CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-936/s-061

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: **18-936,20-101,20-974**
Sponsor: **Lilly**

Generic Name **fluoxetine**
Trade Name **Prozac**
Material Reviewed: **Labeling submissions for bulimia relapse (S-065), PD indication (S-061), and the pediatric indication (S-064, MDD changes only)**
Clinical Reviewer: **Earl D. Hearst, M.D.**

I. Review:

We have received a copy of Lilly's labeling incorporating the bulimia relapse, PD indication, and the pediatric indication (MDD changes).

Lilly agrees to the draft labeling contained in the FDA approvable letter for bulimia. The only changes are two minor editorial corrections in the language proposed in the approvable letter and other minor editorial changes throughout to bring the labeling into conformance with current Lilly standards. In the Clinical Trials section, (b) (4) The basis for this draft labeling is the current approved Prozac labeling based on the Agency letter of May 25,2001. Finally, the changes requested in the Agency approvable letter of July 12, 2001 for supplemental application 18-936/S-064 concerning the terms "depression" and "antidepressant" also been implemented.

In addition Lilly has changed the label as requested in the Prozac for panic disorder letter.

Lilly has confirmed that the changes are, verbatim, as that contained in the Agency AE letters for bulimia relapse, PD indication, and the pediatric indication (MDD changes). I have reviewed the changes and agree that they are as requested. I will deal with bulimia submission in more detail later in this review as this contained a safety update.

Foreign labeling: As requested in the approvable letter, Attachment 2 contains the Clinical Particulars sections of European Summary of Product Characteristics for 16 EU member states. The sponsor notes that (b) (4) Thus, specific reference to this study and its results will not be found in these SPCs or other foreign labeling for fluoxetine.

Postmarketing adverse events: Contained in Attachment 3 is a report that contains the methodology of search, a brief statement of results and conclusions, and tables comparing adverse event information for patients taking fluoxetine for bulimia versus those taking it for other indications. This report was prepared by Lilly's pharmacovigilance group and concludes that the pattern of adverse events in patients with bulimia is not substantially different from that in other patient populations and no labeling changes are warranted based on this analysis.

Literature update: Attachment 4 contains search methodology, a bibliography and copies of the relevant articles for bulimia relapse with fluoxetine.

A search of the available medical literature was conducted to compile a list of pertinent publications discussing bulimia relapse along with fluoxetine therapy. This search included the search terms fluoxetine and bulimia in conjunction with relapse, recurrence, or long-term. The search evaluated publications from 1974 into January of 2002 utilizing the following databases: Embase, :MEDLINE (combined representing 4900 biomedical journals), Derwent Drug Files (representing 1200 pharmaceutical journals),- BIOSIS Previews (representing 6000 life sciences journals), PsychInfo (representing 1300 psychiatric journals), and SciSearch (representing approximately 5600 science, technology, and medical journals).

17 studies have been provided. I do not see any study that would affect the current labeling for Prozac.

DISTRIBUTION: Attachment 5 contains a summary of quantity of fluoxetine distributed in the US and foreign markets for the period December l 2000 through November 2001, by product (pulvules, liquid, and tablets). This information is identical to that which will be provided in the fluoxetine annual report

for this period and is similar to that provided in annual reports for other years. Lilly does not track this use by indication.

Promotional Materials: Lilly does not plan to prepare promotional materials concerning the use of fluoxetine in bulimia, including the results of the study in relapse prevention. Thus, they feel there is nothing to submit to the Division or to the Division of Drug Marketing, Advertising, and Communications with regard to this supplement.

INTRODUCTION POSTMARKETING ADVERSE EVENTS

This report has been done in order to provide the FDA with a post-marketing review of adverse events reported in patients treated with fluoxetine for bulimia.

The report provides a cumulative review of all fluoxetine spontaneous adverse events, where the indication for use of fluoxetine has been reported as "bulimia" or "bulimia nervosa" in the Lilly global safety database from launch and up to a cut-off date of 15th January 2002. In addition, the report provides a comparison of adverse events reported in patients treated for bulimia with all other patients reported in the Lilly safety database.

Methodology

Spontaneous Adverse Event Data Sources

The Lilly Safety Database (b) (4) is a computerized safety database, implemented in 1998, but containing data from 1983, for the world-wide collection, storage and reporting of adverse events involving Lilly products. It includes serious and non-serious events reported spontaneously from post-marketing experience (including literature and regulatory reports) and clinical trial events described as "serious". The term "serious" refers to any adverse event that results in death, is life-threatening, is permanently or severely disabling, requires or prolongs inpatient hospitalization, results in congenital anomaly or is significant for any other reason.

Eli Lilly and Company have now changed to MedDRA Coding Dictionary Version 4.0. In this process Lilly has retrospectively re-coded all adverse events in the (b) (4) database to reflect a current MedDRA term. Some medical terms that do not exist in COST ART are available in MedDRA. Therefore, direct comparison with previous pharmacovigilance reviews performed in COSTART dictionary is not appropriate.

Database Search Criteria

The (b) (4) safety database was searched for all fluoxetine reports (spontaneous, clinical trial and post-marketing studies) in patients where the indication for fluoxetine were reported as bulimia to a cut-off date of 15th January 2002. Furthermore, the database was searched for adverse events occurring in all other patients.

The rate of adverse events for each MedDRA Preferred Term (PT) occurring in bulimia patients was compared to the rate of adverse events occurring in all other patients. Adverse event reports with unknown indication were excluded as these reports may have concerned bulimic patients. Finally, the ratio of adverse events occurring in bulimic patients to adverse events occurring in all other patients was calculated.

RESULTS

The search identified 742 adverse event reports associated with the use of fluoxetine in bulimic patients. There were 1442 adverse events reported in these 742 case reports. A line listing of these 742 adverse event reports are presented in Appendix 1.

A total of 166535 adverse events were identified for patients treated for all other indications than bulimia.

The number and rate of adverse events by MedDRA PT reported in patients treated with fluoxetine for bulimia and patients treated for all other indications are presented in appendix 2. In addition, the ratio of adverse events in bulimic patients to adverse events in patients with all other indications has also been presented.

Table 1 lists the MedDRA PTs that were reported with a ratio of bulimia to all other indications of greater than 1.00 and where the absolute relative rate of adverse events among bulimic patients were higher than 1.0%.

All other adverse events reported in bulimic patients have a absolute relative rate of less than 1.0 percent.

Table 1: MedDRA PTs Reported within bulimic patient of Greater than Reported in patients with other indications and an Absolute Rate ≥ 1.0%

MedDRA PT	Rate of Event within bulimic patients		Rate of Event within patients of all other indication		Ratio of bulimic patients to all other patients
	No.	%	No	%	
Pregnancy NOS	45	3.12	2009	1.20	2.59
Rash NOS*	42	2.91	3982	2.39	1.22
Overdose NOS*	39	2.70	2045	1.23	2.20
Headache NOS	32	2.21	3488	2.09	1.06
Urticaria NOS*	24	1.66	1914	1.15	1.45
Convulsions NOS	20	1.39	1427	0.86	1.62
Weight increased NOS*	20	1.39	1933	1.16	1.19
Fatigue NOS*	19	1.31	1646	0.99	1.33
Pruritus NOS*	18	1.25	2011	1.21	1.03
Contusion*	17	1.18	470	0.28	4.18
Unintended pregnancy	16	1.11	1209	0.72	1.52
Arthralgia*	15	1.04	1317	0.79	1.31
Sweating increased*	15	1.04	1661	0.10	1.04

*Listed reaction according to fluoxetine labelling

All the MedDRA PTs included in table 1 with the exception of “pregnancy NOS", "overdose NOS" and "contusion" have been reported in bulimic patients with less than twice the rate of that reported in patients of all other indications. These events were reported proportionally higher in bulimic patients. However, the total number of adverse event_for each of these terms was relatively low. Therefore, the sponsor feels no conclusion can be drawn on the basis of these results.

The majority of events listed in Table 1 are listed adverse reactions according to the current fluoxetine labeling with the exception of "pregnancy NOS", "headache NOS", "convulsions NOS" and "unintended pregnancy".

I do not see any additional safety events which would effect the labeling.

II. Recommendation:

The safety update for bulimia does not materially effect the labeling. I recommend the labeling submitted be accepted for bulimia relapse prevwntion, PD indication, and the pediatric indication (MDD changes).

Earl D. Hearst, M.D.

Medical Reviewer

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CC:file, tlaughren,ehearst,pdavid

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/s/

Earl Hearst
5/29/02 02:35:03 PM
MEDICAL OFFICER

Thomas Laughren
5/30/02 01:07:06 PM
MEDICAL OFFICER
I agree that these supplements can now be approved.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA: 18-936
Sponsor: Lilly

Drug Name

Generic Name fluoxetine
Trade Name Prozac

Material Submitted: Response to non-approvable letter

Reviewer Information

Clinical Reviewer: Earl D. Hearst, M.D.
Review Completion Date: 10/15/2001

I. Review:

We have received the response to our non-approvable letter dated 5/22/01. On Aug 1st we meet with Lilly and agreed to approve this submission pending submission of post-hoc analyses of secondary endpoints for eastern European and western European sites along with a discussion of Study HCJB.

In a document that preceded a 01 August 2001 meeting with the FDA, Lilly demonstrated that the primary endpoint remained statistically significant even when data from Eastern Europe sites were removed from the analysis. At our meeting, Dr.Michelson pointed out that an analysis of Western Europe sites only (specifically Austria and Sweden) show a statistically significant difference in favor of fluoxetine based on the primary outcome. This primary outcome was a better choice than other potential primary outcomes that did not reach statistical significance.

I have reviewed the secondary endpoint data and find little difference between the eastern European and western European sites.
Please see table one in this submission included as an appendix in this review. The interpretability of these data is compromised by the small patient population and by the study not being statically powered for subset analyses of secondary endpoints. The results of the secondary measures show that the mean change at endpoint for the measures was very similar for fluoxetine-treated patients at both Eastern and Western European sites.

The sponsor has repeated their basic argument about Study HCJB maintaining that it is a positive study even though the secondary variables do reach statistical significance.

Tables R.3 compares the number of panic-free patients at endpoint between the Eastern and Western European sites. Statistical analyses were also performed to determine whether country-by-treatment interactions (Austria, Sweden, Macedonia, and Yugoslavia) or geographic location-by-treatment interactions (Western versus Eastern Europe) may have had an effect on study results. Interactions were not statistically significant in either analysis: country-by-treatment interaction, p=.66; geographic location-by-treatment interaction, p=.178.

Only 5 percent of fluoxetine-treated patients at the Macedonian site and 43 percent at the Yugoslavian sites were reported as panic free at endpoint whereas 79 percent of Austrian and 57% of Swedish fluoxetuine-treated patients were panic free. See below.

Table R.3. Panic-Free Patients at Endpoint

Analysis by Country and Geographic Locations
Study HCJC

	Fluoxetine			Placebo			
	Total Patients	Panic-Free Patients		Total Patients	Panic-Free Patients		p-Valuea
Country	N	n	%	N	n	%	
Austria	14	11	79	14	7	50	.236
Sweden	14	8	57	13	3	23	.120
Macedonia	20	1	5	19	0	0	1.00
Yugoslavia	42	18	43	44	15	34	.507
Overall	90	38	42	90	25	28	**.018**
Geographic Locations							
Western Europe (Austria and Sweden)	28	19	68	27	10	37	**.03**
Eastern Europe (Macedonia and Yugoslavia)	62	19	31	63	15	24	.427

*Based on Fisher's exact test, with the exception of the Overall analysis, which utilizes logistic regression.

II. RECOMMEDATION:

Based on our meeting with the sponsor and the new data submitted I recommend we now approve this submission pending agreement on labeling. Their labeling is largely unchanged from the first submission with the exception that [redacted] (b) (4) [redacted] My main labeling concern is that I feel we will have to deal with their use of statements regarding [redacted] (b) (4) "free from panic attacks". [redacted] (b) (4) [redacted]

Earl D. Hearst, M.D.
Medical Reviewer
HFD-120

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

/s/

Earl Hearst
10/15/01 04:01:52 PM
MEDICAL OFFICER

Thomas Laughren
12/27/01 07:50:12 PM
MEDICAL OFFICER
I agree that this supplement is now approvable; see memo to file for more detailed comments.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA: 18-936
Sponsor: Lilly
Clock Date: 07/27/2000

Drug Name

Generic Name fluoxetine
Trade Name Prozac

Drug Characterization

Pharmacological Category: Antidepressant SSRI
Proposed Indication: Panic Disorder with and without Agoraphobia
Dosage Forms, Strengths, and Routes of Administration: Oral Tablets 10mg and 20mg

Reviewer Information

Clinical Reviewer: Earl D. Hearst, M.D.
Review Completion Date: 04/20/2001

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1.0 Material Reviewed

1.1 Material from NDA

The sponsor has submitted 117 volumes (07/20/00) plus a 1-volume safety update (11/14/00) consisting of the extension phase of study HCJB. There are three CD-ROMs with summaries, CRFs and case report tabulations. I have reviewed all narratives for patients meeting the criteria for adverse events leading to discontinuation and serious adverse events. I have also reviewed case report forms for all subjects who discontinued due to an adverse event. The case report forms are consistent with the narratives and clinical summaries provided by the sponsor.

1.2 Related Review

There is a statistical review by Yeh-Fong Chen Ph.D.(HFD-710).

2.0 Background

2.1 Indication

Panic Disorder with and without Agoraphobia

2.2 Related INDs and NDAs

IND 12,274 was submitted on 26 February 1976.
IND 53,079 for the delayed-release fluoxetine was submitted on 10 April 1997.

NDA 18-936 was submitted on 6 September 1983, and approved on 29 December 1987. This NDA is for the capsule forms.
NDA 20-101 was submitted on 10 July 1990, and approved on 24 April 1991. This is for the oral liquid form.
NDA 20-974 is for the tablet formulation. This was submitted on 19 March 1998, and approved on 10 March 1999.
NDA 21-235 is for the delayed release formulation. This was submitted on 13 March 2000 and has recently been approved.

2.3 Administrative History

2.3.1 Protocol background

Study B1Y-MC-HCHG (US)

- First patient enrolled: September 1994.
- Last patient completed: August 1996.
- Clinical Study Report written and approved September 1997.

Study B1Y-EW-HCHQ (European)

- First patient enrolled: May 1995.
- Last patient completed: 20 August 1997.

Studies B1Y-MC-HCJB (US)/ B1Y-MC-HCJC (European)

- Original protocols approved by Lilly (PDSS defined as primary outcome measure)
  - HCJB (05 November 1997)
  - HCJC (07 November 1997)
- Letter from FDA to Lilly (12 November 1997)
  - FDA suggests panic attack frequency is preferred primary outcome measure
- Lilly amends protocols (08 December 1997)
  - Protocols HCJB(a) and HCJC(a) declare primary outcome measure as reduction in total panic attacks
- First patient enrolled (assigned to therapy) in study HCJB (24 February 1998)
- Letter from FDA to Lilly (24 February 1998)
  - Clarifies that intent of 07 November 1997 letter was to identify full panic attack frequency as the primary efficacy variable
- First patient enrolled (assigned to therapy) in study HCJC (28 April 1998)
- Letter from FDA to Lilly (16 June 1998)
  - Reiterates that full panic attack frequency should be primary outcome measure
- Lilly amends protocol HCJB (17 December 1998)
  - Protocol HCJB(b) declares full panic attack frequency as primary outcome measure and increases enrollment target from 180 to 214 patients
  - Lilly, in error, does not submit this second amendment to the FDA
- Lilly claims they declared a new primary outcome measure (full panic attack frequency) for protocol HCJC, but enrollment is not increased as it was in HCJB
  - A change is documented in a Note to File 9 April 1999 but the note does not specify what the specifics of the change will be. Nothing is submitted at the time to the FDA

2.3.2 Financial disclosure

The sponsor has provided a listing of investigators for required studies HCJB and HCJC and certified that there were no financial conflicts of interest. Studies HCJG and HCJQ predate the financial disclosure requirement.

2.4 Directions for Use

The sponsor's directions are reproduced below in italics.

Panic Disorder—

Initial Treatment--In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of panic disorder, patients were administered fluoxetine doses in the range of 10 mg to 60 mg/day (see Clinical Trials under Clinical Pharmacology). Treatment should be initiated with a dose of 10 mg/day. After 1 week, the dose should be increased to 20 mg/day. The most frequently administered dose in the two flexible-dose clinical trials was 20 mg/day.

A dose increase may be considered after several weeks if no clinical improvement is observed. Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with panic disorder.

As with the use of Prozac in other indications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (see Geriatric Use under Precautions), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (see Liver Disease and Renal Disease under Clinical Pharmacology, and Use in Patients with Concomitant Illness under Precautions).
Maintenance/Continuation Treatment—While there are no systematic studies that answer the question of how long to continue Prozac, panic disorder is a chronic condition and it is reasonable to consider continuation for a responding patient. (b) (4)

2.5 Foreign Marketing

There is currently no marketing of Prozac for panic disorder in any foreign country.

3.0 Chemistry

There is no change in this section.

4.0 Preclinical Pharmacology

There is no change in this section.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

(b) (4) trials were conducted to evaluate the safety and efficacy of fluoxetine in the treatment of panic disorder: Studies B1Y-MC-HCJC, B1Y-MC-HCJB, (b) (4). The cutoff date for data in the original panic submission is December 28, 1999. For the 120-day Safety Update submitted to the FDA on November 14, 2000 the cutoff date for data is June 27, 2000.

The safety (b) (4) of fluoxetine for the acute treatment of panic disorder has been evaluated for 767 patients (425 patients exposed to doses of fluoxetine of 10 to 60 mg/day, 342 patients exposed to placebo) in four placebo-controlled trials.

Studies HCJC and HCJB are the key studies relied on by the sponsor to provide the primary data for assessing the effectiveness of fluoxetine in the treatment of panic disorder. The sponsor feels that (b) (4) I will summarize these studies briefly below.

B1Y-MC-HCJC: A double-blind, randomized, parallel, placebo-controlled, multicenter study conducted in Europe to determine whether fluoxetine 20 to 60 mg/day was more effective than placebo in decreasing full panic attack frequency during acute treatment in patients with panic disorder with or without agoraphobia, according to DSM-IV criteria.

B1Y-MC-HCJB: A double-blind, randomized, parallel, placebo-

controlled, multicenter study conducted in the United States (US) to determine whether fluoxetine 20 to 60 mg/day was more effective than placebo in decreasing full panic attack frequency during acute treatment in patients with panic disorder with or without agoraphobia, according to DSM-IV criteria.

B1Y-MC-HCHG: A double-blind, randomized, parallel, placebo-controlled, multicenter study conducted in the United States to (b) (4) of fluoxetine 20 mg/day, fluoxetine 10 mg/day, and placebo in the treatment of patients with panic disorder with or without agoraphobia according to modified DSM-III-R criteria.

B1Y-EW-HCHQ: A double-blind, randomized, parallel, placebo- and active comparator-controlled, multicenter study conducted in Europe to (b) (4) of fixed doses of fluoxetine 20 mg/day, clomipramine 100 mg/day, and placebo in the treatment of panic disorder with or without agoraphobia according to modified DSM-III-R criteria.

(b) (4)

There are 425 fluoxetine and 342 placebo patients in the database for this submission. Cut-off dates are listed in the table below.

Cutoff Dates for Data in Panic Submission

Protocol	First patient enrolled (assigned to therapy)	Last patient completed	Interim Analyses	Database validated and locked
B1Y-MC-HCHG	Sept 1994	Aug 1996	17 Jun 1996 (DMB)	22 Apr 1997
B1Y-EW-HCHQ	May 1995	20 Aug 1997	• 16 Aug 1996 (acute phase) • 12 May 1997 (final analysis of acute phase, interim analysis of maintenance phase)	• 17 Oct 1997 • 12 Jan 2000 (re-locked)

B1Y-MC-HCJC	28 Apr 1998	07 Oct 1999	NA	20 Nov 1999
B1Y-MC-HCJB (acute phase only)	24 Feb 1998	28 Dec 1999	NA	• 11 Feb 2000 • 7 Mar 2000 (re-locked)
B1Y-MC-HCJB (extension phase)	26 May 1998	27 Jun 2000	NA	14 Aug 2000 (final HCJB database)

The sponsor provided the following table enumerating patients.

ENUMERATION OF ALL PATIENTS BY STUDY

Study	Location/Centers	Acute Phase Randomized/Completed/ Discontinued	Continuation Phase Entered/Completed	Maintenance Phase Entered/Completed	Discontinuation Phase Entered/Completed
B1Y-MC-HCJC	Europe 8 Investigators 9 Study Centers	**Fluoxetine** Randomized N=90 Completed N=75 Discontinued N=15 **Placebo** Randomized N=90 Completed N=80 Discontinued N=10 **Total** Randomized N=180 Completed N=155 Discontinued N=25	NA	NA	NA
B1Y-MC-HCJB	US 17 Investigators 20 Study Centers	**Fluoxetine** Randomized N=108 Completed N=67 Discontinued N=41	**Fluoxetine**[a] Entered N=47 Completed N=26 Discontinued N=21	NA	NA

		Placebo Randomized N=106 Completed N=71 Discontinued N=35 **Total** Randomized N=114 Completed N=138 Discontinued N=76	**Placebo**[a] Entered N=34 Completed N=16 Discontinued N=18 **Total**[a] Entered N=81 Completed N=42 Discontinued N=39		

[a] HCJB Continuation Phase data submitted as 120-day Safety Update. Data not included in ISS, ISE

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ENUMERATION OF ALL PATIENTS BY STUDY (continued)

Study	Location/Investigators	Acute Phase Randomized/Completed	Continuation Phase Entered/Completed	Maintenance Phase Entered/Completed	Discontinuation Phase Entered/Completed
B1Y-MC-HCHQ	Europe 34 Investigators 34 Centers	**Fluoxetine** Randomized N=62 Completed N=37 Discontinued N=25 **Clomipramine** Randomized N=70 Completed N=47 Discontinued N=23 **Placebo** Randomized N=68 Completed N=46 Discontinued N=22 **Total** Randomized N=200 Completed N=130 Discontinued N=70	NA	**Fluoxetine** Entered N=37 Completed N=31 Discontinued N=6 **Clomipramine** Entered N=47 Completed N=38 Discontinued N=9 **Placebo** Entered N=46 Completed N=30 Discontinued N=16 **Total** Entered N=130 Completed N=99 Discontinued N=31	**Fluoxetine** Entered N=31 Completed N=25 Discontinued N=6 **Clomipramine** Entered N=38 Completed N=35 Discontinued N=3 **Placebo** Entered N=30 Completed N=23 Discontinued N=7 **Total** Entered N=99 Completed N=83 Discontinued N=16

HCJB Continuation Phase data submitted as 120-day Safety Update. Data not included in ISS, ISE

5.1.2 Demographics

A summary of patient baseline characteristics is presented in Table 2.2. Patients were between the ages of 16 and 79 years with a mean age of approximately 37 years. Patients were predominately female (63%) and Caucasian (91%). There were no statistically significant differences between treatment groups in age, gender, or origin.

