[redacted]

To Call Writer Direct
Phone [redacted]

July 1, 1985

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J. W. Wernicke, Ph.D., M.D.
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307 E. McCarty Street
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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. These 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. [redacted] and [redacted] for evaluation. Dr. [redacted] 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. [redacted]. Dr. [redacted] obtained a copy of the data and looked it over. Dr. [redacted] also evaluated the data, and I believe you have a letter from him which he handed to you in Indianapolis.

Reporter I.D. ☒
Patient I.D. ☐
Other Confidential ☐

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It became apparent to me that one of the things which was necessary was a systematic evaluation of the patients who were said to have attempted suicide in order to determine whether we would agree that these were suicide attempts. There was, of course, one completed suicide in the group.

As a consequence, I asked you for the charts on the patients and after you sent them to me I went over them. Out of the total group of charts I identified eight cases in which there might be considerable controversy as to whether these were indeed suicide attempts at all. These are:

1) [redacted] who was a polydrug abuser. He took cocaine, heroin, fluoxetine, and alcohol at one time and was eliminated from the study. He denied this was a suicide attempt. He had a history of having abused drugs in the past. I did not believe that should be considered a suicide attempt. Dr. [redacted] was presented this data in Indianapolis, and he agreed.

2) [redacted] This person used cocaine, was never very suicidal and engaged in self-mutilation with broken glass. There was no evidence that this was a suicide attempt. The data were not too good, but both Dr. [redacted] and I agreed on going over the material in Indianapolis that this was not a suicide attempt.

3) [redacted] At the start of the study, this person had no suicide ideation according to the Hamilton Rating Scale. The patient said that the overdose was taken because "I needed help", and the psychiatrist who evaluated the patient said, "This denies a specific suicide attempt and she

currently has no suicide ideation." I rated this person as not making a suicide attempt, but Dr. [redacted] looking at another evaluation was enough in doubt that he thought it might be considered a suicide attempt.

4) [redacted] This patient took an overdose of chloralhydrate, 8 capsules four weeks after stopping medication. At the start of the study, this person had considerable suicide ideation on the Hamilton Rating score but at visit 10 suicide ideation was rated a 0. Visit 11 did not occur but was scheduled for April 12, 1983. The drug was stopped by the patient herself on March 3 as she felt well. She stopped herself on the drug rather than being stopped by a physician. Thus, she was not on any drug for four weeks before this suicide attempt. Both Dr. [redacted] and I agreed this could not be related to any treatment.

5) [redacted] The patient had considerable suicide ideation prior to the onset of the study. The suicide attempt was by wrist slashing. The patient stopped medication March 13, and the suicide attempt was March 15. As the half-life of the drug is three-four days, we agreed that this in fact could be related to the drug.

6) [redacted] This person had no suicide ideation at onset of study. The patient drank a bottle of rum and then took 10 fluoxetine capsules in divided doses of 2-hour intervals. Dr. [redacted] and I agreed this was not a suicide attempt.

7) [redacted] This person had mild suicidal ideation at the beginning of the study. There was some question as to whether this was a suicide attempt

in my mind; but when Dr. [redacted] and I evaluated it together in Indianapolis, we agreed on a positive.

8) [redacted] or [redacted] The patient had suicidal ideation at the beginning of the study and made a self-inflicted laceration of the skin with a razor blade. Dr. [redacted] and I agreed that this was not a suicide attempt.

Thus, of the eight cases there was agreement that there was no suicide attempt in five, a positive suicide attempt in two and a divided vote in one [redacted].

To be evaluated as a suicide attempt, the attending doctor on seeing the patient had to comment that the behavior in fact was related to suicide intention. In other words, if a patient said "I cut my wrist because I was mad at my boyfriend and wanted to gain his attention" we did not consider it a suicide attempt. If, on the other hand, the patient said "I intended to take my life" or the doctor felt that the person had any intent at all to take his/her life, it was counted as a positive. Thus, at least five cases did not meet those criteria.

