rate of clinical significance. Overall, despite a tendency for fluoxetine to cause a decrease in heart rate, there was no pattern suggestive of clinically important HR changes in association with fluoxetine use.

Data on temperature change in association with fluoxetine use were available for approximately 2600 fluoxetine patients, and comparative data were available for approximately 700 patients taking placebo and 500 patients taking TCA's. A clinically significant temperature change was defined as an increase or decrease of 1.5°F. Percentages of patients meeting these criteria for a clinically significant change were as follows: fluoxetine-4.6%; placebo-3.2%; TCA's-3.8%. In all three groups, the numbers with increases were approximately equal to the numbers with decreases. No fluoxetine patients were identified as being discontinued primarily due to temperature changes. Thus, there was no pattern suggesting clinically important temperature changes in association with fluoxetine use.

5. Weight Changes:

Overall, data on weight change were available for 3865 patients who were treated with fluoxetine, of whom 18% experienced weight changes of at least 5% of body weight (5% increased, 13% decreased), compared to 5% of placebo patients (1% increased, 4% decreased) and 14% of patients treated with tricyclic antidepressants (11% increased, 3% decreased). However, in the entire development program, only eight fluoxetine patients had to be discontinued due to weight loss, and in two of these cases, the weight loss was associated with worsening depression.

Data from double blind, controlled trials revealed that the extent of weight loss associated with fluoxetine treatment was related to baseline weight, with overweight patients losing an average of four pounds over six weeks, compared to only a two pound weight loss in normal weight patients.

6. ECG Changes:

ECG tracings were reviewed for 370 fluoxetine patients in the development program who had ECGs at baseline and at least one followup visit. For 312 of these fluoxetine patients, the data were obtained in controlled comparisons of fluoxetine with placebo, imipramine, amitriptyline or doxepin. Among the total sample of patients participating in these controlled studies (N = 753), intraventricular conduction delays were noted in one amitriptyline and five imipramine patients, but in none of the fluoxetine, doxepin or placebo patients. The remaining ECG data for fluoxetine were obtained from 58 patients participating in open studies.

Of the 370 fluoxetine patients whose ECGs were reviewed, 14 were noted to have either changes from normal to abnormal, or had abnormalities at both baseline and followup visits. The ECG changes included A-V nodal rhythm, nonspecific ST-T changes, occasional VPCs, and in one patient, more prominent Q3 and AVF, which were interpreted as a normal variant associated with obesity. In none of these cases were patients discontinued because of the ECG changes.

7. Observed Adverse Events:

a. Commonly Observed:

The most commonly observed adverse events associated with the use of fluoxetine and not seen at an equivalent incidence among placebo treated patients were: nervous system complaints, including anxiety, nervousness and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea and diarrhea; and dizziness or lightheadedness.

b. Associated with Discontinuation of Treatment:

Fifteen percent of approximately 4000 patients who received fluoxetine in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritis.

c. Incidence in Controlled Clinical Trials:

The table that follows enumerates adverse events that occurred at a frequency of 1% or more among fluoxetine patients who participated in controlled trials comparing fluoxetine with placebo. These figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics, methods of adverse event detection, and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event[a]	Percentage of Patients Reporting Event fluoxetine (n=1730)	Placebo (n=799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	--
Lightheadedness	1.6	--
Concentration decreased	1.5	--
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	--
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4

[a]Events reported by at least 1% of fluoxetine patients are included.
--Incidence less than 1%.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event[a]	Percentage of Patients Reporting Event fluoxetine (n=1730)	Placebo (n=799)
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	--
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.5
Dyspnea	1.4	--
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.4
Sexual dysfunction	1.9	--
Frequent micturition	1.6	--
Urinary tract infection	1.2	--
Special Senses		
Vision disturbance	2.8	1.8

[a]Events reported by at least 1% of fluoxetine patients are included.
--Incidence less than 1%.

d. Other Events Observed During the Premarketing Evaluation of fluoxetine:

During clinical testing in the US, multiple doses of fluoxetine were administered to approximately 5600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (i.e., reduced) number of standardized event catagories.