Table 2.2. Summary of Patient Characteristics
Panic Integrated Safety Population
Acute Treatment Phase

Variable	Flx (N=425)	Plac (N=342)	Total (N=767)	p-Value
Sex: No. (%)				
No. Patients	425	342	767	.452*
Female	263 (61.9)	221 (64.6)	484 (63.1)	
Male	162 (38.1)	121 (35.4)	283 (36.9)	
Origin: No. (%)				
No. Patients	425	342	767	.087*
AFRICAN DESCENT	22 (5.2)	14 (4.1)	36 (4.7)	
ASIAN	0	3 (0.9)	3 (0.4)	
CAUCASIAN	382 (89.9)	314 (91.8)	696 (90.7)	
EAST/SE ASIAN	0	1 (0.3)	1 (0.1)	
HISPANIC	6 (1.4)	6 (1.8)	12 (1.6)	
OTHER	14 (3.3)	4 (1.2)	18 (2.3)	
WESTERN ASIAN	1 (0.2)	0	1 (0.1)	
Age: yrs.				
No. Patients	425	342	767	.935**
Mean	37.04	37.23	37.13	
Median	35.86	36.37	36.16	
Standard Dev.	10.75	11.01	10.86	
Minimum	16.49	15.77	15.77	
Maximum	70.40	79.21	79.21	

Flx = fluoxetine; Plac = placebo;
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=investigator and treatment.

Table 3.1 presents the baseline severity of illness of the randomly assigned patients in each study. The treatment groups were comparable in the mean number of full and total panic attacks per week, HAMA score, and HAMD17 score. In comparisons of the mean number of full and total panic attacks per week between studies, studies HCJC and HCJB were comparable. There are no significant differences noted.

Table 3.1. Baseline Severity of Illness
All Randomized Patients
All Panic Studies

(b) (4)

Variable	Study HCJC	Study HCJB
Mean Number of Full Panic Attacks per Week		
Fluoxetine	3.94	3.46
Placebo	3.78	3.10
p-Value	.576	.537
Mean Number of Total Panic Attacks per Week		
Fluoxetine	4.41	3.91
Placebo	4.43	3.31
p-Value	.531	.263
Mean HAMA Score		
Fluoxetine	23.13	18.94
Placebo	23.60	19.71
p-Value	.420	.233
$^{\text{Mean HAMD}}_{17}$ Score		
Fluoxetine	10.87	11.31
Placebo	11.56	11.40
p-Value	.231	.882

(b) (4)

5.1.3 Extent of Exposure (dose/duration)

In the four studies included in this submission, patients received fluoxetine dosages of 5 mg/day to 60 mg/day. In Studies HCJC, HCJB, and HCHG, patients initially received fluoxetine 10 mg/day. After 1 week of treatment, the dosage was titrated to 20 mg/day. In Studies HCJC and HCJB, after 5 weeks of treatment at 20 mg/day, the dosage could have been increased in 20-mg increments to a maximum dose of 60 mg/day. In Studies HCJC and HCJB, analyses were performed on the data at 6 weeks, at which point all patients in the fluoxetine treatment group were receiving fluoxetine 20 mg/day.

The final mean fluoxetine dose in Study HCJC was 29 mg/day. The final

mean dose in Study HCJB was 39 mg/day.

Table 2.3 summarizes patient exposure (mean total number of days) to study drug during the acute treatment phase. Fluoxetine-treated patients were exposed to study drug for a mean of 68 days while placebo-treated patients were exposed to study drug for a mean of 72 days.

Table 2.3. Exposure to Therapy
Panic Integrated Safety Population
Acute Treatment Phase

Variable	Flx (N=425)	Plac (N=342)	Total (N=767)
Total days of exposure to study drug			
No. Patients	**425**	**342**	**767**
Mean	**67.53**	**71.62**	**69.36**
Median	**76.00**	**84.00**	**81.00**
Standard Dev.	**26.12**	**25.19**	**25.77**
Minimum	**1.00**	**1.00**	**1.00**
Maximum	**163.00**	**113.00**	**163.00**

Flx = fluoxetine; Plac = placebo;

The final and modal dosing is displayed below for the two key studies.

Table 3.10. Summary of Prescribed Dosage Acute Treatment Phase All Randomized Patients B1Y-MC-HCJC and B1Y-MC-HCJB

Clinical	Fluoxetine Final Dose (mg)			Fluoxetine Modal Dose (mg)	
	N	Mean	Median	Mean	Median
HCJC	89	29.44	20.00	21.44	20.00
HCJB	107	38.79	40.00	21.59	20.00

N = number of patients receiving fluoxetine in the study.

5.1.4 Disposition

Table 2.1 summarizes patient disposition during the acute treatment phase. Sixty-three percent of the fluoxetine-treated patients and 67% of the placebo-treated patients completed the acute treatment phase. The percentage of patients who completed treatment was not statistically significantly different between groups. The most common reason for discontinuation in the fluoxetine treatment group was adverse events (8%). The most common reason for discontinuation among placebo-treated patients was lack of efficacy (9%). There were no statistically

significant differences between treatment groups for any reason discontinued.

Table 2.1. Summary of Reasons for Discontinuation
Panic Integrated Safety Population
Acute Treatment Phase

Primary Reason for Discontinuation	Flx (N=425) n (%)	Plac (N=342) n (%)	Total (N=767) n (%)	p-Value*
Reporting Interval Complete	267 (62.8)	229 (67.0)	496 (64.7)	.255
Adverse Event	34 (8.0)	17 (5.0)	51 (6.6)	.109
Satisfactory Response	2 (0.5)	0	2 (0.3)	.505
Lack of Efficacy	29 (6.8)	30 (8.8)	59 (7.7)	.341
Lost to Follow-up	33 (7.8)	18 (5.3)	51 (6.6)	.190
Patient Decision	25 (5.9)	29 (8.5)	54 (7.0)	.201
Physician Decision	1 (0.2)	1 (0.3)	2 (0.3)	1.00
Protocol Requirement	33 (7.8)	18 (5.3)	51 (6.6)	.190

Flx = fluoxetine; Plac = placebo
* Frequencies are analyzed using a Fisher's Exact test.

5.2 Secondary Sources

5.2.1 Non-IND Studies

Eli Lilly and Company is not aware of any studies of fluoxetine for panic disorder conducted by Eli Lilly and Company outside the fluoxetine IND (IND 12,274).

However, they are aware of one study conducted by a non-Lilly investigator under (b) (4) Franklin Schneier, M.D. investigated the efficacy of fluoxetine compared to imipramine and placebo in the treatment of panic disorder.

Data from the acute phase of the trial were presented by the investigator at the 1998 meetings of the Anxiety Disorders Association of America, and the American Psychiatric Association (a copy of the abstract is in the appendix). Based upon a search of the National Library of Medicine PubMed database, no additional published data from this study are available at this time.

5.2.2 Post-Marketing Experience

Prozac has not been approved for this indication anywhere.

5.2.3 Literature

A search of the medical literature was conducted by the sponsor to identify published reports of fluoxetine in the treatment of patients with panic disorder. The literature search was completed on March 20, 2000, and includes reports published in the online databases during the time period 1969 to March 13, 2000.

The following databases were used to complete the comprehensive searches: Medline, Biosis Previews, SciSearch, Derwent Drug File, PsycInfo, Embase. The following search strategy was employed to identify the publications: Keywords: {panic} OR {Panic—Drug Effects—DE} OR {panic - complication} OR {panic - complication -maj} OR {panic - diagnosis} OR {panic - diagnosis -maj} OR {panic - disease management} OR {panic - disease management -maj} OR {panic – drug resistance -maj} OR {panic - drug therapy} OR {panic - drug therapy -maj} OR {panic –epidemiology OR {panic - epidemiology -maj} OR {panic - etiology} OR {panic –etiology -maj} OR {panic - prevention -maj} OR {panic - side effect} OR {panic – side effect -maj} OR {panic - therapy} OR {panic - therapy -maj} OR {panic -maj} OR {Panic Disorder—Complications} OR {Panic Disorder—Drug Therapy} OR {PANIC DISORDER—physiopathology} OR {Panic Disorder—Psychology} OR {Panic Disorder—Chemically Induced—CI} OR {Panic Disorder—Diagnosis—DI} OR {Panic Disorder—Drug Therapy—DT} OR {Panic Disorder—Etiology—ET} OR {Panic Disorder—Prevention and Control—PC} OR {Panic Disorder—Psychology—PX}OR Titles: panic NOT Keywords: {rat} OR {rabbit} OR {rabbit -maj} OR {Rabbits} OR {dog} OR {dog -maj} OR {Dogs} OR {Dogs—Psychology—PX} OR {cat} OR {cat -maj} OR {Cat Diseases—Drug Therapy} OR {Cat Diseases—Psychology} AND Keywords: fluoxetine The initial search identified 480 publications. Review articles and publications focused solely on other pharmacological

management options for panic disorder were excluded from further review. Fifty-six publications were determined to be clinical studies or case reports concerning the use of fluoxetine in panic disorder.

I have reviewed the summaries of these publications provided by the sponsor and do see any significant data pertinent to this review.

5.3 Adequacy of Clinical Experience

The exposure to Prozac appears to be of an adequate duration and dosage and the clinical experience is otherwise satisfactory.

5.4 Data Quality and Completeness

The data appears to be complete and of adequate quality to provide efficacy and safety information for evaluation.

6.0 Summary of Human Pharmacokinetics

There is no change in this section.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

HCJC

Title: Fluoxetine Versus Placebo in Panic Disorder

Investigators: This multicenter study included eight principal investigators.

Study Centers: Nine study centers in central and eastern Europe were used.

Dates of Study: 28 April 1998 through 7 October 1999

Objectives:

The primary objective was to determine whether fluoxetine 20 to 60 mg/day was more effective than placebo in decreasing full panic attack frequency during acute treatment of patients who, according to DSM-IV criteria,

had panic disorder with or without agoraphobia.

Study Design

This study was a double-blind, randomized, parallel, placebo-controlled, multicenter trial, which compared the efficacy of fluoxetine versus placebo in decreasing full panic attack frequency in patients diagnosed with panic disorder with or without agoraphobia according to DSM-IV criteria.

Study B1Y-MC-HCJC was conducted concurrently with another pivotal study, B1Y-MC-HCJB. The protocols were similar in study design and used the same statistical and analytical methods. Both studies included an evaluation phase and an acute treatment phase (Study Periods I and II). Study B1Y-MC-HCJB also included a 6-month, double-blind, optional extension phase (Study Period III). Study B1Y-MC-HCJC consisted of two study periods, which are briefly described below:

Study Period I was a 2-week evaluation period during which patients received single-blind placebo treatment. Baseline values were established and patients were evaluated for eligibility to enter the study.

Study Period II was a 12-week, double-blind, acute treatment period during which patients were randomly assigned to either fluoxetine or placebo treatment. Fluoxetine-treated patients received fluoxetine 10 mg/day for the first week of treatment. After this 1-week treatment period, all fluoxetine-treated patients underwent a forced titration to fluoxetine 20 mg/day. At fixed intervals (Visits 5, 6, and 7), patients were titrated up to a maximum dose of fluoxetine 60 mg/day based on predefined titration criteria (CGI-Severity score >2).

Number of Subjects:

Fluoxetine: Male 43, Female 47, Total 90.
Placebo: Male 37, Female 53, Total 90.

Diagnosis and Inclusion Criteria:

Eligible patients were male or female outpatients aged 18 years or older who met DSM-IV criteria for panic disorder with or without agoraphobia and who had at least four full panic attacks during the 4 weeks prior to study entry; all four attacks must not have occurred in the same week. Additionally, patients must have had scores of 12 on the PDSS and 4 on the CGI-Severity scale.

Duration of Treatment:

Study Period I: single-blind, placebo evaluation phase, 2 weeks
Study Period II: double-blind, randomized treatment phase, 12 weeks

Criteria for Evaluation:

Efficacy: The primary outcome measure was the percentage of patients panic-free at endpoint. Efficacy was also evaluated by comparing the percentage of patients experiencing at least a 50% reduction in full panic attacks and the mean reduction in full panic attacks per week. Data on panic attack frequency was collected using a patient diary.

Safety: To assess safety, a physical examination and clinical laboratory tests were performed, patient medical and psychiatric histories, vital signs, weight, and height were recorded, and adverse events and concomitant medications were monitored.

Statistical Methods: Efficacy: The primary analysis used logistic regression analysis to compare the percentage of patients with zero full panic attacks. Additional analyses included logistic regression analysis to compare the percentage of patients having at least a 50% reduction from baseline in the number of full panic attacks and analysis of variance (ANOVA) on mean change from baseline to endpoint in the number of full panic attacks per week.

Safety: Fisher’s exact test was used to analyze treatment-emergent adverse events during the double-blind, acute treatment phase.

Rating Scales

The primary efficacy measure was the frequency of full panic attacks. A full panic attack met at least 4 of the 13 possible symptoms of a panic attack according to the DSM-IV criteria. The primary efficacy endpoint was the percentage of patients panic-free during the final visit interval. Additional efficacy analyses were the percentage of patients experiencing at least a 50% reduction in full panic-attack frequency from baseline to endpoint and the mean change from baseline to endpoint in the number of full and total panic attacks per week. Total panic attacks were defined as the number of full panic attacks and limited-symptom panic attacks. A limited-symptom panic attack was defined as a panic attack that met 1, 2, or 3 of the 13 symptoms of a panic attack. Patients recorded the incidence of full and limited-symptom panic attacks along with the severity of the symptoms in a patient diary, and these data were used to calculate the panic attack frequency (number of attacks per week) for each visit interval.

Secondary efficacy measures included the following:

7-Item Multicenter Collaborative Panic Disorder Severity Scale (PDSS; Shear et al. 1997): A clinician-rated instrument administered to assess the severity of panic disorder and its improvement during the course of treatment. This index of illness severity is specific to panic disorder.

Clinical Global Impression of Severity (CGI-Severity): A clinician-rated instrument administered to assess the global severity of the disorder and its change over the course of the study.

Panic and Phobic Disorder Scale (PPDS; NIMH 1976) -Clinician and -Patient: Administered to assess the patient's and the clinician's impression of the severity of symptom domains specific to panic disorder.

Hamilton Anxiety Rating Scale (HAMA): Administered by the clinician to assess the patient's severity of anxiety, its improvement during the course of treatment, and the timing of such improvement.

17-item Hamilton Depression Rating Scale, modified (HAMD17 ; Hamilton 1960): This scale was administered to assess the severity of depression and its change during the course of treatment. It is completed by the efficacy rater.

State-Trait Anxiety Inventory (STAI; Spielberger 1983): Completed by the patient to assess anxiety and change in anxiety over time.

Analysis

The primary efficacy measure was the reduction in full panic attacks (used interchangeable with frequency of full panic attacks), which was defined as the percentage of patients with zero panic attacks during the final visit interval.

The primary efficacy and safety analyses were based upon the intent-to-treat principle. All treatment effects were to be tested at a two-sided alpha level of 0.05. Investigators with fewer than 2 randomized patients per treatment group were to be pooled for statistical analysis purposes.

Changes were made to the protocol on two occasions. These changes are documented as a protocol amendment and as a note-to-file. The amendment to the protocol was made on 8 December 1997, approximately 5 months before patient enrollment began; the note-to-file was made on 9 April, 1999.

The most significant change was necessitated by input from the US Food and Drug Administration (FDA) regarding the primary efficacy measure. In the original protocol, the primary efficacy measure was the PDSS. The FDA informed Lilly that it considered panic attack frequency as the standard measure for clinical trials assessing panic disorder.

The protocol was amended so that the study's primary efficacy measure became frequency of total panic attacks. Later input from the FDA clarified that it meant full panic attack frequency. As a result, full panic attack frequency as assessed by the percentage of patients panic free at endpoint was declared as the primary outcome measure. This change was documented in a note-to-file dated 9 April 1999 according to the sponsor. I have reviewed this note and placed it in the appendix. This note does not specify the exact nature of the change to the primary efficacy variable but does say a change will be made and implies it will be similar to the change in HCJB.

Other changes made included the following: The original protocol required that patients be blinded to changes in their dosage by requiring them to take three capsules daily. Because of difficulties in providing clinical trial materials to the investigational sites under blinded conditions, the dosage and administration scheme were modified. Instead of blinding patients to changes in their dosage, following Visit 5, patients could take from one to three capsules daily in both study arms. The amendment also added the PDSS to the list of secondary efficacy measures.

I have asked the sponsor if there was a formal protocol change for HCJC involving a signed document as was done for HCJB. They informed me there was no signed document other than the 4/9/99 note to file.

STUDY RESULTS:

Protocol

Investigators/Sites

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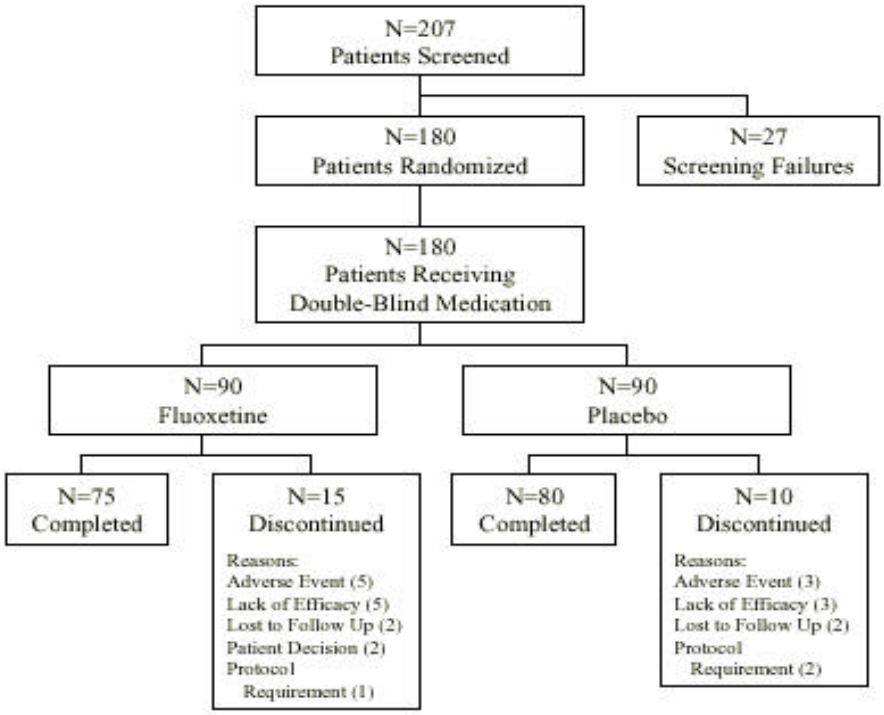
Disposition

207 patients were screened for eligibility and 180 patients were enrolled into the 12-week, double-blind acute treatment phase. Twenty-five patients (14%) discontinued during the acute treatment phase: 15 from the fluoxetine treatment group and 10 from the placebo group. One hundred fifty-five patients (86%) finished the study.



Discontinuations

Table 10.1 presents a summary by treatment group of reasons for discontinuation during the acute treatment phase. The most common reasons for discontinuation for all patients were adverse events (4%) and lack of efficacy (4%). Differences in the reasons for discontinuation between treatment groups were not statistically significant.

Table 10.1. Reasons for Discontinuation
All Randomized Patients
Acute Treatment Phase
B1Y-MC-HCJC

Primary Reason for Discontinuation	Flx (N=90) n (%)	Plac (N=90) n (%)	Total (N=180) n (%)	p-Value*
PROTOCOL COMPLETE	75 (83.3)	80 (88.9)	155 (86.1)	.389
ADVERSE EVENT	5 (5.6)	3 (3.3)	8 (4.4)	.720
LACK OF EFFICACY	5 (5.6)	3 (3.3)	8 (4.4)	.720
LOST TO FOLLOW-UP	2 (2.2)	2 (2.2)	4 (2.2)	1.00
PATIENT DECISION	2 (2.2)	0	2 (1.1)	.497
PROTOCOL REQUIREMENT	1 (1.1)	2 (2.2)	3 (1.7)	1.00

* Frequencies are analyzed using a Fisher's Exact test.

Demographics

Table 11.1 summarizes patient physical characteristics by treatment group. The mean age of patients was 36 years. All 180 patients were Caucasian, and 100 (56%) were female. There was no significant difference between the two treatment groups in age or gender.

Table 11.1. Patient Demographic Characteristics
All Randomized Patients
B1Y-MC-HCJC

Variable	Flx (N=90)	Plac (N=90)	Total (N=180)	p-Value
Sex: No. (%)				
No. Patients	90	90	180	.453*
Female	47 (52.2)	53 (58.9)	100 (55.6)	
Male	43 (47.8)	37 (41.1)	80 (44.4)	
Origin: No. (%)				
No. Patients	90	90	180	.*
CAUCASIAN	90 (100)	90 (100)	180 (100)	

* Frequencies are analyzed using a Fishers-Exact test.

**** Means are analyzed using a Type III Sum of Squares analysis of variance**

Severity of illness

The patients showed little difference is the baseline severity of illness. See table 11.4.

Table 11.4. Baseline Severity of Illness: Frequency of Panic Attacks
All Randomized Patients
B1Y-MC-HCJC

Variable	Fluoxetine (N=90)	Placebo (N=90)	Total (N=180)	p-Value
Number of Full Panic Attacks/Week (Visit: 2)				
Mean	3.94	3.78	3.86	.576
Median	3.00	2.60	2.76	
Standard Dev.	3.46	3.02	3.24	
Minimum	0.00	0.50	0.00	
Maximum	17.27	19.60	19.60	
Number of Total Panic Attacks/Week (Visit: 2)				
Mean	4.41	4.43	4.42	.531
Median	3.17	3.25	3.23	
Standard Dev.	3.88	3.48	3.68	
Minimum	0.54	0.78	0.54	
Maximum	21.93	20.07	21.93	

Exposure

The study drug exposure is given in the table below.

Table 12.1. Duration of Study Drug Exposure
All Randomized Patients
B1Y-MC-HCJC

Variable	Flx (N=90)	Plac (N=90)	Total (N=180)	p-Value
Total days of exposure to study drug				
No. Patients	90	90	180	.214**
Mean	75.66	80.98	78.32	
Median	85.00	85.00	85.00	
Standard Dev.	22.38	17.43	20.18	
Minimum	8.00	3.00	3.00	
Maximum	97.00	99.00	99.00	

**** Means are analyzed using a Type III Sum of Squares analysis of variance**

Dosing Information

Table 12.1 summarizes patient exposure to fluoxetine and placebo

during the acute treatment phase. The mean length of exposure to study drug was 76 days for the fluoxetine treatment group and 81 days for the placebo group. Minimum exposure time was 8 days for the fluoxetine group and 3 days for the placebo group.

Table 12.1. Duration of Study Drug Exposure
All Randomized Patients
B1Y-MC-HCJC

Variable	Flx (N=90)	Plac (N=90)	Total (N=180)	p-Value
Total days of exposure to study drug				
No. Patients	90	90	180	.214**
Mean	75.66	80.98	78.32	
Median	85.00	85.00	85.00	
Standard Dev.	22.38	17.43	20.18	
Minimum	8.00	3.00	3.00	
Maximum	97.00	99.00	99.00	

** Means are analyzed using a Type III Sum of Squares analysis of variance

Table 12.2 summarizes fluoxetine dosages administered during the study.

Table 12.2. Summary of Prescribed Dosage
All Randomized Patients
B1Y-MC-HCJC

Variable	Flx (N=90)	Plac (N=90)	Total (N=180)
Mean Dose			
No. Patients	90	90	180
Mean	22.78	0.00	11.39
Median	19.17	0.00	5.00
Standard Dev.	6.83	0.00	12.40
Minimum	10.00	0.00	0.00
Maximum	36.12	0.00	36.12
Modal Dose			
No. Patients	90	90	180
Mean	21.44	0.00	10.72
Median	20.00	0.00	5.00
Standard Dev.	6.63	0.00	11.72
Minimum	10.00	0.00	0.00
Maximum	40.00	0.00	40.00

Concomitant Medications

Table 11.7 summarizes the use of concomitant medications during the study. Of the 180 patients randomized, 28 (16%) reported using concomitant medications. The most commonly used medication was acetylsalicylic acid.