Prior to coming to [redacted] Dr. [redacted] Dr. [redacted] and I met for an hour. We determined that there was a series of things which could be of some interest and might clarify the issue. First, it was possible that the patients who were on one or the other treatments were more suicidal than patients in other groups. We had no information on this and needed to get it in Indianapolis. Second, if the physicians could somehow break the blind because of the side effects and had more confidence that the fluoxetine patients were

taking a drug which would not be lethal, they might keep suicidal patients on fluoxetine longer than on comparator drugs. Was it possible that in the course of the studies the more suicide inclined patients were terminated from comparator drugs earlier than those from fluoxetine; thus accounting for an eventually higher rate of attempts in the fluoxetine group? This is still something which needs to be looked at, and the way to do this is determine if there is a differential change over time in baseline suicide ratings between fluoxetine and comparator groups. Another way to look at this is to look at the five point Hamilton Scale and determine the dropouts over time for each point, associating the drop outs with particular treatments. Finally we questioned whether clinicians, in fact, could guess which drugs the patients were on. We do not know the answer to this. Perhaps there was some evaluation.

Upon arrival in Indianapolis, we looked at the baseline suicide scores between the various groups. There were no differences. Thus, there was no reason to believe that there was misassignment. One of the most interesting things, however, is the fact that in all groups there was an enormous amount of suicide ideation. Thus, if one looks at the Hamilton Rating Scale and the 0 score only between 0% and 39% of the groups were rated as having no suicide ideation of any kind. This, of course, is the one item on the Hamilton Rating. What this means is that the patients had considerable suicide inclinations according to that measure. It is interesting that there is such a low suicide attempt rate under those circumstances. Of course, the physicians were supposed to evaluate the suicide potential as well. They were supposed to include patients only if they did not believe they were suicide risks. Nevertheless, in a systematic evaluation, there were suicide ideas and

thoughts. In evaluating over the various groups, there were 3% to 28% of the patients who had a rating of 3 on the Hamilton Rating Scale. This indicates considerable suicide ideation. So, by my criterion some of these patients were suicidal when they entered the study and I continue to be surprised at the low number of suicide attempts in the study.

In evaluating the end points, it was clear that there was a decrease in suicide ideation on the Hamilton Rating Score in the fluoxetine groups and also in the groups which were treated with comparator drugs. On the other hand, such a decrease did not occur in the placebo groups. There was no significant difference between the fluoxetine groups and the imipramine group as an example in terms of decrease of suicide ideation. The placebo group, however, did not show this salutory effect.

The conclusion of this set of findings is that the cognitive aspects of suicide are not increased in the fluoxetine group as opposed to the comparator drug groups. This is a very important point.

Next, there is the question of whether there are increased suicide attempts in the fluoxetine group as opposed to the comparator groups. We decided that the appropriate way to look at this was to look at the amount of weeks at risk for the various groups. The reason for this is that the fluoxetine groups were associated with more weeks at risk than the other groups and this had to be taken into account as the more weeks at risk would give the fluoxetine group a better chance of having a suicide attempt. Dr. [redacted] made an effort to do this in [redacted] and we made another effort to do this in [redacted] However, there were such divergent viewpoints as to how many weeks at risk

should be attributed to each group that we have to go over this again in a more systematic fashion. There were marked discrepancies with each new evaluation of weeks at risk and this turns out to be something which must be clarified. One statistical workup which was suggested was Fisher's Exact Probability between the fluoxetine group and the comparative drugs plus placebo. Dr. [redacted] suggested using a binomal expansion. Both of these should be done but the fact is that both are dependent on knowing an exact number of weeks at risk for the various groups. The original evaluations, both in [redacted] and in [redacted] were questionable because of the possibility that we were counting some weeks at risk twice. In any event, the significance favoring the fact that fluoxetine was associated with more attempts varied with P numbers of .011, .056 and .19. Thus there is considerable variability and we must assume that we do not have a final answer to this question. It is of major importance that this be clarified.

There are some qualitative points that should be noted. 1) In any group the presence of suicide attempts is a very rare event, probably less common than you would see in other studies. 2) If it turned out that the fluoxetine group in fact had significantly more suicide attempts per weeks at risk, we would have an interesting finding. It would indicate that the cognitive suicide data does not separate the groups, but the behavioral suicide data does. The meaning of that is something which should be pursued vigorously. A possibility which comes to mind is that fluoxetine might be somewhat more stimulating as a drug and that individuals might be slightly more impulsive although their thinking was not changed. In any event, this is only meaningful if we have a significance difference between groups in terms of suicide attempts per unit of observation.

Anyway, there is somewhat more to be done before we reach a final conclusion. It may be that when appropriate evaluations of time at risk are taken into account there will be no differences of any significance at all.

Please let us state at this point that this has been an interesting exercise and we stand ready to continue to help in the evaluation.

Sincerely,