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FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Background Comments for February 2, 2004 Meeting of Psychopharmacological
Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-
Infective Drugs Advisory Committee (Peds AC)

TO: Members of PDAC and Peds AC

Background on Suicidality Associated with Antidepressant Drug Treatment

Longstanding Concern that Antidepressants May be Associated with the Induction of Suicidality
Early in Treatment

One of the goals of the February 2, 2004 meeting of the Psychopharmacological Drugs Advisory
Committee (PDAC) and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory
Committee (Peds AC) is to give you an update on the current status of our efforts to better
understand the suicidality data we have received from various drug development programs
involving the use of antidepressant drug products in pediatric patients.

The occurrence of suicidality in the context of treating patients with depression and other
psychiatric illnesses has been a concern and a topic of interest and debate for decades. In fact,
antidepressant labeling has, for many decades, carried the following standard language under
Precautions, alerting clinicians to closely monitor patients during initial drug therapy out of
concern for the possible emergence of suicidality:

> "Suicide: The possibility of a suicide attempt is inherent in major depressive disorder
> and may persist until significant remission occurs. Close supervision of high-risk patients
> should accompany initial drug therapy. Prescriptions for Drug X should be written for the
> smallest quantity of tablets consistent with good patient management, in order to reduce the
> risk of overdose."

Of course, this standard Precautions statement does not explicitly warn of the possibility that
antidepressant drugs may have a causal role in the emergence of suicidality early in treatment.
While it is likely impossible at this point to trace the history of the addition of this language to

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antidepressant labeling, I believe that, whether explicit or not, the statement allows for that interpretation. In fact, as early as medical school, many physicians learn of this concern, and it has been part of medical lore for many decades that antidepressants may have an early activating effect that perhaps gives depressed patients the energy to follow through on suicidal impulses before the mood improvement associated with antidepressant treatment takes effect. Following is a statement from a textbook of psychiatry published over 40 years ago that is referring to observations in patients during initial treatment with tricyclic antidepressants [**Slater and Roth's Clinical Psychiatry, by Bailliere, Tindall and Cassell; London, 1960, p. 231**]:

> "With beginning convalescence (following initiation of treatment with tricyclic antidepressants), the risk of suicide once more becomes serious as retardation fades."

In fact, this particular mechanism proposed to explain a possible increase in suicidality early in antidepressant treatment is so well known that it is referred to as the "roll back" phenomenon. However, it is but one of several mechanisms that have been proposed to explain the clinical observation that some patients being treated with antidepressants, particularly early in treatment, may have an increase in suicidality. This topic was discussed at the September, 1991 meeting of the PDAC on this same issue, and Dr. Martin Teicher provided a comprehensive list of the various mechanisms that have been proposed:

- o Roll back phenomenon: view that antidepressants with prominent energizing effects may actually increase suicidal behavior in severely depressed patients who are suicidal but also have psychomotor retardation and are thus inhibited from acting on their suicidal thoughts.
- o Paradoxical worsening of depression: view that, in rare patients, the depressed mood may actually worsen as a result of antidepressant treatment.
- o Akathisia: view that some antidepressants are associated with akathisia, and the belief that akathisia may lead to suicidal behavior in certain depressed patients.
- o Induction of anxiety and panic attacks: view that certain antidepressants may induce anxiety and panic attacks, and that these may lead to suicidal behavior in certain depressed patients.
- o Stage shifts: view that antidepressants may lead to switch from depression into mixed states in bipolar depressed patients, and this may lead to suicidality.
- o Insomnia: view that insomnia associated with certain antidepressants may lead to suicidal behavior in certain depressed patients.

While all of these have some plausibility as mechanisms for explaining the clinical observation of worsening depression or suicidality in depressed patients being treated with antidepressants, proposing a mechanism is quite a different matter from demonstrating empirically that there is a causal association between antidepressant use and induction of suicidality. Of course, this is the key question we hope to be able to address with the suicidality data coming from the studies done with various antidepressant drugs in pediatric patients, i.e., is there a causal link between antidepressant drug use and suicidality in pediatric patients with major depressive disorder or other psychiatric disorders. This is a critically important question to answer, but it is equally important to answer it in a careful, thoughtful manner. Erring in either direction would have adverse consequences. Missing a signal of increased risk of suicidality would result in greater comfort than is warranted in the safety of these drugs in treating pediatric depression. On the other

hand, a premature decision on the strength of the signal could result in the overly conservative use of these drugs, or their lack of availability entirely for the pediatric population. Prematurely reducing therapeutic options for this serious disease with well established morbidity and mortality, quite apart from any role that antidepressant drugs may have, does not seem like a good approach. In any case, the question is obviously timely and important to fully address in order to understand how best to use these drugs in the treatment of pediatric MDD.