Table 11.7. Concomitant Medication Use
All Randomized Patients
B1Y-MC-HCJC

Drug Name	Flx (N=90) n (%)	Plac (N=90) n (%)	Total (N=180) n (%)
PATIENTS WITH >= 1 DRUG	11 (12.2)	13 (14.4)	24 (13.3)
PATIENTS WITH NO DRUGS	79 (87.8)	77 (85.6)	156 (86.7)
ACETYLSALICYLIC ACID	0	3 (3.3)	3 (1.7)
ALUMINIUM PHOSPHATE GEL	1 (1.1)	1 (1.1)	2 (1.1)
FAMOTIDINE	1 (1.1)	1 (1.1)	2 (1.1)
LEVOTHYROXINE SODIUM	2 (2.2)	0	2 (1.1)
METHYCLOTHIAZIDE/AMILORIDE/AMI	1 (1.1)	1 (1.1)	2 (1.1)
METOCLOPRAMIDE	2 (2.2)	0	2 (1.1)
ACETYLCYSTEINE	0	1 (1.1)	1 (0.6)
ACETYLSALICYLIC ACID/CAFFEINE/	0	1 (1.1)	1 (0.6)
ATENOLOL	0	1 (1.1)	1 (0.6)
CAPTOPRIL	0	1 (1.1)	1 (0.6)
EBASTINE	0	1 (1.1)	1 (0.6)
ESTRADIOL	1 (1.1)	0	1 (0.6)
ESTRADIOL/NORETHISTERONE	0	1 (1.1)	1 (0.6)
ETHINYLESTRADIOL	0	1 (1.1)	1 (0.6)
ETHINYLESTRADIOL/DESOGESTREL	1 (1.1)	0	1 (0.6)
FOLIC ACID/FERROUS SULFATE	1 (1.1)	0	1 (0.6)
IBUPROFEN	0	1 (1.1)	1 (0.6)
ITRACONAZOLE	1 (1.1)	0	1 (0.6)
LEVONORGESTREL	0	1 (1.1)	1 (0.6)
LISINOPRIL	0	1 (1.1)	1 (0.6)
NORFLOXACIN	1 (1.1)	0	1 (0.6)
OMEPRAZOLE	1 (1.1)	0	1 (0.6)
ORAL CONTRACEPTIVE NOS	0	1 (1.1)	1 (0.6)
PYRIDOXINE	0	1 (1.1)	1 (0.6)
RANITIDINE	0	1 (1.1)	1 (0.6)
SIMVASTATIN	0	1 (1.1)	1 (0.6)
TRIMETHOPRIM	1 (1.1)	0	1 (0.6)

RESULTS:

Forty-two percent of fluoxetine-treated patients were panic free at endpoint versus 28% of placebo-treated patients (p=.018); 82% of fluoxetine-treated patients experienced a 50% or greater reduction in panic attacks versus 61% of placebo-treated patients (p=.001).

Our Statistical reviewer feels a more reasonable primary endpoint and analysis should be the full panic attack frequency and the ANOVA on ranked change from baseline to endpoint in full panic attack

frequency using LOCF. If this primary endpoint and analysis were to be considered Studies HCJC is not significant. Table 3 is prepared by Yeh-Fong Chen Ph.D.

Table 3. Summaries of Supportive Efficacy Analyses Results for Study B1Y-MC-HCJC

Variables	Fluoxetine	Placebo	p-value
Percentage of Patients Having ≥ 50% Reduction in Frequency of Full Panic Attacks from Baseline	82% (n=90)	61% (n=90)	**0.001**
Mean Change from Baseline to Endpoint in Frequency of Full Panic Attacks	-2.9 (n=90)	-2.2 (n=90)	0.078
Mean Change from Baseline to Endpoint in Frequency of Total Panic Attacks	-3.2 (n=90)	-2.5 (n=90)	0.263

The analysis results for some secondary endpoints are shown in Table 4, prepared by Yeh-Fong Chen Ph.D.

Table 4. Summaries of Some Secondary Efficacy Analyses Results for Study B1Y-MC-HCJC

Variables	Fluoxetine	Placebo	p-value
Mean Change from Baseline to Endpoint in PDSS Average Score	-1.64 (n=88)	-1.09 (n=90)	**0.009**
Mean Change from Baseline to Endpoint in CGI-Severity Score	-2.61 (n=88)	-1.82 (n=90)	**0.037**
Mean of PPDS Endpoint Analyses on Clinician-Rated Scales	1.977 (n=88)	2.600 (n=90)	0.186

(Overall Functioning-Clinician)			
Mean of PPDS Endpoint Analyses on Patient-Rated Scales (Overall Functioning-Clinician)	2.068 (n=88)	2.622 (n=90)	0.477
Mean Change from Baseline to Endpoint in HAMA Total Score	-14.86 (n=85)	-9.97 (n=88)	**0.043**
Mean Change from Baseline to Endpoint in STAI Total Score	-15.32 (n=85)	-7.48 (n=88)	**0.005**
Mean Change from Baseline to Endpoint in $HAMD_{17}$ Total Score	-6.482 (n=85)	-4.227 (n=88)	0.137

EFFICACY CONCLUSION STUDY I

This study would appear to be positive for efficacy if the sponsor's failure to submit the final protocol changes prior to writing the final study report is overlooked. This study in fact never had a signed protocol amendment. It did have a signed memo-to-file implying a change to the protocol similar to study HCJB (which also did not submit the key protocol amendment until the final study report was submitted). There may also be a statistical issue concerning multiple primary endpoints or additional analyses as the sponsor calls them.

HCJB

Title: Fluoxetine Versus Placebo in Panic Disorder

Investigators:

Seventeen principal investigators participated in this multicenter study.

Study Centers:

There were 20 study centers. All centers were in the United States (US). Investigators 001, 007, and 008 each used two centers.

Dates of Study:

24 February 1998 through 28 December 1999

Objectives:

The primary objective was to determine whether fluoxetine (20 to 60 mg/day)is more effective than placebo in decreasing full panic attack frequency during acute treatment of patients who, according to DSM-IV criteria, had panic disorder with or without agoraphobia.

Methodology:

The study was a multicenter, double-blind, randomized, parallel, placebo-controlled study consisting of three study periods. Study Period I was a single-blind, placebo lead-in, evaluation phase. Study Period II was a double-blind, acute treatment phase during which patients were randomly assigned to fluoxetine or placebo treatment. During this period, a flexible dose-escalation scheme was employed. Fluoxetine-treated patients were initially given 10 mg/day; after 1 week, a forced titration occurred that raised the dosage to 20 mg/day. Based on predefined titration criteria, patients could have had their dosage increased from fluoxetine 20 mg/day to a maximum of fluoxetine 60 mg/day. Study Period III was an optional, 6-month, double-blind, extension phase. Note: Study Period III was ongoing at the time this report was written; thus data for this study period were not analyzed and will not be presented here but will be presented in the safety update section of this review.

Number of Subjects:

Fluoxetine: Male 41, Female 67, Total 108.
Placebo: Male 35, Female 71, Total 106.

Diagnosis and Inclusion Criteria:

Eligible patients were male or female outpatients, aged 18 years or older, who met DSM-IV criteria for panic disorder with or without agoraphobia and who had experienced at least four full panic attacks during the 4 weeks prior to study entry; all four attacks must not have occurred in the same week. Patients must also have had scores of 12 on the 7-Item Multicenter Collaborative Panic Disorder Severity Scale (PDSS) and 4 on the Clinical Global Impressions of Severity (CGI-Severity) scale.

Dosage and Administration:

Test Product
Study Period II:
10-mg capsules of fluoxetine hydrochloride CT07620
20-mg capsules of fluoxetine hydrochloride CT07618

Study Period III:
20-mg capsules of fluoxetine hydrochloride CT09678
Reference Therapy
Study Periods I and II:
Placebo capsules CT07619 and CT10799
Study Period III:
Placebo capsules CT09679

Duration of Treatment:

Single-blind, placebo lead-in evaluation phase (Study Period I): 2 weeks
Double-blind, randomized, acute treatment phase (Study Period II): 12 weeks
Double-blind, optional extension phase (Study Period III): 6 months

Criteria for Evaluation:

Efficacy: The primary outcome measure was the percentage of patients panic free at the acute treatment phase endpoint. Efficacy was also evaluated by comparing the percentage of patients experiencing at least a 50% reduction in full panic attacks and the mean reduction in full panic attacks per week. Data on panic attack frequency was collected using a patient diary.

Safety: To assess safety, a physical examination and clinical laboratory tests were performed, patient medical and psychiatric histories, vital signs, weight, and height were recorded, and adverse events and concomitant medications were monitored.

Statistical Methods:

Efficacy: The primary analysis was a logistic regression analysis that compared the percentage of patients in each treatment group who were panic free during the last visit interval of the acute treatment phase. Additional analyses included a logistic regression analysis that compared the percentage of patients who experienced at least a 50% reduction from baseline in the number of full panic attacks and analysis of variance (ANOVA) on mean change from baseline to endpoint in the number of full panic attacks.

Safety: Fisher’s exact test was used to analyze treatment-emergent adverse events during the acute treatment phase.

Rating Scales

The primary efficacy measure was the frequency of full panic attacks. A full panic attack met at least 4 of the 13 possible symptoms of a panic attack according to the DSM-IV criteria. The primary efficacy endpoint was the percentage of patients panic-free during the final visit interval. Additional efficacy analyses were conducted on the percentage of patients who experienced at least a 50% reduction in full panic-attack frequency from baseline to endpoint and the mean change from baseline to endpoint in the number of full and total panic attacks per week. Total panic attacks were defined as the number of full plus limited-symptom panic attacks. Panic attacks recorded with no symptoms were also included in total panic attacks. A limited-symptom panic attack was defined as a panic attack that met 1, 2, or 3 of the 13 symptoms of a panic attack. Patients recorded their full and limited-symptom panic attacks along with the severity of the symptoms in a patient diary, and these data were used to calculate the panic attack frequency per week for each visit interval.

Secondary efficacy measures included the following:

7-Item Multicenter Collaborative Panic Disorder Severity Scale (PDSS; Shear et al. 1997): Administered to assess the severity of panic disorder and its improvement during the course of treatment. This index of illness severity is specific to panic disorder and was completed by the clinician.

Clinical Global Impression of Severity (CGI-Severity): A clinician-rated instrument administered to assess the global severity of the disorder and its change over the course of the study.

Panic and Phobic Disorder Scale (PPDS-Clinician and -Patient; NIMH 1976): Administered to assess the patient’s and the clinician’s impression of the severity of symptom domains specific to panic disorder.

Hamilton Anxiety Rating Scale (HAMA): Administered by the clinician to assess the patient’s severity of anxiety, its improvement during the course of treatment, and the timing of such improvement.

17-item Hamilton Depression Rating Scale, modified (HAMD17 ; Hamilton 1960): This scale was administered to assess the severity of depression and its change during the course of treatment. It is completed by the efficacy rater.

State-Trait Anxiety Inventory (STAI; Spielberger 1983): Completed by

the patient to assess anxiety and change in anxiety over time.

Analysis

The primary efficacy measure was the reduction in full panic attacks(used interchangeable with frequency of full panic attacks), which was defined as the percentage of patients with zero panic attacks during the final visit interval.

Objectives

The primary objective was to determine whether fluoxetine 20 to 60 mg/day is more effective than placebo in decreasing full panic attack frequency during acute treatment in patients with panic disorder with or without agoraphobia, according to DSM-IV criteria. A full panic attack was defined as an attack that meets at least 4 of the 13 symptoms for panic attack presented in DSM-IV.

The secondary objectives of this study were to determine the following:

The effectiveness of fluoxetine (20 to 60 mg/day) compared with placebo in improving global response, mood, and anxiety during acute treatment in patients who have panic disorder with or without agoraphobia according to DSM-IV criteria. Outcomes were assessed using the 7-Item Multicenter Collaborative Panic Disorder Severity Scale (PDSS), Clinical Global Impressions of Severity (CGI-Severity) scale, Panic and Phobic Disorders Scale (PPDS-Clinician and -Patient), Hamilton Anxiety Rating Scale (HAMA), State-Trait Anxiety Inventory (STAI), and the 17-item Hamilton Depression Rating Scale, modified (HAMD17). The effectiveness of fluoxetine (20 to 60 mg/day) compared with placebo in improving quality of life scores as assessed by the Sheehan Disability Scale.

The safety of fluoxetine (20 to 60 mg/day) as a treatment for patients who have panic disorder with or without agoraphobia based on assessment of the incidence of treatment-emergent adverse events during 12 weeks of double-blind treatment.

Protocol Amendment 8 December 1997.

The primary efficacy measure in the original protocol was the PDSS. The FDA informed Lilly through two letters full panic attack frequency

should be the primary outcome measure. As a result, full panic attack frequency as assessed by the percentage of patients panic free at endpoint was declared as the primary outcome measure in an Amendment dated 17 December 1998. This amendment was not sent to the FDA at the time it was changed. I have reviewed this amendment when it was sent with the final submission and it is changed as stated and signed off as of DEC 17th by Gary Tolefson, M.D. of Lilly. Five other Lilly employees have signed the document as of 12/10/98.

STUDY RESULTS:

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Disposition

Table 10.1 presents a summary of reasons for discontinuation for all 214 randomized patients. Among fluoxetine-treated patients, 62% completed the acute phase of the study; the most common reason for discontinuation was lost to follow up (11%). Among placebo-treated patients, 67% completed the acute phase; the most common reason for discontinuation was patient decision (12%). There were no statistically significant differences in the reasons for discontinuation between treatment groups.

Table 10.1. Summary of Reasons for Discontinuation
All Randomized Patients
Acute Treatment Phase
B1Y-MC-HCJB

Primary Reason for Discontinuation	Flx (N=108) n (%)	Plac (N=106) n (%)	Total (N=214) n (%)	p-Value*
Reporting Interval Complete	67 (62.0)	71 (67.0)	138 (64.5)	.477
Adverse Event	9 (8.3)	7 (6.6)	16 (7.5)	.796

Lack of Efficacy	5 (4.6)	9 (8.5)	14 (6.5)	.282
Lost to Follow-up	12 (11.1)	4 (3.8)	16 (7.5)	.066
Patient Decision	9 (8.3)	13 (12.3)	22 (10.3)	.376
Protocol Requirement	6 (5.6)	2 (1.9)	8 (3.7)	.280

POOLED INVESTIGATORS (003,005,006,015)=999
* Frequencies are analyzed using a Fisher's Exact test.

Table 10.2 provides a summary of the primary reason for patient discontinuation by visit. Most fluoxetine-treated patients who discontinued early left the study at Visits 3, 4, and 5 (11, 9, and 10 patients, respectively).

Table 10.2. Patient Disposition by Visit
All Randomized Patients
Acute Treatment Phase
B1Y-MC-HCJB

Treatment Group: Flx
Number of patients in the therapy group: (N=108)

	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Primary Reason for Discontinuation	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Reporting Interval Complete	0	0	0	0	0	0	68 (63.0
Adverse Event	0	2 (1.9)	1 (0.9)	2 (1.9)	1 (0.9)	2 (1.9)	0
Lack of Efficacy	0	1 (0.9)	2 (1.9)	1 (0.9)	1 (0.9)	0	0
Lost to Follow-up	0	3 (2.8)	2 (1.9)	3 (2.8)	1 (0.9)	3 (2.8)	0
Patient Decision	0	3 (2.8)	2 (1.9)	3 (2.8)	1 (0.9)	0	0
Protocol Requirement	1 (0.9)	2 (1.9)	2 (1.9)	1 (0.9)	0	0	0

POOLED INVESTIGATORS (003,005,006,015)=999

Demographics:

Table 11.1 summarizes patient physical characteristics by treatment group. The mean age of patients was 38 years. One hundred eighty patients (84%) were Caucasian, and 138 (65%) were female. The treatment groups were comparable at baseline (Visit 2) with respect to age, origin, and gender.

Table 11.1. Patient Demographic Characteristics
All Randomized Patients
Acute Treatment Phase
B1Y-MC-HCJB

Variable	Flx (N=108)	Plac (N=106)	Total (N=214)	p-Value
Sex: No. (%)				
No. Patients	108	106	214	.477*
Female	67 (62.0)	71 (67.0)	138 (64.5)	
Male	41 (38.0)	35 (33.0)	76 (35.5)	
Origin: No. (%)				
No. Patients	108	106	214	.957*
AFRICAN DESCENT	11 (10.2)	9 (8.5)	20 (9.3)	
CAUCASIAN	90 (83.3)	90 (84.9)	180 (84.1)	
EAST/SE ASIAN	0	1 (0.9)	1 (0.5)	
HISPANIC	6 (5.6)	6 (5.7)	12 (5.6)	
WESTERN ASIAN	1 (0.9)	0	1 (0.5)	
Age: yrs.				
No. Patients	108	106	214	.493**
Mean	37.23	38.80	38.01	
Median	36.28	37.58	36.82	
Standard Dev.	11.32	11.19	11.26	
Minimum	18.40	19.53	18.40	

```
  Maximum                   65.09         74.24         74.24
POOLED INVESTIGATORS (003,005,006,015)=999
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance
```

Severity of illness

Table 11.4 presents the frequency of panic attacks experienced by randomized patients during the 2-week evaluation phase. During this phase, all patients received single-blind placebo treatment. The mean number of full panic attacks per week for all patients was 3.28 attacks; the mean number of total panic attacks during the same period was 3.61 attacks. There were no statistically significant differences between the two treatment groups.

Table 11.4. Baseline Severity of Illness: Frequency of Panic Attacks
All Randomized Patients
Acute Treatment Phase
B1Y-MC-HCJB

Variable	Fluoxetine (N=108)	Placebo (N=106)	Total (N=214)	p-Value
Number of Full Panic Attacks/Week (Visit: 2)				
Mean	3.46	3.10	3.28	.537
Median	2.00	2.00	2.00	
Standard Dev.	3.81	3.25	3.54	
Minimum	0.00	0.00	0.00	
Maximum	21.00	26.92	26.92	
Number of Total Panic Attacks/Week (Visit: 2)				
Mean	3.91	3.31	3.61	.263
Median	2.39	2.08	2.33	
Standard Dev.	4.57	3.54	4.09	
Minimum	0.00	0.00	0.00	
Maximum	31.11	28.54	31.11	

Abbreviation: Dev. = deviation; N = number of patients.
Note: These analyses were performed on rank-transformed data.

Exposure

Exposure was based on the number of days that patients participated in the acute phase of the study (Study Period II) and represented the potential exposure to study drug during that period only. Table 12.1 summarizes patient exposure to fluoxetine and placebo treatment. The mean length of exposure to study drug was 72 days for both the fluoxetine and placebo treatment groups. Minimum exposure time was 1 day for the fluoxetine and placebo.

Table 12.1. Duration of Study Drug Exposure
All Randomized Patients
Acute Treatment Phase
B1Y-MC-HCJB

Variable	Flx (N=108)	Plac (N=106)	Total (N=214)	p-Value
Total days of exposure to study drug				
No. Patients	108	106	214	.595**
Mean	71.91	71.83	71.87	
Median	85.00	85.00	85.00	
Standard Dev.	29.11	28.19	28.59	
Minimum	1.00	1.00	1.00	
Maximum	163.00	113.00	163.00	

POOLED INVESTIGATORS (003,005,006,015)=999
** Means are analyzed using a Type III Sum of Squares analysis of variance

Table 12.2 summarizes fluoxetine dosages administered during the study. The mean modal and median modal doses were 21.59 mg and 20.00 mg, respectively. The modal dose for an individual patient is the most frequently administered dose for that patient.

Table 12.2. Summary of Prescribed Dosage
All Randomized Patients

Acute Treatment Phase
B1Y-MC-HCJB

Variable	Flx (N=108)	Plac (N=106)	Total (N=214)
Mean Dose			
No. Patients	107	104	211
Mean	25.96	0.00	13.16
Median	22.71	0.00	12.22
Standard Dev.	8.68	0.00	14.40
Minimum	10.00	0.00	0.00
Maximum	44.44	0.00	44.44
Modal Dose			
No. Patients	107	104	211
Mean	21.59	0.00	10.95
Median	20.00	0.00	10.00
Standard Dev.	8.48	0.00	12.38
Minimum	10.00	0.00	0.00
Maximum	60.00	0.00	60.00

POOLED INVESTIGATORS (003,005,006,015)=999

Concomitant medication:

Table 11.7 summarizes the use of concomitant medication during the study. Of the 214 patients randomized in the acute treatment phase, 176 (83%) reported using concomitant medications. The most frequently reported concomitant medications used were paracetamol (24%), ibuprofen (23%), and ergocalciferol/ascorbic acid (16%).

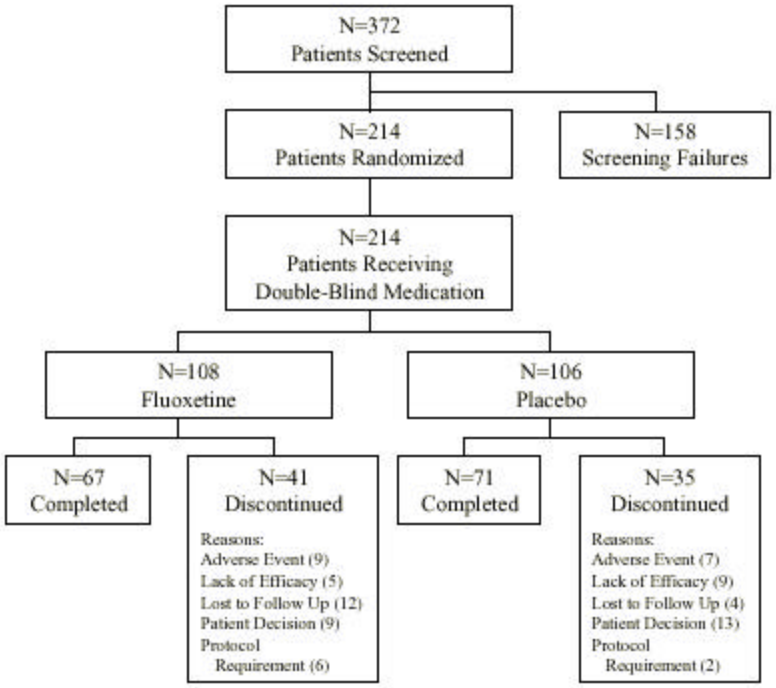
Table 11.7. Summary of Concomitant Medication Use
All Randomized Patients
Acute Treatment Phase
B1Y-MC-HCJB

Drug Name	Flx (N=107) n (%)	Plac (N=104) n (%)	Total (N=211) n (%)
PATIENTS WITH >= 1 DRUG	90 (84.1)	86 (82.7)	176 (83.4)
PATIENTS WITH NO DRUGS	17 (15.9)	18 (17.3)	35 (16.6)
PARACETAMOL	22 (20.6)	28 (26.9)	50 (23.7)
IBUPROFEN	24 (22.4)	24 (23.1)	48 (22.7)
ERGOCALCIFEROL/ASCORBIC ACID/F	15 (14.0)	18 (17.3)	33 (15.6)
ACETYLSALICYLIC ACID	13 (12.1)	10 (9.6)	23 (10.9)
LORATADINE	5 (4.7)	7 (6.7)	12 (5.7)
ASCORBIC ACID	7 (6.5)	4 (3.8)	11 (5.2)
TOCOPHEROL	6 (5.6)	5 (4.8)	11 (5.2)
NAPROXEN SODIUM	4 (3.7)	6 (5.8)	10 (4.7)
ACETYLSALICYLIC ACID/CAFFEINE/	3 (2.8)	6 (5.8)	9 (4.3)
AMOXICILLIN	4 (3.7)	4 (3.8)	8 (3.8)
ESTROGENS CONJUGATED	1 (0.9)	6 (5.8)	7 (3.3)
RANITIDINE HYDROCHLORIDE	2 (1.9)	5 (4.8)	7 (3.3)
SALBUTAMOL	4 (3.7)	3 (2.9)	7 (3.3)
FAMOTIDINE	3 (2.8)	3 (2.9)	6 (2.8)
MAGNESIUM/ALUMINIUM HYDROXIDE	3 (2.8)	3 (2.9)	6 (2.8)

```
NAPROXEN                          1 (0.9)    5 (4.8)    6 (2.8)
OMEPRAZOLE                        4 (3.7)    2 (1.9)    6 (2.8)
POOLED INVESTIGATORS (003,005,006,015)=999
```

Dispostion:

372 patients were screened for eligibility at Visit 1 for Study Period I. Of these, 214 patients (58%) met study criteria and were entered into the 12-week, double-blind, acute treatment phase (Study Period II). Of the 214 patients enrolled, 138 (65%) patients completed the study and 76 (35%) patients discontinued from the study.



