

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-235

MEDICAL REVIEW



NDA 21-235

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated March 13, received March 14, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prozac Weekly (fluoxetine HCl) Delayed-Release 90 mg Capsules.

We acknowledge receipt of your submissions dated March 24, March 28, April 13, May 1, May 12, May 13, May 18, May 22, May 26, June 16, July 3, July 5, July 11, July 19, August 3, August 4, August 25, August 30, September 6, September 22, October 11, October 12 (2), and October 13, 2000.

We have completed the review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following information and respond to the following issues.

CLINICAL

Labeling

Accompanying this letter (Attachment) is the Agency's proposal for the labeling of Prozac Weekly. We note that the Prozac Weekly formulation will share the same labeling as that of the immediate release fluoxetine products. Therefore, we have used, as our base labeling, the most recently approved fluoxetine labeling (approved in an Agency letter dated November 28, 2000). Double underline font denotes additions to the labeling, and strikeout font denotes deletions to the labeling. Brackets [] embedded within the text that follows include comments and explanations concerning our proposed labeling. The Agency's revisions are based on the labeling changes proposed in your March 14, 2000 submission and your September 29, 2000 submission providing for a revised tradename. For some sections, few changes were proposed, while others required extensive modification.

Container Packaging

We note your agreement in a telephone call between Mr. Paul David, of this Agency, and Dr. Reed Tarwater, of your firm, in a telephone conversation dated November 17, 2000, to only market the 4 and 12 quantity blister packages. Our major safety concern with this proposed name and formulation is the possibility that a practitioner will dispense 90 mg of the immediate release Prozac for a weekly dose (10 mg - 9 capsules every week or a combination of the 20 mg and 10 mg). The clinical consequences of this error would most likely not result in any serious outcomes, but would result in the patient receiving the wrong product that was intended. With this in mind, we are restricting the packaging of this product to a unit-of-use "blister" packages (e.g., 4's and 12's) with adequate instructions to the patient that this is a once-a-week dosage. This packaging configuration will also lessen the possibility of patients taking the 90 mg capsule on a daily basis. Having package sizes in containers of 4's, 12's

_____ for this formulation may not result in the safest use of the product.

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Based on the individual dissolution data for the batches used in the pivotal bioequivalence study, we request that you adopt a dissolution specification of $Q = \text{---}$ in 45 minutes.

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

Attachment

/s/

Russell Katz
2/26/01 09:40:08 AM

APPEARS THIS WAY
ON ORIGINAL

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-235

SPONSOR: LILLY

DRUG: PROZAC WEEKLY 90 MG (Delayed Release 90 mg Fluoxetine HCl capsules)

MATERIAL SUBMITTED: RESPONSE TO APPROVABLE LETTER

DATE SUBMITTED:

DATE RECEIVED:

Please refer to the agency's approvable letter for this drug product, issued 1/8/01. The sponsor's response does not include any new clinical data, but does include some proposed modifications to the agency's labeling. Lilly submitted (by email on 1/31/01) a second version of labeling incorporating the changes mutually agreed to by Division staff and Lilly. I will summarize the labeling changes at issue below.

1. Incidence of diarrhea (Adverse Reactions section). Lilly pointed out that the correct incidence of diarrhea in the clinical study for fluoxetine 20 mg daily patients was 5%, rather than ~~10%~~. I believe this was a typographical error in our approvable letter labeling. The sentence in question will now read, "In a placebo-controlled clinical trial, more patients taking Prozac Weekly reported diarrhea than patients taking placebo (10% vs. 3%, respectively) or taking Prozac 20 mg daily (10% vs. 5%, respectively)."
2. In the Clinical Pharmacology/Weekly Dosing section, the C_{min} for norfluoxetine will now be included in addition to the C_{min} for fluoxetine. The sentence will now read, "Average trough concentrations are 76% lower for fluoxetine and 47% lower for norfluoxetine than the concentrations maintained by 20 mg once-daily dosing." This additional information seems worth including to me, and Dr. Sekar of HFD-860 also find this acceptable (please see her review dated 1/31/01).
3. Lilly proposes substituting "transition the next day" for "~~the next day~~" in the second and sixth lines of the second paragraph under Clinical Pharmacology/Weekly Dosing. The sentences in question will now read: " C_{max} for fluoxetine following the 90 mg dose was approximately 1.7 fold higher than the C_{max} value for the established 20 mg once-daily regimen *following transition the next day* to the once-weekly regimen...Also, there was a transient increase in the average steady-state concentrations of fluoxetine observed *following transition the next day* to the once-weekly regimen." I agree with these proposed changes.
4. In the Dosage and Administration/Weekly Dosing section Lilly proposes deleting the portion of the second paragraph that repeats language from the Clinical Pharmacology/Weekly Dosing section. The paragraph will now read: "Weekly dosing with Prozac Weekly capsule is recommended to be initiated 7 days after the last dose of Prozac 20 mg (see CLINICAL PHARMACOLOGY)." I agree with this change.
5. Other issues: Lilly has agreed to unit-of-use blister packages to discourage confusion with daily fluoxetine dosage forms. Lilly has also agreed to the dissolution specification of $Q =$ ~~10~~ in 45 minutes stipulated in the approvable letter.

In conclusion, this is an adequate response to the approvable letter, from a clinical standpoint.

Andrew Mosholder, M.D.

Medical Officer, HFD-120

CC: Laughren, David, Mosholder

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/s/

Andy Mosholder
2/2/01 04:47:38 PM
MEDICAL OFFICER

Thomas Laughren
2/3/01 11:39:38 AM
MEDICAL OFFICER
I agree that this NDA can now be approved.--TPL

APPEARS THIS WAY
ON ORIGINAL

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA 21-235

Sponsor: Eli Lilly and Company

Clock Date: March 13, 2000

User Fee Due Date: January 14, 2001

Drug Name

Generic Name: Fluoxetine HCl _____

Trade Name: Prozac _____

Drug Categorization

Pharmacological Class: Selective Serotonin Reuptake Inhibitor

Proposed Indication: Weekly Treatment of Depression

Dosage Forms: 90 mg capsules

Route: oral

Reviewer Information:

Clinical Reviewer: Kathy J. Smith, M.D.

Completion Date: November 9, 2000

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ON ORIGINAL

TABLE OF CONTENTS FOR CLINICAL REVIEW OF NDA 21-235

1.0 Material Used in Review

2.0 Background

2.1 Indication

2.2 Administrative History

2.3 Proposed Labeling

2.4 Foreign Marketing

3.0 Chemistry

4.0 Animal Pharmacology

5.0 Clinical Data Sources

6.0 Human Pharmacokinetics

6.1 Overview of Clinical Pharmacology Studies

6.2 Summary of Clinical Pharmacology Studies

6.2.1 Study B1Y-LC-HCIX

6.2.2 Study B1Y-LC-HCJO

6.3 Conclusions Regarding Human Pharmacokinetics

7.0 Efficacy Findings

7.1 Summary of Study Pertinent to Efficacy

7.1.1 Study B1Y-MC-HCIZ

7.2 Conclusions Regarding Efficacy

7.3 Additional Study in Labeling

7.3.1 Adherence Study B1Y-MC-HCJR

8.0 Integrated Review of Safety

8.1 Methods and Findings for Safety Review

8.1.1 Deaths

8.1.2 Serious Adverse Events

8.1.3 Dropouts and Other Serious Adverse Events

8.1.4 Other Search Strategies

8.1.5 Common Adverse Events

8.1.6 Laboratory Findings

8.1.7 Vital Signs

8.1.8 Electrocardiograms

8.1.9 Special Studies

8.1.10 Human Reproduction Studies

8.1.11 Overdose Experience

8.2 Adequacy of Patient Exposures and Safety Assessments

8.2.1 Adequacy of Clinical Exposure

8.2.2 Assessment of Quality and Completeness of Data

8.3 Summary of Adverse Event Findings

9.0 Special Populations

9.1 Pediatric Population

10.0 Labeling Review Recommendations

11.0 Conclusions

12.0 Recommendations

Appendices

1.0 Material Used in Review

1.1 Materials from NDA/IND

The studies in this NDA application were conducted under IND 53,079. IND 53,079 was submitted on April 10, 1997 for fluoxetine hydrochloride weekly dosing. NDA 21-235 was submitted on March 15, 2000. The complete chemistry, manufacturing and controls section of NDA 21-235 was submitted on February 15, 2000 for early review. The submission was a paper copy except for two items, the case report tabulations and the case report forms were submitted in the electronic format. The original fluoxetine hydrochloride IND and NDA were IND 12,274 and NDA 18-936 for treatment of depression, respectively.

1.2 Related reviews and consultations for the NDA.

The following reviews were completed for NDA 21-235:

Dr. Barry Rosloff completed the Pharmacology and Toxicology review.

Dr. Vanitha Sekar completed the Pharmacokinetics and Metabolic review.

Dr. Gurpreet Gill-Sangha completed the Chemistry Manufacturing and Control review.

Dr. Ohidul Siddiqui completed the Statistical review.

A consultation was obtained from the Office of Post-Marketing Drug Risk Assessment to review the proposed proprietary name "Prozac" to determine the potential for confusion with approved and pending proprietary and generic names.

2.0 Background

2.1 Indication

Fluoxetine hydrochloride 90 mg was developed as a new dosage formulation to be given weekly. It was developed for less frequent administration and clinically tested in patients who demonstrated an adequate response to 20 mg daily fluoxetine. The 90 mg formulation consists of enteric-coated pellets in a capsule. The enteric-coating delays absorption by 1 to 2 hours until the pellets reach the segment of the gastrointestinal tract with a pH of 5.5 where the drug substance is released.

2.2 Administrative History

IND 53,079 was submitted on April 10, 1997.

During a meeting on July 24, 1997, the Agency and Lilly agreed that only a single study would be needed to distinguish the weekly enteric-coated 90 mg formulation from placebo and to demonstrate non-inferiority of the weekly enteric-coated 90 mg formulation compared to 20 mg daily of Prozac. A delta of 15% was accepted as the threshold for testing non-inferiority.

The pre-NDA meeting was held on October 4, 1999. Lilly presented the results of the pivotal trial HCIZ. The primary outcome measure, the relapse rate at 16 weeks for WEEKLY-90, had a p value of 0.093. In addition, the 20 mg daily Prozac was superior on the test for non-inferiority. Non-inferiority was tested at week 16, using a difference of 15%.

The agency said they would file the NDA application but Lilly had to make an argument for

why HCIZ should be considered to have demonstrated efficacy given that it failed on its primary outcome and on the test for non-inferiority compared to 20 mg daily. On April 14, 1999, the Agency and the sponsor met to discuss the use of the enteric-coated ~~_____~~, in humans.

2.3 Proposed Labeling

The sponsors proposed additions to labeling are in italics and deletions are in strikeout.

[Redacted content]

CLINICAL PHARMACOLOGY

[Redacted content]

DOSAGE AND ADMINISTRATION

Weekly Dosing—Systematic evaluation of Prozac _____ has shown that its anti-depressant efficacy is maintained for periods up to 25 weeks with once-weekly dosing following 13 weeks of open-label treatment with Prozac 20 mg once-daily _____

Weekly dosing with Prozac _____ capsule is recommended to be initiated _____ 7 days after the last daily dose of Prozac 20 mg. _____

2.4 Foreign Marketing

The enteric-coated 90 mg formulation of fluoxetine has not been marketed outside the US.

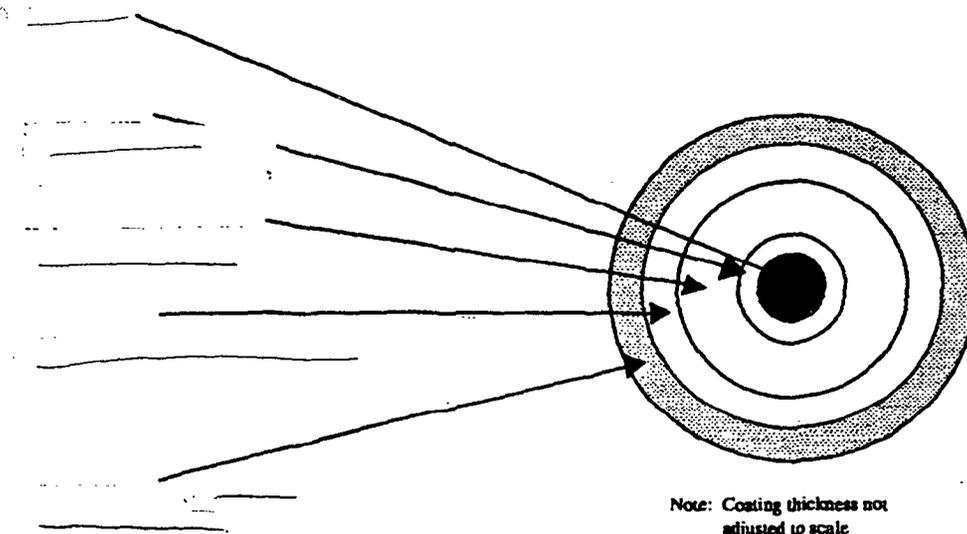
3.0 Chemistry, Manufacturing and Controls

Prozac _____ is classified as a _____ formulation. The enteric coating prevents release of the fluoxetine in an acidic environment with a pH less than 5.5 by virtue of the pH dissolution dependent _____ coating. _____

Because the enteric-coating of the small pellets containing fluoxetine only begins to dissolve at pH values above 5.5, preventing release of fluoxetine in the acidic environment of the stomach is prevented.

As a cellulose _____ this excipient is not expected to be absorbed in humans, thus having no systemic adverse events. _____ has been approved for use in Germany and Japan. The sponsor's diagram below illustrates the composition of the individual pellets.

Diagram of the Enteric-Coated Pellets



The 90 mg enteric-coated pellet formulation will be distinguishable from the immediate release capsules. The new formulation is a larger capsule. One-half of the cap has a clear body with visible pellets. The second half is an opaque green cap. It is possible to distinguish visually between the green cap of the new formulation and the marketed formulations.

4.0 Animal Pharmacology and Toxicology

The animal pharmacology and toxicology studies conducted for fluoxetine hydrochloride are contained in NDA 18-936.

The sponsor submitted two animal studies, one to demonstrate that the 90 mg enteric-coated formulation was bioequivalent to the 90 mg immediate release formulation and the second, to demonstrate that the excipient _____ was not absorbed into the systemic circulation.

The sponsor submitted a history of pharmacology and toxicology studies conducted with _____, the excipient used in this formulation. Please refer to the pharmacology/toxicology review by Dr. Barry Rosloff for the evaluation of this portion of the sponsor's submission.