In the tabulations which follow, standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5600 fluoxetine exposed individuals who experienced an event of the type cited on at least one occasion while receiving fluoxetine. All reported events are included except those already listed in tables, those costart terms so general as to be uninformative and those events where a drug-cause was remote. It is important to emphasize that, although the events reported did occur during treatment with fluoxetine, they were not necessarily caused by it.

Events are further classified within body system catagories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: Frequent-chills; Infrequent-chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; Rare-abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System: Infrequent-angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; Rare-AV block first degree, bradycardia, bundle branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System: Frequent-increased appetite
Infrequent-aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, thirst; Rare-bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, tongue edema.

Endocrine System: Infrequent-hypothyroidism; Rare-goiter, hyperthyroidism.

Hemic and Lymphatic System: Infrequent-anemia and lymphadenopathy; Rare-bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, thrombocythemia.

Metabolic and Nutritional: Frequent-weight loss; Infrequent-generalized edema, hypoglycemia, peripheral edema, and weight gain; Rare-dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, iron deficiency anemia.

Musculoskeletal System: Infrequent-arthritis, bone pain, bursitis, tenosynovitis, and twitching; Rare-bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System: Frequent-abnormal dreams and agitation; Infrequent-abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; Rare-abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidial syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System: Frequent-bronchitis, rhinitis, and yawn; Infrequent-asthma, epistaxis, hiccup, hyperventilation, pneumonia; Rare-apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, pleural effusion.

Skin and Appendages: Infrequent-acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; Rare-eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses: Infrequent-amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; Rare-blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Endocrine System: Infrequent-hypothyroidism; Rare-goiter, hyperthyroidism.

Hemic and Lymphatic System: Infrequent-anemia and lymphadenopathy; Rare-bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, thrombocythemia.

Metabolic and Nutritional: Frequent-weight loss; Infrequent-generalized edema, hypoglycemia, peripheral edema, and weight gain; Rare-dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, iron deficiency anemia.

Musculoskeletal System: Infrequent-arthritis, bone pain, bursitis, tenosynovitis, and twitching; Rare-bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System: Frequent-abnormal dreams and agitation; Infrequent-abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; Rare-abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidial syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System: Frequent-bronchitis, rhinitis, and yawn; Infrequent-asthma, epistaxis, hiccup, hyperventilation, pneumonia; Rare-apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, pleural effusion.

Skin and Appendages: Infrequent-acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; Rare-eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses: Infrequent-amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; Rare-blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System: Infrequent-abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; Rare-abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, vaginal hemorrhage.

8. Special Safety Considerations:

a. Death:

Fatalities in temporal association with the use of fluoxetine were reported in 27 patients as of October 15, 1987 (16 suicides, 1 homocide and 10 other medical events). None of these deaths were known or believed to be a direct consequence of treatment with fluoxetine. Of the 16 suicides, only two clearly involved an overdose with fluoxetine, and both involved at least one other drug as well (see b, Fluoxetine Overdose). Of the ten other fatal medical events, four were primarily cardiac, three were carcinomas, and one each of the remaining deaths was associated with hematemesis, ruptured aneurysm and fractured hip with fat embolism. In none of these ten cases was there any plausible link to fluoxetine.

b. Fluoxetine Overdose:

As of December, 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respectively. A second death involved 3 drugs, yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment. The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

c. Cutaneous Adverse Events:

The primary data regarding cutaneous adverse events were from 5620 US patients who were treated with fluoxetine and were included in the sponsor's database as of July 31, 1987. In addition, 1324 patients received placebo and 803 received comparator substances (usually tricyclic agents). Of these US cases, 235 fluoxetine-treated patients (4.2%) experienced treatment emergent events subsumed under the terms rash or urticaria.