Results:

Only the percentage of full panic free patients at endpoint is statistically significant in this study. All other analyses of efficacy variables fail to reach statistical significance.

Yeh-Fong Chen Ph.D. prepared the following tables.

Table 5. Summary of Primary Efficacy Analysis Results for Study B1Y-MC-HCJB

Variables	Fluoxet	Placebo	p-value

	ine		
Percentage of Panic-Free Patients at Endpoint	62% (n=107)	44% (n=104)	**0.008**

Table 6. Summary of Supportive Efficacy Analyses Results for Study B1Y-MC-HCJB

Variables	Fluoxetine	Placebo	p-value
Percentage of Patients Having ≥ 50% Reduction in Frequency of Full Panic Attacks from Baseline	83% (n=107)	74% (n=104)	0.120
Mean Change from Baseline to Endpoint in Frequency of Full Panic Attacks	-2.7 (n=107)	-1.9 (n=104)	0.129
Mean Change from Baseline to Endpoint in Frequency of Total Panic Attacks	-3.03 (n=107)	-2.07 (n=104)	0.057

Table 7. Summary of Some Secondary Efficacy Analyses Results for Study B1Y-MC-HCJB

Variables	Fluoxetine	Placebo	p-value
Mean Change from Baseline to Endpoint in PDSS Average Score	-1.17 (n=99)	-1.01 (n=96)	0.118
Mean Change from Baseline to Endpoint in CGI-Severity Score	-1.79 (n=99)	-1.57 (n=96)	0.226

Mean of PPDS Endpoint Analyses on Clinician-Rated Scales (Overall Functioning-Clinician)	2.317 (n=101)	2.542 (n=96)	0.185
Mean of PPDS Endpoint Analyses on Patient-Rated Scales (Overall Functioning-Clinician)	2.539 (n=102)	2.438 (n=96)	0.853
Mean Change from Baseline to Endpoint in HAMA Total Score	-7.024 (n=83)	-6.417 (n=84)	0.362
Mean Change from Baseline to Endpoint in STAI Total Score	-6.59 (n=83)	-6.5 (n=85)	0.833
Mean Change from Baseline to Endpoint in $HAMD_{17}$ Total Score	-2.18 (n=84)	-1.55 (n=84)	0.323

Conclusion

To consider this study one must again accept the sponsor's explanation that the signed protocol amendment was in place prior to breaking the blind and writing the study report. They do have a signed protocol amendment but did not submit it to us until the final report was submitted. This key protocol change and the associated signature page are included in the appendix of this review.

If one accepts these conditions then the study was positive for the amended final primary outcome measure. However it was not positive for any other evaluation of efficacy that might have been a reasonable alternative. Please see my discussion above and our statistical review.
In addition all secondary efficacy measures were not statistically positive. There may also be a statistical issue concerning multiple primary endpoints or additional analyses as the sponsor calls them.

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7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

In Studies HCJC and HCJB, the sponsor performed subgroup analyses to examine the consistency of treatment effects across the strata of various populations: gender, age (<50, > 50), agoraphobia status (yes or no), and racial origin (Caucasian or non-Caucasian).

In Study HCJC, all patients were Caucasian; therefore, analyses on this subgroup were not conducted. Logistic regression was used to analyze the proportion of patients who were full panic attack free during the last visit interval or who experienced at least a 50% decrease in full panic attacks per week from baseline to the last visit interval. Therapy-Within-Subgroup p-values were obtained using a reduced model with therapy as the only effect. The other p-values (Therapy-by-Subgroup Interaction and Subgroup Term) were obtained from the analysis conducted with a full model (therapy, investigator, subgroup, and therapy-by-subgroup interaction).

The sponsor states that the therapy-by-gender interaction for study HCJC approached significance in the analysis of the proportion of patients who were full panic attack free during the last visit interval (p=.013). See tables to follow. A greater percentage of both male and female fluoxetine-treated patients were panic free compared with placebo-treated patients. No statistically significant treatment-by-subgroup interactions were found in the age and agoraphobia subgroup analyses.

The subgroup analyses for Study HCJB evaluate the proportion of patients who were full panic attack free at the last visit interval and the proportion of patients having a 50% or greater reduction from baseline in the number of full panic attacks per week while accounting for subgroup effect and the outcome measure within subgroup strata. No statistically significant treatment-by-subgroup interactions were found for any subgroup. The treatment effect of fluoxetine was consistent across all subgroups examined.

Table 5.1. **Subgroup Analyses: Study HCJC**
Percentage of Full Panic Attack Free Patients at Endpoint
All Randomized Patients
Acute Treatment Phase

Subgroup	Therapy by Subgroup Interaction	Subgroup Term	Strata	Total Number of Patients in Subgroup	Therapy	Number of Patients by Therapy and Subgroup	Number of Panic-Free Patients by Therapy and Subgroup	%	Therapy Within Subgroup
Gender	0.013	0.334	Female	100	Fluoxetine	47	17	36.2	0.973
					Placebo	53	19	35.9	
			Male	80	Fluoxetine	43	21	48.8	0.002
					Placebo	37	6	16.2	
Age	0.743	0.332	<50	162	Fluoxetine	79	35	44.3	0.027
					Placebo	83	23	27.7	
			50	18	Fluoxetine	11	3	27.3	0.952
					Placebo	7	2	28.6	
Agoraphobia Status	0.888	0.332	Yes	128	Fluoxetine	63	24	38.1	0.099
					Placebo	65	16	24.6	
			No	52	Fluoxetine	27	14	51.9	0.249
					Placebo	25	9	36.0	

% = Percentage of patients by subgroup and therapy who are full panic attack free at endpoint.

Table 5.3. Subgroup Analyses: Study HCJB
Percentage of Full Panic Attack Free Patients at Endpoint
All Randomized Patients
Acute Treatment Phase

Subgroup	Therapy by Subgroup Interaction	Subgroup Term	Strata	Total Number of Patients in Subgroup	Therapy	Number of Patients by Therapy and Subgroup	Number of Panic-Free Patients by Therapy and Subgroup	%	Therapy Within Subgroup
Gender	0.360	0.993	Female	136	Fluoxetine	66	42	63.6	0.015
					Placebo	70	30	42.9	
			Male	75	Fluoxetine	41	24	58.5	0.321
					Placebo	34	16	47.1	
Age	0.464	0.886	<50	180	Fluoxetine	92	58	63.0	0.007
					Placebo	88	38	43.2	
			50	31	Fluoxetine	15	8	53.3	0.853
					Placebo	16	8	50.0	
Origin	0.374	0.159	Caucasian	177	Fluoxetine	89	55	61.8	0.042
					Placebo	88	41	46.6	
			Non-Caucasian	34	Fluoxetine	18	11	61.1	0.079
					Placebo	16	5	31.3	
Agoraphobia Status	0.097	0.020	Yes	145	Fluoxetine	75	39	52.0	0.147
					Placebo	70	28	40.0	
			No	66	Fluoxetine	32	27	84.4	0.005
					Placebo	34	18	52.9	

% = Percentage of patients by subgroup and therapy who are full panic attack free at endpoint.

7.3.2 Size of Treatment Effect

One measure of treatment effect could be the frequency of full panic attacks from baseline to endpoint. The sponsor has three analyses of this measure (this is explained in Yeh-Fong Chen's review). Table 3.4 gives us a look at the size of the full and total panic frequency change in study HCJC. Prozac patients had a slightly larger improvement than placebo patients but it did not reach statistical significance by this measure.

Table 3.4. Analyses of Panic Attack Frequency
Mean Change from Baseline to Endpoint
Acute Treatment Phase
All Randomized Patients
B1Y-MC-HCJC

	Analysis A					Analysis B					Protocol-Defined Analysis				
	Fluoxetine		Placebo		p-	Fluoxetine		Placebo		p-	Fluoxetine		Placebo		p-
Variable	N	Change	N	Change	Value	N	Change	N	Change	Value	N	Change	N	Change	Value
Full Panic Attacks	88	-2.92	90	-2.18	.294	89	-2.89	90	-2.18	.304	90	-2.90	90	-2.18	.078
Total Panic Attacks	88	-3.25	90	-2.48	.225	89	-3.22	90	-2.48	.234	90	-3.24	90	-2.49	.263

Abbreviations: Fluoxetine columns: N = total number of fluoxetine-treated patients; Change = mean change in frequency in the measure for fluoxetine-treated patients from baseline to acute-phase endpoint; Placebo columns: N = total number of placebo-treated patients; Change = mean change in frequency in the measure for placebo-treated patients from baseline to acute-phase endpoint.

Sources: LAS3JCBC, LAS3JCBD, LAS3JCBE, LAS3JCBF, LAS3JCCD, LAS3JC30.

7.3.3 Choice of Dose

Studies HCJC and HCJB employed flexible dose escalation schemes that allowed fluoxetine dosages to

be titrated from 20 mg/day to a maximum of 60 mg/day. Table 3.10 summarizes the fluoxetine dosages administered during the acute treatment phases of these studies.

**Table 3.10. Summary of Prescribed Dosage
Acute Treatment Phase
All Randomized Patients
B1Y-MC-HCJC and B1Y-MC-HCJB**

Clinical Study	N	Fluoxetine Final Dose (mg) Mean	Fluoxetine Final Dose (mg) Median	Fluoxetine Modal Dose (mg) Mean	Fluoxetine Modal Dose (mg) Median
HCJC	89	29.44	20.00	21.44	20.00
HCJB	107	38.79	40.00	21.59	20.00

N = number of patients receiving fluoxetine in the study.

7.3.4 Duration of Treatment

Three panic disorder studies had long-term extension of fluoxetine in the continuation treatment of panic disorder: Studies HCJB, HCHG, and HCHQ. Study Period III of HCJB was ongoing at the time of this submission; therefore, analyses of that study's extension phase are included in the safety update. Long-term safety data are available from the maintenance treatment phases of Studies B1Y-MC-HCHG and B1Y-EW-HCHQ. Both studies included a 24-week maintenance treatment phase. (b) (4) All patients with at least one maintenance treatment phase visit are included in the safety analyses. Data from patients treated with fluoxetine during both the acute and maintenance treatment phases were pooled to create the Fluoxetine/Fluoxetine treatment group. The Fluoxetine/Fluoxetine treatment group was exposed to study drug for a mean of 148 days.

7.4 Conclusions Regarding Efficacy Data

Regarding the primary efficacy measure, in Study HCJC, 42% of fluoxetine-treated patients were panic free during the last visit interval versus 28% of placebo-treated patients (p=.018). In Study HCJB, the percentage of panic free patients was 62% for the fluoxetine group and 44% for the placebo group (p=.008). (b) (4)

In Study HCJC, a statistically significantly greater number of patients in the fluoxetine treatment group had at least a 50% reduction in the frequency of full panic attacks per week compared with the placebo group (82% of fluoxetine-treated patients versus 61% of placebo-treated patients; p=.001). (b) (4) HCJB, (b) (4) demonstrated no statistically significant difference between fluoxetine and placebo treatment groups in this measure.

In all studies, there were no statistically significant differences between treatment groups in the mean change from baseline to endpoint in full panic attacks per week.

(b) (4)

Tables of primary and secondary efficacy measures are presented below.

Table 3.2. Summary of Primary and Supportive Efficacy Measu (b) (4)
Panic Studies

Efficacy Measure	HCJC	HCJB
Panic free status at endpoint	**p=0.018**	**p=0.008**
≥50% reduction in full panic attacks from baseline to endpoint	**p=0.001**	+
Mean change in full panic attacks from baseline to endpoint	+	+
Mean change in total panic attacks from baseline to endpoint	+	+
PPDS: CGI-Improvement	+	+

Note: The primary efficacy analyses were panic-free status at endpoint for HCJC and HCJB and mean change in total panic attacks and mean endpoint (b) (4) Abbreviations: + means numerically favoring fluoxetine (b) (4)

Table 3.7. Summary of Secondary Efficacy Measures
Acute Treatment Phase
All Randomized Patients
All Panic Studies

Efficacy Measure	HCJC	HCJB	(b) (4)
Mean change in CGI-Severity	p=.037	+	
Mean change in PDSS average score	p=.009	+	
Mean change in PDSS frequency of panic attacks (Item 1)	p=.008	p=.017	
Mean change in HAMA	p=.043	+	
Mean change in $HAMD_{17}$	+	+	

Abbreviations: + means numerically favoring fluoxetine; (b) (4)

The conclusion regarding efficacy partly depends on accepting and forgiving the sponsor's failure to submit timely protocol amendments. Please see my final conclusions at the end of this review.

8.0 Safety Findings

8.1 Methods

The cutoff date for data in the original panic submission is December 28, 1999. For the 120-day

Safety Update submitted to the FDA on November 14, 2000 the cutoff date for data is June 27, 2000.

The safety of fluoxetine for the acute treatment of panic disorder has been evaluated for 767 patients (425 patients exposed to doses of fluoxetine of 10 to 60 mg/day, 342 patients exposed to placebo) in four placebo-controlled trials. The safety of fluoxetine in the long-term treatment of panic disorder was evaluated for 203 patients in two placebo-controlled trials. Of these, 75 were exposed to 10, 20, or 40 mg of fluoxetine during both the acute and maintenance treatment phases.

8.2 Deaths

There were no deaths for patients taking Prozac in this database.

8.3 Assessment of Dropouts

8.3.1 Overall Pattern of Dropouts

There were no statistically significant differences in the overall pattern for dropouts between placebo and fluoxetine. Fluoxetine had a higher percentage of adverse event dropouts and placebo led with dropouts due to lack of efficacy. See below.

	Flx		Plac		Total		p-Value*
		(N= 425)		(N= 342)	(N= 767)		
Primary Reason for Discontinuation	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	
Reporting Interval Complete		**267 (62.8)**		**229 (67.0)**	**496 (64.7)**		**.255**
Adverse Event	**34**	**(8.0)**	**17**	**(5.0)**	**51**	**(6.6)**	**.109**
Satisfactory	**2**	**(0.5)**	**0**		**2**	**(0.3**	**.505**

Response						**)**	
Lack of Efficacy	**29**	**(6.8)**	**30**	**(8.8)**	**59**	**(7.7)**	**.341**
Lost to Follow- up	**33**	**(7.8)**	**18**	**(5.3)**	**51**	**(6.6)**	**.190**
Patient Decision	**25**	**(5.9)**	**29**	**(8.5)**	**54**	**(7.0)**	**.201**
Physician Decision	**1**	**(0.2)**	**1**	**(0.3)**	**2**	**(0.3)**	**1.00**
Protocol Requirement	**33**	**(7.8)**	**18**	**(5.3)**	**51**	**(6.6)**	**.190**

8.3.2 Adverse Events Associated with Dropout

Fifty patients (7%) discontinued from the studies due to an adverse event during the acute treatment phase: 33 (8%) patients in the fluoxetine treatment group and 17 (5%) patients in the placebo treatment group. The percentages of patients discontinuing were not statistically significantly different between the two treatment groups. The most common adverse event leading to discontinuation in the fluoxetine treatment group was anxiety, which was reported by 9 (2%) patients. A statistically significantly higher percentage of fluoxetine-treated patients than placebo-treated patients discontinued due to anxiety (p=.049). The most common adverse event leading to discontinuation in the placebo treatment group was asthenia, reported by 4 (1%) patients. This percentage was statistically significantly higher than that for fluoxetine-treated patients (p=.039). See appendix table.

Eleven patients (5%) discontinued from the studies due to an adverse event during the maintenance treatment phase: 4 (5%) patients in the Fluoxetine/Fluoxetine treatment group, 4 (8%) patients in the Fluoxetine/Placebo treatment group, and 3 (4%) patients in the Placebo/Placebo treatment group. The percentages of patients discontinuing were not statistically significantly different across the three treatment groups. The most common adverse event leading to discontinuation in the Fluoxetine/Fluoxetine treatment group (3% of patients) and the Fluoxetine/Placebo

treatment group (4% of patients) was depression. Each of the adverse events that led to discontinuation in the Placebo/Placebo treatment group were reported by 1 patient. There were no statistically significant differences across the treatment groups in the incidence
of any adverse event leading to discontinuation.
See appendix table.

I have reviewed these tables and the narratives and do not feel there are any noteworthy events.

8.4 Search for Serious Adverse Events

12 (7 on prozac) patients reported 16 SAE during the acute treatment phase. These events are not different from the normal pattern and I have reviewed the narratives. See table.

Table 2.6. Patients Experiencing Serious Adverse Events Acute Treatment Phase Panic Integrated Safety Population

Study	Inv- Pt	Age (yrs)	Treatment Group	Event Classification (Reported Term)	Days Post-Randomization	Related to Study Drug*	Serious Criteria	Patient Discontinued
HCJC	003- 3011	44	Fluoxetine	Pervasive anxiety	9	Yes	Hospitalization	Yes
HCJB	002- 0219	30	Placebo	Viral meningitis	81	No	Hospitalization	No
HCJB	006- 0602	45	Fluoxetine	Suicidal ideation	38	Yes	Hospitalization	Yes
HCHG	004- 4002	40	Placebo	Confusion	35	No	Other a	Yes
HCHG	006- 6516	32	Placebo	Intentional overdose	42	No	Overdose b	Yes
HCHG	009- 8011	34	Fluoxetine	Streptococcal pneumoniae	11	No	Hospitalization	No
				Bacteremia sepsis				
				Tracheobronchitis				
HCHQ	204- 2155	36	Placebo	Suicidal ideation	19	No	Hospitalization	No
HCHQ	204- 2156	32	Fluoxetine	Anxiety	10	Yes	Hospitalization	No
HCHQ	291- 2907	39	Fluoxetine	Aggravation of panic	25	No	Hospitalization	No
				disorder				
HCHQ	303- 3101	50	Fluoxetine	Bronchitis	-13	No	Hospitalization	No
HCHQ	501- 5001	21	Placebo	Fracture of the coccyx	50	No	Hospitalization	No
HCHQ	501- 5003	20	Fluoxetine	Colic, abdominal	32	No	Hospitalization	Yes
				SGOT increased				
				SGPT increased				

Six patients reported nine serious adverse events during the maintenance treatment phase.

Table 6.5. Patients with Serious Adverse Events
Panic Integrated Safety Population
Maintenance Treatment Phase

Study	Inv-Pt	Age (yrs)	Treatment Group	Event Classification (*Reported Term*)	Days Post-Randomization	Related to Study Drug*	Serious Criteria	Discontinued
HCHG	001-1526	48	Fluoxetine/Fluoxetine	Gall Bladder Surgery	157	No	Hospitalization	No
HCHG	001-1552	26	Placebo/Placebo	Gunshot Wound to the Abdomen	142	No	Hospitalization	Yes
HCHG	002-2001	41	Placebo/Placebo	Kidney Calculus	167	No	Hospitalization	No
HCHG	008-7511	79	Placebo/Placebo	Coronary Artery Stenosis Heart Block	218	No	Hospitalization	Yes
HCHQ	202-2055	56	Placebo/Placebo	Abdominal Pain Bowel Adherences and Surgery	263	No	Hospitalization	Yes
HCHQ	303-3102	28	Fluoxetine/Fluoxetine	Anxiety Depressive State	104	No	Hospitalization	Yes

*As assessed by the investigator
Abbreviations: Inv-Pt = investigator number-patient number.

8.5 Other Safety Findings

8.5.1 ADR Incidence Tables

8.5.1.1 Appropriateness of Adverse Event Categorization and Preferred Terms

The appropriateness of adverse events and preferred terms appear to be adequate with no unusual terms.

8.5.1.2 Incidence in Controlled Clinical Trials

465 patients (61%) reported at least one treatment-emergent adverse event. Statistically significantly more fluoxetine-treated patients than placebo-treated patients reported at least one treatment-emergent adverse event (66% versus 54%, respectively; p=.001). Events that occurred in > 10% of patients in the fluoxetine treatment group included headache (17%), nausea (13%), and insomnia (10%). Only one event, headache (14%), occurred in > 10% of placebo-treated patients. Events that occurred statistically significantly more frequently in fluoxetine-treated patients than in placebo-treated patients were nausea, diarrhea, dyspesia, anxiety, anorexia, tremor, gastrointestinal disorder, thinking abnormal, and allergic reaction. Events occurring at twice the placebo rate in Prozac patients are listed below in a table the sponsor places in their suggested labeling.

The sponsor feels the adverse event profile of fluoxetine in patients receiving acute treatment for panic disorder was clinically comparable to the treatment-emergent adverse event profile established in the Prozac product labeling. They also feel the adverse event profile of fluoxetine from patients receiving maintenance treatment for panic disorder was clinically comparable to the treatment-emergent adverse event profile established in long-term studies of depression, OCD, and bulimia. I have compared these events with the adverse event profile in labeling and agree with the sponsor's statements above.

8.5.1.3 Post Marketing Spontaneous Reports

Prozac is not yet marketed for Panic disorder in any country.

8.5.2 Laboratory Findings

Laboratory assessment, including hematology, clinical chemistry and urinalysis, was performed at baseline (Visit 1), at the end of the acute treatment phase (Visit 8), and at the end of the study (Visit 15) or

at early discontinuation for patients in Study B1Y-MC-HCHG. In Study B1Y-EW-HCHQ, laboratory assessment was performed at baseline (Visit 1) and at the end of the study (Visit 17) or at early discontinuation. In Studies B1Y-MC-HCJC and B1Y-MC-HCJB, laboratory assessment was performed only at baseline.

8.5.2.1 Clinical Chemistry Findings

There were no clinically significant abnormal laboratory results.

8.5.2.2 Hematology Findings

There were no clinically significant abnormal hematology results.

8.5.2.3 Urinalysis

There were no clinically significant abnormal urinalysis results.

8.5.3 Vital Signs

There were no statistically significant between-group differences in vital signs. Fluoxetine-treated patients demonstrated a statistically significant within-group decrease in heart rate (-0.98 beats/min, p=.045). Fluoxetine-treated patients demonstrated a statistically significant within-group decrease in weight (-0.51 kg, $p < .001$) while placebo-treated patients demonstrated a statistically significant within-group increase in weight (0.29 kg, p=.045). The changes in weight were statistically significant between treatment groups ($p < .001$). None of the changes in vital signs or weight were considered clinically significant.