The sponsor's bioequivalence study was a cross over design in six beagle dogs comparing the 90 mg immediate release formulation of fluoxetine to the 90 mg enteric-coated formulation. Plasma pharmacokinetic parameters of fluoxetine and norfluoxetine were compared after an oral 90 mg dose was administered with both the immediate release and the enteric-coated formulation. Six weeks were allowed between treatments.

The results demonstrated that there were no appreciable differences in the mean pharmacokinetic parameters of fluoxetine and norfluoxetine when dosed with either formulation. The 90 mg immediate release formulation and the 90 mg enteric-coated pellet formulation had comparable bioavailability in dogs.

The elimination profile of [¹⁴C] _____ in male Fischer 344 rats was studied to determine if _____ or its radio-labeled metabolites were absorbed into the systemic circulation after oral administration. In one study with the rats, 92.78% of a single 1000 mg/kg oral dose of [¹⁴C] _____ was eliminated in the feces in 48 hours, increasing to 93.17% by 96 hours. Urine contained 0.23% of the dose.

In a second study, in bile duct cannulated rats, the percentage of the dose eliminated in the bile was 0.03%. Plasma samples collected up to 8 hours after the [¹⁴C] _____ dose contained <0.003% of the dose in any sample. The predominant recovery of radioactivity in the feces and lack of radioactivity in the bile and plasma indicates that _____ was not absorbed when administered orally to rats.

5.0 Clinical Data Sources

The clinical data for the 90 mg enteric-coated formulation includes four studies: two pharmacokinetic studies, B1Y-LC-HCIX and B1Y-LC-HCJO, in healthy volunteers and two studies in patients with Major Depressive Disorder, one efficacy trial, B1Y-MC-HCIZ, and study B1Y-MC-HCJR which measured patient adherence.

292 subjects were exposed to WEEKLY-90. There have been 71 patient-years (3688 patient-weeks) of exposure to the 90 mg enteric-coated formulation given once weekly and 26 patient-years (1358 patient-weeks) of exposure to the 90 mg enteric-coated formulation given twice-weekly. Only patients in the optional rescue therapy phase of study B1Y-MC-HCIZ received the 90 mg enteric-coated formulation twice-weekly. The exposure to the 90 mg enteric-coated formulation was during the continuation treatment phase of the double blind study B1Y-MC-HCIZ and during the continuation treatment phase of the open-label study B1Y-MC-HCJR.

122 patients were exposed to placebo; patients received placebo only in the continuation treatment phase of the double-blind study B1Y-MC-HCIZ. During the continuation treatment phase of the double-blind study B1Y-MC-HCIZ, 189 patients were exposed to fluoxetine 20 mg daily and during the continuation treatment phase of the open-label study B1Y-MC-HCJR, 53 patients were exposed to fluoxetine 20 mg daily.

Study B1Y-MC-HCKN, begun in July 2000, is the only on-going study with the 90 mg enteric-coated formulation. This study is designed to assess the safety of switching patients from an SSRI (citalopram, paroxetine, or sertraline) to once-weekly fluoxetine 90 mg. No data is available from this study at this time.

Table of all studies

| | |
|-------------|--|
| B1Y-LC-HCIX | Single oral dose, open-label, randomized, two-period, crossover design to assess the bioavailability of the 90 mg enteric-coated formulation compared to immediate release fluoxetine and to assess the effect of food on the bioavailability of the enteric-coated formulation. N=24 healthy adults |
| B1Y-LC-HCJO | Multiple dose, randomized, open-label study to characterize the steady-state pharmacokinetic profile of the |

| | |
|-------------|---|
| | enteric-coated 90 mg formulation given once a week and to assess the safety and pharmacokinetics of the period of transition between the 20 mg once daily regimen and the 90 mg once weekly dosage regimen. N=25 healthy adults |
| B1Y-LC-HCIZ | Multi-center study designed to measure the efficacy of the 90 mg enteric-coated formulation for the continuation treatment of Major Depressive Disorder. After a remission of depression, on 20 mg fluoxetine, patients were randomized to double-blind, 25-week, continuation treatment with the 90 mg enteric-coated formulation once weekly, 20 mg fluoxetine daily, or placebo. N=501 adult outpatients randomized in the continuation treatment phase. |
| B1Y-MC-HCJR | Multi-center, open-label, randomized, parallel group study in patients with major depressive disorder designed to measure adherence to treatment. After remission in depression on 20 mg fluoxetine daily, patients went on to randomization to the 90 mg enteric-coated formulation once weekly or 20 mg fluoxetine daily in Study Period II, the 12-week continuation treatment phase. Adherence to treatment was measured by electronic monitoring in a bottle that recorded each time the cap was removed and replaced. N=109 adult patients |

Summary of Patient Demography for Clinical Trials

Baseline patient characteristics for the clinical trials with patients with Major Depressive Disorder- B1Y-MC-HCIZ and B1Y-MC-HCJR are summarized in the table below. Clinical trial subjects were predominantly female and Caucasian.

| Variable | WEEKLY-90 N=246 | Placebo N=122 | DAILY-20 N=242 |
|----------------------|--------------------|------------------|-------------------|
| Ethnicity- Caucasian | 230 (93.5%) | 111 (91%) | 217 (89.7%) |
| Hispanic | 8 (3.3%) | 1 (0.8%) | 8 (3.3%) |
| African-American | 5 (2.0%) | 6 (4.9%) | 14 (5.8%) |
| Asian | 3 (1.2%) | 2 (1.6%) | 3 (1.2%) |
| Other | 0 | 2 (1.6%) | 0 |
| Gender- Male | 70 (28.5%) | 44 (36.1%) | 65 (26.9%) |
| Female | 176 (71.5%) | 78 (63.9%) | 177 (73.1%) |
| Age- Mean | 42.281 | 41.952 | 42.533 |
| Median | 41.755 | 41.696 | 42.945 |
| Range | 19- 77 | 20- 75 | 19- 70 |

Baseline subject characteristics for the healthy volunteers in the pharmacokinetic trials, B1Y-LC-HCIX and B1Y-LC-HCJO are given in the table below.

| Variable | 90 mg enteric-coated formulation N=73 |
|----------------------|---|
| Ethnicity- Caucasian | 67 |
| Hispanic | 2 |
| African-American | 3 |
| Asian | 1 |
| Gender- Male | 28 |

| | |
|-----------|--------|
| Female | 45 |
| Age- Mean | 37.33 |
| Median | 31.17 |
| Range | 19- 72 |

6.0 Human Pharmacokinetics

6.1 Overview of Clinical Pharmacology Studies

The two clinical pharmacology studies, B1Y-LC-HCIX and B1Y-LC-HCJO, were conducted to assess the safety, pharmacokinetics, bioavailability and bioequivalence of the 90 mg enteric-coated pellet formulation of fluoxetine.

6.2 Summary of Clinical Pharmacology Studies

6.2.1 Study B1Y-LC-HCIX

Investigator and Location

This was a single-center US study; the investigator was _____ at _____

Objective

The bioavailability, safety, and tolerability of a single dose of the 90 mg enteric-coated formulation of fluoxetine were compared to a single dose of the marketed immediate-release formulation (one 10 mg and four 20 mg capsules). In part 2, the effect of food on the oral bioavailability of the enteric-coated pellet formulation was assessed.

Study Population

Subjects were 48 healthy men and women, ages 19 to 75.

Design

This study had a single-dose, open-label, randomized, two-period, crossover design. The In part 1, the two treatment sequences were the 90 mg enteric-coated pellet formulation and 90 mg of the immediate release fluoxetine (one 10 mg and four 20 mg capsules) with a washout period between. In part 2, each subject was randomized to a treatment sequence with the 90 mg enteric-coated formulation after an eight-hour fast and after a high-fat breakfast.

Results

Patient Disposition

48 subjects were enrolled 24 in group 1 and 24 group 2.

Pharmacokinetic Analysis

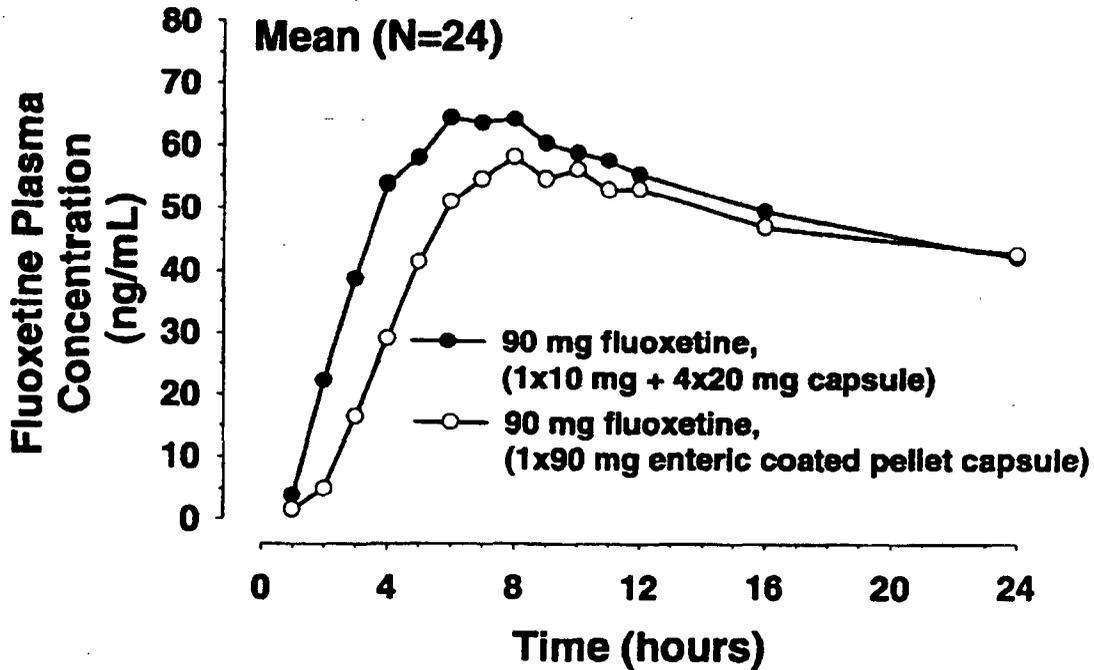
Plasma concentration data for fluoxetine and its metabolite norfluoxetine were analyzed for maximum plasma concentration (C_{max}) and the corresponding time of maximum concentration (T_{max}). The time from the administration of the dose until the first plasma sample that had a measurable concentration of fluoxetine is the estimated lag time for the onset of absorption

Results

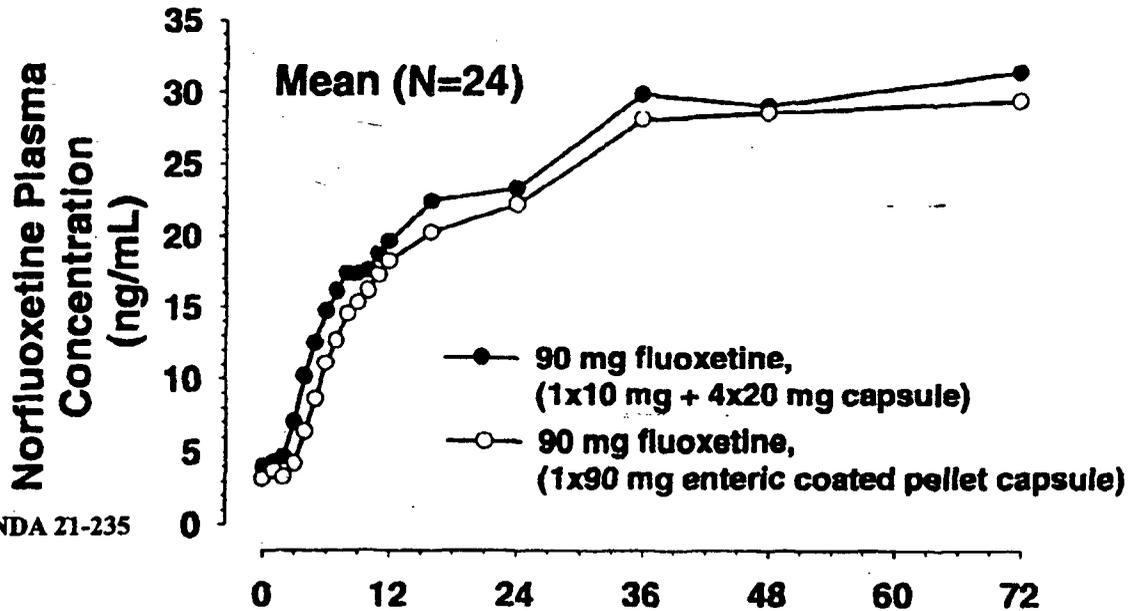
The single dose C_{max} and the AUC were equivalent between the 90 mg enteric-coated pellet formulation and the marketed immediate release capsules of fluoxetine (total dose of 90 mg). However, the T_{max} was delayed by 1 to 2 hours suggesting a 1 to 2 hour delay in absorption.

The sponsor's figures below compare fluoxetine and norfluoxetine plasma levels in the enteric-coated formulation to the immediate release formulation.