Utilizing the July 31, 1987 database, a survey was made of all cases of rash occurring among patients treated with fluoxetine, placebo, or comparator antidepressants. The results of this survey are displayed in the following table:

Cases of Rash and/ or Urticaria*

Number of Patients

	Fluoxetine		Comparator		Placebo	
		(%)		(%)		(%)
TOTAL	279	(100.0)	34	(100.0)	59	(100.0)
Severe Rash	49	(17.6)	5	(14.7)	6	(10.2)
Moderate Rash	104	(37.3)	14	(41.2)	22	(37.3)
Mild Rash	124	(44.4)	15	(44.1)	31	(52.5)
Severity Unknown	2	(0.7)	0	(0.0)	0	(0.0)
Overall Incidence of Rash &/or Urticaria	5.0 %		4.2 %		4.5 %	
On Concomitant Medication	183	(65.6)	13	(38.2)	31	(52.5)
Discontinued treatment	62	(22.2)	14	(41.2)	6	(10.2)
Received Rx for Rash	99	(35.5)	5	(14.7)	14	(23.7)

*The data in this table include patients with treatment emergent events and those with events present at the baseline assessment.

Nearly two-thirds of patients treated with fluoxetine received concomitant medications, including, among others, penicillin, sulfonamides and quinidine; thus it was frequently difficult to determine which of the multiple drugs might be the cause of the event. Some of the cases were later rediagnosed as contact dermatitis, scabies or herpes simplex.

c. Cutaneous Adverse Events:

The primary data regarding cutaneous adverse events were from 5620 US patients who were treated with fluoxetine and were included in the sponsor's database as of July 31, 1987. In addition, 1324 patients received placebo and 803 received comparator substances (usually tricyclic agents). Of these US cases, 235 fluoxetine-treated patients (4.2%) experienced treatment emergent events subsumed under the terms rash or urticaria.

Utilizing the July 31, 1987 database, a survey was made of all cases of rash occurring among patients treated with fluoxetine, placebo, or comparator antidepressants. The results of this survey are displayed in the following table:

Cases of Rash and/ or Urticaria*

Number of Patients

	Fluoxetine		Comparator		Placebo	
		(%)		(%)		(%)
TOTAL	279	(100.0)	34	(100.0)	59	(100.0)
Severe Rash	49	(17.6)	5	(14.7)	6	(10.2)
Moderate Rash	104	(37.3)	14	(41.2)	22	(37.3)
Mild Rash	124	(44.4)	15	(44.1)	31	(52.5)
Severity Unknown	2	(0.7)	0	(0.0)	0	(0.0)
Overall Incidence of Rash &/or Urticaria	5.0 %		4.2 %		4.5 %	
On Concomitant Medication	183	(65.6)	13	(38.2)	31	(52.5)
Discontinued treatment	62	(22.2)	14	(41.2)	6	(10.2)
Received Rx for Rash	99	(35.5)	5	(14.7)	14	(23.7)

*The data in this table include patients with treatment emergent events and those with events present at the baseline assessment.

Nearly two-thirds of patients treated with fluoxetine received concomitant medications, including, among others, penicillin, sulfonamides and quinidine; thus it was frequently difficult to determine which of the multiple drugs might be the cause of the event. Some of the cases were later rediagnosed as contact dermatitis, scabies or herpes simplex.

In a minority of fluoxetine-treated cases (less than 10%), associated events were reported, including arthralgia, edema, leukocytosis, mild elevation of transaminases, fever, and proteinuria. Two cases of erythema multiforme were reported, and in four cases (including one of the former), the treating physician used the term "serum sickness". Adjunctive medications administered for the treatment of the cutaneous event included, most commonly, antihistamines, and less frequently, steroids. Most patients with rash continued fluoxetine treatment without ill effect, while others responded promptly to discontinuation and/or treatment, and no patient who experienced rash was known to have suffered lasting injury as a result of the event.