Table 2.9. Vital Signs and Weight
Mean Change from Baseline to Endpoint
Panic Integrated Safety Polpulation
Acute Treatment Phase

Variable Treatment	N	Baseline		Change		Overall p-Value
Systolic Blood Pressure						
Fluoxetine	401	121.47	14.67	-0.13	12.10	.957
Placebo	328	121.57	14.38	-0.23	11.62	
Diastolic Blood Pressure						
Fluoxetine	401	78.21	9.67	0.20	10.61	.334
Placebo	328	77.77	9.36	-0.57	8.80	
Heart Rate						
Fluoxetine	401	74.57	9.10	-0.98	9.71*	.535
Placebo	328	74.95	9.67	-0.41	10.07	
Weight (kg)						
Fluoxetine	384	75.04	18.38	-0.51	2.43*	<.001
Placebo	317	73.22	17.62	0.29	2.40*	

Abbreviations: N = number of patients with a baseline and at least one postbaseline measurement.
*within group p-value <.05.

8.5.4 ECGs

No ECGs were obtained routinely in these studies.

8.5.5 Special Studies

There were no special studies.

8.5.6 Withdrawal Phenomena/Abuse Potential

There was no new data related to this area.

8.5.7 Human Reproduction Data

There was no new data related to this area.

8.6 Overdose Experience

There was no new data related to this area.

8.7 Summary of Important Events Considered Drug Related

There are no indications of any important drug related events different from the labeling database.

8.8 Important Events Considered Not Drug Related

Certain events have been discussed elsewhere in this document and have been excluded from this category (i.e., deaths, overdoses, dropouts and changes in laboratory values).

The rest of the serious adverse events are considered not drug related and they are displayed in the serious adverse events tables.

8.9 Summary of Drug Interactions

8.9.1 Drug-Demographic Interactions

Treatment-emergent adverse events were analyzed by the sponsor in subgroups according to age (< 50 years, > 50 years), gender, and origin (Caucasian, non-Caucasian). Patients were predominately less than 50 years old (88%), female (63%), and Caucasian (91%). The sponsor reports that treatment-emergent adverse events was similar between subgroups of age, gender, and origin. There was no evidence of increased risk

for fluoxetine-treated patients in any of these subgroups.

8.9.2 Drug-Disease Interactions

Patients with unstable medical illness were excluded from all four studies, and the majority of patients who did enroll were medically healthy. No formal subgroup analyses among the relatively small number of patients with concurrent stable medical illness were performed. There is no evidence in these studies to suggest that fluoxetine was poorly tolerated or associated with increased safety concerns among patients with stable medical illness.

8.9.3 Drug-Drug Interactions

No new data was obtained regarding drug interactions.

8.10.0 SAFETY UPDATE

This update consists of the extension phase of Study HCJB with a cut-off date of 14 Aug 2000. One hundred thirty-eight patients completed the acute phase (Study Period II). The 6-month, double-blind, extension period (Study Period III) was an optional phase of the study. Patients achieving at least a 50% decrease in PDSS scores from baseline to endpoint and CGI-Severity scores 3 at endpoint of Study Period II could choose to continue in the study and enter the 6-month extension period at the dosage assigned at Visit 8. Of the 81 patients enrolled, 42 (52%) patients completed the study and 39 (48%)
patients discontinued during the extension period.

The mean length of exposure was 112 days for the fluoxetine treatment group and 106 days for the placebo treatment group. The minimum exposure time was 1 day for both the fluoxetine and placebo treatment groups.

The administered doses ranged from 20 to 60 mg/day. The average mean and modal doses were 40.37 mg/day and 41.74 mg/day, respectively. The duration of study drug exposure is given in the table below.

Table HCJBe.12.1. Duration of Study Drug Exposure
All Patients
Extension Treatment Period

Variable	Flx (N=47)	Plac (N=34)	Total (N=81)	p-Value
Total days of exposure				
No. Patients	47	34	81	.570**
Mean	111.55	106.35	109.37	
Median	141.00	126.50	141.00	
Standard Dev.	58.50	56.43	57.34	
Minimum	1.00	1.00	1.00	
Maximum	179.00	169.00	179.00	

Of the 81 patients in the extension period, 44 (54%) patients reported at least one treatment-emergent adverse event. Of the 47 fluoxetine-treated patients, 26 (55%)
patients experienced at least one treatment-emergent adverse event; the most frequently reported adverse events being flu syndrome, asthenia, sinusitis, and surgical procedure (all 6%).

No patients died and no serious adverse events were reported during the extension period of the study.

Seven patients (5 fluoxetine-treated, 2 placebo-treated patients) discontinued due to an adverse event during the extension period. The adverse events leading to discontinuation of the 5 fluoxetine-treated patients were depression (1 patient), libido decreased (1 patient), pruritus (1 patient), and unintended pregnancy (2 patients). The adverse events leading to discontinuation of the 2 placebo-treated patients were infection (1 patient) and depression (1 patient).

No laboratory measurements were collected during the extension period of the study. There were no clinically relevant changes in vital signs from Visit 8.

9.0 Labeling Review

9.1 Proposed labeling changes

The sponsor's proposed labeling changes are presented below.

(b) (4)

9 pages immediately following withheld - Draft Labeling b(4)

(b) (4)

[redacted]

9.2 Labeling comments

It may be premature to suggest final labeling changes as I am not sure the sponsor has provided two acceptable studies to support their proposed changes. If they meet this standard I feel we will have to deal with their use of statements regarding (b) (4) [redacted] "free from panic attacks". (b) (4) [redacted]

10.0 Conclusions

Assuming the final protocol amendments are acceptable, only study HCJC is comfortably positive. HCJB taken as a whole does not have statistically significant results except for the final amended primary efficacy variable. Both of these studies were allegedly amended without submitting documentation prior to filing this supplement. See more complete discussion regarding this issue in the individual study reviews. There may also be a statistical issue concerning multiple primary endpoints or additional analyses as the sponsor calls them. (b) (4) [redacted]

There are no safety problems in this review.

11.0 Recommendations

An administrative decision must be made on the acceptability of the two key studies and the undocumented nature of their final protocol amendments. If they are acceptable the sponsor may have provided minimal evidence of efficacy although study HCJB is questionable.

Earl D. Hearst, M.D.
Medical Reviewer

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APPENDIX

Additional Efficacy tables are below.

Table 3.4. **Analyses of Panic Attack Frequency**
Mean Change from Baseline to Endpoint
Acute Treatment Phase
All Randomized Patients
B1Y-MC-HCJC

	Analysis A					Analysis B					Protocol-Defined Analysis				
	Fluoxetine		Placebo		p-	Fluoxetine		Placebo		p-	Fluoxetine		Placebo		p-
Variable	N	Change	N	Change	Value	N	Change	N	Change	Value	N	Change	N	Change	Value
Full Panic Attacks	88	-2.92	90	-2.18	.294	89	-2.89	90	-2.18	.304	90	-2.90	90	-2.18	.078
Total Panic Attacks	88	-3.25	90	-2.48	.225	89	-3.22	90	-2.48	.234	90	-3.24	90	-2.49	.263

Abbreviations: Fluoxetine columns: N = total number of fluoxetine-treated patients; Change = mean change in frequency in the measure for fluoxetine-treated patients from baseline to acute-phase endpoint; Placebo columns: N = total number of placebo-treated patients; Change = mean change in frequency in the measure for placebo-treated patients from baseline to acute-phase endpoint.
Sources: LAS3JCBC, LAS3JCBD, LAS3JCBE, LAS3JCBF, LAS3JCCD, LAS3JC30.

Table 3.5. **Endpoint Analyses of Panic Attack Frequency**
Acute Treatment Phase
All Randomized Patients
B1Y-MC-HCJB

	Analysis A						Analysis B						Protocol-Defined Analysis					
	Fluoxetine			Placebo			Fluoxetine			Placebo			Fluoxetine			Placebo		
Variable	N	n	%	N	n	%	p-Value	N	n	%	N	n	%	p-Value	N	n	%	N	n	%	p-Value
Patients who were Full Panic Attack Free	102	57	56%	96	40	42%	.027	103	57	55%	102	40	39%	.012	107	66	62%	104	46	44%	.008
Patients with ≥50% Reduction in Full Panic Attacks	102	80	78%	96	70	73%	.399	103	82	80%	102	74	73%	.240	107	89	83%	104	77	74%	.120

Abbreviations: Fluoxetine columns: N = total number of fluoxetine-treated patients; n = number of fluoxetine-treated patients who met the variable criteria; % = percentage of fluoxetine-treated patients who met the variable criteria; Placebo columns: N = total number of placebo-treated patients; n = number of placebo-treated patients who met the variable criteria; % = percentage of placebo-treated patients who met the variable criteria.
Sources: GENJBPF, GENJBPFB, GENJB50, GENJB50B, EFFN01RX.

Table 3.6. **Analyses of Panic Attack Frequency**
Mean Change from Baseline to Endpoint
Acute Treatment Phase
All Randomized Patients
B1Y-MC-HCJB

	Analysis A					Analysis B					Protocol-Defined Analysis				
	Fluoxetine		Placebo		p-	Fluoxetine		Placebo		p-	Fluoxetine		Placebo		p-
Variable	N	Change	N	Change	Value	N	Change	N	Change	Value	N	Change	N	Change	Value
Full Panic Attacks	102	-2.34	96	-1.97	.259	103	-2.56	102	-1.91	.184	107	-2.68	104	-1.91	.129
Total Panic Attacks	102	-2.72	96	-2.11	.096	103	-2.92	102	-2.05	.066	107	-3.03	104	-2.07	.057

Abbreviations: Fluoxetine columns: N = total number of fluoxetine-treated patients; Change = mean change in frequency in the measure for fluoxetine-treated patients from baseline to acute-phase endpoint; Placebo columns: N = total number of placebo-treated patients; Change = mean change in frequency in the measure for placebo-treated patients from baseline to acute-phase endpoint.
Sources: LAS3JBAV, LAS3JBAW, LAS3JBAX, LAS3JBAY, LAS3JB26, LAS3JB30.

Adverse event drop-out table for Acute Phase Studies

Event Classification	Flx (N=425) n (%)	Plac (N=342) n (%)	Total (N=767) n (%)	p-Value*
PATIENTS DISCONTINUED	33 (7.8)	17 (5.0)	50 (6.5)	.141

Event Classification	Flx (N=425) n (%)	Plac (N=342) n (%)	Total (N=767) n (%)	p-Value*
ANXIETY	9 (2.1)	1 (0.3)	10 (1.3)	.049
Patient(s):	B1Y-MC-HCHG 1-1014, 1-1502, 1-1504, 1-1590; B1Y-MC-HCHQ 241-2422; B1Y-MC-HCJB 1- 140, 1- 142, 17-1711; B1Y-MC-HCJC 3-3011	B1Y-MC-HCJB 1- 143		
NERVOUSNESS	5 (1.2)	0	5 (0.7)	.069
Patient(s):	B1Y-MC-HCHG 1-1573, 2-2002, 6-6515; B1Y-MC-HCHQ 241-2404; B1Y-MC-HCJB 12-1204			

Event Classification	Flx (N=425) n (%)	Plac (N=342) n (%)	Total (N=767) n (%)	p-Value*
ASTHENIA	0	4 (1.2)	4 (0.5)	.039
Patient(s):		B1Y-MC-HCJB 1- 112, 2- 221; B1Y-MC-HCJC		

		3-3013 6-6006		
ABDOMINAL PAIN	2 (0.5)	1 (0.3)	3 (0.4) 1.00	
Patient(s):	B1Y-MC-HCHQ 501-5003	B1Y-MC-HCHQ 242-2454		

Event Classification	8-8020 n (%)	n (%)	n (%)	
AGITATION	1 (0.2)	1 (0.3)	2 (0.3) 1.00	
Patient(s):	B1Y-MC-HCHG 3-3034	B1Y-MC-HCHQ 242-2451		
CONFUSION	1 (0.2)	1 (0.3)	2 (0.3) 1.00	
Patient(s):	B1Y-MC-HCHG 1-1001	B1Y-MC-HCHG 4-4002		
THINKING ABNORMAL	2 (0.5)	0	2 (0.3) .505	
Patient(s):	B1Y-MC-HCHG 1-1023 B1Y-MC-HCHQ 801-8001			

Event Classification	n (%)	n (%)	n (%)	
ALLERGIC REACTION	1 (0.2)	0	1 (0.1) 1.00	
Patient(s):	B1Y-MC-HCHQ 604-6158			
BACK PAIN	0	1 (0.3)	1 (0.1) .446	
Patient(s):		B1Y-MC-HCHG 6-6025		
CONSTIPATION	1 (0.2)	0	1 (0.1) 1.00	
Patient(s):	B1Y-MC-HCHG 5-5009			

Event Classification	n (%)	n (%)	n (%)	
DEPERSONALIZATION	1 (0.2)	0	1 (0.1) 1.00	
Patient(s):	B1Y-MC-HCHG 3-3038			
DEPRESSION	1 (0.2)	0	1 (0.1) 1.00	
Patient(s):	B1Y-MC-HCJB 6- 602			

DYSPEPSIA	1 (0.2)	0	1 (0.1)	1.00
Patient(s):	B1Y-MC-HCHQ 141-1402			
Event Classification	n (%)	n (%)	n (%)	
FLATULENCE	0	1 (0.3)	1 (0.1)	.446
Patient(s):		B1Y-MC-HCJB 9- 909		
HALLUCINATIONS	0	1 (0.3)	1 (0.1)	.446
Patient(s):		B1Y-MC-HCHQ 241-2401		
HEADACHE	0	1 (0.3)	1 (0.1)	.446
Patient(s):		B1Y-MC-HCJC 8-8066		
Event Classification	n (%)	n (%)	n (%)	
HYPERCHLORHYDRIA	1 (0.2)	0	1 (0.1)	1.00
Patient(s):	B1Y-MC-HCJC 8-8005			
HYPERTENSION	1 (0.2)	0	1 (0.1)	1.00
Patient(s):	B1Y-MC-HCJB 13-1315			
INFECTION	0	1 (0.3)	1 (0.1)	.446
Patient(s):		B1Y-MC-HCJB 2- 219		
Event Classification	n (%)	n (%)	n (%)	
INTENTIONAL OVERDOSE	0	1 (0.3)	1 (0.1)	.446
Patient(s):		B1Y-MC-HCHG 6-6516		
LIBIDO DECREASED	1 (0.2)	0	1 (0.1)	1.00
Patient(s):	B1Y-MC-HCJB 10-1014			
PALPITATION	0	1 (0.3)	1 (0.1)	.446
Patient(s):		B1Y-MC-HCJB 11-1106		
Event Classification	n (%)	n (%)	n (%)	
PEPTIC ULCER	1 (0.2)	0	1 (0.1)	1.00

Patient(s):	B1Y-MC-HCJC 8-8037			
SOMNOLENCE	1 (0.2)	0	1 (0.1)	1.00
Patient(s):	B1Y-MC-HCJB 7- 701			
TACHYCARDIA	0	1 (0.3)	1 (0.1)	.446
Patient(s):		B1Y-MC-HCHQ 502-5055		
Event Classification	n (%)	n (%)	n (%)	
TREMOR	1 (0.2)	0	1 (0.1)	1.00
Patient(s):	B1Y-MC-HCJB 1- 109			
VERTIGO	1 (0.2)	0	1 (0.1)	1.00
Patient(s):	B1Y-MC-HCHG 1-1005			
VOMITING	1 (0.2)	0	1 (0.1)	1.00
Patient(s):	B1Y-MC-HCJC 8-8014			
Event Classification	n (%)	n (%)	n (%)	
WEIGHT GAIN	0	1 (0.3)	1 (0.1)	.446
Patient(s):		B1Y-MC-HCJB 7- 710		

Flx = fluoxetine; Plac = placebo;
* Frequencies are analyzed using a Fisher's Exact test.

Table 6.1. Summary of Reasons for Discontinuation
Panic Integrated Safety Population
Maintenance Treatment Phase

Primary Reason for Discontinuation	Flx/Plc (N=50) n (%)	Flx/Flx (N=75) n (%)	Plc/Plc (N=78) n (%)	Total (N=203) n (%)	p-Value*
Reporting Interval Complete	22 (44.0)	55 (73.3)	49 (62.8)	126 (62.1)	.004
Adverse Event	4 (8.0)	4 (5.3)	3 (3.8)	11 (5.4)	.626
Lack of Efficacy	7 (14.0)	3 (4.0)	12 (15.4)	22 (10.8)	.045

Lost to Follow-up	4	(8.0)	6	(8.0)	4	(5.1)	14	(6.9)	.777
Patient Decision	6	(12.0)	2	(2.7)	5	(6.4)	13	(6.4)	.108
Protocol Requirement	7	(14.0)	4	(5.3)	5	(6.4)	16	(7.9)	.214
Relapse	0		1	(1.3)	0		1	(0.5)	.616

Reporting Interval Complete - defined as completing visit 15 study HCHG and visit 14 for study HCHQ.
RMP.B1YP.JCLLIB3(RDS1JCAB)
RMP.B1YO.HCJCISS(RDS1JCAB)
* Frequencies are analyzed using a Fisher's Exact test.
XRDS0001

Table 6.6. Summary of Discontinuations Due to an Adverse Event or Death

Panic Integrated Safety Population
Maintenance Treatment Phase

Event Classification	Flx/Plc (N=50) n (%)	Flx/Flx (N=75) n (%)	Plc/Plc (N=78) n (%)	Total (N=203) n (%)	p-Value*
PATIENTS DISCONTINUED	4 (8.0)	4 (5.3)	3 (3.8)	11 (5.4)	.626
DEPRESSION	2 (4.0)	2 (2.7)	1 (1.3)	5 (2.5)	.642
Patient(s):	B1Y-MC-HCHG 1-1557, 5-5001	B1Y-MC-HCHG 1-1565, B1Y-MC-HCHQ 303-3102	B1Y-MC-HCHQ 801-8005		
ACCIDENTAL INJURY	0	0	1 (1.3)	1 (0.5)	1.00
Patient(s):			B1Y-MC-HCHG 1-1552		

Event Classification	Flx/Plc (N=50) n (%)	Flx/Flx (N=75) n (%)	Plc/Plc (N=78) n (%)	Total (N=203) n (%)	p-Value*
ANORGASMIA	0	1 (1.3)	0	1 (0.5)	.616
Patient(s):		B1Y-MC-HCHG 1-1524			
HEART BLOCK	0	0	1 (1.3)	1 (0.5)	1.00
Patient(s):			B1Y-MC-HCHG 8-7511		
PERSONALITY DISORDER	1 (2.0)	0	0	1 (0.5)	.246
Patient(s):	B1Y-MC-HCHG 6-6005				

Event Classification	Flx/Plc (N=50) n (%)	Flx/Flx (N=75) n (%)	Plc/Plc (N=78) n (%)	Total (N=203) n (%)	p-Value*
SOMNOLENCE	0	1 (1.3)	0	1 (0.5)	.616
Patient(s):		B1Y-MC-HCHQ 806-8256			
UNINTENDED PREGNANCY	1 (2.0)	0	0	1 (0.5)	.246

Patient(s): B1Y-MC-HCHG
1-1558

Flx/Flx = fluoxetine treatment in the acute phase, and fluoxetine treatment in the maintenance phase;
Flx/Plc = fluoxetine treatment in the acute phase, and placebo treatment in the maintenance phase;
Plc/Plc = placebo treatment in the acute phase, and placebo treatment in the maintenance phase;
*** Frequencies are analyzed using a Fisher's Exact test.**

Study HCJB final amendment submitted after blind was broken.

3.9.1.2. **Efficacy Criteria** (pages 19-20)

The primary efficacy measure will be the frequency of ~~total (~~full ~~plus limited symptom~~ panic attacks~~)~~ ~~panic attack frequency~~ which will be used to determine if the patient is a responder in the acute phase. For the acute phase, a patient is a responder if he has zero full panic attacks in his final visit interval of the acute phase.

This amendment for HCJB was signed-off on 12/18/98, see next page. The 4/9/99 note-to-file for HCJC follows below.

LILLY MEDICAL GLOBAL DOCUMENT PREPARATION AND APPROVAL FORM

Version 2Q97.1. Numbers in parentheses refer to the Type of Document. For some documents, indicated preparers may not be applicable. In this case, please insert "not applicable" in the field.

	Type of Document	LY 110140
		LY# of Compound
	Clinical investigator's brochure (1)	Fluoxetine Hydrochloride
	Risks profile (1a)	Generic Name
X	Protocol (plus amendments, addenda) (2)	Prozac®
	Protocol-specific ICD (2a)	Trade Name
	Change to ICD legal sections (2b)	B1Y
	Change to risks section in ICD (2c)	Project Code
	Clinical report (plus amendments)* (3)	MC
	Global registration brochure (4)	Site Code (2, 2a, 3)
		HCJB(b)
	*Type of clinical report: (eg, clinical study report, integrated summary, etc)	Study Code (2, 2a, 3)

APPROVED BY:

Name	*Signature*	*Date*
Gary Tollefson MD, PhD		12/17/98
Therapeutic area medical director (or designee)* (1,2,2a,3,4)		

* After signing, please return approved document to (b) (6) Mail/Drop Code 2423 for distribution to preparers and reviewers.

PREPARED BY:

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Medical Writer (1,2,2a,3,4) (if available)		
(b) (6)		Dec 10, 1998
Pharmaceutical Project Manager (1)		
Other		
Lilly Legal in Indianapolis (2a)		

REVIEWED BY:

The following individuals may be consulted during the preparation of the document. Please indicate reviews by placing a check mark in the appropriate boxes. The signatures of the reviewers need not be obtained.

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o Clinical Pharmacologist (1,2,3,4)	o Division Attorney (2a & on request)	o Systems Analyst (2,3,4)
o Clinical Project Manager (2,2a,3)	o Pharmaceutical Project Manager (2,4)	o Other
o Clinical Laboratory Medicine (2,3)	o Project Microbiologist (1,2,3,4)	
o Global CDU Physician (1,2,3,4)	o Project Pharmacokineticist (1,2,3,4)	
o Data Collection Coordinator (2)	o Project Toxicologist (1,4)	
o Data Management Coordinator (2,3)	o Regulatory Scientist (1,2,3,4)	

\TEMPLATE\DOCAPPRV.DOT Date Form Printed: 12 November 1998

Note-To-File

Project Code: **B1Y-MC-HCJC(a)**

Protocol Title **Prozac vs. Placebo in the Treatment of Panic Disorder**

Reason for Note-To-File:

The United States study protocol (HCJB) was amended to increase the enrollment target from 162 to 214. This increase was related to a change in the declared primary outcome measure. Although the declaration of the new primary outcome measure was made for the European study (HCJC) as well, no protocol amendment was put forward to increase the study size. Enrollment in the European study was not increased for several reasons related both to the clinical characteristics of the study population as well as the logistics of completing the study:

1. The rationale for choosing the European sites was that in a previous panic study they had demonstrated very low placebo response and better separation from active drug compared with our US experience. This suggests that the number of patients needed to discriminate fluoxetine from placebo will be lower than in the United States.
2. The European study started later and initially enrolled more slowly than the US study, and increasing the enrollment to match the US enrollment target could require as much as an additional 6-12 months of patient accrual.
3. The option of adding extra sites to compensate for the increased enrollment target (as was done in the US) was not available due to a lack of resources as well as the technical difficulties which different languages and patterns of practice impose on a European study.
4. The Hungarian sites, which were initially envisioned as providing as much as 40% of the enrollment target, did not receive regulatory approval to participate in the study, compounding patient recruitment issues.