Bioequivalence of the 90 mg Enteric-Coated Formulation vs. Immediate Release Capsules



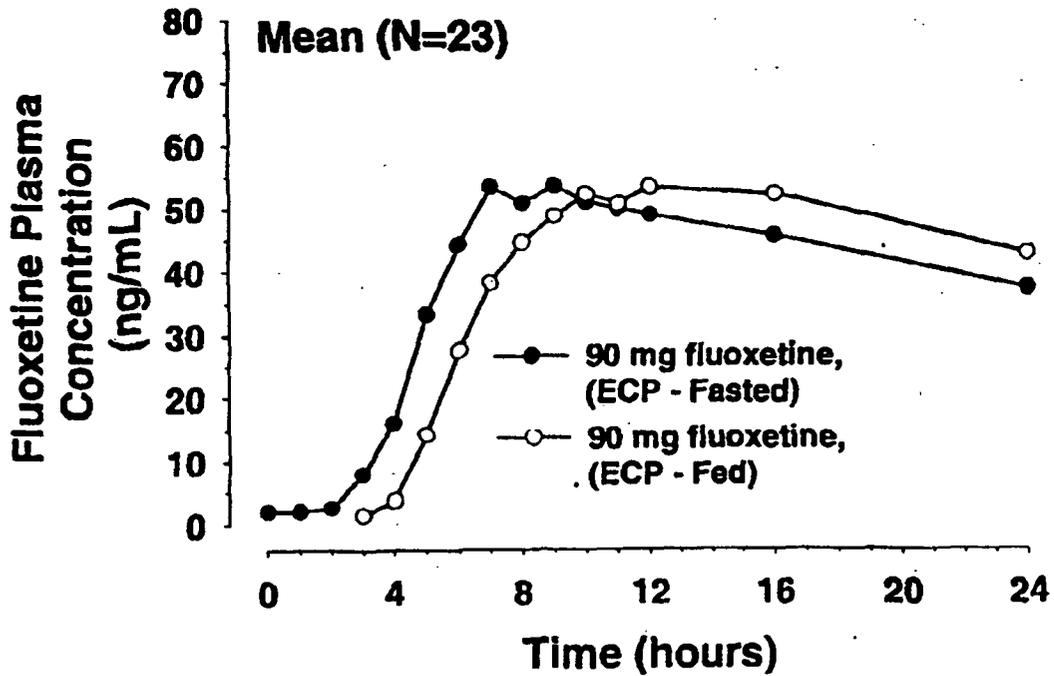
Bioequivalence of the 90 mg Enteric-Coated Formulation vs. Immediate Release Capsules



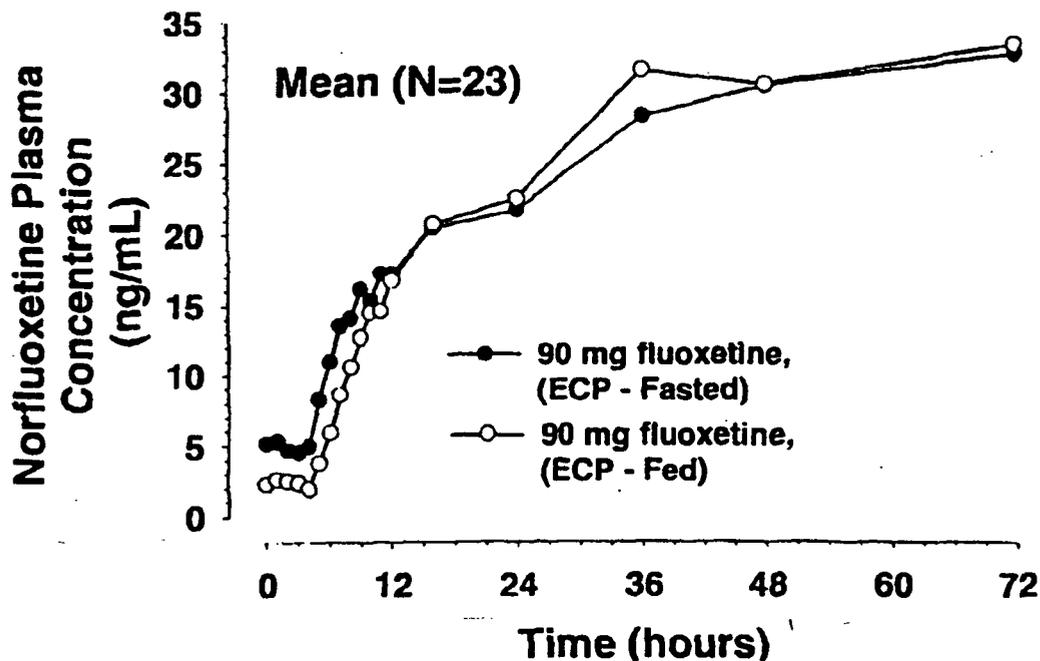
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In part 2, food delayed the onset of absorption of the enteric-coated formulation an additional 1 to 2 hours, but C_{max} and AUC were equivalent in the fed and fasting states. The sponsor's figure below compares fluoxetine and norfluoxetine levels after an 8 hour fast and after a high fat breakfast.

**Bioequivalence of the 90 mg Enteric-Coated Formulation
Under Fed vs. Fasting States**



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**Bioequivalence of the 90 mg Enteric-Coated Formulation
Under Fed vs. Fasting States**

Conclusions

The enteric-coated pellet formulation of fluoxetine is equivalent to the immediate release fluoxetine capsules in the rate and the extent of absorption. The enteric-coating delays the onset of absorption until the pellets reach a segment of the gastrointestinal tract where the pH exceeds 5.5, delaying the absorption 1 to 2 hours. Food delays the onset of absorption of the enteric-coated formulation an additional 1 to 2 hours. The total effect is a delay in absorption of 3 to 4 hours. With once a week dosing, this delay in the onset of absorption would not have a clinical effect. The enteric-coated formulation can be administered with or without food.

6.2.2 Study B1Y-LC-HCJO

Investigator and Location

This was a single-center US study; the investigator was _____ at _____

Objective

This study characterized the steady-state pharmacokinetic profile of the enteric-coated 90 mg formulation given once a week compared to the 20 mg capsule given once daily. The study also assessed the safety and pharmacokinetics of the period of transition between the 20 mg once daily regimen and the 90 mg once weekly dosage regimen. The impact of the _____ was assessed in 3 participants who were classified as poor metabolizers.

Study Population

25 healthy male and female adults, ages 19 to 80.

Design

This study had a multiple dose, gender stratified, randomized, open-label design. In phase 1, fluoxetine 60 mg was given daily for 7 days to approach steady state more quickly. In phase 2, 20 mg of fluoxetine was given daily for 14 days to establish steady state. In phase 3, the subjects were randomized to two groups, either switching to the 90 mg enteric-coated formulation the day following the last 20 mg daily dose or switching to 90 mg seven days after the last daily 20 mg dose.

Pharmacokinetic Assessment

The steady-state pharmacokinetic profile of the enteric-coated 90 mg formulation vs. 20 mg given once daily was measured. The pharmacokinetic profile was measured during the transition from 20 mg daily to the 90 mg dose given one day vs. given 7 days after the last 20 mg dose.

Safety Assessment

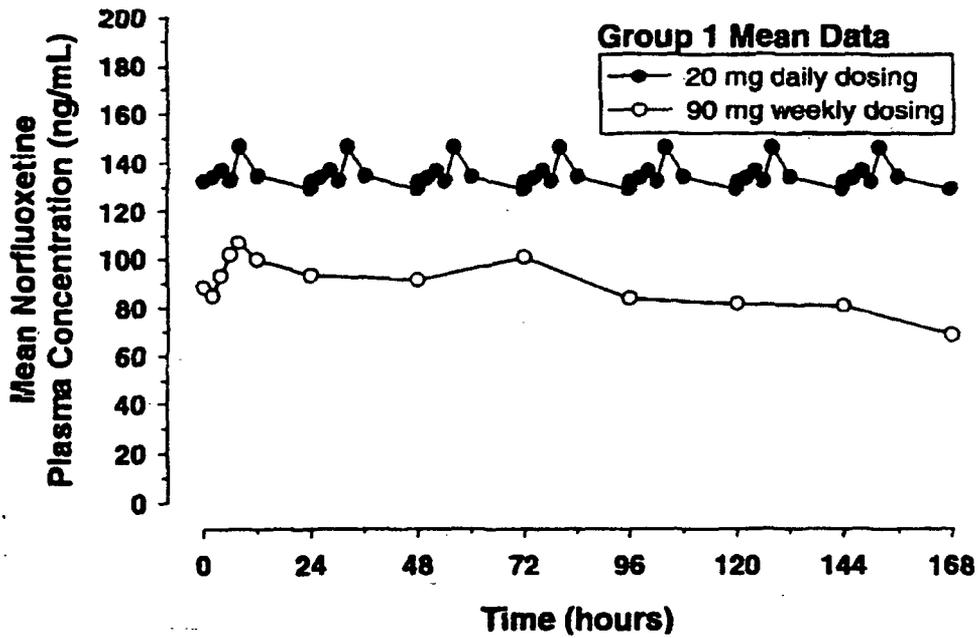
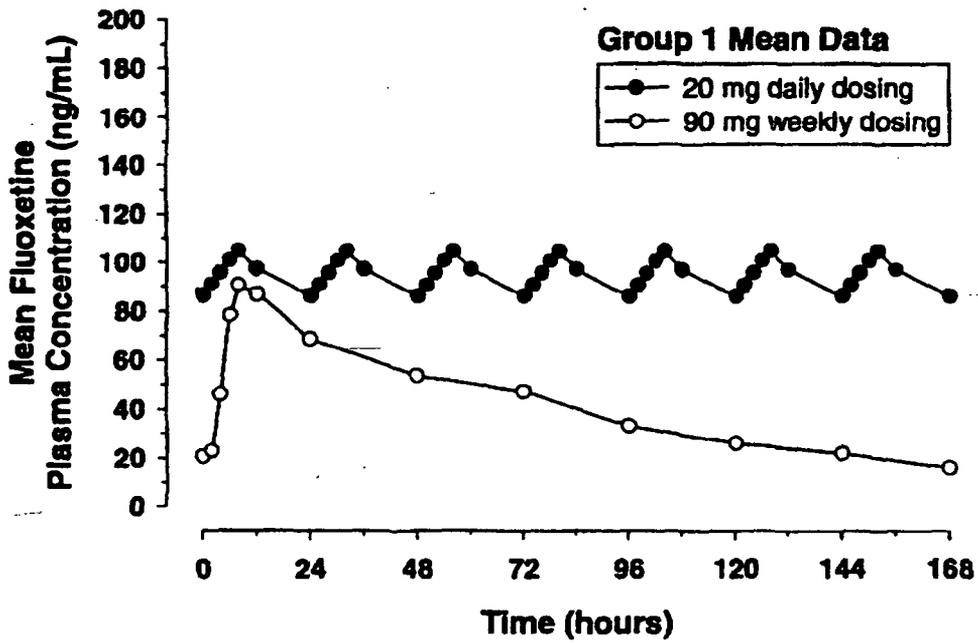
Vital signs were monitored prior to drug administration, prior to release from the inpatient unit (24 hours after drug administration), and at study completion. A 12 lead ECG was performed at the completion of the study. Clinical Laboratory testing was performed at screening, study day 19, and at the end of the study.

Results**Patient Disposition**

Of the initial 25 subjects, 22 completed phase 1 and 2 and entered phase 3 treatment with enteric-coated 90 mg fluoxetine given once weekly for 6 doses. Nineteen of the 25 subjects who entered the study completed the trial.

Results

This study provided a steady-state evaluation of the pharmacokinetic characteristics of weekly dosing versus daily dosing in healthy subjects. The 90 mg weekly dose maintains a lower average steady-state concentration. Average steady-state concentrations for daily and weekly dosing were in relative proportion to the total weekly dose given. The 90 mg weekly dose of fluoxetine had steady-state plasma concentrations of fluoxetine and norfluoxetine that were approximately 46% and 62% of the steady-state concentrations of daily 20 mg dosing, respectively. The steady-state concentrations following weekly dosing fluctuate more than those for daily dosing. The fluctuation in steady-state concentrations between peak and trough values was greater in the weekly dosing compared with the daily dosing. The figures below are copied from the sponsor's NDA submission.



**Steady-State Plasma Concentrations of Fluoxetine and Norfluoxetine
90 mg Weekly Dosing vs. 20 mg Daily Dosing**

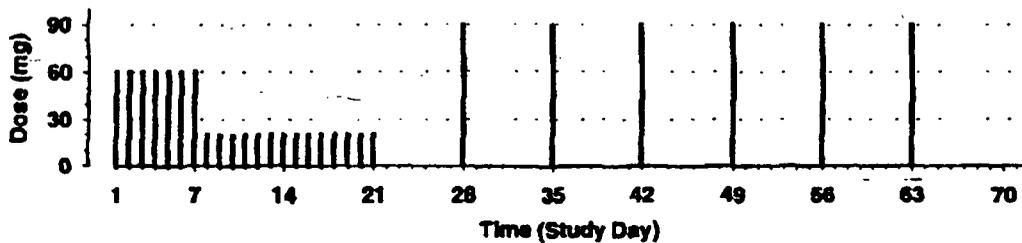
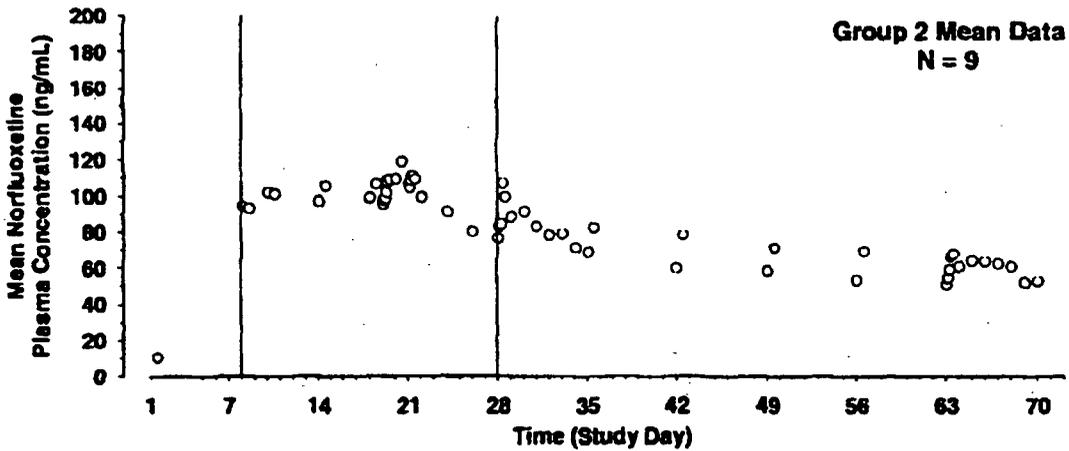
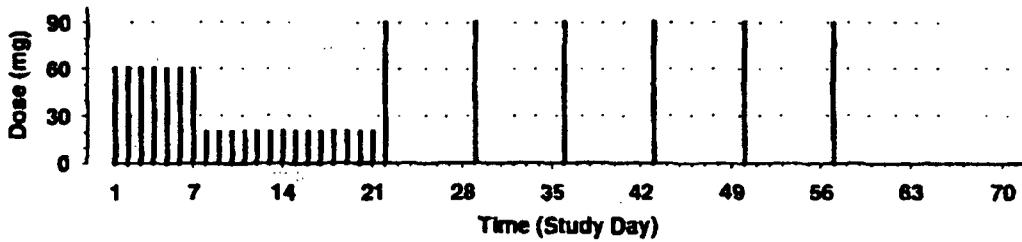
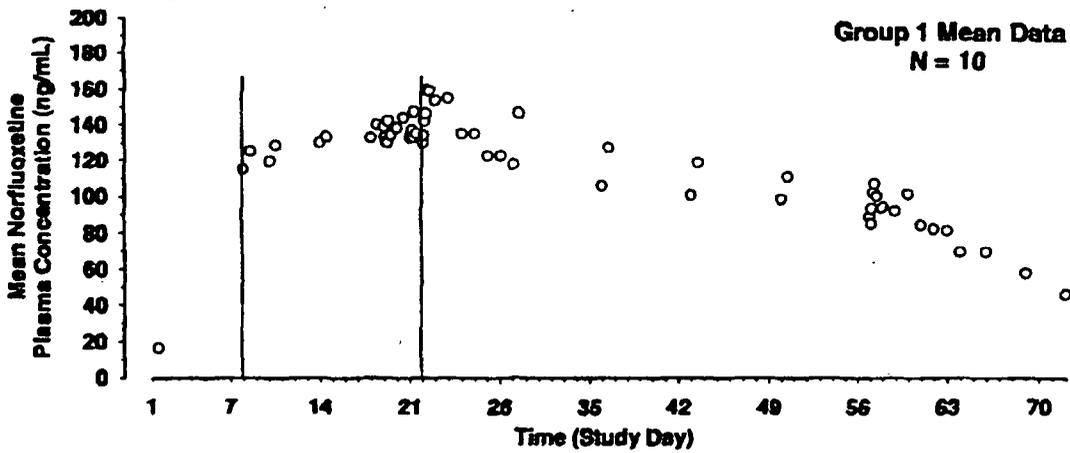
The sponsor's table below gives the mean pharmacokinetic values at steady state for fluoxetine 20 mg daily and the 90 mg enteric-coated formulation.

