Reporter I.D. ☒
Patient I.D. ☐
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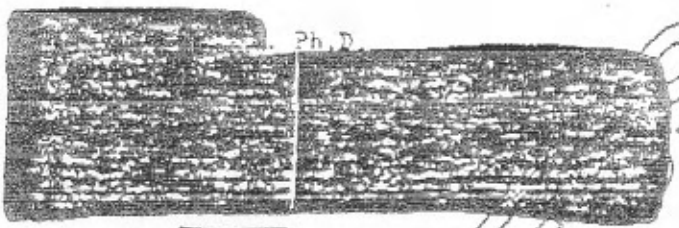
LETTERHEAD (DRAFT)

July 18, 1985



Dear Dr. [redacted]

The following tables summarize our current statistical analyses to determine if there are increased suicide attempts associated with fluoxetine, in comparison to the comparator group (imipramine, doxepin, amitriptyline, placebo), for the pooled double-blind and open-label studies. All computations are based on our current knowledge of the number of weeks at risk for the various groups, and on the revised number of suicide attempts for the combined studies (6 in fluoxetine and 1 in the comparator group). These values are reflected in the tables. Following Dr. [redacted]'s suggestion of using a binomial distribution, 2 p-values are initially calculated. The first considers fluoxetine and comparator exposure to week 54, while the second considers comparator exposure to week 54 and fluoxetine exposure to week 174. From our computations, there appear to be no significant differences between fluoxetine and the comparator group ($p=0.165$ for exposure to week 54, $p=0.208$ for exposure to week 174) for suicide attempts, based on patient exposure.

If we perform a binomial analysis considering fluoxetine and comparator exposures only to week 5, thereby producing a "balanced" exposure comparison between fluoxetine and all 4 comparators, we reduce the total number of suicide attempts to 5 (4 in fluoxetine, 1 in the comparator group). The p-value obtained for this computation is equal to 0.190. Similarly, comparing fluoxetine exposure to week 54 with only imipramine and doxepin in the comparator group, thereby producing a "balanced" exposure comparison and reducing the number of suicides to 6 (6 in fluoxetine and 0 in the comparator group), we obtain a p-value from the binomial expansion equal to 0.079.

Fisher's Exact Test was also suggested as an alternative methodology to assess differences in suicide attempts between fluoxetine and the comparator group. Although we question its applicability for this situation in which patient weeks are considered as experimental units (lack of independence between units, mixing of suicides which are in patient units with units of patient exposure), we are providing the results from our analysis:

Exposure Units	Duration	P-value (1-tail test)
Patient weeks	Week 54	0.165
Patient weeks	Week 174	0.208

The above results agree almost exactly with those obtained from the binomial expansion for exposure to weeks 54 and 174, using all 4 comparators and 7 suicide attempts (5 in fluoxetine and 2 in the comparator group).

Using Fisher's Exact test (1-tail) and strictly patients as experimental units, and comparing fluoxetine to all comparators until week 5, we have 5 suicide attempts (4 in fluoxetine, 1 in the comparator group). Fisher's Exact Test for these data provide a p-value equal to 0.166. Similarly, a comparison of fluoxetine to only imipramine and doxepin in the comparator group, to week 54, and using patients as experimental units and a total of 6 suicide attempts (6 in fluoxetine and 0 in the comparator group) provides a p-value equal to 0.058 by Fisher's Exact Test.

An alternative approach, which also utilizes exposure time, is to compare the survival curves for the fluoxetine group with the comparator group for the pooled double-blind and open-label studies. The log-rank test (2-tails) provides a chi-square value of 2.60 (df=1) with a corresponding p-value equal to 0.107. Any conclusions drawn from this analysis must be considered in light of the fact that the number of events (suicide attempts) is extremely small for each group. This forces us to question the suitability of any survival analysis for these data.

In summary, we are analyzing a pooled group of Phase II & III clinical trials, as though it is a traditional "observational" study for which such variable as suicides were not considered but "observed" as part of the adverse events recording mechanism. Hence a wide range of p-values are possible, depending on the analysis. Since we have analyzed a variety of ad hoc groupings we came up with a widely varying set of p-values. This should not be surprising.