If this view that initial antidepressant treatment may be associated with an actual increase in risk of suicidality is in fact empirically established, this would, in a sense, confirm a view that is already widely prevalent in clinical lore, whatever the proposed mechanism. Despite this fairly widely held view, however, the use of antidepressants has obviously increased over the years rather than declined. This fact suggests that, as a group, clinicians may place more weight on their beliefs in the longer-term benefits of antidepressants than their concerns about possible early risks of actually increased suicidal behavior. In fact, the dual findings of an early increase in the risk of suicidality but also a longer-term benefit for this same risk with antidepressant treatment would, if both true, not necessarily be inconsistent. It is quite possible for a drug to have opposite effects over time, even within the same domain.

Debate in Recent Years on the Question of Antidepressant-Induced Suicidality in Adults

The debate on this question with regard to adult depression intensified in 1990, at which time Martin Teicher, a psychiatrist from Harvard Medical School, along with several colleagues, published a paper describing a series of 6 adult patients with depression who, in their view, became suicidal as a result of being treated with Prozac (fluoxetine) **(Teicher, et al, 1990)**. This paper and the ensuing discussion led Lilly, the manufacturer of Prozac, to conduct new analyses of their controlled trials data for Prozac to explore for the emergence of suicidality. This renewed interest in the possible induction of suicidality in association with the use of antidepressant treatment also led FDA to fully re-evaluate its spontaneous reports database to try to detect whether or not a signal of increased risk could be observed. Ultimately, this issue was brought to a PDAC meeting in September, 1991. This one-day meeting consisted of several hours of statements made by family members and others in the open public session, and presentations by representatives from FDA, Lilly, and NIMH. Statements in the open session were made mostly by family members of suicide victims whose deaths the families attributed to their taking Prozac. FDA gave an update on the very substantial number of spontaneous reports of suicidality in association with Prozac use, but also showed how the pattern of reporting was clearly linked to the publication of the Teicher, et al, paper and other publicity about this concern. A representative from NIMH gave that agency's perspective on this issue, essentially making the case that depression is a serious disorder that itself is associated with suicidality, and arguing that the data available to date did not support the view that antidepressants further increase the risks of suicidality in this population. Finally, Lilly presented the results of its analysis of data pooled over its extensive clinical trials, revealing no signal of increased suicidality in association with the use of Prozac **(Beasley, et al, 1991)**. At the end of a long day, a majority of the committee concluded that there was no clear evidence of an increased risk of suicidality in association with the use of Prozac, and they did not recommend any changes to Prozac labeling with regard to this issue.

Over the next several years, additional data were accumulated as applications for newer antidepressants were submitted and reviewed, and these drugs came to market. Several groups have, in recent years, conducted pooled analyses for adult data on completed or attempted suicides from these programs, in order to continue the search for a possible signal of risk, either by virtue of being assigned to placebo, since the ethics of conducting placebo controlled trials in depression were being challenged, or due to assignment to drug treatment. Arif Khan, a psychiatrist from the Northwest Clinical Research Center, Bellevue, Washington, published a paper in 2000 based on adult data he obtained under FOI from FDA reviews. He concluded that the risk of completed suicide was the same, regardless of treatment assignment **(Khan, et al, 2000)**. Jitschak Storosum, a physician from the Medicines Evaluation Board of the Netherlands, did an analysis of attempted suicides from adult data available to his group, and he reached the same conclusion **(Storosum, et al, 2001)**. FDA has done several analyses on completed suicides for adult data sets provided to us in response to a request for patient level data sets[1] for all relevant studies involving 20 antidepressant drugs studied in 234 randomized controlled trials with MDD. Based on our initial analyses of these data, we have reached a similar conclusion, i.e., that there does not appear to be an increased risk of completed suicide associated with assignment to either active drug or placebo in adults with MDD **(Hammad, et al, 2003)**.

Source of Pediatric Suicidality Data

Regarding pediatric suicidality, it is important first of all to understand how it is that the various pediatric trials happen to have been done. These trials were done largely in response to a change in the Food, Drug and Cosmetic Act that authorized FDA to grant additional marketing exclusivity (referred to as pediatric exclusivity) to pharmaceutical manufacturers who were willing to conduct studies of their drugs as requested by the FDA in pediatric populations. The first law permitting the pediatric exclusivity incentive was the FDA Modernization Act (FDAMA, 1997), and this authority to attach additional marketing exclusivity for such studies was renewed in the Best Pharmaceuticals for Children Act (BCPA, 2001). In order to qualify for pediatric exclusivity, sponsors had to conduct pediatric studies according to the terms of a Written Request from FDA, and submit the results of those studies in a pediatric supplement. We have reviewed 8 pediatric supplements over the past few years for pediatric drug development programs involving antidepressant drugs that were conducted to gain additional marketing exclusivity, and these supplements are the source of the pediatric suicidality data that are at issue for this meeting. For completeness, we have included in our review of pediatric suicidality two studies for a ninth antidepressant drug for which the studies were not done for exclusivity. Our review includes a total of 24 studies for these 9 drugs, involving a total of over 4000 pediatric patients.