(b) (6) 4/9/99
(4/9/99)

(b) (6)
4/9/99)

Distribution: White copy - Lilly
Bottom copy - Investigator

USMD Note-To-File Template
Created May 2, 1997

Pattern Analysis of a Clinical Trial of Fluoxetine in Panic Disorder

Franklin R. Schneier, M.D., Dept. of Therapeutics, NY State Psychiatric Institute, 722 West 168th Street, Unit 13, New York NY 10032; Brian A. Fallon, M.D., Shu-Hsing Lin, Ph.D., Randall D. Marshall, M.D., Donna Vermes, R.N., Jose Arturo Sanchez-Lacay, M.D., Michael R. Liebowitz, M.D.

Summary:

Objective: To assess the utility of application of pattern analysis to a panic disorder clinical trial with a high placebo response rate.

Method: This double-blind, placebo-controlled eight-week clinical trial of fluoxetine and imipramine for 102 patients with panic disorder was conducted in an anxiety disorders clinic. It used standard outcome measures such as global response and change in panic attack frequency, as well as the novel application of longitudinal pattern of panic response, which was adapted from studies of major depression. Panic response at each weekly visit for each patient was defined by a 1 or 2 (much or very much improved) on a 7-point scale of change in panic attacks. Delayed persistent response was defined by onset of responder status after three weeks or more, with responder status maintained at all later visits.

Results: In the intent-to-treat sample there was no significant group difference in overall response rates at endpoint; however, delayed persistent response was more common for patients taking fluoxetine (33%) or imipramine (26%) than placebo (7%), $X^2 = 7.7$, $p = .02$.

Conclusion: Pattern analysis may be a sensitive method of detecting drug-placebo differences in panic disorder.

Funded by NIMH RO1 MH45846 and Eli Lilly Co.

This is the only non-IND study reported.

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

/s/

Earl Hearst
4/20/01 01:43:55 PM
MEDICAL OFFICER

Thomas Laughren
4/27/01 11:19:42 AM
MEDICAL OFFICER
I do consider this supplement approvable; see memo to file for more de
tailed comments.--TPL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-936/s-061

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
(Addendum)

NDA#:	18-936 (SE1-061)
APPLICANT:	Eli Lilly and Company
NAME OF DRUG:	Prozac
INDICATION:	Panic Disorder
DOCUMENT REVIEWED:	9/12/01
MEDICAL OFFICER:	Earl Hearst M.D. (HFD-120)
STATISTICAL REVIEWER:	Yeh-Fong Chen Ph.D. (HFD-710)

I. Background

On 22 May 2001, Eli Lilly and Company (Lilly) received from the FDA a non-approvable letter for the use of fluoxetine in the treatment of panic disorder. On 01 August 2001, representatives of the FDA and Lilly met to discuss the FDA's position on issues relating to the panic submission specifically and broader issues regarding the use the submission of data from clinical study sites in Eastern Europe.

Lilly's July 2000 submission regarding fluoxetine in the treatment of panic disorder featured two pivotal trials (U.S. Study HCJB and European Study HCJC) in which fluoxetine statistically significantly separated from placebo in the primary endpoint of the number of panic-free patients at endpoint. In the letter dated 22 May 2001, the FDA expressed a lack of familiarity with the study sites in Eastern Europe. However, in the document provided by Lilly for the 01 August 2001 meeting with the FDA, Lilly demonstrated that the primary endpoint - which is the basis for approvability – remained statistically significant even when data from Eastern European sites were removed from the analysis (p=.03). So, the agency went on to list the additional information that Lilly needed to submit in order to meet the FDA's requirements for final approval. They are the post-hoc analyses on secondary endpoints for the Western and Eastern European sites and a discussion for the results of Study HCJB, i.e., the study conducted in the U.S.

Since the sponsor did not provide any new discussion of the results for the HCJB study in this re-submission, this review will be mainly focusing on the evaluation of the sponsor's post-hoc analyses on secondary endpoints for Western and Eastern European sites in the HCJC study.

II. The Sponsor's Results of Secondary Efficacy Measures for Western and Eastern European Study Sites in Study BIY-MC-HCJC

Tables 1 and 2 below (abstracted from Table 1 in the sponsor's submission) present statistical analyses of the results from Eastern and Western European study sites for each secondary efficacy measure in Study HCJC. The sponsor mentioned in their report that the results of the secondary measures show that the mean change at endpoint for the measures was very similar for fluoxetine-treated patients at both Eastern and Western European sites. In other words, the fluoxetine treatment group in Western Europe showed clinically comparable levels of improvement as the fluoxetine group in Eastern Europe.

In some cases, such as the Frequency of Panic Attacks sub-term of the Panic Disorder Severity Scale, the fluoxetine group for the Western European sites showed a greater mean change than the Eastern European fluoxetine group.

The sponsor also commented that the differences in results for these measures between the fluoxetine and placebo treatment groups for the Western European sites were not always statistically significant. It was most likely because the small patient population size in Western Europe (55 total fluoxetine and placebo patients) decreases statistical sensitivity to detecting treatment differences. The high placebo response commonly recognized in clinical studies of this disorder may also confound the results of these analyses.

They concluded that these secondary analyses from Study HCJC support the comparability of Eastern and Western European data and the conclusion that fluoxetine is effective in the treatment of panic disorder.

Table 1. Mean Change from Baseline to Endpoint for Some Secondary Measures in Study HCJC

Eastern European Sites					**Western European Sites**				
Therapy	**n**	**Mean**	**SD**	**p-value**	**Therapy**	**n**	**Mean**	**SD**	**p-value**
Number of Full Panic Attacks per Week:									
Fluoxetine	62	-3.113	3.371	.162	Fluoxetine	28	-2.443	2.879	.329
Placebo	63	-2.603	3.203		Placebo	27	-1.207	3.172	
Number of Total Panic Attacks per Week:									
Fluoxetine	62	-3.405	3.788	.098	Fluoxetine	28	-2.862	3.823	.839
Placebo	63	-2.759	3.696		Placebo	27	-1.870	4.184	
Panic Disorder Severity Scale-Frequency of Panic Attacks:									
Fluoxetine	61	-1.623	1.083	.007	Fluoxetine	27	-1.889	1.121	.184
Placebo	63	-1.063	1.045		Placebo	27	-1.148	1.262	
Panic Disorder Severity Scale-Distress During Attacks:									
Fluoxetine	61	-1.705	1.160	.012	Fluoxetine	27	-2.148	1.512	.328
Placebo	63	-1.143	1.162		Placebo	27	-1.444	1.188	
Panic Disorder Severity Scale-Anticipatory Anxiety									
Fluoxetine	61	-1.705	1.085	.018	Fluoxetine	27	-1.481	1.221	.707
Placebo	63	-1.016	1.100		Placebo	27	-1.222	1.013	
Panic Disorder Severity Scale-Phobic Avoidance Situations:									
Fluoxetine	61	-1.508	1.043	.001	Fluoxetine	27	-1.333	1.441	.755
Placebo	63	-0.889	1.094		Placebo	27	-0.926	1.141	
Panic Disorder Severity Scale-Phobic Avoidance Sensations:									
Fluoxetine	61	-1.459	1.058	.029	Fluoxetine	27	-1.074	1.439	.590
Placebo	63	-0.952	0.974		Placebo	27	-0.926	1.174	
Panic Disorder Severity Scale-Interference with Work:									
Fluoxetine	61	-1.885	1.142	.004	Fluoxetine	27	-1.556	1.577	.733
Placebo	63	-1.175	1.225		Placebo	27	-1.296	1.436	

Eastern European Sites					Western European Sites				
Therapy	**n**	**Mean**	**SD**	**p-value**	**Therapy**	**n**	**Mean**	**SD**	**p-value**
Panic Disorder Severity Scale-Interference with Social:									
Fluoxetine	61	-1.721	1.019	.023	Fluoxetine	27	-1.667	1.301	.214
Placebo	63	-1.111	1.271		Placebo	27	-1.296	1.137	
Panic Disorder Severity Scale-Average Score (Items 1-7):									
Fluoxetine	61	-1.658	0.858	<.001	Fluoxetine	27	-1.593	1.075	.355
Placebo	63	-1.050	0.914		Placebo	27	-1.180	0.894	
Panic Disorder Severity Scale-Total Score (Items 1-7)									
Fluoxetine	61	-11.607	6.006	<.001	Fluoxetine	27	-11.148	7.528	.355
Placebo	63	-7.349	6.396		Placebo	27	-8.259	6.255	
Clinical Global Impression of Severity Scale (CGI-Severity)									
Fluoxetine	61	-2.574	1.420	.002	Fluoxetine	27	-2.704	1.857	.624
Placebo	63	-1.651	1.439		Placebo	27	-2.222	1.396	
Hamilton Anxiety Rating Scale (HAMA):									
Fluoxetine	59	-16.305	9.278	.008	Fluoxetine	26	-11.577	8.031	.503
Placebo	61	-10.098	10.361		Placebo	27	-9.667	9.081	
17-Item Hamilton Depression Rating Scale ($HAMD_{17}$):									
Fluoxetine	59	-7.644	4.444	.007	Fluoxetine	26	-3.846	4.192	.933
Placebo	61	-4.393	6.144		Placebo	27	-3.852	4.889	
State-Trait Anxiety Inventory (STAI)									
Fluoxetine	59	-17.068	12.972	<.001	Fluoxetine	26	-11.346	14.497	.343
Placebo	61	-8.607	14.602		Placebo	27	-4.926	14.655	

Table 2. Endpoint for Some Secondary Measures in Study HCJC

Eastern European Sites					Western European Sites				
Therapy	**n**	**Mean**	**SD**	**p-value**	**Therapy**	**n**	**Mean**	**SD**	**p-value**
Panic and Phobic Disorders Scale-Clinician-Rated Endpoint in Overall Functioning:									
Fluoxetine	61	1.836	1.267	.005	Fluoxetine	27	2.296	1.793	.982
Placebo	63	2.556	1.389		Placebo	27	2.704	1.877	
Panic and Phobic Disorders Scale-Clinician-Rated Endpoint in Panic Attacks:									
Fluoxetine	61	1.934	1.138	.013	Fluoxetine	27	2.074	1.542	.805
Placebo	63	2.619	1.442		Placebo	27	2.481	1.909	
Panic and Phobic Disorders Scale-Clinician-Rated Endpoint in Phobic Avoidance:									
Fluoxetine	61	1.951	1.203	.010	Fluoxetine	27	2.296	1.772	.882
Placebo	63	2.651	1.483		Placebo	27	2.741	1.631	
Panic and Phobic Disorders Scale-Clinician-Rated Anticipatory Anxiety:									
Fluoxetine	61	2.000	1.304	.039	Fluoxetine	27	2.444	1.826	.822
Placebo	63	2.683	1.412		Placebo	27	2.889	1.805	
Panic and Phobic Disorders Scale-Clinician-Rated Change in Clinical Global Improvement:									
Fluoxetine	61	1.984	1.204	.006	Fluoxetine	27	2.333	1.776	.933
Placebo	63	2.683	1.318		Placebo	27	2.778	1.948	

Eastern European Sites					Western European Sites				
Therapy	**n**	**Mean**	**SD**	**p-value**	**Therapy**	**n**	**Mean**	**SD**	**p-value**
Panic and Phobic Disorders Scale-Patient-Rated Change in Overall Functioning:									
Fluoxetine	61	1.902	1.287	.009	Fluoxetine	27	2.444	1.847	.648
Placebo	63	2.571	1.411		Placebo	27	2.741	1.933	
Panic and Phobic Disorders Scale-Patient-Rated Change in Panic Attacks:									
Fluoxetine	61	1.852	1.195	.015	Fluoxetine	27	2.037	1.556	.887
Placebo	63	2.540	1.490		Placebo	27	2.519	2.045	
Panic and Phobic Disorders Scale-Patient-Rated Change in Phobic Avoidance:									
Fluoxetine	61	1.820	1.088	.001	Fluoxetine	27	2.222	1.601	.482
Placebo	63	2.667	1.503		Placebo	27	2.963	1.829	
Panic and Phobic Disorders Scale-Patient-Rated Anticipatory Anxiety:									
Fluoxetine	61	2.016	1.204	.054	Fluoxetine	27	2.593	1.824	.942
Placebo	63	2.651	1.370		Placebo	27	3.074	1.979	
Panic and Phobic Disorders Scale-Patient-Rated Change in Global Improvement:									
Fluoxetine	61	1.934	1.223	.009	Fluoxetine	27	2.481	1.889	.524
Placebo	63	2.619	1.408		Placebo	27	2.815	2.001	

III. The Sponsor's Other Studies in the Submission and Overall Conclusions

Other (b) (4) in the Submission

(b) (4) other adequate and well-controlled (b) (4) included in Lilly's submission for fluoxetine in the treatment of panic disorder. Study B1Y-MC-HCJB was conducted in the U.S. and served as an additional pivotal trial alongside the European Study HCJC. (b) (4)

The Sponsor's Overall Conclusions

This document reaffirms that fluoxetine is effective in the treatment of panic disorder, and that Lilly's submission of July 2000 contains sufficient evidence to this effect. The data from Study HCJC, a European study, is valid and consistent regardless of its originating site or region. Study HCJB was conducted in the U.S., and the results of the study's primary and secondary efficacy measures strongly support the use of fluoxetine for the indication. (b) (4)

With the analyses presented in this document as well as in preceding briefing documents, Lilly petitions the FDA to agree that the data submitted to date provide adequate and sufficient information for the agency to approve the use of fluoxetine in the treatment of panic disorder.

IV. The Reviewer's Comments

1. This reviewer was able to duplicate the sponsor's values shown on Table 1 and 2. There was no error found by this reviewer about the sponsor's values in the tables. However, the sponsor made the wrong titles for the endpoints shown on this review's Table 2. For the sub-items of the Panic and Phobic Disorders Scales, the comparisons between the fluoxetine and placebo groups was the endpoints not the change from the baselines to the endpoints.

2. This reviewer does not agree on what the sponsor mentioned in their report about the similarity of the results of the secondary measures for fluoxetine-treated patients at both Eastern and Western European sites. The sponsor did not show any statistical analyses results to support this statement. This reviewer performed the two sample T tests for all the secondary measures and found two statistical significant results. They are comparisons on the Hamilton Anxiety Rating Scale (HAMA) and 17-Item Hamilton Depression Rating Scale ($HAMD_{17}$). The corresponding p-values are .027 and .004.

3. The sponsor mentioned that the differences in results for the secondary measures between the fluoxetine and placebo groups for the Western European sites were not always statistically significant. In fact, none of the secondary measures show statistical significance for the Western European sites. With only less than 55 patients in the Western European sites, the power is certainly a concern. However, we should also notice that almost all p-values are much greater than .05. Moreover, the efficacy results for the primary endpoint as well as the secondary endpoints from the Western European sites only in Study HCJC are highly similar to the results shown in the HCJB-USA study.

4. The sponsor mentioned in the submission that in addition to the post-hoc analyses on secondary endpoints for the Western and Eastern European sites, the agency asked them to provide a discussion for the results of Study HCJB in the 01 August 2001 meeting. It was noticed that the sponsor did not provide any more discussion than what was already known and discussed before the meeting.

_____

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

Concurrence:

Dr. Jin Dr. Chi

cc: NDA 18-936 (SE1-061)
HFD-120/Dr. Katz
HFD-120/Dr. Laughren
HFD-120/Dr. Hearst
HFD-120/MS. Shin
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Chen
This review consists of 6 pages. MS Word: C:/yfchen/nda18936/review2.doc

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/s/

Yeh-Fong Chen
12/5/01 03:33:12 PM
BIOMETRICS

Kun Jin
12/5/01 03:58:13 PM
BIOMETRICS

George Chi
12/6/01 10:18:07 AM
BIOMETRICS

Statistical Review and Evaluation

NDA#:	18-936 (SE1-061)
APPLICANT:	Eli Lilly and Company
NAME OF DRUG:	Prozac
INDICATION:	Panic Disorder
DOCUMENT REVIEWED:	July-27-00
MEDICAL OFFICER:	Earl Hearst M.D. (HFD-120)
STATISTICAL REVIEWER:	Yeh-Fong Chen Ph.D. (HFD-710)

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(b) (4)

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I. Introduction and Summary of Sponsor's Results

In this submission, Eli Lilly and Company (Lilly) evaluated the safety and efficacy of fluoxetine in the treatment of panic disorder. They concluded that they had two large, positive, double-blind, randomized, placebo-controlled trials (B1Y-MC-HCJC and B1Y-MC-HCJB), (b) (4) Since it involves changing the primary efficacy endpoint but without sending the official amendment (See details in Section III) to the agency, this reviewer does not concur with the sponsor's primary endpoint, i.e., panic free status at endpoint. If the other endpoint was considered as primary, i.e., mean change in full panic attacks from baseline to endpoint, then the sponsor's two positive studies, however, would become negative studies.

The detailed summary of primary and supportive efficacy measures according to the sponsor for these (b) (4) studies are shown in Table 1.

Table 1. Summary of Primary and Supportive Efficacy Measures for All Panic Studies

Efficacy Measure	HCJC	HCJB	(b) (4)
Panic free status at endpoint	p=0.018	p=0.008	
≥50% reduction in full panic attacks from baseline to endpoint	p=0.001	+	
Mean change in full panic attacks from baseline to endpoint	p=0.078	p=0.129	
Mean change in total panic attacks from baseline to endpoint	+	+	
PPDS: CGI-Improvement	+	+	

Note:

- The primary efficacy analyses were panic-free status at endpoint for HCJC and HCJB (b) (4)
- Abbreviations: + means numerically favoring fluoxetine; (b) (4)

II. Summaries of Study B1Y-MC-HCJC and Study B1Y-MC-HCJB

Studies B1Y-MC-HCJC and B1Y-MC-HCJB had common study objectives, similar designs, same primary endpoints and analyses, but used different sample sizes and locations. Study B1Y-MC-HCJC was conducted in Europe and Study B1Y-MC-HCJB was done in the U.S.A.

1. Study Objectives

The primary objective of this study was to determine whether fluoxetine 20 to 60 mg/day is more effective than placebo in decreasing full panic attack frequency during acute treatment in patients with panic disorder with or without agoraphobia, according to DSM-IV criteria. Notice that a full panic attack was defined as an attack that meets at least 4 of the 13 symptoms for panic attack presented in DSM-IV.

The secondary objectives of this study were to determine the following:

- The effectiveness of fluoxetine (20 to 60 mg/day) compared with placebo in improving global response, mood and anxiety during acute treatment in patients who have panic disorder with or without agoraphobia according to DSM-IV criteria. Outcomes were assessed using the 7-Item Multicenter Collaborative Panic Disorder Severity Scale (PDSS), Clinical Golbal Impressions of Severity (CGI-Severity) Scale, Panic and Phobic Disorder Scale (PPDS-Clinician and –Patient-rated), Hamilton Anxiety Rating Scale (HAMA), State-Trait Anxiety Inventory (STAI), and the 17-item Hamilton Depression Rating Scale, modified ($HAMD_{17}$).

- The effectiveness of fluoxetine (20 to 60 mg/day) compared with placebo in improving quality of life scores as assessed by the Sheehan Disability Scale.

- The safety of fluoxetine (20 to 60 mg/day) as a treatment for patients who have panic disorder with or without agoraphobia based on assessment of the incidence of treatment-emergent adverse events during 12 weeks of double-blind treatment.

2. Overview of the Sponsor's Study Design and Methodology

These two studies were double-blind, randomized, parallel, placebo-controlled, multi-center trials with two arms of a fluoxetine and a placebo. There are three study periods included.

- Study Period I was a 2-week evaluation period during which patients received single-blind placebo treatment. Baseline values were established and patients were evaluated for eligibility to enter the study.

- Study Period II was a 12-week double-blind, acute treatment phase in which patients were randomly assigned to either the fluoxetine or placebo treatment group. Fluoxetine-treated patients received fluoxetine 10 mg/day for the first week of treatment in Study Period II. After this 1-week treatment period, all fluoxetine-treated patients underwent a forced titration to fluoxetine 20 mg/day. At fixed intervals (Visit 5, 6, or 7), patients were titrated up to a maximum dose of fluoxetine 60 mg/day based on predefined titration criteria (CGI-Severity score >2).

- Study Period III was a double-blinded optional 6-month extension phase (For Study B1Y-MCJB only).

3. Efficacy Measures

Primary Efficacy Measure:

The primary efficacy measure was the frequency of full panic attacks. The primary efficacy endpoint was the percentage of patients panic-free during the final visit interval.

Additional supporting efficacy analyses were conducted on the percentage of patients experiencing at least a 50% reduction in full panic-attack frequency from baseline to endpoint and on the mean change from baseline to endpoint in the number of full and total panic attacks per week. Total panic attacks were defined as the number of full panic attacks and limited-symptom panic attacks. Note that panic attacks with no symptoms recorded were not considered as full panic attacks but were included in the calculation of the total panic attacks. A limited-symptom panic attack met fewer than 4 of the 13 symptoms of a panic attack.

Patients recorded the incidence of full and limited-symptom attacks along with the severity of the symptoms, and these data were used to calculate the panic attack frequency (number of attacks per week) for each visit interval.

Secondary Efficacy Measures:

Secondary efficacy measures included the Panic Disorder Severity Scale (PDSS), Clinical Global Impression of Severity (CGI-Severity), Panic and Phobic Disorder Scale-Clinician and Patient (PPDS-Clinician and PPDS-Patient), Hamilton Anxiety Rating Scale (HAMA), State Anxiety Inventory (STAI), and the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$).

4. Efficacy Analyses

Logistic regression model with treatment, investigator, and treatment-by-investigator interaction (if it is significant at 0.1 level of significance) was used as the primary analysis to compare the percentage of responders at endpoint. A patient was considered as a responder if he had no full panic attack in his final visit interval of the acute phase. This logistic regression model was also used to compare percentage of subjects having at least 50% reduction from baseline to endpoint. Note that investigators with fewer than 2 randomized patients per treatment group were pooled for statistical purposes.

Because of non-normal behavior, efficacy analysis on mean change from baseline to endpoint for the number of full panic attacks was done on the rank-transformed data. Treatment groups were compared using the F-test in an ANOVA model. Independent variables are treatment, investigator, and treatment-by-investigator (if it is significant at 0.1 level of significance) and the dependent variable is the last observation carried forward (LOCF) change from baseline to endpoint of the acute phase.

5. Subgroup Analyses

The following efficacy variables were assessed for subgroup analyses during the acute treatment phase: Panic Disorder Severity Scale average score, CGI-Severity, total and full panic attacks, HAMA total, State Anxiety total, and HAMD total score. The subgroups analyses were performed based on age (<50, ≥50), gender, racial origin (Caucasian, non-Caucasian). For each variable and each subgroup, the LOCF change from baseline to acute phase endpoint were analyzed using the ANOVA with treatment, investigator, investigator-by-treatment interaction, subgroup, and subgroup-by-treatment interaction as independent variables. The subgroup-by-treatment interaction F-test was used to screen for possible differential subgroup behavior. Because of the large number of efficacy variables and subgroups, the subgroup-by-treatment interaction was assessed at the α level of 0.01.

6. Subjects

There are 80 male and 100 female patients randomized for Study B1Y-MC-HCJC and 76 male and 138 female patients for Study B1Y-MC-HCJB. However, only 155 patients completed for Study B1Y-MC-HCJC and 142 patients for Study B1Y-MC-HCJB.

7. Sponsor's Results on Efficacy Evaluation

7.1 For Study B1Y-MC-HCJC

7.1.1. Demographic and Other Baseline Characteristic

Table I.1 in Appendix I summarizes patient demographic characteristics by treatment groups. The mean age of patients was 36 years. All 180 patients were Caucasian, and 100 (56%) were female. There was no significant difference between the two treatment groups in age or gender. On the other hand, according to the patients' consumptive habits which were recorded at Visit 1. There were no significant differences between the two treatment groups in caffeine, alcohol, or tobacco consumption.