Table 1. Mean (range) of Pharmacokinetic Values for Steady-State Fluoxetine and Norfluoxetine Concentration Parameters After Giving Fluoxetine at a Dose of 20 mg Once Daily or 90 mg Once Weekly (Study HCJO).

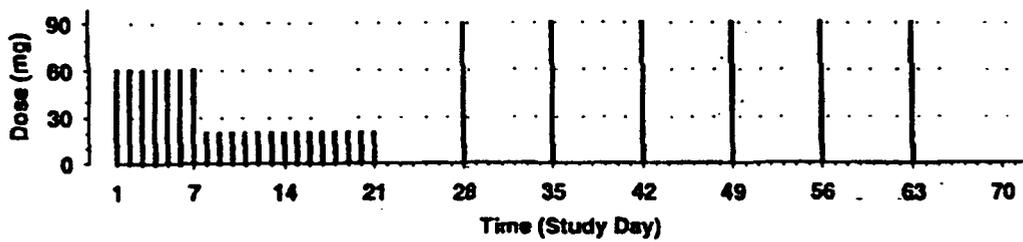
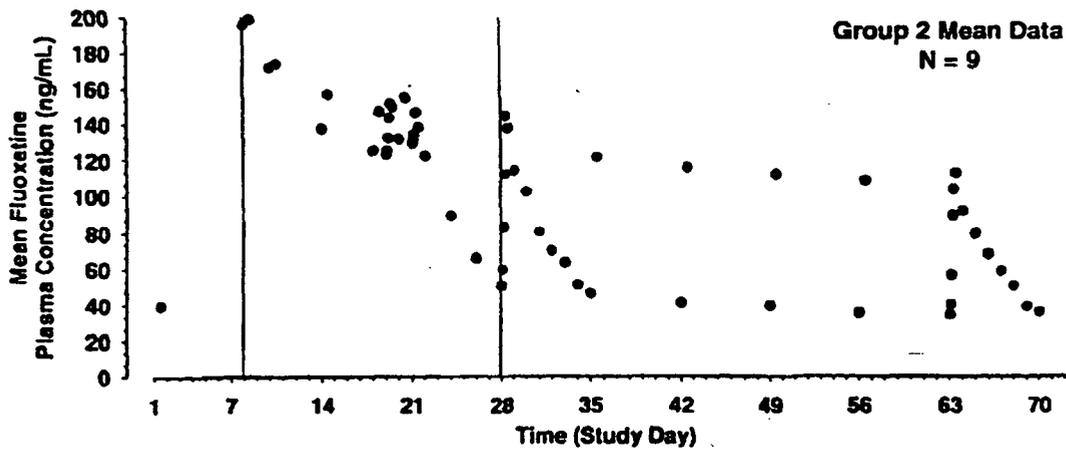
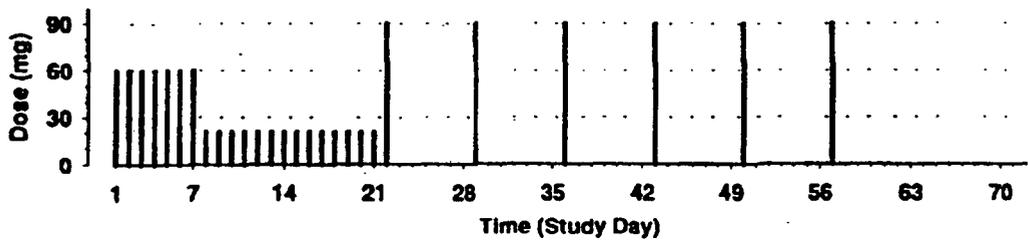
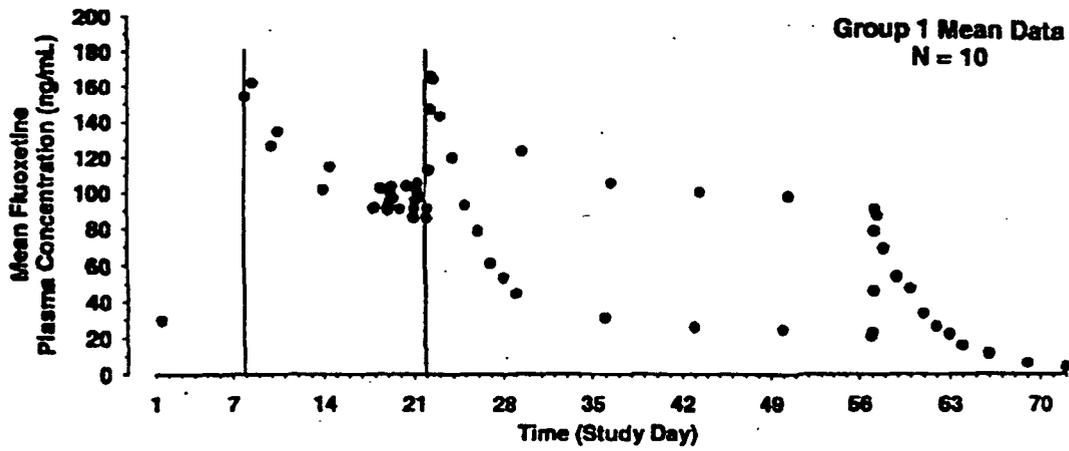
| Pharmacokinetic Parameter (N=19 Subjects) | Fluoxetine Concentrations | | | Norfluoxetine Concentrations | | |
|--|--|--------------------------------|--|--|--------------------------------|--|
| | 20 mg Once Daily Mean (range) | 90 mg Once Weekly Mean (range) | 90 mg Weekly as a Percent of 20 mg Daily | 20 mg Once Daily Mean (range) | 90 mg Once Weekly Mean (range) | 90 mg Weekly as a Percent of 20 mg Daily |
| $C_{p_{max}}^{ss}$ (ng/mL) Maximum Steady-State | 127 (52 to 238) | 103 (53 to 194) | 81% | 132 (60 to 227) | 92 (37 to 188) | 70% |
| \bar{C}_p^{ss} (ng/mL) Average Steady-State | 114 (46 to 217) | 53 (21 to 118) | 46% | 121 (56 to 214) | 75 (32 to 138) | 62% |
| $C_{p_{min}}^{ss}$ (ng/mL) Minimum Steady-State | 100 (38 to 206) | 24 (4.4 to 75) | 24% | 112 (51 to 203) | 59 (21 to 108) | 53% |
| F_{min}^{max} (%) Fluctuation | 24 (11 to 36) | 164 (91 to 236) | --- | 17 (10 to 27) | 43 (29 to 62) | --- |
| AUC_{0-168} (ng·hr/mL) 7 day Area Under the Curve | 19080 ^a (7800 to 36490) ^a | 8830 (3490 to 19740) | 46% | 20400 ^a (9420 to 35980) ^a | 12600 (5380 to 23120) | 62% |

^a AUC_{0-24} multiplied times 7.

The study also evaluated the pharmacokinetic characteristics during the transition from 20 mg daily to 90 mg weekly. The plasma concentration profiles resulting when the first weekly dose was given the next day after the last 20 mg dose (group 1) as well as the profile when the first 90 mg fluoxetine dose was given after 7 days (group 2). There is a transient overshoot in plasma concentrations initially when the subjects in group one switch to once weekly dosing. The overshoot is greater for fluoxetine than for norfluoxetine because norfluoxetine has a longer half-life. The plasma concentrations during the transition in group 2 did not exceed the maximum plasma concentration range for the once daily dosing. The transition from once daily to once weekly dosing was less abrupt and more on target when subjects had a period of 7 days between their last dose of daily fluoxetine and their first dose of 90 mg weekly. Therefore, by waiting an interval of 7 days between the last 20 mg dose and the first 90 mg weekly dose a transient overshoot in the steady-state concentrations is avoided. The sponsor's figures below plot the mean plasma concentration data for fluoxetine and norfluoxetine.



Mean Norfluoxetine Plasma Concentration Data



Mean Fluoxetine Plasma Concentration Data

The impact of the _____ was not affected by the weekly dosing regimen. From prior studies, it is known that the difference between poor metabolizers and extensive metabolizers is largest with single doses and becomes less obvious under multiple dose steady-state conditions. This is because fluoxetine and norfluoxetine are themselves inhibitors of _____

Conclusion

The 90 mg enteric-coated formulation given once a week has a different steady-state profile for fluoxetine and norfluoxetine plasma concentrations compared to the 20 mg immediate release capsule given daily. The fluctuation in plasma concentration is larger and the average steady-state concentration is lower for the weekly enteric-coated formulation compared with the 20 mg capsule given daily. Average steady-state concentrations for daily and weekly dosing were in relative proportion to the total weekly dose given. The 90 mg weekly dose of fluoxetine had steady-state plasma concentrations of fluoxetine and norfluoxetine that were approximately 46% and 62% of the steady-state concentrations of daily 20 mg dosing.

There is a transient overshoot in steady-state plasma concentrations seen when the first 90 mg weekly dose is given the day after the last 20 mg daily dose compared with waiting 7 days after the last 20 mg daily dose.

6.3 Conclusions Regarding Human Pharmacokinetics

The enteric-coated formulation was demonstrated to be bioequivalent to the immediate release fluoxetine capsules in terms of the extent of absorption. The enteric-coating delays the onset of absorption until the pellets reach a segment of the gastrointestinal tract where the pH exceeds 5.5, delaying the absorption 1 to 2 hours. Food delays the onset of absorption of the enteric-coated formulation an additional 1 to 2 hours. The total effect would be a delay in absorption of _____ hours. When dosing once weekly, this delay in the onset of absorption would not have a clinical effect. The 90 mg enteric-coated formulation given once a week has a different steady-state profile for fluoxetine and norfluoxetine plasma concentrations compared to the 20 mg immediate release capsule given daily. The fluctuation in plasma concentration is larger and the average steady state concentration is lower for the weekly enteric-coated formulation compared with the 20 mg capsule given daily.

7.0 Efficacy Findings

7.1 Study B1Y-MC-HCIZ

Investigators and Locations

This multi-center study included 43 centers and 43 primary investigators. See the appendix for a list of the primary investigators, center number, and number of patients enrolled into study B1Y-MC-HCIZ.

Objectives

This study tested the efficacy of the enteric-coated 90 mg formulation of fluoxetine hydrochloride given once weekly for the continuation treatment of depression.

Primary Objectives

The two primary objectives of this study were

1. To determine if the relapse rate of patients given fluoxetine 90 mg once weekly was lower than those given placebo after 16 weeks of continuation therapy.
2. To determine whether the 90 mg formulation given once weekly (WEEKLY-90) was non-inferior to standard treatment with 20 mg daily (DAILY-20) for the continuation treatment of depression. Non-inferiority was measured by testing whether the relapse rate of patients given WEEKLY-90 was no more than 15 percentage points higher than for patients given DAILY-20, after 16 weeks of continuation therapy.

Study Population

The protocol required screening 1027 patients in order to enter 862 patients into Study Phase I. Subjects were male or female outpatients, ages 18-80 years, with a DSM-IV diagnosis of non-psychotic Major Depressive Disorder (MDD), single episode or recurrent. The diagnosis of major depressive episode was determined by the Structured Clinical Interview for DSM-IV, Patient version (SCID-P). The duration of the current episode of depression was required to be 4 weeks or longer. Subjects had to demonstrate at least moderate depression on the 17 item Hamilton Depression Rating Scale (HAMD) (score ≥ 18) and receive a score ≥ 4 on the Clinical Global Impression (CGI) of Severity scale. Patients were excluded if the current episode of depression was non-responsive to two courses of anti-depressant treatment or if there was any past history of depression that was non-responsive to fluoxetine. Patients were excluded if they met criteria for an anxiety disorder that was the primary focus of treatment, at any point in the last 6 months. Other exclusion criteria were a history of schizophrenia, a psychotic disorder, mania, hypomania or substance abuse. Exclusion criteria also included serious cardiovascular, renal, respiratory, hepatic, hematological, endocrine or neurological disease and clinically significant laboratory abnormality.

Design

This is a multi-center study in outpatients with major depressive disorder. The study was designed with the four study periods summarized below. Study Period III, the continuation treatment phase was designed to measure the efficacy of the 90 mg enteric-coated formulation.

Study Period I The Assessment Phase (Visits 1 and 2)

Patients with depression were screened for eligibility.

Study Period II Open-Label Acute Treatment Phase (Visits 3 to 9)

In this open-label, 13-week, acute treatment phase, all patients were treated with fluoxetine 20 mg daily. If patients were unable to tolerate 20 mg daily by visit 4, they were discontinued from the study. To continue into Study Period III, a positive response to fluoxetine 20 mg needed to be demonstrated at both visits 8 and 9. Response was defined as no longer meeting the DSM-IV diagnostic criteria for a major depressive episode and receiving a score ≤ 9 on the HAMD17 and a score ≤ 2 on the CGI.

Study Period III Double Blind Continuation Treatment Phase (Visits 10 to 18)

Patients who responded to treatment with fluoxetine 20 mg daily were randomly assigned to one of three treatment groups- WEEKLY-90, DAILY-20, or placebo. During this

double blind, 25-week period of continuation treatment, patients were monitored for relapse. (See assessments for the definition of relapse.)