Sincerely,

LILLY RESEARCH LABORATORIES
A Division of Eli Lilly and Company

Bruce E. Dornseif, Ph.D.
Senior Statistician

drr

Attachments

bcc: Mr. [illegible] B. Houck
Dr. [illegible] C. Kuster
Dr. [illegible] W. Offen
Dr. C. B. Sampson
Dr. [illegible] F. Wernicke

The evidence in the form of the p-values are summarized in the following table:

Test	Experimental Units	Exposure Duration	Total Suicide Attempts	p-value
B	Patient weeks	Week 54	7	0.165
B	Patient weeks	Week 174	7	0.208
FE	Patient weeks	Week 54	7	0.165
FE	Patients weeks	Week 174	7	0.208
B	Patient weeks	Week 5	5	0.190
B*	Patient weeks	Week 54	6	0.079
FE	Patients	Week 5	5	0.166
FE*	Patients	Week 54	6	0.058

*Comparator group consists only of imipramine and doxepin.

B=Binomial
FE=Fisher's Exact

Comparator Exposure Rates

Week	Imipramine Pt Weeks	Doxepin Pt Weeks	Amitriptyline Pt Weeks	Placebo Pt Weeks
1	326	134	70	283
2	286	113	61	260
3	247	99	56	196
4	213	89	53	165
5	189	81	49	137
6	156	71		96
10	412	176		
14	336	156		
22	528	222		
30	472	208		
38	392	176		
46	312	128		
54	240	104		
Total	4109	1807	289	1137

Exposure Rates

	Fluoxetine			Comparators		
Week	Weeks at Risk	Patients at Risk	Patients Weeks	Weeks at Risk	Patients at Risk	Patients Weeks
1	1	758	758	1	813	813
2	1	699	699	1	720	720
3	1	627	627	1	598	598
4	1	553	553	1	520	520
5	1	499	499	1	456	456
6	1	422	422	1	323	323
10	4	321	1284	4	147	588
14	4	275	1100	4	123	492
22	8	195	1560	8	100	800
30	8	152	1216	8	85	680
38	8	124	992	8	71	568
46	8	103	824	8	55	440
54	8	88	704	Total	43	344
62	8	30	240	11238	43	344
70	8	28	224		Total	7342
78	8	24	192			
86	8	22	176			
94	8	17	136			
102	8	14	112			
110	8	12	96			
118	8	10	80			
126	8	7	56			
134	8	7	56			
142	8	5	40			
150	8	4	32			
158	8	3	24			
166	8	2	16			
174	8	1	8			
			Total 12726			

Suicides and Suicide Attempts During Fluoxetine Studies

This document contains data on suicides and suicide attempts observed during U.S. and Canadian Fluoxetine Studies. The first section is a summary of suicide/attempt data and similar tables for each study. The second section contains individual patient description and plots of HAMD total as well as plots of HAMD subfactor scores for depressed mood, suicide ideation, agitation and psychic anxiety.

C. D. Hardison
5773

J. F. Wernicke
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To Call Writer Direct
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July 1, 1985

Copies mailed 7/11/85

JFW JUL 9 1985

J. W. Wernicke, Ph.D., M.D.
Clinical Investigator
Lilly Research Laboratories
307 E. McCarty Street
Indianapolis, IN 46285

Dear Dr. Wernicke:

This is a report on our efforts to evaluate the clinical material on fluoxetine.

Let me recapitulate the circumstances. You have my letter of May 8 which I sent after I had an opportunity to evaluate a series of tables and graphs that you sent me. Those data were relevant to the question of whether or not fluoxetine was associated with an increased number of suicide attempts when compared to placebo controls and comparator drug controls. The issue appeared complex enough to require further evaluation, and I sent the material to Drs. Coryell and Pfohl for evaluation. Dr. Pfohl who is no mean statistician himself dropped out of the evaluation after putting a short amount of time into it. He decided that what was necessary was a person who is better in statistics than he and suggested Dr. Robert Woolson. Dr. Woolson obtained a copy of the data and looked it over. Dr. Coryell also evaluated the data, and I believe you have a letter from him which he handed to you in Indianapolis.

Summarizing opinion

1. The claimed indication "depressive disorders" can not be accepted in this form. The entire studies have to be reworked with consideration of the criteria of the science of depression effective in the Federal Republic of Germany as well as with reference to the WHO criteria, so that they are understandable for the physician and the patient.