Five cases, representing significant morbidity, will be described in detail:

1. The most severe case of rash involved a 73 year old female who developed a localized eruption five weeks after starting fluoxetine. Diphenhydramine was prescribed, but treatment with fluoxetine continued for two more weeks. Just before fluoxetine was discontinued, the rash progressed to involve the entire body with target lesions typical of erythema multiforme. This was accompanied by mild elevation of SGOT. Hospitalized and treated with steroids, the patient subsequently developed peripheral edema, arthralgia, and arthritis, in addition to rash and pruritis. Her temperature reached 102°F, with white count 19,000 mm^{-3} with 28% bands and 15% eosinophils. There were accompanying elevations of SGOT, SGPT and alkaline phosphatase, between 3 and 5 times upper limit of normal, along with mild elevations of BUN and creatinine and trace proteinuria. One month after onset she suffered desquammation of her entire epidermis. By 32 days after onset, the patient was discharged from the hospital, the episode having subsided and laboratory values returning to normal. A treating allergist diagnosed the episode as a case of allergic vasculitis. One consultant suggested that the case might represent toxic epidermal necrolysis (although there was no histological confirmation). At the time of onset, the patient was also taking chloral hydrate, so it was unclear which of the two agents was responsible.

2. Carpal tunnel syndrome occurred as a consequence of rash-associated swelling in a 48 year old woman treated with fluoxetine for 23 days. Initially she developed large coalescent urticarial lesions lasting 5 days after drug discontinuation. However just as rash abated, she developed swollen hands and arthralgia of left wrist, and right elbow, knee and foot, and had difficulty walking which required use of a cane. Some adenopathy was observed

in her right axilla. The patient was treated with diphenhydramine, ACTH, ibuprofen, and cyproheptadine, but swelling and and multiple arthralgias persisted for two more weeks, at which time a rash reappeared at the neck and diminished sensation developed in her right hand. She was treated with a splint, but the diminished sensation lasted 6 weeks, along with continued localized arthralgias and rashes; however she recovered and surgery was not needed.

3. A 55 year old man developed rash, arthritis, arthralgia, a white count as high as 17,400 mm^{-3}, 3+ proteinuria, and mildly elevated alkaline phosphatase and bilirubin.

4. A 72 year old woman suffered a rash on her lower legs and calf pain, and was given a clinical diagnosis of leukocytoclastic vasculitis (without histological confirmation). A direct Coombs test was positive but all other tests were normal. She responded promptly to treatment (diphenhydramine and steroids) and fully recovered. This reaction began 10 days after the patient was started simultaneously on fluoxetine and trazodone.

5. A 37 year old woman developed rash and angioneurotic edema after three weeks on fluoxetine. After self-administering diphenhydramine, she sought treatment in an ER and received norepinephrine and methylprednisolone. Laboratory studies showed elevations of ESR and WBC count, and mild elevations of SGPT and GGT; a skin biopsy revealed a perivascular and interstitial infiltrate of neutrophils and eosinophils. Dyspnea also occurred during this episode and was treated with steroids.

d. Mania and Hypomania:

There were 39 reports of manic reaction among fluoxetine treated patients as of July 31, 1987. These reports included typical cases of mania and hypomania, as well as cases designated manic psychosis and manic reaction. Although fluoxetine was discontinued in a majority of cases symptoms resolved despite continued treatment in the remaining cases.

e. Seizure:

As of October 15, 1987, there were 16 reports of seizure among fluoxetine-treated patients (0.2%). Ten of these cases could be categorized as probable or definite, while in six other cases other diagnoses were considered, including anxiety, transient ischemic attack, migraine and vasovagal episode. At least five of these patients continued on fluoxetine, despite the diagnosis of seizure. One of the seizures was reported in a patient who overdosed (See b, Fluoxetine Overdose), while the remainder occurred at doses within the proposed therapeutic dose range.

3. Safety Data

1. Adverse effects

(All adverse experi[ences whether believed to be drug related or not are included in [the following discussion.)