Optional Rescue Treatment Phase

Participation was optional in this double-blind rescue treatment phase. Patients who had relapsed had their dose escalated as follows:

1. Patients who had received WEEKLY-90 were treated with 90 mg twice per week.
2. Patients who had received DAILY-20 were treated with 40 mg daily.
3. Patients who received placebo were treated with 20 mg daily.

The sponsor's illustration of the study design can be found in the appendix.

Assessments

As noted above, the diagnosis of Major Depressive Disorder was confirmed using the Structured Clinical Interview for DSM-IV, Patient version (SCID-P) Major Depressive Episode Module.

The 28 item Hamilton Depression Rating Scale (HAMD) was administered, from which a modified 17 item HAMD (HAMD17) was used to establish eligibility, treatment response, and relapse. The sponsor chose 17 items from the 28 item HAMD. The sponsor's 17-item scale is not identical to the 17 item HAMD typically used in depression research. The sponsor defined their HAMD17 as a combination of items 1, 2, 3, 7, 8, 9, 10, 11, 13, 14, 15, and 17 for all patients; and items 4, 5, 6, 12, and 16 for patients with depression with neurovegetative signs or items 22, 23, 24, 25, and 26 for patients with depression with atypical symptoms. The higher score of these two combinations determined protocol eligibility, response and relapse. The Clinical Global Impressions of Severity (CGI-Severity) rating scale was also used to monitor treatment response and relapse.

The primary efficacy measure was time-to-relapse. Relapse was the physician's categorical determination that the patient met the symptom criteria for major depressive disorder, as determined by the Major Depressive Episode module of the SCID-P. In addition, there needed to be an increase from baseline in CGI-Severity score of at least 2. Relapse was assumed to have occurred if the patient had 6 unscheduled visits for the reemergence of symptoms along with a HAMD17 score >9 and CGI-Severity score >2. The sponsor's schedule for the administration of efficacy and safety instruments during all four periods of the study is listed in the appendix.

Analysis Plan

Study Period III, the randomized continuation treatment phase, was the study period analyzed for efficacy.

The primary analysis planned to use confidence intervals to estimate and compare the relapse rates of patients given WEEKLY-90, DAILY-20, or placebo at visit 15 (after 16 weeks of continuation treatment). The confidence intervals were to be constructed using estimates of the relapse rate and standard error for each group obtained using the Kaplan-Meier survival analysis (with time to relapse as the dependent variable). Efficacy of WEEKLY-90 compared to placebo was to be assessed using two-tailed confidence intervals for the difference in relapse rates. The non-inferiority of WEEKLY-90 compared with DAILY-20 was to be assessed using a one-tailed confidence interval for

the difference in relapse rates. The range of non-inferiority was defined as 0.15. The WEEKLY-90 relapse rate was to be no more than 15% higher than DAILY-20 at a one-tailed 95% confidence limit.

Protocol Amendments

In the original protocol there was a single primary objective as follows: "To determine if the relapse rate of patients given enteric coated fluoxetine 90 mg/week (WEEKLY-90) is lower than the relapse rate of patients given placebo (PLACEBO) after 25 weeks of continuation therapy."

Protocol amendments changed the primary objective to the following: 1.) "To determine if the relapse rate of patients given enteric coated fluoxetine 90 mg once weekly (WEEKLY-90) or fluoxetine 20/mg a day (DAILY-20) is lower than the relapse rate of patients given placebo (PLACEBO) after 16 weeks of continuation therapy" 2.) "To determine if the relapse rate of patients given (WEEKLY-90) is not appreciably higher than the relapse rate of patients given placebo (DAILY-20) after 16 weeks of continuation therapy".

The study design was modified and the study size increased to allow for testing non-inferiority of the long-term antidepressant effect of weekly dosing with 90 mg fluoxetine (enteric coated) versus daily dosing with 20 mg fluoxetine.

A 12 lead ECG was recorded if the patient was ≥ 50 years old. The optional rescue treatment for patients who relapse during Study Period III was more fully detailed. The primary analysis was changed to read as follows. "The primary analysis will use confidence intervals to estimate and compare the relapse rates after 16 weeks of continuation treatment of patients given WEEKLY-90, DAILY-20 or PLACEBO. The confidence intervals will be constructed using estimates of relapse rates and standard error for each group obtained using Kaplan-Meier survival analysis (with time to relapse as the dependent variable). Efficacy of WEEKLY-90 compared with PLACEBO and efficacy of DAILY-20 compared with PLACEBO will be assessed using $100(1-\alpha)\%$ two-tailed confidence intervals for the difference in relapse rates. The non-inferiority of WEEKLY-90 compared with DAILY-20 will be assessed using a $100(1-\alpha)\%$ two-tailed confidence intervals for the difference in relapse rates. The range of non-inferiority is defined as .15."

The protocol allowed for a planned interim analysis, which was not performed as written in the protocol. However, an interim analysis was conducted after all patients attained the primary endpoint (or had discontinued) but 38 patients had not yet completed Study Period III. No adjustment was made to α (significance level).

Results

Baseline Demography

Baseline characteristics of gender, age, and origin are summarized below for each treatment group.

Subject Demography Study Period III- Randomized Patients

| Variable | WEEKLY-90 N=190 | Placebo N=122 | DAILY-20 N=189 |
|----------|--------------------|------------------|-------------------|
| | | | |

| | | | |
|----------------------|-------------|------------|-------------|
| Ethnicity- Caucasian | 174 (91.6%) | 111 (91%) | 164 (86.8%) |
| Hispanic | 8 (4.2%) | 1 (0.8%) | 8 (4.2%) |
| African-American | 5 (2.6%) | 6 (4.9%) | 14 (7.4%) |
| Asian | 3 (1.6%) | 2 (1.6%) | 3 (1.6%) |
| Other | 0 | 2 (1.6%) | 0 |
| Gender- Male | 60 (31.6%) | 44 (36.1%) | 55(29.1%) |
| Female | 130 (68.4%) | 78 (63.9%) | 134(70.9%) |
| Age- Mean | 41 | 42 | 42 |
| Median | 41 | 42 | 42 |
| Range | 19- 73 | 20- 75 | 19- 65 |

The majority of patients in this study are Caucasian (88%) females (66%) with a mean age of 41. In Study Period III, there were no statistically significant differences in age, gender, or ethnicity among treatment groups.

Baseline Severity of Depression

At entry to Study Phase II, based on the SCID-P, 43.9% had a typical Major Depressive Disorder; 28.3% of patients had Major Depressive Disorder with atypical features; 15.2% had Major Depressive Disorder with melancholic features; 0.4% had Major Depressive Disorder with seasonal features. 72% of patients entering Study Phase III reported a previous episode of depression. There were no significant differences in the number of previous episodes of depression among treatment groups during Study Period III.

The past psychiatric history of patients at enrollment into Study Phase II included 4.6% who had a history of an anxiety disorder, 4.1% had a history of drug dependence, and 2.5% of patients had a history of a suicide attempt. The past psychiatric history was similar at the time of randomization into Study Phase III. There were no statistically significant differences between treatment groups, however, a few more patients with a history of a suicide attempt were randomly assigned to 20 mg daily and a few less to 90 mg weekly and placebo groups (p=0.062).

Patient Disposition

Of the 1186 patients who were screened in Study Period I (screening), 932 patients were enrolled in Study Period II. 502 patients responded to 20 mg fluoxetine and continued to visit 10. Of the 501 patients randomized to Study Period III, 2 patients were excluded from the primary efficacy analysis of time-to-relapse, because they had no post baseline measure. Both patients were lost to follow up prior to visit 10.

Reasons for Discontinuation Study Period III-Continuation Treatment Phase

| Reason for Discontinuation | WEEKLY-90 N=190 | PLACEBO N=122 | DAILY-20 N=189 | p-value |
|----------------------------|--------------------|------------------|-------------------|---------|
| | N (%) | N (%) | N (%) | |
| Relapse | 68 (35.8) | 57 (46.7) | 51 (30.2%) | 0.012 |
| Adverse Event | 8 (4.2) | 2 (1.6) | 4 (2.1%) | 0.313 |
| Lack of Efficacy | 3 (1.6) | 4 (3.3) | 3 (1.6%) | 0.508 |
| Lost to follow-up | 13 (6.8) | 5 (4.1) | 14 (7.4%) | 0.481 |

| | | | | |
|--------------------|----------|-----------|-----------|-------|
| Patient Decision | 17 (8.9) | 15 (12.3) | 16 (8.5%) | 0.497 |
| Physician Decision | 2 (1.1) | 3 (2.5) | 4 (2.1%) | 0.604 |
| Protocol violation | 8 (4.2) | 1 (0.8) | 7 (3.7%) | 0.221 |

178 of 182 eligible patients opted to enter the optional rescue treatment phase and 118(66.3%) of these patients completed this phase of the study. 47 patients treated with WEEKLY-90 given twice a week completed the rescue treatment phase; 32 receiving 40 mg daily completed; and 35 receiving placebo completed.

Concomitant Medications

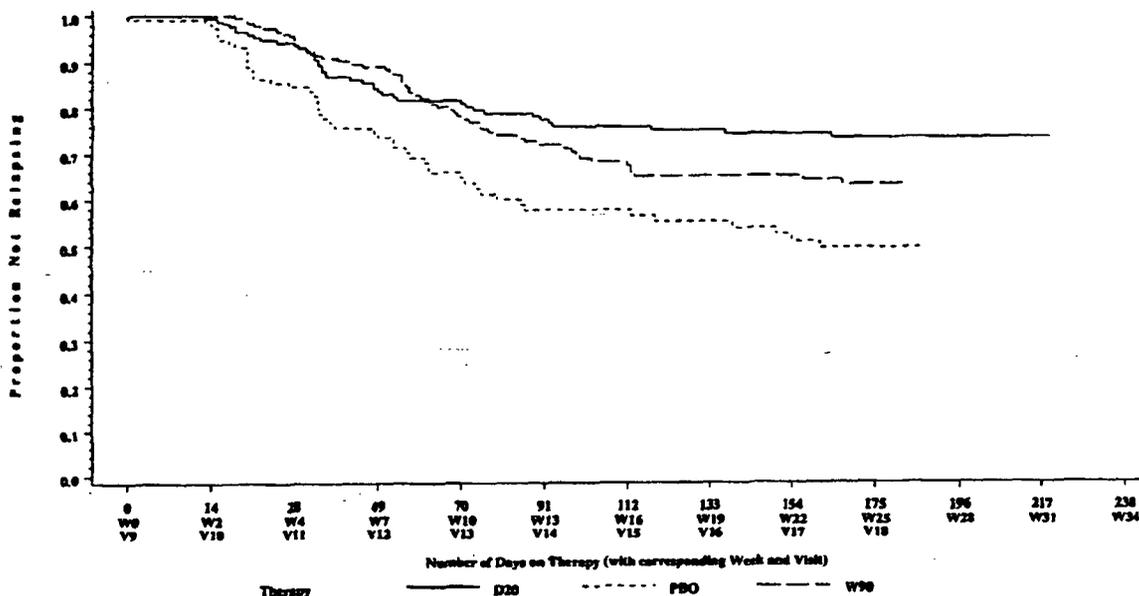
Temazepam and zolpidem were allowed for insomnia for up to 8 nights in Study Period II, but no hypnotics were allowed in Study Phase III after randomization. Sedating anti-histamines were allowed for allergies and upper respiratory infections 3 days per month in Study Phase III after randomization but no limit was placed on non-sedating anti-histamines. Allowable medications were acetaminophen, multivitamins, antacids, laxatives, kaolin and pectin containing antidiarrheals, over-the-counter nonsteroidal anti-inflammatory agents, and birth control. For patients with migraine headaches prescription NSAID's were allowed. The most commonly used class of medication during any treatment phase was non-narcotic analgesics (ibuprofen 36.2%, paracetamol 27.7%, acetylsalicylic acid 20.1%). During Study Period III 34.7% took ibuprofen, 21.0% took paracetamol, 21.0% ergocalciferol/ascorbic acid. In Study Period III, there was a statistically significant difference in the use of two medications when comparing WEEKLY-90 to placebo. Acetylsalicylic acid/caffeine was consumed significantly more frequently in the WEEKLY-90 group compared with the group on placebo (p=0.015). Loperamide hydrochloride was consumed significantly more frequently in the WEEKLY-90 group (3.7%) than in the placebo group (0.0%). The use of loperamide reflects the rate of reports of diarrhea in the two treatment groups. For the analysis to compare WEEKLY-90 to DAILY-20, the sponsor pooled the data from these two treatment groups in this study with the data from the WEEKLY-90 and DAILY-20 in study BIY-MC-HCJR. Acetylsalicylic acid/caffeine was consumed significantly more frequently in the WEEKLY-90 group compared with the DAILY-20 group (p=0.013).

Efficacy Results

As noted previously, there were two primary objectives in this study: The first was to determine whether the 90 mg formulation given once weekly (WEEKLY-90) was non-inferior to standard treatment with 20 mg daily (DAILY-20) for the continuation treatment of depression. Non-inferiority was measured by testing whether the relapse rate of patients given WEEKLY-90 was not higher (less than 15 percentage points) than those of patients given DAILY-20 after 16 weeks of continuation therapy. The second was to determine if the relapse rate of patients given fluoxetine 90mg once weekly was lower than the relapse rate for patients given placebo after 16 weeks of continuation therapy.

Using the Kaplan-Meier analysis of time-to-relapse, the primary endpoint compared the proportion of patients in each treatment group who relapsed 16 weeks after randomization to continuation treatment. The sponsor's Kaplan Meier Curve plot below shows the proportion of patients not relapsing on the vertical axis and time on treatment along the horizontal axis. At visit 15, after 16 weeks of treatment, the proportion of

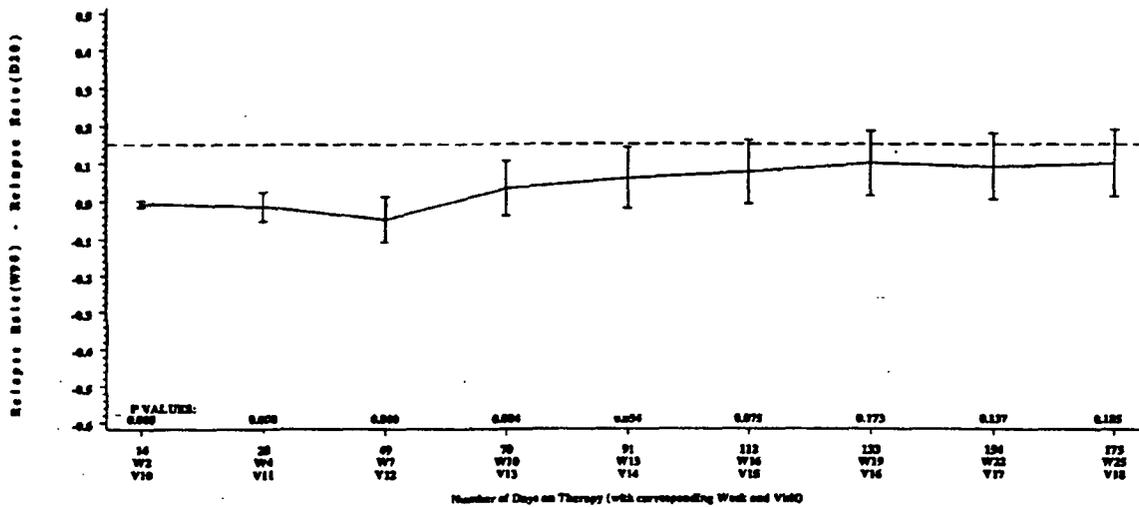
patients not relapsing (\pm Standard Error) was as follows: Weekly-90 was 0.68 (\pm 0.038); placebo was 0.58 (\pm 0.050); and Daily-20 was 0.76 (\pm 0.043). (The confidence intervals described below were constructed using estimates of the relapse rate and standard error for each group obtained using the Kaplan-Meier analysis.)