The 9 drugs involved in our review are:
- Prozac (fluoxetine)
- Zoloft (sertraline)

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[1] I will distinguish between what I will refer to as <u>summary data</u> and <u>patient level data</u>. Summary data will refer to data tables provided by sponsors that include only numbers of events as numerators and either total patients exposed or total accumulated person-time as denominators. Patient level data will refer to data sets provided by sponsors in response to detailed requests made by FDA for electronic data sets structured to include one row per patient participating in each study, with multiple variables for each patient. Patient level data sets permit adjustments for potentially important covariates, while summary data do not.

- Paxil (paroxetine)
- Luvox (fluvoxamine)
- Celexa (citalopram)
- Wellbutrin (bupropion)
- Effexor (venlafaxine)
- Serzone (nefazodone)
- Remeron (mirtazapine)

Of the 24 studies for these 9 drugs, 15 were in MDD, 4 in OCD, 2 in GAD, 1 in SAD, and 2 in ADHD.

Effectiveness Data for Antidepressants in Pediatric MDD

While the focus of the discussion at the Feb 2nd PDAC meeting will be on pediatric suicidality data, it is important to consider the effectiveness data for these drugs as part of the overall context for this discussion. Ultimately, this is a risk benefit assessment, so it is important to know where we stand on the benefit side of this issue. Of the 7 programs in pediatric MDD (Prozac; Zoloft; Paxil; Celexa; Effexor; Serzone; Remeron), FDA's reviews of the effectiveness data resulted in only 1 approval for pediatric MDD, i.e., for Prozac. The efficacy results from the 15 studies in pediatric MDD are summarized in **Appendix 1**.

These are sobering findings and certainly raise a question about the benefits of these drugs in pediatric depression, however, the findings need to be considered in the context of several other facts.

(1) In all but one case for the failed programs, there were only 2 studies in MDD; for the remaining failed program, there were 3 MDD studies. Among the failed programs there was one program where 1 of the studies was positive (citalopram), and 2 others where the results, while negative by the usual standards, were at least trending toward positive for 1 of the 2 studies (sertraline and nefazodone). Of note, the published literature gives a somewhat different perspective, suggesting more positivity in 2 of these programs than was the conclusion at FDA. One paper describes one of the Paxil studies as positive on most of the secondary endpoints, while acknowledging that it failed on the primary endpoint **(Keller, et al, 2001)**. Another paper describes the Zoloft program as positive, based on a pooling of 2 similarly designed studies that, when looked at individually, failed **(Wagner, et al, 2003)**.

In adult MDD programs for drugs that are approved for this indication, overall, the failure rate for studies that appear in every respect to be adequate trials is about 50%. Thus, if the failure rate were the same in pediatric MDD, it would not be unexpected to have either 1 or both studies fail. In fact, since the studies can be considered independent of one another, the probability of having one or both studies fail in the 2-study programs is actually 0.75 [3(0.5 X 0.5)]; the probability of both succeeding would be only 0.25 (0.5 X 0.5). Thus, under the best of circumstances, these very limited programs may have been expected to mostly fail regarding the goal of obtaining 2 positive studies. Nevertheless, the overall success rate for positive studies of 20% (3/15) is clearly a concern.

(2) The history of pediatric MDD studies with the tricyclic antidepressants (TCAs) is uniformly negative. This finding may have several possible explanations, including flaws in design or conduct, or the possibility that TCAs simply do not work in pediatric MDD. It is also possible, however, that there is even greater heterogeneity among pediatric patients who meet criteria for MDD than is true for adults. If true, this would also work against obtaining positive studies in pediatric MDD.

(3) The context in which these studies were conducted was not ideal, in the sense that there was no need to obtain positive results in order to gain exclusivity. The programs simply had to be conducted according to the terms of the Written Requests, and the results submitted to meet deadlines specified in those requests. This is not to suggest that sponsors of these studies did not design and conduct them with good intent and according to high standards, but rather, that the mindset was different than the usual mindset for registration trials. Ordinarily, a failure of a registration trial to show a drug effect is a complete loss. That was not the case here and this reality could have influenced the conduct of the study in subtle ways that might have worked against getting a positive result, e.g., in recruitment of patients.

(4) Finally, there was not the kind of preliminary phase 2 dose finding exploration for these studies that typically precedes definitive trials in adult studies. We are routinely asking for such exploration as part of the Written Requests we are now issuing.