2. Considering the benefit and the risk, we think this preparation totally unsuitable for the treatment of depression.

25. Mai 1984
BvK/AM

Excludes suicides
Not. should be included

Attachment VIII.6

Summary Listing of Patients with Suicidal Acts Not Meeting the Case Definition

Double-Blind Therapy Portion of Placebo- and Active Comparator-Controlled International Depression Trials

Double-Blind Therapy Portion of Controlled Fluoxetine-Only International Fluoxetine Depression Clinical Trials

Open-Label Portion of Controlled Fluoxetine-Only International Depression Clinical Trials

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TABLE I

SUMMARY OF PATIENTS NOT MEETING CASE DEFINITION OF SUICIDAL ACT

Double-Blind Therapy Portion of Placebo- and Active Comparator Controlled International Fluoxetine Depression Trials

Patient Identification	Case Finding	Visit	Description of Possible Event	Reason for Not Meeting Case Definition
BP HC26 [redacted]	Clinical Comments	Summary	Two suicide attempts on 3/9/87 with 20-25 tablets of mogadon and on 3/10/87 with 20 tablets of unknown antidepressant	Study drug was discontinued 6 days prior to first overdose. Discontinued due to severe rash
BP HC31 [redacted]	Clinical Comments	Summary	Nonfatal overdose of Rohypnol on 1/28/87	Patient was last seen on 12/18/86. Patient had failed to keep appointments. Comments state "no further anti-depressants since last visit". Overdose occurred 6 weeks later.
BX HC04 [redacted]	Note to the file		Abused oxazepam with a minimal dose of 10 capsules (15 mg) per day since 8/11/87.	Patient was last seen on 8/10/87; was lost to follow-up. Information obtained from rehospitalization. No intent; addiction to benzodiazepines.

active med longer

still possible

Table 1 (continued)

SUMMARY OF PATIENTS NOT MEETING CASE DEFINITION OF SUICIDAL ACT

Double Blind Therapy Portion of Placebo and Active Comparator Controlled

International Fluoxetine Depression Trials

Patient Identification	Case Finding	Visit	Description of Possible Event	Reason for Not Meeting Case Definition
SB6066 [redacted]	Note to the file		Two months after discontinuing study patient overdosed on a tranquilizer. The suicide attempt was not life-threatening and he recovered.	Overdose occurred 2 months after discontinuation due to good improvement.
BP1IC22 [redacted]	Other Drug Therapy Clinical Comments	4.5	Patient was prescribed fluoxetine for aggression particularly towards her brother who she wanted to kill. Her boyfriend destroyed the tablets as she "tried to overdose".	No overdose; tablets destroyed when she "tried to overdose".
BP1IC21 [redacted]	Summary Note to the File		Patient entered trial on 9/18/84. He remained in the study as an outpatient being discharged from the hospital on 10/19/84. His body was found on 10/24/84. Death probably occurred on 10/22/84. Probable cause of death: overdose of chlormethimazole and alcohol	Caretaker's office note indicates no capsules or sachets of study drug were taken

		Three months after discontinuing double blind portion of study, patient overdosed with 5 to 60 mg fluoxetine and 15 aspirin tablets prior to drinking with friends. She was admitted to hospital approximately 9 hours after overdose. Patient experienced 2 grand mal seizures. She made an uncomplicated recovery.	Overdose occurred 3 months after discontinuation of double blind therapy. The patient was in open label portion of study. Overdose was a manipulative attempt to gain readmission. Patient had been in fluoxetine only controlled trial.
KW 8004 [redacted]	Note to File Summary	Six months after discontinuation of the double blind portion of the study, this patient died of an overdose. Report notes fluoxetine not suspected in overdose. If compliant, patient should have had only 8 (60 mg) capsules.	Overdose occurred approximately 6 months after discontinuation of double-blind portion of the study. The patient was in open label phase of the study. Patient had been in a fluoxetine only study.

ATTACHMENT VIII 6
Fluoxetine Hydrochloride (Prozac®) Safety Experience
June 18, 1991

Ended up

CASE

1 — Prozac - overdose
2 — Prozac - exc
3 — Prozac - exp
4 — Prozac - ex
5 — IN
6 — Prozac — ex
7 — IF
8 — Prozac — e

Ended up excluding 6 Prizes, 7 now included

CASE

1 — Prize - excluded
2 — Prize - excluded
3 — Prize - excluded / included [included]
4 — Prize - excluded
(5) — — included - 3 days ½ life - ? Not Prize
6 — Prize — excluded
(7) — — included [illegible]
8 — Prize — excluded