**Time-to-Relapse
Kaplan-Meier Estimates**

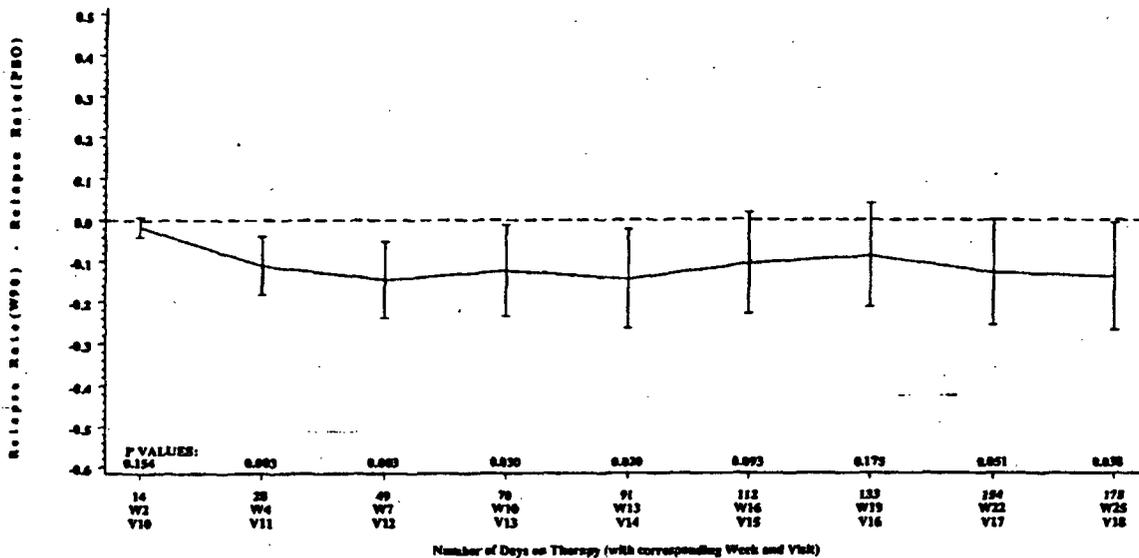
The non-inferiority of WEEKLY-90 compared with DAILY-20 was assessed using a one-tailed confidence interval for the difference in relapse rates. The range of non-inferiority was defined as 0.15. Comparing the non-inferiority of WEEKLY-90 relative to DAILY-20, at visit 15, after 16 weeks of treatment, the upper end of the confidence interval fell above 0.15. At 16 weeks of treatment, the difference in the relapse rate was 0.08, in favor of DAILY-20, with an upper limit of 0.16. (See the sponsor's figure below.)

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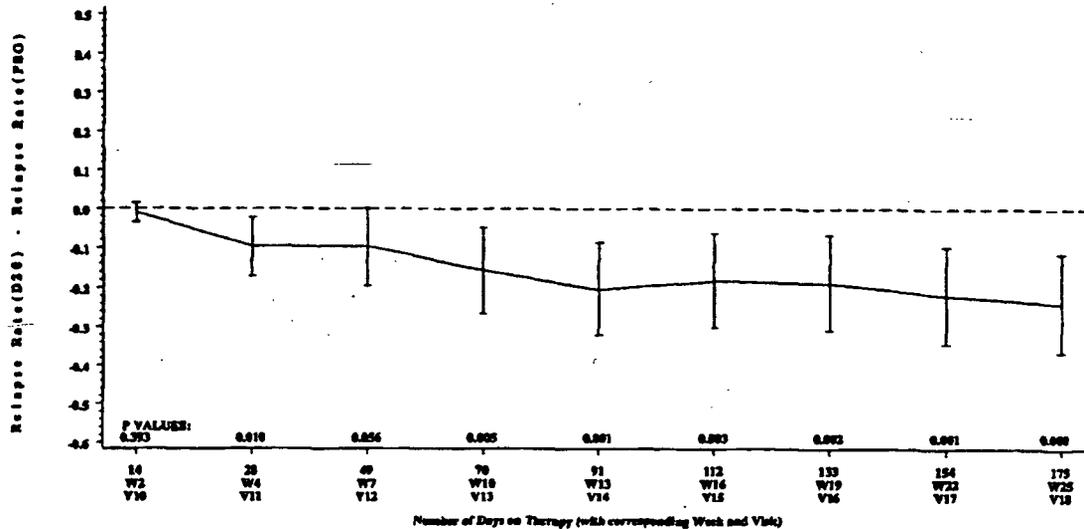
**Non-Inferiority of WEEKLY-90 to DAILY-20
Upper Tailed 95% Confidence Interval for the Difference in
Relapse Rates of WEEKLY-90 and DAILY-20**

The efficacy of WEEKLY-90 was compared to placebo using a two-tailed confidence interval for the difference in relapse rates. (See the sponsor's figure below.) After 16 weeks of treatment, the difference in relapse rate was -0.11 with an upper limit of 0.02 and a lower limit of -0.23 . Up to week 13, WEEKLY-90 was superior to placebo by a statistically significant margin. However, at the primary end-point of 16 weeks, Weekly-90 did not demonstrate statistically significant superiority (although it remained numerically superior.)



**Two-tailed 95% Confidence Interval for the Difference in
Relapse Rates of WEEKLY-90 and PLACEBO**

The confidence interval plot that assesses the superiority of DAILY-20 to placebo is shown in the sponsor's figure below. The estimated relapse rate of DAILY-20 was significantly less than the estimated relapse rate for placebo at every time point except at visit 12.



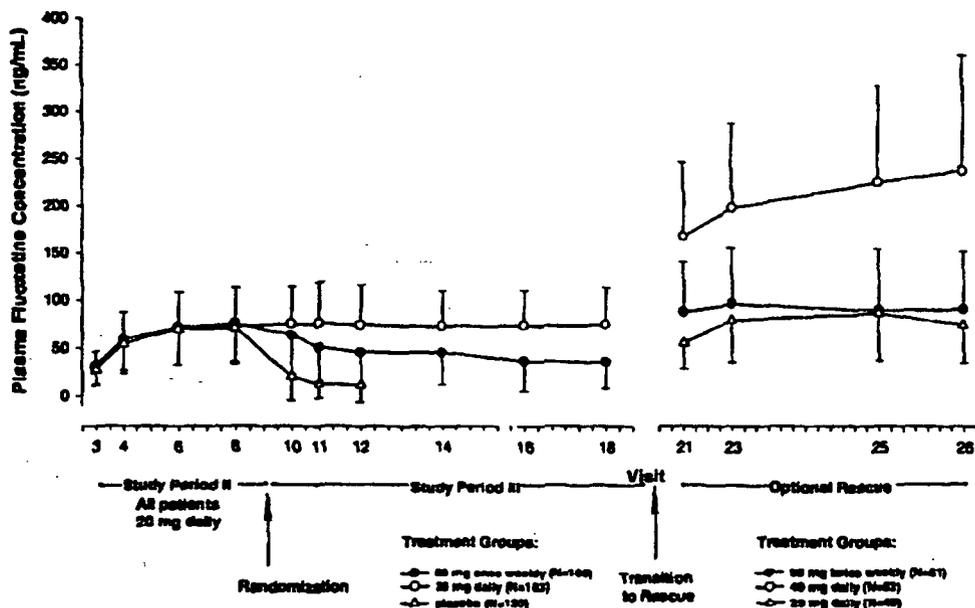
Two-Tailed Confidence Interval for the Difference in Relapse Rates of DAILY-20 and PLACEBO

Log-Rank test: This test showed WEEKLY-90 to be superior to placebo ($p=0.007$) and DAILY-20 to be superior to placebo ($p<0.001$) comparison of WEEKLY-90 to DAILY-20 yielded $p=0.164$.

Pharmacokinetic Data

Plasma concentration levels of fluoxetine and norfluoxetine were drawn in Study Period II, Study Period III, and the Optional Rescue Treatment phase. In Study Period II, 20 mg given daily took 3-7 weeks to reach an average steady state concentration of fluoxetine 73 ng/mL and norfluoxetine 107 ng/mL. In Study Period III, placebo plasma concentration washout was within 7 weeks and DAILY-20 maintained pre-randomization drug concentration levels. However, WEEKLY-90 declined to a new lower level average steady state concentration of fluoxetine 43 ng/mL (57% of levels in Study Period II) and norfluoxetine 69 ng/mL (66% of levels in Study Period II) within 4-7 weeks. The new steady-state concentrations of fluoxetine and norfluoxetine, 57% and 64% of corresponding concentrations in Study Period II is consistent with a WEEKLY-90 dose that is 64% of DAILY-20, 140 mg/week dose. For patients who relapsed in Study Period II and entered the Optional Rescue Treatment Phase, fluoxetine and norfluoxetine levels concentrations increased in accordance with the increase in dosage for each treatment group. With an increase in dose from placebo to 20 mg daily, fluoxetine and norfluoxetine concentration levels returned to levels similar to pre-randomization levels. With an increase from 20 mg a day to 40 mg a day, a three-fold increase in the average steady-state concentration was seen. Patients who went from WEEKLY-90 to twice

weekly WEEKLY-90 had a doubling in their average steady-state concentration to fluoxetine, 94 ng/mL and norfluoxetine, 112 ng/mL. (The figures below were both taken from the sponsor's submission.)



**Mean (+SD) Plasma Concentrations of Fluoxetine (ng/mL)
Study Periods II, III, and the Optional Rescue Treatment Phase
Study B1Y-MC-HCZ**

7.2 Conclusions Regarding Efficacy

WEEKLY-90 failed to show efficacy based on the a priori primary outcome measure at week 16, chosen by Lilly ($p=.09$). Whereas, DAILY-20 did show efficacy compared with placebo.

In testing for non-inferiority, based on confidence intervals, WEEKLY-90 could be more than 15% less effective than DAILY-20 when measuring number of relapses prevented.

The more robust efficacy of DAILY-20 compared with WEEKLY-90, corresponded with the higher plasma concentration of DAILY-20.

By log rank analysis, both treatments were favored over placebo.

7.3 Additional Study in Labeling

7.3.1 Adherence Study B1Y-MC-HCJR

Investigators and Locations

This was a multi-center study conducted at 18 centers in the United Kingdom.

Objective

This study assessed patient adherence to a regimen of the enteric-coated fluoxetine 90 mg given weekly (WEEKLY-90) against a regimen of fluoxetine 20 mg daily (DAILY-20).

The primary objective was to determine if the level of patient adherence to WEEKLY-90 was not significantly inferior to patient adherence to DAILY-20 for up to 12 weeks of continuation treatment of major depressive disorder. This study was not designed to prove efficacy.

Study Population

Subjects were male or female outpatients, ages 18 to 80, who met DSM -IV criteria for non-psychotic Major Depressive Disorder and who had received treatment for 6 to 16 weeks with fluoxetine. Patients needed to have a past history of depression treated with an anti-depressant on at least one other occasion. As a measure of response to the fluoxetine, patients had to score 12 or less on the Montgomery-Asberg Depression Rating Scale and a score of 2 or less on the CGI-severity rating scale.

Design

This study was a multi-center, open-label, randomized, parallel group design in patients with major depressive disorder. In Study Period I, patients received four weeks of fluoxetine 20 mg daily, then were randomized to Weekly-90 or Daily-20. Adherence to treatment was separately assessed in the two study periods by electronic monitoring. Fluoxetine was distributed in a bottle with a special cap equipped with micro-circuitry that recorded each time the cap was removed and replaced.

Results

Patient Disposition

The protocol specified screening 150 patients in order to enter 50 patients in each of the two treatment arms. 117 subjects (20 males and 97 females) entered Study Period I and received four weeks of fluoxetine 20 mg daily. Eight discontinued in Study Period I. 109 subjects were randomized to the two treatment arms in Study Period II. 56 patients received Weekly-90 and 53 patients received Daily-20. Eleven patients discontinued in Study Period II.

Baseline Patient Demography

109 patients, ranging in age from 21 to 77 were randomized in Study Period II. 56 patients, 10 male and 46 female, with a mean age of 47, were assigned to WEEKLY-90. 53 patients, 10 male and 43 female, with a mean age of 46, were assigned to DAILY-20. All patients were Caucasian.

Analysis

The primary endpoint in this study is adherence to the dosing regimen. Each single dose was coded as adherent or not adherent with a window of $\pm 25\%$. The percent of adherent doses was calculated for each patient and then averaged for each treatment group. Non-inferiority was tested to demonstrate that mean adherence to the weekly regimen was no worse than 20% lower than the mean adherence to daily fluoxetine.

Blood samples for fluoxetine and norfluoxetine were obtained at visit 2 and 5 for objective measurement of drug ingestion.

Weighting was not used to adjust for missing adherence data, for subjects who discontinued prior to Visit 5. The patient level denominator was adjusted to reflect the

early discontinuation date. For patients who discontinued early for any reason, the number of doses prescribed (the denominator) was calculated from the date of enrollment to the date of early discontinuation.

An intent-to-treat analysis of randomized patients included patients who did not take the assigned treatment, did not receive the correct treatment or other protocol violators.

Results

Mean adherence to WEEKLY-90 was 85.91 ±21. Mean adherence to DAILY-20 was 79.42 ±16. Adherence to WEEKLY-90 was not significantly inferior to that with DAILY-20. The ratio of WEEKLY-90 to DAILY-20 adherence was 1.08. This study was not designed to prove efficacy.