The point I am making is that there are several plausible reasons for all but one of these programs failing, other than the possibility that these drugs may have no benefits in pediatric MDD. It is understandable how some may have reached the conclusion that these studies represent proof that these drugs, with the exception of Prozac, have no benefits in pediatric MDD. We at FDA, however, do not view negative studies as proof of no benefit. In our view, absence of evidence for effectiveness in most of these programs does not constitute evidence of absence of benefit for these drugs in pediatric patients, for all the reasons noted above. Nevertheless, the failure of most of these programs to show a benefit in MDD does heighten the concern about the possibility of certain risks that may be associated with these drugs, in particular the concern about induction of suicidality. In any case, the burden is clearly upon those who believe these drugs do have benefits in pediatric MDD to design and conduct studies that are capable of demonstrating such benefits. I will return later to a possible alternative approach to acute efficacy studies for demonstrating antidepressant benefits of these drugs.

Origins of Present Concern About the Emergence of Pediatric Suicidality in Association with Antidepressant Use; Initial Regulatory Response

Background to May, 2003 Paroxetine Report

After this brief look at the effectiveness issue, I want now to return to the issue of the origins of the present concerns about pediatric suicidality. My approach will be to give a temporal perspective on how this issue has evolved over the past approximately 7 months. The focus will be on certain adverse events that were reported in the pediatric supplements for the various antidepressants, in particular, adverse events considered to represent suicidality.

First, it is important to comment on the approach used to elicit treatment emergent suicidality in these trials. In part, investigators relied on very general prompts, e.g., asking the general question of "how have things been" at each visit. While this approach is perhaps somewhat superior to spontaneous reporting, it is likely a distinctly insensitive approach to eliciting adverse events related to suicidality. Even in adults with MDD, it generally requires a skilled clinician to elicit patient reporting of suicidal ideation or behavior, and this tendency to conceal such ideation and behavior may be even more prominent in adolescents. On the other hand, all of these trials also utilized formal instruments for assessing depressive symptoms, each of them including a suicidality item. However, it is not clear what elicitation approaches were used in completing these instruments, and thus, it is not clear whether or not there was specific elicitation with regard to suicidality. Furthermore, these instruments were not always done at the times that patients were experiencing events of interest, since such events occurred at random times. In order to adequately assess for such emergence of suicidal ideation and/or behaviors, it is important to have methods that are sensitive to detecting such effects.

In any case, verbatim (investigator) adverse events in any drug development program, however they are elicited, are coded by subsuming them under preferred terms in order to capture like events under the same term, even if patients or investigators had used variable language to describe the events. For these pediatric trials, adverse events suggestive of suicidality were coded by the various sponsors for their programs, using approaches unique to each program, and these data were examined, along with numerous other adverse events, in the course of our reviews of the pediatric supplements. FDA's clinical reviews for these supplements, conducted over a several year period prior to our becoming aware of a possible signal for the paroxetine program, did not, overall, suggest a signal for drug treatment-induced suicidality.

The Paxil review, however, did raise a question of data management. The clinical reviewer for the Paxil supplement noticed that events suggestive of possible suicidality were subsumed under the preferred term "emotional lability," rather than under a preferred term more directly suggestive of suicidality. Other verbatim terms were also subsumed under "emotional lability," so one of our requests to GSK in our response letter to their pediatric supplement for Paxil was to ask them to separate out for us the verbatim terms suggestive of suicidality. This request was the basis for the additional work done by GSK on this issue of suicidality that resulted in their submission of a report on suicidality, first to the UK, and shortly thereafter, to FDA, on May 22, 2003.

This May 22, 2003 report suggested an increased risk (paroxetine vs placebo) of various thoughts and behaviors coded as events considered "possibly suicide related" and also for the subgroup of these events that met the sponsor's criteria for representing "suicide attempts." The signal for increased risk was clearest for 1 of the 3 trials involving pediatric patients with MDD. A summary of the sponsor's findings for the MDD trials in the Paxil program is included in **Appendix 2.**

<u>Initial Regulatory Response to Signal of Increased Risk of Suicidality for Paroxetine</u>

The reaction to this report by the MHRA in the UK was very prompt, resulting in:
- A public statement explicitly stating that paroxetine "should not be used in children and adolescents under the age of 18 years to treat depressive illness," and
- A labeling change contraindicating paroxetine in pediatric MDD.

FDA's response was soon to follow, with:
- A public health advisory, stating that: "Although the FDA has not completed its evaluation of the new safety data, FDA is recommending that Paxil not be used in children and adolescents for the treatment of MDD."
- Despite the strong advisory, we did not take any labeling action, and in fact have not taken any action on labeling as of the date of this memo.