Table I.2 presents the frequency of panic attacks experienced by randomized patients during the 2-week evaluation phase. During this phase, all patients received single-blind placebo treatment. The mean number of full panic attacks per week was 3.86 attacks and the mean number of total panic attacks during the same period was 4.42 attacks. There were no statistically significant differences between the two treatment groups.

Regarding the baseline severity of illness characteristics for the secondary efficacy measures of the CGI-Severity scale, STAI, HAMA, HAMD17, PDSS Frequency of Panic Attacks, and PDSS Average score and on the Sheehan Disability Scale individual items,

there were no significant differences between treatment groups on any of these measures or individual items.

7.1.2. Primary Efficacy Analysis: Patients with Zero Full Panic Attacks Per Week

A logistic regression model with treatment, investigator, and treatment-by-investigator interaction effects was originally suggested in the protocol to compare the percentage of full panic-free patients receiving fluoxetine or placebo at endpoint. Because of sparse data, inclusion of the treatment-by-investigator interaction in the model caused non-convergence problems. Further analysis with only treatment and investigator effects in the model was conducted.

A statistically significantly greater percentage of patients from the fluoxetine treatment group were panic-free at endpoint (p=0.018, likelihood ratio test) compared with the placebo treatment group. Forty-two percent of fluoxetine-treated patients and 28% of placebo-treated patients were panic free at endpoint. The estimated odds of achieving panic-free status at endpoint were 2.29 times higher for fluoxetine-treated patients compared to patients receiving placebo. The 95% confidence interval for the estimate of odds ratio is (1.14,4.59). Table 2.1 shows the detailed numbers of panic-free patients by investigators.

Table 2. Summary of Primary Efficacy Analysis Results for Study B1Y-MC-HCJ**C**

Variables	Fluoxetine	Placebo	p-value
Percentage of Panic-Free Patients at Endpoint	42% (n=90)	28% (n=90)	**0.018**

Table 2.1. Numbers of Panic-Free Patients by Investigator for Study B1Y-MC-HCJC

Fluoxetine:

Investigator	Total Patient Number	Panic-Free Number	Percent of responder
001	14	11	78.6
003	6	3	50.0
004	3	2	66.7
005	20	1	5.0
006	8	3	37.5
007	6	3	50.0
008	28	12	42.9
009	5	3	60.0
Total	90	38	42.2

Placebo:

Investigator	Total Patient Number	Panic-Free Number	Percent of responder
001	14	7	50.0
003	5	1	20.0
004	2	0	0.0
005	19	0	0.0
006	8	1	12.5
007	7	4	57.1
008	29	10	34.5
009	6	2	33.3
Total	90	25	27.8

7.1.3. Supportive Efficacy Analyses

7.1.3.1. Patients With at Least 50% Reduction from Baseline in Number of Full Panic Attacks

The percentage of patients receiving fluoxetine who had at least a 50% reduction from baseline in the number of full panic attacks per week was compared with the percentage of those patients receiving placebo who experienced the same effect. For this comparison, a logistic regression model with treatment, investigator, and treatment-by-investigator interaction effects was originally planned. However, because of sparse data, inclusion of the treatment-by-investigator effect in the model led to non-convergence problems. Therefore, results based on a reduced model with just the treatment and investigator effects are presented.

A statistically significantly greater percentage of patients from the fluoxetine group (p=0.001, likelihood ratio test) had at least a 50% reduction from baseline compared with the placebo group. Eighty-two percent of patients in the fluoxetine treatment group demonstrated at least a 50% reduction compared with 61% for the placebo treatment group. The estimated odds of having at least a 50% or greater reduction from baseline in the number of full panic attacks per week was 3.23 times higher for the fluoxetine-treated patients compared with placebo-treated patients. The 95% confidence interval is (1.57, 6.63).

7.1.3.2. Mean Change from Baseline in Full Panic Attacks per Week

The LOCF change from baseline to endpoint in the weekly number of full panic attacks was planned to be analyzed by ANOVA. Since previous studies had indicated that non-normal behavior was likely, the ANOVA was conducted on the rank-transformed data of change from baseline to endpoint. The treatment-by-investigator interaction was not statistically significant at a significance level of 0.10, so as planned in the protocol, it was dropped from the ANOVA model.

The mean change in the weekly number of full panic attacks was –2.90 for fluoxetine group and –2.18 for the placebo group. However, the difference between the two treatment groups was not statistically significant (p=0.078).

7.1.3.3. Mean Change from Baseline in Total Panic Attacks per Week

Panic attacks in which the patient reported a panic attack, but failed to enumerate the symptoms, were included in the calculation of total panic attacks. Because of the extreme non-normality problem on residual errors, the ANOVA was conducted on the rank transformation of change from baseline to endpoint.

Although fluoxetine-treated patients demonstrated numerically greater reduction in the number of total panic attacks per week compared with placebo-treated patients, the difference between the two treatment groups was not statistically significant.

Table 3. Summaries the Supportive Efficacy Analyses Results for Study B1Y-MC-HCJC.

Variables	Fluoxetine	Placebo	p-value
Percentage of Patients Having ≥ 50% Reduction in Frequency of Full Panic Attacks from Baseline	82% (n=90)	61% (n=90)	**0.001**
Mean Change from Baseline to Endpoint in Frequency of Full Panic Attacks	-2.9 (n=90)	-2.2 (n=90)	0.078
Mean Change from Baseline to Endpoint in Frequency of Total Panic Attacks	-3.2 (n=90)	-2.5 (n=90)	0.263

7.1.4. Secondary Efficacy Analyses

The analysis results for some secondary endpoints are shown in Table 4. In measurements of symptoms associated with panic disorder, fluoxetine-treated patients experienced significantly greater improvement compared with placebo-treated patients on PDSS Average score (p=0.009) and on the CGI-Severity total score (p=0.037). On measures for assessing the severity of anxiety, the HAMA and STAI, fluoxetine-treated patients showed significantly greater improvement compared with placebo-treated patients (p=0.043 and p=0.005, respectively).

Table 4. Summaries of Some Secondary Efficacy Analyses Results for Study B1Y-MC-HCJC

Variables	Fluoxetine	Placebo	p-value
Mean Change from Baseline to Endpoint in PDSS Average Score	-1.64 (n=88)	-1.09 (n=90)	**0.009**
Mean Change from Baseline to Endpoint in CGI-Severity Score	-2.61 (n=88)	-1.82 (n=90)	**0.037**
Mean of PPDS Endpoint Analyses on Clinician-Rated Scales (Overall Functioning-Clinician)	1.977 (n=88)	2.600 (n=90)	0.186
Mean of PPDS Endpoint Analyses on Patient-Rated Scales (Overall Functioning-Clinician)	2.068 (n=88)	2.622 (n=90)	0.477

Mean Change from Baseline to Endpoint in HAMA Total Score	-14.86 (n=85)	-9.97 (n=88)	**0.043**
Mean Change from Baseline to Endpoint in STAI Total Score	-15.32 (n=85)	-7.48 (n=88)	**0.005**
Mean Change from Baseline to Endpoint in $HAMD_{17}$ Total Score	-6.482 (n=85)	-4.227 (n=88)	0.137

7.1.5. Subgroup Analyses

Subgroup analyses based on the patient subgroups of age (<50 or ≥50 years) and gender (male or female) are summarized in tables of Appendix II (Recall that all 180 patients were Caucasian, so racial subgroup was not analyzed). As it was shown on the tables, fluoxetine-treated patients were numerically superior to placebo-treated patients for all subgroups in each efficacy measure. Fluoxetine-treated patients <50 year old experienced statistically significantly greater improvement at endpoint than did placebo-treated patients in all the efficacy measures analyzed. The number of patients in the ≥ 50 subgroup was small and it would not be expected to see statistical significance in this subgroup. Female fluoxetine-treated patients experienced statistically significantly greater improvement at endpoint than did placebo-treated patients for each efficacy variable.

7.2. For Study B1Y-MC-HCJB

7.2.1. Demographic and Other Baseline Characteristics

Table III.1 summarizes patient demographic characteristics by treatment groups. The mean age of patients was 38 years. One hundred eighty patients (84%) were Caucasian, and 138 (65%) were female. The treatment groups were comparable at baseline (Visit 2) with respect to age, origin, and gender.

Patient consumptive habits were recorded at Visit 1. There were no significant differences between the two treatment groups in caffeine or tobacco consumption; however, a higher percentage of placebo-treated patients consumed alcohol at baseline compared with fluoxetine-treated patients (64% and 50%, respectively; p=.039).

Table III.2 presents the frequency of panic attacks experienced by randomized patients during the 2-week evaluation phase. During this single-blind placebo treatment phase, the mean number of full panic attacks per week for all patients was 3.28 attacks and 3.61 attacks for total panic attacks. There were no statistically significant differences between two treatment groups.

Regarding the baseline illness characteristics for the secondary efficacy measures and on the Sheehan Disability Scale individual items, there were no significant differences between treatment groups on any of measures or items.

7.2.2. Primary Efficacy Analysis: Patients with Zero Full Panic Attacks Per Week

Same as Study B1Y-MC-MCJC, logistic regression analysis was used as the primary efficacy analysis to compare the percentage of panic-free patients in each treatment group at endpoint. Each investigator having 2 or fewer randomized patients in each treatment group was pooled for this analysis. So, Investigators 003, 005, 006, and 015 were pooled. The logistic regression model included treatment, investigator, and treatment-by-investigator interaction effects. Since the interaction term was not significant at the 0.1 level, it was dropped from the model as planned in the protocol. The treatment differences were tested using the reduced model.

A statistically significantly greater percentage of patients from the fluoxetine treatment group were panic free at endpoint compared with the placebo group (p=0.008, likelihood ratio test). The percentage of panic-free patients at endpoint was 62% for the fluoxetine group and 44% for the placebo group. The estimated odds of achieving panic-free status at endpoint were 2.15 times higher for fluoxetine-treated patients compared with placebo-treated patients. The treatment-by-investigator interaction was not significant. The 95% confidence interval for the estimate of odds ratio is (1.21, 3.80). The detailed numbers of panic-free patients by investigator is shown in Table 5.1.

Table 5. Summary of Primary Efficacy Analysis Results for Study B1Y-MC-HCJB

Variables	Fluoxetine	Placebo	p-value
Percentage of Panic-Free Patients at Endpoint	62% (n=107)	44% (n=104)	**0.008**

Table 5.1. Numbers of Panic-Free Patients by Investigator for Study B1Y-MC-HCJB

Fluoxetine:

Investigator	Total Patient Number	Panic-Free Number	Percent of responder
001	14	6	42.86
002	6	2	33.33
004	10	7	70.00
007	8	3	37.50
008	4	2	50.00
009	6	3	50.00
010	6	5	83.33
011	2	2	100.00
012	12	6	50.00
013	13	10	76.92
014	7	7	100.00
016	5	3	60.00
017	7	5	71.43
999[a]	7	5	71.43
Total	107	66	61.68

Placebo:

Investigator	Total Patient Number	Panic-Free Number	Percent of responder
001	12	6	50.00
002	6	3	50.00
004	8	3	37.50
007	8	2	25.00
008	6	3	50.00
009	6	2	33.33
010	5	3	60.00
011	4	2	50.00
012	11	5	45.45
013	12	5	41.67
014	7	4	57.14
016	4	2	50.00
017	8	4	50.00
999[a]	7	2	28.57
Total	104	46	44.23

[a] Investigator 999 includes Sites 003, 005, 006 and 015.

7.2.3. Supportive Efficacy Analyses

7.2.3.1. Patients with at Least a 50% Reduction from Baseline in Number of Full Panic Attacks

Although a higher percentage of fluoxetine-treated patients who experienced at least a 50% reduction from baseline to endpoint compared with placebo-treated patients, the treatment difference was not significant (83% and 74%, respectively; p=0.120, likelihood ratio test). The estimated odds of having a 50% or greater reduction from baseline in the number of full panic attacks per week were 1.74 times higher for the fluoxetine-treated patients compared with placebo-treated patients. The 95% confidence interval for the estimate of odds ratio is (0.86, 3.50).

7.2.3.2. Full Panic Attacks Per Week

As it was shown in Table 6 there was no statistically significant difference between the two treatment groups. However, the mean change from baseline to endpoint in frequency of full panic attacks was greater for the fluoxetine group compared with the placebo group. The ANOVA for this variable was conducted on the rank transformation of changes due to the non-normal error structure of the data.

7.2.3.3. Total Panic Attack Frequency Analyses

As with the number of full panic attacks per week, preliminary analyses of the original scale data indicated extreme non-normality of the residual errors, suggesting that some transformation of the data was needed. The ANOVA for this variable was conducted on the rank transformation of change from baseline to endpoint.

Although the treatment comparison was not significant, fluoxetine-treated patients showed numerically greater decreases (improvement) from baseline as compared with placebo-treated patients. At this case, the treatment-by-investigator interaction was statistically significant.

Table 6. Summary of Supportive Efficacy Analyses Results for Study B1Y-MC-HCJB

Variables	Fluoxetine	Placebo	p-value
Percentage of Patients Having ≥ 50% Reduction in Frequency of Full Panic Attacks from Baseline	83% (n=107)	74% (n=104)	0.120
Mean Change from Baseline to Endpoint in Frequency of Full Panic Attacks	-2.7 (n=107)	-1.9 (n=104)	0.129
Mean Change from Baseline to Endpoint in Frequency of Total Panic Attacks	-3.03 (n=107)	-2.07 (n=104)	0.057

7.2.4. Secondary Efficacy Analyses

As it was shown on Table 7, none of the secondary points below had statistically significant difference between the treatment group and placebo group.

Table 7. Summary of Some Secondary Efficacy Analyses Results for Study B1Y-MC-HCJB

Variables	Fluoxetine	Placebo	p-value
Mean Change from Baseline to Endpoint in PDSS Average Score	-1.17 (n=99)	-1.01 (n=96)	0.118
Mean Change from Baseline to Endpoint in CGI-Severity Score	-1.79 (n=99)	-1.57 (n=96)	0.226
Mean of PPDS Endpoint Analyses on Clinician-Rated Scales (Overall Functioning-Clinician)	2.317 (n=101)	2.542 (n=96)	0.185
Mean of PPDS Endpoint Analyses on Patient-Rated Scales (Overall Functioning-Clinician)	2.539 (n=102)	2.438 (n=96)	0.853
Mean Change from Baseline to Endpoint in HAMA Total Score	-7.024 (n=83)	-6.417 (n=84)	0.362
Mean Change from Baseline to Endpoint in STAI Total Score	-6.59 (n=83)	-6.49 (n=85)	0.833
Mean Change from Baseline to Endpoint in $HAMD_{17}$ Total Score	-2.18 (n=84)	-1.55 (n=84)	0.323

7.2.5. Subgroup Analyses

As Study B1Y-MC-HCJC, subgroup analyses based on the patient subgroups of age (<50 or ≥ 50 years), gender (male or female), and origin (Caucasian or non-Caucasian) were performed and are summarized in the tables of Appendix IV. Analyses were conducted on rank-transformed data for total and full panic attacks per week. All other analyses

were conducted on original-scale data. The subgroup effect was not statistically significant for any of the efficacy variables, nor was the treatment-by-subgroup interaction significant at the 0.01 level. This indicates that treatment effects as measured by these scales were consistent within subgroup strata.

Among patients stratified by age, fluoxetine-treated patients less than 50 years old experienced statistically significantly greater improvement at endpoint than did the placebo-treated patients less than 50 years old in total panic attack frequency (p=0.033). There were no treatment differences within age categories for other efficacy measures.

Among patients stratified by gender, female fluoxetine-treated patients experienced statistically significantly greater improvement at endpoint than did female placebo-treated patients in the full panic attack frequency (p=0.045). There were no significant treatment differences within gender categories for other efficacy measures.
Among patients stratified by racial origin, Caucasian fluoxetine-treated patients experienced statistically significantly greater improvement at endpoint than did Caucasian placebo-treated patients in total panic attack frequency (p=0.048). There were no significant treatment differences within racial origin categories for other efficacy measures.

III. Reviewer's Findings and Comments for Study B1Y-MC-HCJC and Study B1Y-MC-HCJB (two studies are abbreviated as HCJC and HCJB, respectively)

1. The primary endpoint and statistical analysis utilized for both Study HCJC and HCJB by the sponsor were based on Amendment (b) to the protocol of HCJB. However, this amendment was not submitted to the agency before the submission of this supplemental NDA.

   The sponsor amended the protocol fluoxetine IND 12,274 twice for Study HCJB but only once for Study HCJC, although two studies HCJC and HCJB are similar. According to the sponsor's explanations, Amendment (b) of Study HCJB was made to increase the number of patients to be enrolled in the study and to change the designation of the primary efficacy measure for the study and consequently, to change the primary efficacy analysis. These changes were made after several interactions between Lilly and the Division to clarify the most appropriate primary measure for panic disorder. After amendment (b) to HCJB was made, Lilly decided to change the designation of the primary efficacy measure for Study HCJC also, but not to adjust the sample size in this study. Lilly also determined that a change in the designation of the primary efficacy measure for Study HCJC did not require a protocol amendment and, thus, protocol of HCJC was not amended to reflect this change. Although, according to Lilly, Amendment (b) to HCJB was approved on December 17, 1998 by Lilly and implemented by the investigator shortly thereafter, Lilly inadvertently did not have it sent to the agency.

2. Two studies HCJC and HCJB are positive only when the endpoint is the percentage of patients panic-free during the final visit interval. If the mean change from baseline to endpoint in frequency of full panic attacks were to be considered as the primary endpoint instead, then both studies would fail to be considered positive studies (p=0.078 and 0.129, respectively).

   As it was mentioned in the previous comment, the sponsor amended the protocol twice for determining the most appropriate primary endpoint and analysis for both studies. In the original protocols of HCJC and HCJB, the primary efficacy variable and analysis were the total score on the Panic Disorder Severity Scale (PDSS) and ANOVA on change from baseline to endpoint using Last Observation Carried Forward (LOCF) analysis. They were later changed to the total (full plus limited symptom attacks) panic attack frequency and ANOVA on ranked change from baseline to endpoint in total panic attacks using LOCF in Amendment (a) to both studies. According to the sponsor and the letter of June 16, 1998 from FDA to Lilly, the sponsor was again asked to consider only full panic attack frequency as the primary outcome measure. So the sponsor finally used the percentage of patients panic-free during the final visit interval as the primary endpoint in this submission of supplemental NDA and the study became positive. Since the earlier primary endpoint and analysis were the total panic frequency and ANOVA on ranked change from baseline to endpoint shown in the Amendment (a) of both studies, it lacked a reasonable explanation why the sponsor finally chose a kind of dichotomized primary endpoint instead.

3. For both studies, HCJC and HCJB, this reviewer's analysis results are pretty much consistent with the sponsor's on primary efficacy analysis, supportive efficacy analyses and some secondary efficacy analyses. For subgroup analyses, however, this reviewer found that none of p-values shown for variables of total panic attacks per week and full panic attacks per week are correct in both studies.

   For Study HCJC, the most crucial errors are p-values for female patients on the variable of total panic attacks per week as well as for the group of age <50 patients and the group of female patients on the variable of full panic attacks per week. They should be 0.0594, 0.0951, and 0.1522 not 0.013, 0.010, and 0.048, respectively (see Appendix II).

   For Study HCJB, on the variable of total panic attacks per week, p-values should be 0.4623 and 0.1904 not 0.033 and 0.048 for age <50 patients and Caucasian patients, respectively (see Appendix IV). For the variable of full panic attacks per week, the p-value of female patients should be 0.5485 not 0.045.

   With all these changes on p-values, we notice that the conclusions are changed accordingly. Since the sample sizes are not powered for subgroup analysis, we can only conclude that the group of age <50 patients in Study HCJC shows the significant difference between fluoxetine and placebo comparisons on the variables of total panic attack per week.

4. Although for Study HCJC the p-value showed 0.018 (<0.05) when the variable of percentage of panic-free patients at endpoint was analyzed by the logistic regression, this result was found to be method dependent. By using the simple chi-square test, p-values showed 0.061.

5. One should notice that for Study HCJB, the sponsor's primary endpoint from their study report, i.e., the percentage of panic-free patients at endpoint, is the **only** endpoint that had significant test result. For their supportive and almost all of secondary endpoints, p-values were greater than 0.05.

6. In the first volume of this submission, the sponsor attached a 'NOTE TO REVIEWERS', which mentioned some additional clinical efficacy analyses. This reviewer evaluated the sponsor's analyses and had consistent results.

   According to the sponsor, in studies HCJC and HCJB, patients recorded panic attack information in an electronic diary. Patients were required to enter a diary record only if they experienced a panic attack. Therefore, patients who did not have any diary entries during their last visit interval were assumed to be panic attack free. Some patients who discontinued from the study did not have any data at their final visit from other efficacy measures, such as the PDSS, PPDS, and HAMA. Therefore, additional analyses were conducted to investigate the robustness of the efficacy conclusions to this assumption regarding panic-free status. These analyses were conducted on four efficacy variables: full panic attack free status, at least a 50% reduction from baseline in the number of full panic attacks per week, and mean change from baseline to endpoint in the number of full and total panic attacks per week. These variables were analyzed based on the following two scenarios:

   - Analysis A: The final visit was defined as the last visit at which a patient had other efficacy data (such as PDSS, PPDS, and HAMA). At this visit, patients were more clearly actively participating in the trial. However, subsequent panic diary entries are ignored.

   - Analysis B: The final visit was defined as the last visit at which a patient had other efficacy data (such as PDSS, PPDS, and HAMA) only for those patients who did not have panic diary entries during their final visit interval. Final visits for all other patients did not change. In this analysis, any panic attack entries collected in the absence of other efficacy data are still used. However, the absence of panic diary entries was not counted unless other efficacy data were also present.

   Table 8 and 9 show statistical results from the sponsor and this reviewer for analyses A and B. Except a few different p-values shown on variables of mean change from baseline to endpoint for variables of full or total panic attacks and one error happened in the sponsor's number of patients and p-value for the variable of ≥ 50% reduction in full panic attacks of Analysis B for Study HCJB, this reviewer's results agree with the sponsor's results very well. Therefore, as we can observed from the

following two tables, there is no doubt on the robustness of these efficacy conclusions.

Table 8. Additional Clinical Efficacy Analyses for Study HCJC

Analysis A	Fluoxetine			Placebo			
Variable	N	n	%	N	n	%	p-value
Patients Full Panic Attack Free	88	35	40%	90	24	27%	0.027
Patients with ≥ 50 % Reduction in Full Panic Attacks	88	71	81%	90	55	61%	0.003
Mean Change on Full Panic Attacks	88	-2.92		90	-2.18		~~0.294~~ 0.298
Mean Change on Total Panic Attacks	88	-3.25		90	-2.48		~~0.225~~ 0.231

Analysis B	Fluoxetine			Placebo			
Variable	N	n	%	N	n	%	p-value
Patients Full Panic Attack Free	89	35	39%	90	24	27%	0.032
Patients with ≥ 50 % Reduction In Full Panic Attacks	89	71	80%	90	55	61%	0.004
Mean Change on Full Panic Attacks	89	-2.89		90	-2.18		~~0.304~~ 0.308
Mean Change on Total Panic Attacks	89	-3.22		90	-2.48		~~0.234~~ 0.240

Table 9. Additional Clinical Efficacy Analyses for Study HCJB

Analysis A	Fluoxetine			Placebo			
Variable	N	n	%	N	n	%	p-value
Patients Full Panic Attack Free	102	57	56%	96	40	42%	0.027
Patients with ≥ 50 % Reduction In Full Panic Attacks	102	80	78%	96	70	73%	0.399
Mean Change on Full Panic Attacks	102	-2.34		96	-1.97		~~0.259~~ 0.260
Mean Change on Total Panic Attacks	102	-2.72		96	-2.11		0.096

Analysis B	Fluoxetine			Placebo			
Variable	N	n	%	N	n	%	p-value
Patients Full Panic Attack Free	103	57	55%	102	40	39%	0.012
Patients with ≥ 50 % Reduction In Full Panic Attacks	103	~~82~~ 81	80%	102	74	73%	~~0.240~~ 0.319
Mean Change on Full Panic Attacks	103	-2.56		102	-1.91		~~0.184~~ 0.191
Mean Change on Total Panic Attacks	103	-2.92		102	-2.05		0.066

7. It was observed by this reviewer that , in Study HCJB, thirteen patients had protocol violations #34 (according to the sponsor), i.e., <2 full panic attacks during the first 2 weeks of evaluation period between Visit 1 to Visit 2. Patients 1202 and 1609 were not even had the diary data. Since some of these patients only had few

visits out of 8 but turned out to be responders according to the definition of the method of LOCF (last observation carried forward), this reviewer tried to do analysis again after excluding them from the original data file. Since the p-value showed 0.009, which is still significant (compared with 0.008), it tells us that those 13 patients did not make much influence.