8.0 Integrated Review of Safety

8.1 Methods and Findings for Safety Review

The safety review includes the safety data from the two pharmacokinetic studies, B1Y-LC-HCIX and B1Y-LC-HCJO. The sponsor presented descriptive statistics for the two pharmacokinetic trials and separated this data from the safety data collected in HCIZ and HCJR. This separation of the safety data is justified because of the difference in patient populations, healthy volunteers vs. patients, and because of the shorter exposure in the pharmacokinetic trials. The sponsor presented WEEKLY-90 safety data by comparing WEEKLY-90 vs. placebo from the continuation treatment phase of B1Y-MC-HCIZ. The WEEKLY-90 safety data was also presented comparing WEEKLY-90 vs. DAILY-20 by combining the data from the continuation treatment phases of B1Y-MC-HCIZ and B1Y-MC-HCJR. The continuation treatment phase of B1Y-MC-HCIZ is the only study that compares WEEKLY-90 and placebo.

8.1.1 Deaths

There were no deaths in the four studies of the enteric-coated 90 mg formulation of fluoxetine.

8.1.2 Serious Adverse Events

There were no serious adverse events reported for the pharmacokinetic studies B1Y-LC-HCIX and B1Y-LC-HCJO. Serious Adverse Events reported by patients in the Continuation Treatment Phases of studies B1Y-MC-HCIZ and B1Y-MC-HCJR are listed in the table below.

**Serious Adverse Events
Continuation Treatment Phases
B1Y-MC-HCIZ and B1Y-MC-HCJR**

| Patient Number | Treatment Group | Serious Adverse Event | Actual Terms and Narrative |
|----------------|--------------------------|-----------------------|--|
| 001-100 | WEEKLY-90 B1Y-MC-HCIZ | Hospitalization | Sudden Confusion, Manic Episode, Bizarre Behavior 27 YO female exhibited bizarre and confused behavior, such as taking a bath in bleach and water and stating she was losing weight because she was allergic to something in the lasagna, and she wanted to fly to Georgia. She was seen in the emergency room and given a diagnosis of manic or psychotic episode. Study medication was discontinued and valproate instituted. |

| | | | |
|------------------|--------------------------|-----------------|---|
| 7-208 | WEEKLY-90 B1Y-MC-HCIZ | Hospitalization | Diabetic Ketoacidosis |
| 020-2015 | WEEKLY-90 B1Y-MC-HCIZ | Hospitalization | Suicidal Ideation 26 YO male reported suicidal ideation of 4 days duration. He was hospitalized and discontinued from the study. Drop out from the study was 128 days after fluoxetine 20 mg daily was instituted and 40 days since randomization to WEEKLY-90. Inpatient treatment was with 20 mg fluoxetine daily and then changed to venlafaxine 75 mg bid. |
| 030-3012 3012 | WEEKLY-90 B1Y-MC-HCIZ | Hospitalization | Pulmonary Embolism Onset at visit 7 during open-label treatment with 20 mg Prozac daily, prior to randomization in the continuation treatment phase. The patient continued into the continuation treatment phase. |
| 810-8554 | Weekly-90 B1Y-LC-HCJR | Suicide Attempt | Three weeks after the second visit, the patient attempted suicide by attempting to jump off a bridge into a river but was stopped by the police. |
| 002-215 | DAILY-20 B1Y-MC-HCIZ | Hospitalization | Passed Kidney Stone |
| 021-2101 | DAILY-20 B1Y-MC-HCIZ | Hospitalization | 53 YO male hospitalized with severe diarrhea, nausea, vomiting, and dehydration, which patient attributed to pizza. A diagnosis of gastroenteritis was made and later revised to myocardial infarction. |
| 021-2101 | DAILY-20 B1Y-MC-HCIZ | Hospitalization | Chest Pain (upper left) 53 YO male, same patient as above, hospitalized with chest pain and had 2 stents placed in the circumflex artery of the heart. |
| 035-3511 | PLACEBO B1Y-MC-HCIZ | Hospitalization | Suicidality 37 YO male hospitalized for suicidal ideation and treated inpatient with 40 mg daily fluoxetine. After 13 weeks of open-label treatment, patient was randomized to placebo on Suicidality was reported from at which time he was dropped from the study. |

8.1.3 Reasons for Discontinuation

No subjects discontinued in study B1Y-LC-HCIX.

Two subjects in the pharmacokinetic study, B1Y-LC-HCJO, discontinued in the daily fluoxetine group, one subject after developing hives and one subject who experienced difficulty breathing. The subject who experienced difficulty breathing was seen in an emergency room and treated with oral prednisone 50 mg daily for five days for itching and benadryl 50 mg IM for itching. In study B1Y-LC-HCJO, no subjects discontinued in the 90 mg enteric-coated fluoxetine group.

The following tables list the reasons for discontinuation in the continuation treatment phase of studies B1Y-MC-HCIZ and B1Y-MC-HCJR.

Reasons for Discontinuation Continuation Treatment Phase B1Y-MC-HCIZ

| Reason for Discontinuation | WEEKLY-90 | PLACEBO | DAILY-20 |
|----------------------------|-----------|-----------|------------|
| | N=190 | N=122 | N=189 |
| | N (%) | N (%) | N (%) |
| Relapse | 68 (35.8) | 57 (46.7) | 51 (30.2%) |
| Adverse Event | 8 (4.2) | 2 (1.6) | 4 (2.1%) |
| Lack of Efficacy | 3 (1.6) | 4 (3.3) | 3 (1.6%) |

NDA 21-235

| | | | |
|--------------------|----------|-----------|-----------|
| Lost to follow-up | 13 (6.8) | 5 (4.1) | 14 (7.4%) |
| Patient Decision | 17 (8.9) | 15 (12.3) | 16 (8.5%) |
| Physician Decision | 2 (1.1) | 3 (2.5) | 4 (2.1%) |
| Protocol violation | 8 (4.2) | 1 (0.8) | 7 (3.7%) |

**Reasons for Discontinuation
Continuation Treatment Phase
B1Y-MC-HCJR**

| Reason for Discontinuation | WEEKLY-90 N=56 | | 20 mg daily N=53 | |
|----------------------------|-------------------|-------|---------------------|-------|
| | N | (%) | N | (%) |
| Adverse Event | 1 | (1.8) | 1 | (1.9) |
| Lack of Efficacy | 8 | (7.3) | 2 | (3.8) |
| Relapse | 1 | (1.8) | 0 | |

The table below summarizes the patients who discontinued due to an adverse event in the continuation treatment phase of studies B1Y-MC-HCIZ and B1Y-MC-HCJR. In the WEEKLY-90 group, two patients dropped due to somnolence, one in HCIZ and one in HCJR. In the HCIZ WEEKLY-90 group, one patient discontinued due to diarrhea. In study B1Y-MC-HCIZ, patient 007-0700, who had been randomized to the WEEKLY-90 group on _____, discontinued on _____. The patient reported that she had been experiencing an irregular heart beat and dyspnea since _____. The patient reported that she had discontinued her study medication on _____. A repeat EKG, _____ revealed multiple premature ventricular complexes.

**Adverse Events Leading to Discontinuation
Continuation Treatment Phase
B1Y-MC-HCIZ and B1Y-MC-HCJR**

| Study | Patient | Age | Treatment Group | Reported Adverse Event | Days Post-Randomization |
|-------|----------|-----|-----------------|---------------------------|-------------------------|
| HCIZ | 001-0100 | 27 | WEEKLY-90 | Manic Episode | Day of randomization |
| HCIZ | 035-3500 | 46 | WEEKLY-90 | Fogginess/ somnolence | 37 |
| HCIZ | 002-0202 | 39 | WEEKLY-90 | Sedation/ somnolence | 9 |
| HCIZ | 007-0700 | 52 | WEEKLY-90 | Irregular Heart Rate | 2 |
| HCIZ | 028-2809 | 63 | WEEKLY-90 | Diarrhea | 8 |
| HCIZ | 013-1320 | 33 | WEEKLY-90 | Dysphagia | 34 |
| HCIZ | 038-3800 | 31 | WEEKLY-90 | Study Medication Overdose | 25 |
| HCIZ | 020-2015 | 26 | WEEKLY-90 | Suicidal Ideation | 37 |
| HCJR | 804-8209 | 27 | WEEKLY-90 | Sleepiness | 8 |
| HCIZ | 004-0411 | 44 | DAILY-20 | Akathisia | 22 |
| HCIZ | 033-3309 | 41 | DAILY-20 | Proptosis | 12 |
| HCIZ | 001-0125 | 56 | DAILY-20 | Restless at Night | 7 |
| HCIZ | 021-2128 | 51 | DAILY-20 | Extremely Tired | 27 |
| HCJR | 811-8614 | 49 | DAILY-20 | Reduced Libido | 62 |
| HCIZ | 013-1321 | 27 | Placebo | Blurred Vision | 6 |
| HCIZ | 001-0111 | 49 | Placebo | Hypomania | 12 |

The table below lists the reasons for discontinuation during the optional rescue treatment phase of HCIZ including adverse events leading to discontinuation. One patient discontinued on the WEEKLY-90 given twice weekly due to worsening diarrhea.

**Reasons for Discontinuation
HCIZ Optional Rescue Treatment Phase**

| Reason for Discontinuation | WEEKLY-90 Twice-weekly N=66 | 20 mg daily N=55 | 40 mg daily N=57 |
|-------------------------------------|-----------------------------------|---------------------|---------------------|
| | N (%) | N (%) | N (%) |
| Lack of Efficacy | 9 (13.6) | 4 (7.3) | 13 (22.8) |
| Lost to follow-up | 5 (7.6) | 2 (3.6) | 4 (7.0) |
| Patient Decision | 3 (4.5) | 7 (12.7) | 5 (8.8%) |
| Protocol violation | 0 | 1 (1.8) | 2 (3.5%) |
| Total Adverse Events | 2 (3.0) | 2 (3.6) | 1 (1.8) |
| Anorgasmia | 0 | 1 (1.8) | 0 |
| Asthenia | 0 | 0 | 1 (1.8) |
| Gastrointestinal Disorder- Diarrhea | 1 (1.5) | 0 | 0 |
| Rash | 1 (1.5) | 0 | 0 |
| Somnolence | 0 | 1 (1.8) | 0 |

In summary, the total number of patients randomized to WEEKLY-90, DAILY-20 and placebo were too small to discern a pattern for the discontinuations from treatment. In addition, patients with intolerance for fluoxetine may have dropped out in the run-in phase with 20 mg daily of fluoxetine.

8.1.5 Common Adverse Events

The sponsor used the COSTART Adverse Event Dictionary for reporting adverse events. Only in the continuation treatment phase of study B1Y-MC-HCIZ can the safety data for WEEKLY-90 be compared to placebo. The table below lists treatment-emergent adverse events reported in the Weekly-90 treatment group with a $\geq 5\%$ frequency. The N of the placebo-controlled population is small [WEEKLY-90 (N=190), placebo (N=122)], thus an incidence $\geq 1\%$ was seen if only two patients reported an adverse event. Therefore, this safety data review emphasizes adverse events with an incidence $\geq 5\%$.

**Treatment-Emergent Adverse Events
With an Incidence of $\geq 5\%$
Continuation Treatment Phase
Study B1Y-MC-HCIZ**

| Adverse Event | WEEKLY-90 N=190 | PLACEBO N=122 | DAILY-20 N=189 |
|---------------|--------------------|------------------|-------------------|
| | N (%) | N (%) | N (%) |
| Nervousness | 26 (13.7) | 14 (11.5) | 12 (6.3) |
| Asthenia | 18 (9.5) | 9 (7.4) | 18 (9.5) |
| Headache | 20 (10.5) | 11 (9.0) | 23 (12.2) |
| Somnolence | 16 (8.4) | 10 (8.2) | 20 (10.6) |

| | | | |
|-------------------|----------|---------|-----------|
| Insomnia | 14 (7.4) | 5 (4.1) | 10 (5.3) |
| Diarrhea | 18 (9.5) | 4 (3.3) | 9 (4.8) |
| Thinking Abnormal | 16 (8.4) | 6 (4.9) | 3 (1.6) |
| Rhinitis | 17 (8.9) | 9 (7.4) | 23 (12.2) |
| Depression | 10 (5.3) | 6 (4.9) | 6 (3.2) |
| Anxiety | 13 (6.8) | 7 (5.7) | 10 (5.3) |
| Nausea | 12 (6.3) | 9 (7.4) | 8 (4.2) |
| Back Pain | 11 (5.8) | 5 (4.1) | 11 (5.8) |
| Abnormal Dreams | 11 (5.8) | 3 (2.5) | 6 (3.2) |
| Apathy | 10 (5.3) | 1 (0.8) | 5 (2.6) |
| Dizziness | 10 (5.3) | 6 (4.9) | 11 (5.8) |

Adverse events attributable to WEEKLY-90 treatment (incidence \geq 5% and a relative rate \geq 2 compared to placebo) were diarrhea, abnormal dreams, and apathy. At all time points, diarrhea was reported more frequently by the WEEKLY-90 group (9.5%) when compared to the placebo group (3.3%) and DAILY-20 group (4.8%). The incidence of diarrhea during the first two weeks post-randomization was WEEKLY-90 (5.3%), placebo (1.6%), and DAILY-20 (1.1%).

Patients in the WEEKLY-90 (13.7%) and placebo (11.5%) groups reported nervousness more often than patients in the DAILY-20 group (6.3%). The increased incidence of nervousness in the WEEKLY-90 and placebo groups may reflect better control of depressive symptoms in the DAILY-20 group or it may reflect fluoxetine withdrawal symptoms in the WEEKLY-90 and placebo groups.

8.1.6 Laboratory Findings

In study B1Y-MC-HCIZ, laboratory samples were collected for clinical chemistry, hematology, and urinalysis at visits 1 (screening), 8 (pre-randomization), and 18. Mean change from baseline (Visit 8) to endpoint (Visit 18) was measured and analyzed using an analysis of variance. Note that baseline is after 13 weeks of treatment with 20 mg daily of fluoxetine. Treatment effects compared WEEKLY-90 to placebo and WEEKLY-90 to DAILY-20.

All three treatment groups had a mean decrease in albumin, with a statistically significant difference ($p= 0.042$) between DAILY-20 (-0.8) and WEEKLY-90 (-0.2). There was a statistically significant difference ($p= 0.016$) in blood potassium values between DAILY-20 (-0.06) and WEEKLY-90 (-0.06). Placebo had a mean change of -0.02. However, the magnitude of change is small and if comparison is made to the placebo group, these changes would not have clinical significance.