Overview of FDA's Ongoing Review of Antidepressants and Pediatric Suicidality

<u>GSK Approach to Accumulating Paroxetine Summary Data</u>

First, I want to describe in some detail the approach GSK took in evaluating their pediatric clinical trials data for suicidality, since we modeled our request to sponsors of other antidepressants after the GSK approach, in order to ensure that we would have similar data from different programs, for comparative purposes. They focused exclusively on placebo controlled trials (there were 6 such trials in the GSK program), and that has been our focus as well. As noted earlier, in their original pediatric supplement, they had subsumed events suggestive of suicidality under the preferred term "emotional lability," along with various other behavioral events. Subsequent to our request for a separate approach to events suggestive of suicidality, they conducted the following searches to find events of potential interest:

- Electronic searches of their database with text strings of particular relevance for suicidality:
  - Search for all events for which the preferred term was either "overdose" or "intentional overdose" (<u>Note</u>: They did not include any events for which the preferred term was "accidental overdose")
  - Search of verbatim (i.e., investigator) terms for events that had originally been coded with the preferred term "emotional lability," in order to find verbatim terms including any of the following 15 text strings: "attempt; cut; gas; hang; hung; jump; mutilat; overdos; self damag; self harm; self inflict; self injur; shoot; slash; suic"
  - Search of all verbatim terms containing the text string "overdose" or "suic" (<u>Note</u>: They specifically excluded any events for which the verbatim term selected was a result of the text string occurring in another word that had no relevance to suicidality.)
- They included in their analyses only patients having events that occurred either during randomized treatment or in the +30 days posttherapy window, and only events they judged to represent treatment-emergent events (However, treatment emergent was not

well-defined and no information was provided for any cases excluded for not being considered treatment-emergent). All events meeting these criteria were included under the broad category "possibly suicide related."

- GSK then created the subset of patients having events meeting their criteria for "suicide attempt" using the following criteria:
    - A text string suggestive of self-harm
    - Preferred term "overdose" or "intentional overdose"
    - They did exclude certain events judged (blindly) by their own staff not to represent suicidality, however, no details were provided on these patients or for the criteria used in excluding cases

Request for Summary Data for Other Antidepressants

Following our initial review of the Paxil suicidality summary data, we decided to ask for similar data for the other 8 antidepressants. We decided that it would be most efficient to ask other sponsors to use a similar approach to that used by GSK in exploring the Paxil data. Thus, we issued a letter on July 22, 2003, requesting such summary data for the placebo controlled pediatric studies for the 8 other antidepressant products for which such studies had been conducted:

- Prozac (fluoxetine)
- Zoloft (sertraline)
- Luvox (fluvoxamine)
- Celexa (citalopram)
- Wellbutrin (bupropion)
- Effexor (venlafaxine)
- Serzone (nefazodone)
- Remeron (mirtazapine)

In this July 22nd letter, we asked the sponsors for these products to identify "suicide-related events" for their pediatric studies, in a "blinded" manner, using two search strategies. Since our request was modeled after the approach GSK had already used, it included many of the same details provided above:

- Electronic searches of their database with text strings of particular relevance for suicidality:
    - Search of preferred terms for the following 2 text strings: "suic" or "overdos"
        - Note: We indicated that they may exclude instances coded as accidental overdoses, but asked them to provide information on these cases in a separate table.
    - Search of verbatim (i.e., investigator) terms for the following 15 text strings: "attempt; cut; gas; hang; hung; jump; mutilat; overdos; self damag; self harm; self inflict; self injur; shoot; slash; suic"
        - Note: We did indicate that terms identified using these electronic searches because one of these text strings was included in a word that had no relevance to suicidality could be excluded.

- In addition, we asked them to blindly review narratives for any deaths and serious adverse events (SAEs) in order to identify any additional possible instances of "suicide-related events"
  - Note: There were no deaths due to any cause in any of the 24 studies included in these pediatric programs
- We also asked the sponsors to blindly select from among the larger set of "suicide-related events" a subset of events that could be consider "suicide attempts," defined to include all patients who exhibited self-injurious behavior.
- We asked sponsors to provide a narrative for each patient identified as having one or more potential events, and also a table including the same information for each such patient.

The letter also asked for analyses for the cases identified using these approaches similar to those described above for Paxil.

<u>Re-Review of Suicidality Data from Pediatric Supplements for Other Antidepressants</u>

While we were waiting for the various sponsors of the antidepressants other than Paxil to respond with their summary data, we went back to the summary adverse event data in the pediatric supplements for these other drugs to re-examine the question of suicidality. The major question of interest was whether or not there were other antidepressants with possible signals of increased risk for suicidality, as was observed for Paxil. There were several limitations to this re-examination. First, the methods for detecting and coding events were not standard across these programs. Second, since we wanted to have similar numerator categories to those used for the Paxil data, for purposes of comparison across drug programs, we classified any events described in the adverse event listings, etc for these drug programs into the two categories of interest: "possibly suicide-related" and "suicide attempt." One obvious flaw in this approach was that the FDA reviewer was not blinded during this reclassification process. Nevertheless, it was hoped that this somewhat crude re-examination of these summary data might shed some light on the possibility of signals emerging from other antidepressant programs.