A listing of the ad[verse experiences for each treatment which led to patients be[ing dropped from the study are given in Table 6 (taken directly [from the sponsor's submission). The number of patients dropped [for adverse effects were 12, 19, and 7 for Fluoxetine, Imipra[mine and placebo, respectively. The difference in inci[dence among the treatments is signi[ficant.

During the double b[lind phase, 80% of fluoxetine patients, 98% of imipramine pati[ents and 63% of placebo patients reported side effects. The most [frequent adverse experiences for fluoxetine were nausea (26%), [dry mouth (23%) and headaches (21%). The most frequent effec[ts for imipramine were dry mouth (62%), dizziness (29%), co[nstipation (26%), drowsiness (22%), nervousness (19%) a[nd headaches and nausea (17%) and for placebo, headaches [(13%) and nervousness (17%). No unexpected or serious effects [were noted in the study.

2. Vital Signs

Fluoxetine tended t[o produce a decrease in pulse rate and systolic blood pres[sure whereas imipramine produced a decrease in pulse rate with [increase in systolic blood pressure. There were approxim[ately equal numbers of increases and decreases in diasto[lic blood pressure for both fluoxetine and imipramine. No co[nsistent trends were noted with [illegible] and weight.

Table 13
Weekly Comparison Between Fluoxetine and Imipramine
Based on Evaluable Patients Only
(Protocol #20: Bremner)

Week	Treatment	HAMD Total	HAMD Retardation	Raskin Depression	Severity of Depression	Global Improvement
1	Fluoxetine (16)#	11.0*	2.4	0.9	0.9	1.1
	Imipramine (19)	10.9	2.1	0.7	0.9	1.4
2	Fluoxetine (16)	18.8	4.4	1.7	1.5	1.9
	Imipramine (19)	16.7	4.1	1.4	1.6	2.1
3	Fluoxetine (15)	24.3	5.5	2.4	2.3	2.5
	Imipramine (18)	22.0	5.3	2.2	2.2	2.4
4	Fluoxetine (15)	25.2	6.4	2.6	2.7	2.5
	Imipramine (16)	25.4	6.2	2.6	2.8	2.8
5	Fluoxetine (16)	31.1	7.6	3.3	3.8	2.9
	Imipramine (17)	24.4	6.5	2.6	2.8	2.6
	Two-sided p-value	0.01+	0.07	<0.01	0.01	0.15

These are sample sizes for HAMD Total. Sample sizes may vary slightly for other efficacy measures.

* Mean difference between 1th week and baseline

+ p-values for comparisons at week 5. All comparisons at weeks 1-4 were not statistically significant ($p>0.20$)

Table 14
A Listing of HAMD Total Scores at Baseline
Weeks 4 and 5 for Fluoxetine and Imipramine Patients
(Protocol #20: Bremner)

Fluoxetine				Imipramine			
Patient No.	Baseline	Week 4	Week 5	Patient No.	Baseline	Week 4	Week 5
61	40	-	7	63+	46	19	13
62*	35	17	4	64+*	36	--	--
66	30	4	2	65+	45	7	11
67+	41	14	3	68	35	11	10
69+*	40	--	-	70+	41	20	19
71	31	4	4	72+	38	12	12
75	32	25	13	73+	40	13	19
76+	44	23	20	74	33	4	10
78*	36	--	--	77+	36	31	35
79	39	15	5	80	30	10	12
81	34	14	8	83+	35	11	16
82	34	17	10	84	36	6	11
87+	40	8	8	85	42	9	11
88	41	3	2	86	42	23	11
89	38	16	5	90*	30	--	--
92	39	7	0	91*	39	--	--
93+	37	12	0	95+	39	13	11
94+*	39	--	-	96+	40	--	20
98+	34	2	0	97	40	6	2
99+	33	5	3	100+	35	12	16
Average #	36.7	11.3	5.6	Average	38.4	12.9	14.1

+ Patients with a secondary diagnosis of psychosis
* Nonevaluable patients
# Average based on evaluable patients only.