For urinalysis, the WEEKLY-90 group had 5.7% RBC and 4.7% occult blood; DAILY-20 had 0.8% RBC and 13.9% occult blood; and placebo 4.1% RBC and 6.9% occult blood. All 11 patients with RBC in the urine and 22 of 24 with occult blood in the urine were female suggesting menstrual blood, however, the presence of menstruation was not recorded.

8.1.7 Vital Signs

In study B1Y-MC-HCIZ, vital signs and weight were recorded at visits 1, 8, 9 (randomization), and 10 through 18. In the table below, the sponsor compares vital signs and weight between WEEKLY-90 and placebo. Only in the Continuation Treatment Phase of HCIZ can WEEKLY-90 be compared to placebo. For this comparison, visit 9 is

baseline. Visit 9 is the point of randomization for the continuation treatment phase after 13 weeks of treatment with Prozac 20 mg daily. The treatment effect of mean change from baseline to endpoint uses an analysis of variance with treatment.

**Mean Change from Baseline to Endpoint in Vital Signs and Weight
WEEKLY-90 vs. Placebo
Study B1Y-MC-HCIZ**

| | Treatment | Mean at baseline | Mean Change at Endpoint | Standard Deviation | p-values pair wise comparison |
|---------------------------------|----------------------------------|------------------|-------------------------|--------------------|-------------------------------|
| Systolic Blood Pressure Sitting | Placebo N=122 WEEKLY-90 N=188 | 121.4 118.7 | -1.8 1.5 | 12.2 12.1 | 0.02 |
| Diastolic Blood Pressure | Placebo N=122 WEEKLY-90 N=188 | 77.5 76.1 | -0.6 0.9 | 9.2 9.0 | 0.15 |
| Heart Rate Sitting | Placebo N=122 WEEKLY-90 N=188 | 74.6 74.0 | 1.2 -0.0 | 10.0 10.2 | 0.31 |
| Weight kg | Placebo N=122 WEEKLY-90 N=187 | 85.1 82 | 1.2 1.4 | 2.9 4.5 | 0.72 |

A statistically significant increase in sitting systolic blood pressure was seen in the WEEKLY-90 treatment group when comparing to patients on placebo. The clinical significance of this finding is not clear. Patients on DAILY-20 compared with placebo had a slight decrease in heart rate, which has been seen in other studies with fluoxetine.

8.1.8 Electrocardiograms

In the multiple dose pharmacokinetic study B1Y-LC-HCJO, ECGs were obtained at screening and at completion of the study. All ECG's were read by the investigators as normal.

In study B1Y-MC-HCIZ, ECG's were done only at screening, if the patient was 50 years or older. Patient 007-0700, age 52, while on WEEKLY-90, during the Continuation Treatment phase of study B1Y-MC-HCIZ, reported an irregular heart beat and dyspnea. The symptoms were first reported at scheduled study visit 11, on _____. The patient reported that the symptoms had begun on _____, two days after randomization to WEEKLY-90. The ECG on _____ reported multiple premature ventricular complexes. The patient was discontinued from the study.

8.1.9 Special Studies

In study B1Y-MC-HCIZ, sexual function was assessed using a 4-item, self-report scale, the Patient's Global Impression of Sexual Function. Patients recorded their level of interest and their impressions of their overall sexual function. No significant differences were found between the three treatment groups. However, baseline is visit 9, after 13 weeks of treatment with Prozac 20 mg daily.

8.1.10 Human Reproduction Studies

There are no human reproduction studies with the enteric-coated 90mg fluoxetine formulation. Pregnancy was an exclusion criterion for entry into the studies. If a subject became pregnant during the study, the patient would be discontinued from the study.

8.1.11 Overdose Experience

The 90 mg enteric-coated formulation has a one to two hour delay in absorption. When managing an overdose this delay in absorption should be considered.

8.2 Summary of Key Adverse Event Findings

Because of the large number of patient years of exposure with the immediate release fluoxetine, a significant amount of safety data has been collected and the safety profile fairly well established for the immediate release formulation. The safety profile for this new formulation is similar to what is known about the immediate release formulation.

Unique to this 90 mg enteric-coated fluoxetine formulation is the enteric coating that delays the release of fluoxetine. The excipient, _____, present in the enteric coating of the new formulation is not present in the immediate release formulation.

In study B1Y-MC-HCIZ, the excipient, _____, present in the enteric coating of the new formulation was not present in the immediate release formulation or the placebo. Again, the continuation treatment phase of study B1Y-MC-HCIZ is the only study where the WEEKLY-90 is compared to placebo. In this study, Adverse events with an incidence $\geq 5\%$ and a relative rate ≥ 2 compared to placebo, therefore likely to be attributable to WEEKLY-90 treatment were diarrhea, abnormal dreams, and apathy. The higher incidence of diarrhea seen in the WEEKLY-90 formulation (9.5%) compared to either the DAILY-20 (4.8%) or placebo (3.3%) may be a result of the new excipient. The higher use of loperamide probably reflected the symptoms of diarrhea.

Also a statistically significant increase in sitting systolic blood pressure was seen in patients on WEEKLY-90 when compared to patients on placebo. The clinical significance of this finding is not clear.

9.0 Special Populations

9.1 Pediatric Studies

10.0 Labeling

The sponsor's proposed labeling is generally acceptable. Detailed comments will be provided separately.

11.0 Financial Disclosure

In the original NDA submission, Form 3454 was signed by Rajinder Judge, MD, Lilly's medical director. Item 1 was checked on Form 3454 with an attached list of the primary NDA 21-235

investigators for trial B1Y-LC-HCIZ. In correspondence from the sponsor received July 12, 2000, the sponsor sent an attachment to Form 3455 that they stated they had inadvertently omitted from the original NDA submission. The attachment was a list of _____ investigators who received a non-grant payment of greater than \$25,000. In correspondence from the sponsor received August 7, 2000, the sponsor made an additional correction to Forms 3455 and 3454. Lilly reported that only _____ received non-grant payments in excess of \$25,000 and that seven of the _____ reported in the July 12, 2000 correspondence did not receive non-grant payments in excess of \$25,000. An amended attachment to form 3455 included only _____ An amended attachment to Form 3454 listed all of the other _____ investigators including the _____ removed from the July 12, 2000 Form 3455 attachment.

Financial disclosure was not reported for the clinical pharmacology studies B1Y-LC-HCIX and HCJO. Financial disclosure was not reported for the adherence trial B1Y-LC-HCJR which was conducted in UK.

Conclusions and Recommendations

WEEKLY-90 failed to show efficacy based on the a priori primary outcome measure chosen by Lilly. Whereas, DAILY-20 did show efficacy compared with placebo. However, both treatments were favored over placebo by the log rank analysis. In testing for non-inferiority, based on confidence intervals, WEEKLY-90 could be more than 15% less effective than DAILY-20 when measuring number of relapses prevented. The purpose of this study was to prove that the new 90 mg formulation given weekly had similar efficacy and could be substituted for 20 mg fluoxetine daily. The planned primary analysis failed to demonstrate that WEEKLY-90 could be used in place of 20 mg of fluoxetine given daily. An increased risk of relapse in maintenance treatment of depression is undesirable because of the morbidity and mortality associated with depression.

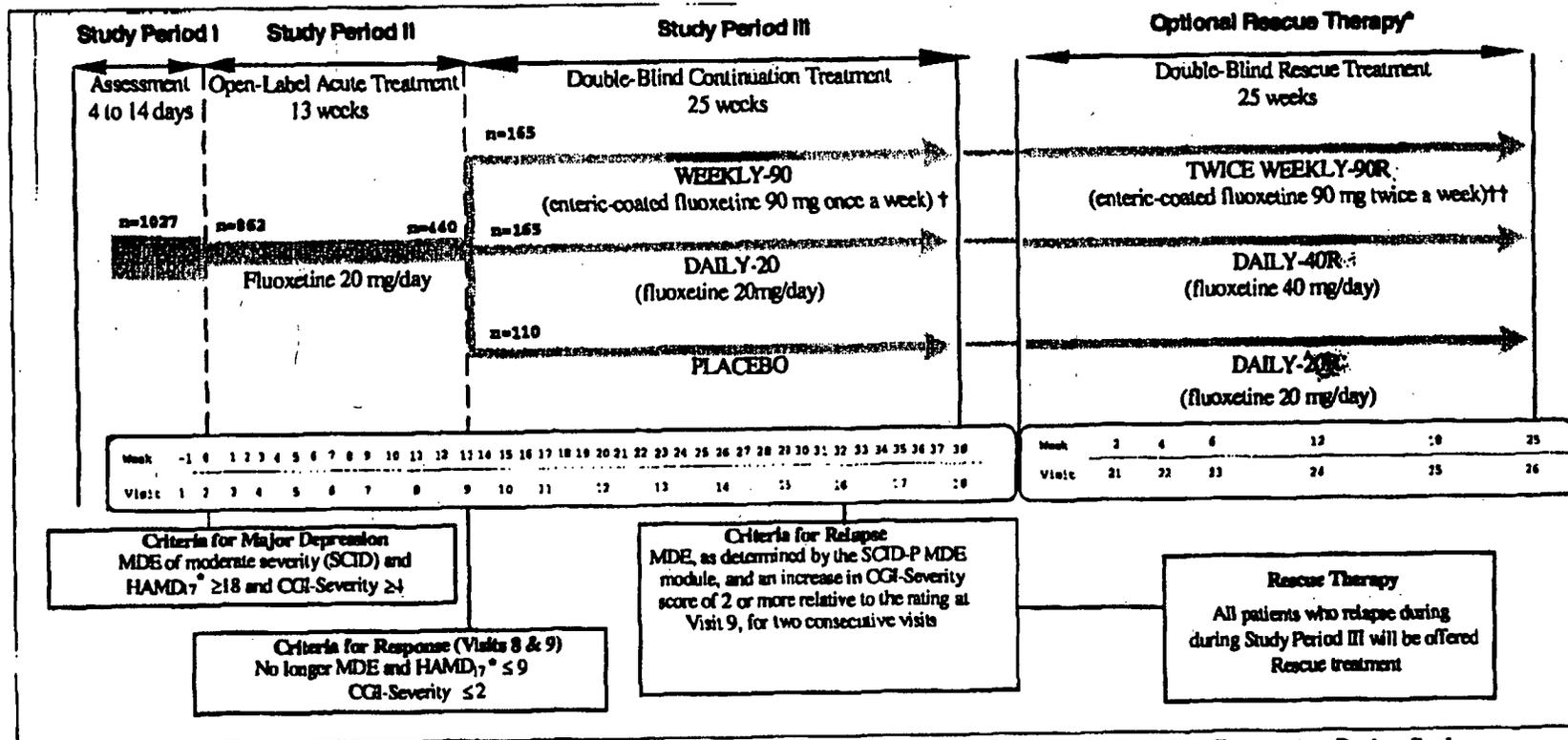
My recommendation based on the available data would be for not approvable action.

[151]
Kathy J Smith, MD
Medical Officer, HFD-120

Cc: Laughren, Mosholder, David, Smith

11-30-00
I think maintenance efficacy for Prozac weekly 90 mg has been demonstrated, and it can be approved with language in labeling describing its limitations. See memo to file for more detailed comments.
[151]
[151]

3 page(s) have been
removed because it
contains
trade secret
and/or
confidential information
that is not disclosable



Abbreviations: CGI-Severity = Clinical Global Impressions of Severity, HAMD₁₇* = modified 17-Item Hamilton Depression Rating Scale, MDE = major depressive episode; SCID-P = Structured Clinical Interview for DSM-IV, Patient version.

- * Optional rescue treatment phase visits begin approximately 2 weeks after relapse is determined and rescue medication is started.
- † The WEEKLY-90 treatment group includes fluoxetine hydrochloride 90 mg once weekly with matching placebo on the remaining days in the week.
- †† The TWICE WEEKLY-90R treatment group includes one capsule of fluoxetine hydrochloride 90 mg twice weekly with one matching placebo. Two of matching placebo were to be taken on the remaining days in the week.

Illustration of the Study Design
Study B1Y-MC-HCIZ

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**Schedule of Events
Study B1Y-MC-HCIZ**

| Activity | Visits | | | | | | | | Unsch. Visit | End of SP III Packet | V 21-26 (Rescue) | Summary |
|--|----------------|----------------|---|-----|---|---|----------------|----------------|----------------|----------------------|------------------|----------------|
| | 1 ^a | 1 ^b | 2 | 3-7 | 8 | 9 | 10 | 11-18 | | | | |
| Informed consent document signed | x | | | | | | | | | | | |
| Patient number assigned | | x | | | | | | | | | | |
| Patient assigned to Study Period II | | | x | | | | | | | | | |
| Patient assigned to Study Period III | | | | | | x | | | | | | |
| Medical history | | x | | | | | | | | | | |
| Consumptive habits | | x | | | x | | | | | x | | |
| Physical examination | | x | | | | | | | | | | x ^d |
| ECG (≥50 years old) | | x | | | | | | | | | | |
| Weight | | x | | | x | x | x | x | x | | x | x ^e |
| Height | | x | | | | | | | | | | |
| Vital signs: blood pressure & heart rate | | x | | | x | x | x | x | x | | x | x ^e |
| HAMD ₂₁ | | x | x | x | x | x | x | x | x | | x | |
| SCID-P for DSM-IV | | x | | | | | | | | | | |
| Diagnosis: SCID-P (depression only) | | | | | | | x ^c | x ^c | x ^c | | | |
| CGI-Severity | | x | x | x | x | x | x | x | x | | x | |
| AMD-P-5 | | | x | | | x | x | | | x | | |
| Zung SDS | | x | x | x | x | x | x | x | x | | x | |
| PGI-Sexual Function | | | x | | | x | x | x | x | | x | |
| SF-36 | | | x | | | x | | | | x | | |
| Preexisting conditions/ Adverse events | | x | x | x | x | x | x | x | x | | x | |
| Concomitant medication | | x | x | x | x | x | x | x | x | | x | |
| Study drug accountability | | | x | x | x | x | x | x | | | x | |
| Patient summary | | | | | | | | | | | | x |

Abbreviations: HAMD₂₁ = Hamilton Depression Rating Scale (this 28-item version allows scoring of the modified Hamilton-17 [HAMD17*]); SCID-P = Structured Clinical Interview for DSM-IV, Patient version; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; SP = Study Period; Unsch. = Unscheduled; Zung SDS = Zung Self-Rating Depression Scale.

- ^a At or before Visit 1.
- ^b Performed by Visit 2.
- ^c Completed if patient had significant re-emergence of depressive symptoms.
- ^d Performed if patient discontinued at Visits 10 through 18 or Visits 21 through 26.
- ^e Completed if patient discontinued at Visits 2 through 7.

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