While the methodology for this initial exploration was necessarily crude, it did provide some further insight into the treatment-emergent suicidality question across these 9 drug programs. There were several findings of particular interest resulting from this crude look at the pediatric supplements data. First, there were signals of increased risk of suicidality for patients assigned to drug for more than the paroxetine program, and second, the findings were not consistent across the studies even within individual programs. Finally, the signals were coming predominantly from the MDD studies within these programs.

<u>Wyeth Labeling Change and Dear Health Care Professional Letter for Effexor, and Regulatory Response</u>

During this period while we were re-examining the suicidality data from the pediatric supplements and beginning to receive responses to our requests for summary data from the sponsors for the other antidepressants, Wyeth, the sponsor for Effexor (venlafaxine) and Effexor XR, decided to make labeling changes for its products with regard to suicidality and hostility. This action was

based on its re-analyses of the Effexor pediatric trials data. The labeling change was the addition of a statement to the Usage in Children/Pediatric Use section of Precautions to note increased reports of hostility and suicidality. This labeling change was accompanied by a Dear Health Care Professional letter (August 22, 2003) noting the findings and also noting that these products are not recommended for use in pediatric patients. It should be noted that sponsors have the authority to make changes of this nature, i.e., that are perceived to strengthen labeling from the standpoint of safety, without prior approval by FDA.

This action by Wyeth was followed in September, 2003 by a regulatory response by the MHRA in the UK similar to their response to the report on paroxetine suicidality data. They issued a public statement advising that these products should not be used in pediatric MDD, accompanied by a change in labeling to contraindicate these products in pediatric MDD. FDA has not taken any regulatory action based on these findings for venlafaxine, since we view these as preliminary data that require the same level of more detailed review needed for the other antidepressant drug products.

FDA Internal Regulatory Briefing

An important milestone in our consideration of the pediatric suicidality data was an internal briefing for upper level CDER management held on September 16, 2003. This briefing was held at a time when we had available to us only a preliminary review of the summary data for the Paxil program and a crude re-analysis of suicidality data from the pediatric supplements, i.e., we had not yet received even the summary data from the pediatric programs other than Paxil. There were several agreements reached at this meeting, including two that were of particular importance for our further plans for addressing this issue. It was acknowledged that a very broad net had been cast in trying to capture events of potential interest with regard to possible suicidality, and questions were raised about what many of these events actually represented. Thus, there was agreement that it would be useful to try to have all events of potential interest blindly reclassified by outside experts in suicidality in order to have greater confidence in what the signals represented. Second, there was acknowledgement that there was inconsistency in the signals across individual studies for the various programs for which signals of increased risk for suicidality emerged, based on the re-analyses of pediatric supplement data. Thus, there was also agreement that it would be useful to attempt to obtain patient level data sets for all of these trials in order to permit a more refined analyses using adjustment for potentially important covariates. These agreements strongly influenced the subsequent course of our efforts to better understand these data.

Updated FDA Public Health Advisory and Talk Paper

We issued an updated public health advisory and talk paper on October 27, 2003, based on our assessment of the pediatric suicidality data at that point in time. We indicated that preliminary data suggested an excess of reports of suicidality for several antidepressant drugs, however, we noted that additional data and analysis would be needed. We also noted that we intended to bring this issue to an advisory committee meeting. We advised caution in the use of any of these drugs in MDD, and reminded prescribers of the standard language already in antidepressant labeling

alerting clinicians to the need for close supervision of high risk patients, particularly during initial drug therapy.

Responses to FDA's Request for Summary Data for Other Antidepressants

Now I want to return to the summary data for the other antidepressant drugs. The responses including the requested data and analyses for these summary data began arriving in late August, and had all arrived by late September, 2003. Unfortunately, as we began reviewing these responses, it became clear that different sponsors had interpreted the July 22nd request differently, resulting in our lack of confidence that the cases of suicidality had been selected for review, classified, and presented to us using similar approaches for all 8 sponsors. This impression was confirmed when we spoke to individual sponsors about their approach to this request. In retrospect, the algorithm we had provided for searching for potential events and selecting patients with events for the summary data analyses was not sufficiently detailed to result in a common understanding. This discovery presented a major hurdle to overcome in our evaluation of these data, since we needed to have confidence in the thoroughness and uniformity of the methods used for gathering and classifying these cases.

I will provide at this point several examples of the kinds of variations in methods we discovered across the different sponsors. This list of variations is just a sampling of the types of variations, and should serve the purpose of making clear why we needed to spend considerably more time ensuring that all relevant cases had been accumulated, and that they had been appropriately classified. We felt this was critical in order for us to complete our assessment of this potential problem.