8. After this reviewer carefully checked the sponsor's data and statistical analyses, it was found that there are some typing errors shown in the diary file for patient 1703 of study HCJB. It shows some inconsistency between diary dates and panic attack dates for that patient. Since the primary endpoint of percentage of patients full panic-free during the final visit interval is a dichotomized variable as well as the variable, percentage of patients having ≥ 50% reduction in frequency of full panic attacks from baseline for supportive analyses, those errors do not make any influence.

   They do make influences on the analyses of variables: mean change from baseline to endpoint in frequency of full panic attacks and total panic attacks for supportive analyses, but changes are found very small (p-value is changed from 0.13 to 0.12 and from 0.06 to 0.05, respectively).

9. This reviewer wants to point out that although it does not show significant mean difference between the fluoxetine treatment group and placebo group in baseline numbers of full panic attack, considering the baseline full panic frequency of patient-wise or not seems to substantially influence the test results. This is the reason why the sponsor has significant test results when the endpoint is the percentage of patients full panic-free during the final visit interval but not when the endpoint is the change on the full panic attack frequency from baseline to the endpoint.

(b) (4)

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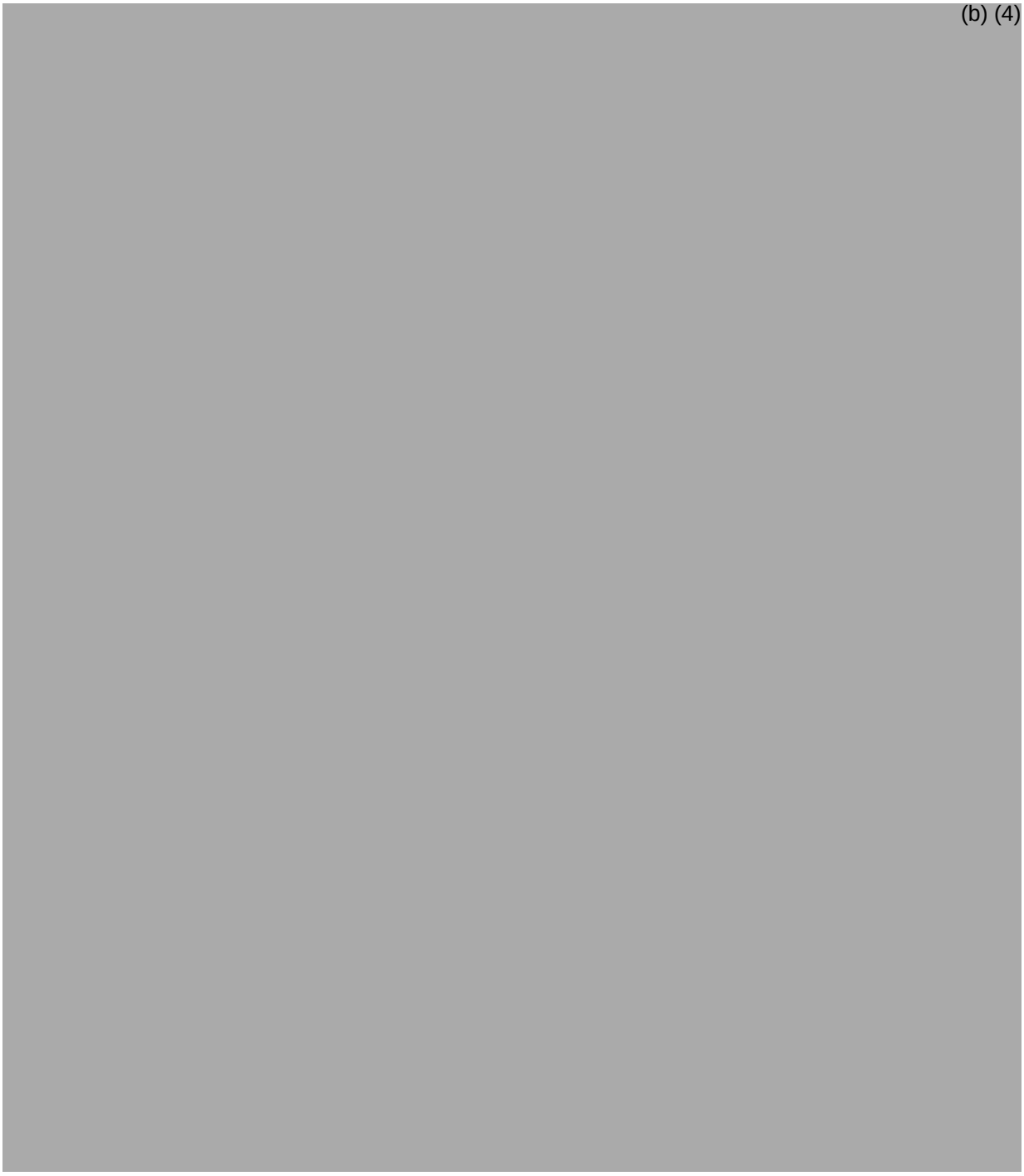

VIII. Reviewer's Overall Conclusions

The **full** panic attack frequency was the primary efficacy measure that FDA insisted for panic disorder. Before the sponsor was asked to consider this primary efficacy measure, the sponsor's primary endpoint and analysis were **total** panic attack frequency and ANOVA on rank transformed change from baseline to endpoint using Last Observation Carried Forward (LOCF). Logically, the sponsor would amend their primary endpoint and analysis to **full** panic attack frequency and ANOVA on rank transformed change

from baseline to endpoint using LOCF. However, the sponsor had primary endpoint and analysis finally specified as the percentage of patients full panic-free during the final visit interval and the logistic regression model with treatment, investigator and treatment-by-investigator interaction (if it had p-value > 0.1) instead in this submission of NDA.

Although they had positive test results on Study HCJC and HCJB according to their specified primary endpoint and analysis, they did not have their amendment submitted to the agency. It lacked any support for using the percentage of patients full panic-free during the final visit interval as their primary endpoint. If the primary endpoint and analysis were full panic attack frequency and ANOVA on rank transformed change from baseline to endpoint using LOCF at endpoint, both studies of HCJC and HCJB became negative.

Even though the percentage of full panic-free patients during the final visit interval is an appropriate primary endpoint, it was noticed that for Study HCJC, the test for it was method dependent. By using chi-square test instead of logistic regression, the p-value showed 0.061. On the other hand, for Study HCJB, the test for this endpoint was the only one showing significant result. Other supportive and almost all of secondary endpoints showed p-values greater than 0.05.

(b) (4)

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Mathematical Statistician

Concurrence:

Dr. Jin Dr. Chi

cc: NDA 18-936 (SE1-061)
HFD-120/Dr. Katz
HFD-120/Dr. Laughren
HFD-120/Dr. Hearst
HFD-120/MS. Shin
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Chen
This review consists of 32 pages. MS Word: C:/yfchen/nda18936/review.doc

VIII. Appendices

Appendix I: Tables of Demographic and Other Baseline Characteristics for Study B1Y-MC-HCJC from Sponsor's Study Report

Table I.1: Patient Demographic Characteristics

Variable	Fluoxetine	Placebo	Total	p-value
Sex: No. (%)				
No. of patient	90	90	180	.453
Female	47 (52.2)	53 (58.9)	100 (55.6)	
Male	43 (47.8)	37 (41.1)	80 (44.4)	
Origin: No. (%)				
No. of patient	90	90	180	
CAUCASIAN	90 (100)	90 (100)	180 (100)	
Age: yrs.				
No. of patient	90	90	180	.584
Mean	36.49	34.83	35.66	
Median	33.95	33.63	33.71	
Standard Dev.	10.35	9.77	10.07	
Minimum	19.19	19.54	19.19	
Maximum	66.77	59.76	66.77	

Table I.2: Baseline Severity of Illness for Frequency of Panic Attacks

Variable	Fluoxetine	Placebo	Total	p-value
No. of Full Panic Attacks/Week (Visit2)				
Mean	3.94	3.78	3.86	.576
Median	3.00	2.60	2.76	
Standard Dev.	3.46	3.02	3.24	
Minimum	0.00	0.50	0.00	
Maximum	17.27	19.60	19.60	
No. of Total Panic Attacks/Week (Visit2)				
Mean	4.41	4.43	4.42	.531
Median	3.17	3.25	3.23	
Standard Dev.	3.88	3.48	3.68	
Minimum	0.54	0.78	0.54	
Maximum	21.93	20.07	21.93	

Appendix II: Age and Gender Subgroup Analysis for Study B1Y-MC-HCJC

1. Total Panic Attacks Per Week

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.715	0.811	< 50	Fluoxetine (79)	-3.24 (3.97)	~~0.005~~ 0.0388
				Placebo (83)	-2.49 (3.94)	
			≥ 50	Fluoxetine (11)	-3.22 (2.12)	~~0.192~~ 0.1665
				Placebo (7)	-2.48 (2.63)	
Gender	0.777	0.614	Female	Fluoxetine (47)	-3.11 (3.54)	~~0.013~~ 0.0594
				Placebo (53)	-2.31 (3.03)	
			Male	Fluoxetine (43)	-3.37 (4.08)	~~0.145~~ 0.2631
				Placebo (37)	-2.75 (4.82)	

2. Full Panic Attacks Per Week

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.658	0.730	< 50	Fluoxetine (79)	-2.88 (3.36)	~~0.010~~ 0.0951
				Placebo (83)	-2.14 (3.29)	
			≥ 50	Fluoxetine (11)	-3.09 (2.11)	~~0.244~~ 0.3615
				Placebo (7)	-2.77 (2.70)	
Gender	0.903	0.873	Female	Fluoxetine (47)	-2.83 (2.98)	~~0.048~~ 0.1522
				Placebo (53)	-2.21 (2.51)	
			Male	Fluoxetine (43)	-2.99 (3.51)	~~0.123~~ 0.2799
				Placebo (37)	-2.14 (4.10)	

3. CGI-Severity

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.511	0.724	< 50	Fluoxetine (77)	-2.61 (1.56)	0.001
				Placebo (83)	-1.86 (1.39)	
			≥ 50	Fluoxetine (11)	-2.64 (1.63)	0.154
				Placebo (7)	-1.43 (2.07)	
Gender	0.331	0.702	Female	Fluoxetine (47)	-2.68 (1.70)	<0.001
				Placebo (53)	-1.68 (1.50)	
			Male	Fluoxetine (41)	-2.54 (1.40)	0.122
				Placebo (37)	-2.03 (1.34)	

4. PDSS Average

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.841	0.723	< 50	Fluoxetine (77)	0.99 (0.95)	<0.001
				Placebo (83)	1.48 (1.05)	
			≥ 50	Fluoxetine (11)	1.05 (1.03)	0.398
				Placebo (7)	1.71 (1.20)	
Gender	0.905	0.609	Female	Fluoxetine (47)	1.02 (1.00)	0.006
				Placebo (53)	1.54 (1.09)	
			Male	Fluoxetine (41)	0.96 (0.91)	0.040
				Placebo (37)	1.44 (1.01)	

5. HAMA Total Score

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.191	0.365	< 50	Fluoxetine (74)	-14.70 (8.89)	0.002
				Placebo (81)	-10.42 (9.89)	
			≥ 50	Fluoxetine (11)	-15.91 (11.08)	0.121
				Placebo (7)	-4.71 (9.60)	
Gender	0.273	0.683	Female	Fluoxetine (45)	-15.56 (9.61)	0.001
				Placebo (51)	-9.82 (10.33)	
			Male	Fluoxetine (40)	-14.08 (8.62)	0.103
				Placebo (37)	-10.16 (9.51)	

6. $HAMD_{17}$ Total Score

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.192	0.690	< 50	Fluoxetine (74)	-6.43 (4.64)	0.010
				Placebo (81)	-4.47 (5.67)	
			≥ 50	Fluoxetine (11)	-6.82 (5.21)	0.211
				Placebo (7)	-1.43 (6.60)	
Gender	0.694	0.205	Female	Fluoxetine (45)	-6.53 (4.43)	0.007
				Placebo (51)	-4.14 (5.52)	
			Male	Fluoxetine (40)	-6.43 (5.01)	0.177
				Placebo (37)	-4.35 (6.16)	

7. STAI Total Score

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.835	0.769	< 50	Fluoxetine (74)	-15.31 (12.91)	<0.001
				Placebo (80)	-7.84 (13.79)	
			≥ 50	Fluoxetine (11)	-15.36 (18.55)	0.304
				Placebo (7)	-7.00 (22.15)	
Gender	0.448	0.807	Female	Fluoxetine (45)	-17.09 (13.25)	0.001
				Placebo (50)	-8.92 (15.70)	
			Male	Fluoxetine (40)	-13.33 (13.94)	0.058
				Placebo (37)	-6.22 (12.63)	

[a] Two columns of Therapy×Subgroup and Subgroup show p-values for the model, response ~ therapy + subgroup + interaction of therapy and subgroup.
[b] The last column shows the p-value for therapy within stratum in the model response ~ therapy + investigator.
Abbreviations: CGI-Severity = Clinical Global Impressions of Severity;
HAMA = Hamilton Anxiety Rating Scale;
HAMD17 = 17-Item Hamilton Depression Rating Scale (modified);
PDSS = 7-Item Multicenter Collaborative panic Disorder Severity Scale
SD = standard deviation;
STAI = State-Trait Anxiety Inventory

Appendix III: Tables of Demographic and Other Baseline Characteristics for Study B1Y-MC-HCJB from Sponsor's Study Report

Table III.1: Patient Demographic Characteristics

Variable	Fluoxetine	Placebo	Total	p-value
Sex: No. (%)				
No. of patient	108	106	214	.477
Female	67 (62.0)	71 (67.0)	138 (64.5)	
Male	41 (38.0)	35 (33.0)	76 (35.5)	
Origin: No. (%)				
No. of patient	108	106	214	.957
AFRICAN DESCENT	11 (10.2)	9 (8.5)	20 (9.3)	
CAUCASIAN	90 (83.3)	90 (84.9)	180 (84.1)	
EAST/SE ASIAN	0	1 (0.9)	1 (0.5)	
HISPANIC	6 (5.6)	6 (5.7)	12 (5.6)	
WESTERN ASIAN	1 (0.9)	0	1 (0.5)	
Age: yrs.				
No. of patient	108	106	214	.493
Mean	37.23	38.80	38.01	
Median	36.28	37.58	36.82	
Standard Dev.	11.32	11.19	11.26	
Minimum	18.40	19.53	18.40	
Maximum	65.09	74.24	74.24	

Table III.2: Baseline Severity of Illness for Frequency of Panic Attacks

Variable	Fluoxetine	Placebo	Total	p-value
No. of Full Panic Attacks/Week (Visit2)				
Mean	3.46	3.10	3.28	.537
Median	2.00	2.00	2.00	
Standard Dev.	3.81	3.25	3.54	
Minimum	0.00	0.00	0.00	
Maximum	21.00	26.92	26.92	
No. of Total Panic Attacks/Week (Visit2)				
Mean	3.91	3.31	3.61	.263
Median	2.39	2.08	2.33	
Standard Dev.	4.57	3.54	4.09	
Minimum	0.00	0.00	0.00	
Maximum	31.11	28.54	31.11	

Appendix IV : Age and Gender Subgroup Analysis for Study B1Y-MC-HCJB

1. Total Panic Attacks Per Week

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.944	0.947	< 50	Fluoxetine (92)	-2.61 (3.29)	~~0.033~~ 0.4623
				Placebo (88)	-1.99 (2.79)	
			≥ 50	Fluoxetine (15)	-5.60 (7.85)	~~0.374~~ 0.2725
				Placebo (16)	-2.50 (3.94)	
Gender	0.934	0.832	Female	Fluoxetine (66)	-3.19 (4.92)	~~0.096~~ 0.4210
				Placebo (70)	-2.34 (3.18)	
			Male	Fluoxetine (41)	-2.77 (3.10)	~~0.165~~ 0.4749
				Placebo (34)	-1.49 (2.45)	
Origin	0.917	0.762	Caucasian	Fluoxetine (89)	-3.03 (4.31)	~~0.048~~ 0.1904
				Placebo (88)	-2.03 (3.16)	
			Non-Caucasian	Fluoxetine (18)	-3.05 (4.42)	~~0.264~~ 0.7712
				Placebo (16)	-2.27 (1.73)	

2. Full Panic Attacks Per Week

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.811	0.795	< 50	Fluoxetine (92)	-2.41 (3.24)	~~0.088~~ 0.6850
				Placebo (88)	-1.83 (2.45)	
			≥ 50	Fluoxetine (15)	-4.36 (5.18)	~~0.325~~ 0.5060
				Placebo (16)	-2.35 (3.68)	
Gender	0.397	0.623	Female	Fluoxetine (66)	-2.81 (4.01)	~~0.045~~ 0.5485
				Placebo (70)	-2.13 (2.75)	
			Male	Fluoxetine (41)	-2.48 (2.88)	~~0.477~~ 0.7290
				Placebo (34)	-1.46 (2.44)	
Origin	0.805	0.488	Caucasian	Fluoxetine (89)	-2.63 (3.44)	~~0.113~~ 0.4122
				Placebo (88)	-1.88 (2.81)	
			Non-Caucasian	Fluoxetine (18)	-2.97 (4.45)	~~0.210~~ 0.7015
				Placebo (16)	-2.06 (1.66)	

3. CGI-Severity

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.431	0.911	< 50	Fluoxetine (85)	-1.81 (1.63)	0.782
				Placebo (80)	-1.64 (1.32)	
			≥ 50	Fluoxetine (14)	-1.64 (1.50)	0.086
				Placebo (16)	-1.25 (1.24)	
Gender	0.590	0.527	Female	Fluoxetine (60)	-1.80 (1.60)	0.417
				Placebo (64)	-1.66 (1.36)	
			Male	Fluoxetine (39)	-1.77 (1.63)	0.501
				Placebo (32)	-1.41 (1.21)	
Origin	0.137	0.432	Caucasian	Fluoxetine (82)	-1.77 (1.54)	0.743
				Placebo (80)	-1.69 (1.34)	
			Non-Caucasian	Fluoxetine (17)	-1.88 (1.93)	0.399
				Placebo (16)	-1.00 (1.03)	

4. PDSS Average

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.711	0.811	< 50	Fluoxetine (85)	0.97 (0.88)	0.139
				Placebo (80)	1.24 (0.93)	
			≥ 50	Fluoxetine (14)	1.10 (1.07)	0.249
				Placebo (16)	1.23 (0.86)	
Gender	0.799	0.892	Female	Fluoxetine (60)	0.98 (0.99)	0.118
				Placebo (64)	1.24 (0.92)	
			Male	Fluoxetine (39)	1.00 (0.76)	0.254
				Placebo (32)	1.24 (0.92)	
Origin	0.070	0.090	Caucasian	Fluoxetine (82)	0.97 (0.87)	0.330
				Placebo (80)	1.10 (0.85)	
			Non-Caucasian	Fluoxetine (17)	1.08 (1.06)	0.356
				Placebo (16)	1.90 (0.95)	

5. HAMA Total Score

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.932	0.273	< 50	Fluoxetine (68)	-7.09 (8.27)	0.745
				Placebo (70)	-6.63 (8.31)	
			≥ 50	Fluoxetine (15)	-6.73 (8.84)	0.673
				Placebo (14)	-5.36 (6.05)	
Gender	0.873	0.179	Female	Fluoxetine (49)	-7.90 (9.50)	0.471
				Placebo (56)	-6.98 (8.72)	
			Male	Fluoxetine (34)	-5.76 (6.17)	0.534
				Placebo (28)	-5.29 (6.18)	
Origin	0.222	0.464	Caucasian	Fluoxetine (71)	-7.15 (8.00)	0.676
				Placebo (69)	-6.68 (8.03)	
			Non-Caucasian	Fluoxetine (12)	-6.25 (10.38)	0.686
				Placebo (15)	-5.20 (7.81)	

6. $HAMD_{17}$ Total Score

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.862	0.881	< 50	Fluoxetine (69)	-2.00 (5.77)	0.717
				Placebo (70)	-1.59 (5.62)	
			≥ 50	Fluoxetine (15)	-3.00 (6.48)	0.869
				Placebo (14)	-1.36 (4.81)	
Gender	0.552	0.674	Female	Fluoxetine (50)	-2.56 (6.92)	0.294
				Placebo (56)	-1.73 (5.61)	
			Male	Fluoxetine (34)	-1.62 (3.88)	0.735
				Placebo (28)	-1.18 (5.25)	
Origin	0.855	0.576	Caucasian	Fluoxetine (72)	-2.43 (5.28)	0.404
				Placebo (69)	-1.71 (5.39)	
			Non-Caucasian	Fluoxetine (12)	-0.67 (8.80)	0.492
				Placebo (15)	-0.80 (5.97)	

7. STAI Total Score

Subgroup of interest	Therapy ×Subgroup[a]	Subgroup[a]	Strata	Therapy (Number of patients)	Change of Mean (SD)	p-value of Therapy[b]
Age	0.961	0.731	< 50	Fluoxetine (67)	-6.09 (13.95)	0.485
				Placebo (71)	-6.62 (17.08)	
			≥ 50	Fluoxetine (15)	-8.47 (20.43)	0.467
				Placebo (14)	-5.86 (15.31)	
Gender	0.201	0.887	Female	Fluoxetine (49)	-8.55 (14.98)	0.812
				Placebo (57)	-4.91 (16.25)	
			Male	Fluoxetine (33)	-3.52 (15.29)	0.482
				Placebo (28)	-9.71 (17.48)	
Origin	0.261	0.845	Caucasian	Fluoxetine (69)	-7.09 (13.56)	0.437
				Placebo (70)	-7.06 (17.18)	
			Non-Caucasian	Fluoxetine (13)	-3.54 (22.57)	0.662
				Placebo (15)	-3.87 (14.63)	

[a] Two columns of Therapy×Subgroup and Subgroup show p-values for the model, response ~ therapy + subgroup + interaction of therapy and subgroup.

[b] The last column shows the p-value for therapy within stratum in the model response ~ therapy + investigator.

Abbreviations: CGI-Severity = Clinical Global Impressions of Severity;
HAMA = Hamilton Anxiety Rating Scale;
HAMD17 = 17-Item Hamilton Depression Rating Scale (modified);
PDSS = 7-Item Multicenter Collaborative panic Disorder Severity Scale
SD = standard deviation;
STAI = State-Trait Anxiety Inventory

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