- We had hoped to have a complete accounting of potential events identified by the search algorithms and SAE narrative reviews, however, in no case did a sponsor provide such an accounting. At one extreme we were provided narratives only for patients judged by the sponsor to have events that represented suicidality, with no explanation as to why other patients identified by the algorithms might have been excluded. In other cases, more details were provided on patients who had been excluded, but none of the reports was completely satisfactory in this regard.
- Although most sponsors conducted the search and selection of cases according to our instructions, in no case did they provide us with the specific criteria used in excluding cases at various levels of the process.
  - o For example, although we invited sponsors to exclude cases that might be considered "false positives" in the sense described above, i.e., where the text string of interest occurred in a longer word that was irrelevant to suicidality, we had expected that excluded cases would have been described. Most sponsors did not provide such a listing.
  - o We had asked for cases coded as accidental overdose, and for the most part received this information, however, we had failed to inquire about cases coded as accidental injury, and most sponsors did not fully address how they handled these cases. In fact, most sponsors simply excluded all cases coded as accidental injury, without further review. As an example, after we began inquiring about the process of excluding cases, we received from one sponsor a line listing of excluded cases

that included a case of a child who was excluded as accidental injury with an event characterized only as "patient stabbed himself in the neck with a pencil while taking a test." While this may have in fact represented an accidental injury, we decided it would be important to know enough details about cases coded as accidental injury in order to be confident that such cases were appropriately classified and excluded.

- o At least one sponsor acknowledged that they had conducted some of the searching and selection of cases with knowledge of treatment assignment, in particular, for the review of narrative summaries of SAEs.

- o Another sponsor acknowledged that they had excluded cases where the events that occurred were not considered "treatment emergent." These were events suggestive of suicidality but for which there was evidence that the event may have also been occurring before randomization. No other information had been provided about the excluded cases in the sponsor's summary submission.

- o Another finding that raised concern about the approach to case exclusion and selection resulted from our comparison of our results of suicidality risk for one drug product based on our re-review of the pediatric supplements with that sponsor's analysis of suicidality based on their reclassification of cases in response to our July 22nd request. In this particular instance, there was a striking difference in the results of the two analysis, i.e., a strong signal emerging from our re-examination of the pediatric supplement for that drug compared to only a weak signal emerging from the sponsor's analysis submitted in response to our July 22nd letter.

- As noted earlier, for many of the events included in the various analyses as representative of suicidality, there were questions about whether or not they were appropriately classified as such. Many of these were described as instances of very minor self injury with no indication of suicidal intent.

- There were also substantial differences across different programs in the selection of cases representing suicide attempts, with some sponsors deciding to include essentially all captured events as suicide attempts, even though there was clearly not enough information in the cases to justify such a classification.

Decision to Seek Outside Review and Reclassification of Cases

During this period when we were re-examining the pediatric supplement data and then beginning to explore the summary data provided to us in response to our July 22nd letter, it was becoming increasingly clear that we could not have confidence in the numerator events for the analyses we were provided by the sponsors, because the methods were not well-articulated, and the limited details available about the methods suggested that they varied substantially for different sponsors. Thus, we essentially confirmed the view already reached tentatively at our internal regulatory briefing that it would be desirable to have potential events blindly reclassified by an independent group. We briefly considered doing this internally, but quickly rejected this idea, since (1) we clearly did not have the expertise in suicidality to conduct such a reclassification, and (2) most of those who might logically be involved in such an effort had already seen many of the cases. Thus, we began to look outside the agency, and we initiated a series of discussions with outside experts. We found several experts interested in such an effort, however, there remained the problem of who

would coordinate the overall effort, establish methods and criteria for reclassification, etc. Among the experts we discovered in our search was a group at Columbia University who not only had well-recognized expertise in adolescent suicidality, but also had developed an approach to classifying events possibly representative of suicidality that precisely fit our needs. Thus we have been involved in extensive discussions with this group in order to establish a contract for having this reclassification of cases accomplished and also to work out the details of a standard approach to both finding all relevant cases and setting up categories for the reclassification effort that would meet our needs from a regulatory standpoint. At the present time, the contract is in place and we are in the process of preparing case material to provide to this group. It is important to note that, while the Columbia group will serve as the coordinating center for this effort, experts in adolescent suicidality from several other academic centers will also participate in the process in order to ensure broad representation from the expert community. Once we have provided the case materials to this group, one of the initial goals will be to try to reach agreement on an approach to classifying events into appropriate categories.

<u>Second Request for Identification of Events of Potential Interest with Regard to Suicidality</u>

As a result of our discussions with sponsors about their submissions in response to our July 22nd request for summary data on suicidality from their pediatric studies, and our discussions with the expert group at Columbia University about the reclassification of these cases, we worked out a more detailed standard method for sponsors to use in assembling their data regarding any cases of potential interest detected in the searches of their pediatric data base. This document was provided to sponsors for all 9 antidepressant products on Nov 24, 2003. Following is a summary of key aspects of this new standard:

- We asked sponsors to confirm that they had conducted an electronic search of their preferred terms and verbatim terms using the text strings specified in our July 22nd letter, or if not, to describe in detail what they had done.
- We next asked sponsors to provide a complete accounting of the winnowing down of the complete list of potential events/patients identified by these electronic searches to arrive at the events that would need to be blindly reclassified by outside experts. Sponsors were asked to provide the total number of patients identified as having 1 or more such potential events suggestive of suicidality, as a starting point. We then requested that they fully describe the exclusions from this list, for the following reasons:
  - o Prerandomization events: Sponsors were to list all patients excluded because all of their potential events occurred prerandomization.
  - o Events occurring more than 30 days beyond the last dose of randomized treatment: Sponsors were to list all patients excluded because all of their potential events occurred more than 30 days beyond the last dose of randomized treatment.
  - o False positive events: Sponsors were to list all patients excluded because all of their potential events could be characterized as "false positives" in the sense that a preferred or verbatim term was selected because one of the text strings occurred within that term and the term has no relevance to suicidality, e.g., "gas" in "gastrointestinal."

- We asked for summary narratives for all remaining patients with potential events, including patients classified as having accidental injury or accidental overdose (i.e., using preferred terms).
- In addition, we asked sponsors to provide narratives for all patients having one or more serious adverse events (SAE, based on regulatory definition) that occurred either in the randomized doubleblind phase of the controlled trials or within the +30 days beyond the last randomized dose period described earlier.

Blinded Reclassification of Potential Suicidality Events

We have now received responses to this Nov 24th request from most of the sponsors, and, as noted, we are in the process of preparing this information to forward to our outside contractors. We expect to be working closely with them over the next month in order to reach agreement on (1) the approach they will use in cleaning and blinding the narratives for information that might bias their assessment (to be done by an independent group who will not be involved in the reclassification of events), (2) the categories into which events will be classified and the criteria for such placements, (3) the process by which disagreements will be resolved, or if not resolved, the process for reaching the best judgement for classifying any particular case. We expect that it will take at least another several months to complete this reclassification effort. A member from the Columbia group will be making a presentation at the Feb 2nd meeting to describe their role in this project in greater detail.

There is one caveat to this effort. It is ultimately limited by 2 significant problems. First, as noted earlier, the approach to eliciting suicidal ideation and behavior was of unknown sensitivity. Second, the approach to identifying potential events may have missed certain events if they were not classified as serious, since detection for the other events depended on matching on certain text strings, and the list of text strings was necessarily limited.

Interim Overview of Results from Sponsors' Analyses of their Original Summary Data (i.e., for drugs other than Paxil)

Given that we are not confident in what the numerator data represent in the summary analyses provided by the sponsors for these pediatric studies, we will not be presenting detailed results from these analyses at this time. However, I have included one summary data table (**Appendix 2**) in order to make two important observations. **Appendix 2** summarizes risk data by individual study for the 15 pediatric major depressive disorder (MDD) studies for which we have data. While we have been provided data both for "on-therapy" and for "on-therapy + 30 days" events, I have focused on the "on-therapy" data, since these are the least problematic from the standpoint of interpretation. While we do sometimes utilize an "on-therapy + 30 days" timeframe for capturing events of interest, this analysis is problematic in this case for two reasons. First, it may be confounded by discontinuation symptoms occurring following withdrawal of medication, and second, different sponsors used different rules in deciding what events to include and exclude from the +30 days period in their analyses. For simplicity, I have provided the data for all ages combined, rather than breaking it out by age group. The table provides risk (percentage of

patients having at least 1 event) and risk ratio (when this can be calculated). Risk is provided both for the category "possibly suicide-related" and the subgroup of events classified as "suicide attempts."

I think there are two important observations from this table:
(1) A signal of increased risk on drug is apparent for at least 4 of the 7 programs, i.e., paroxetine, sertraline, venlafaxine, and citalopram, with perhaps a weak signal for nefazodone.
(2) There is inconsistency across the individual studies within the programs for which there is an apparent signal, with the exception of venlafaxine, where both studies reveal a signal. For paroxetine, a signal emerges from 1 study (329), but without even a weak signal for the other 2 studies in the program. This is also the case for sertraline and citalopram, where a signal emerges from 1 of 2 studies in each case, with no signal emerging in the other study. While fluoxetine is generally without a signal, in the "suicide attempts" analysis for study X065 there is actually a signal for drug. There are several instances where the risk ratio favors drug over placebo.

Overall, I think **Appendix 2** reveals that, while there are signals of increased risk of events suggestive of suicidality for several of these drugs, the signals for the most part are coming from a single trial within each of these programs. An important additional point, however, is that we are not yet confident in what the identified events represent.

Planned Analyses of Patient Level Data for Pediatric Suicidality

As noted earlier, the observation of inconsistency of the signal across studies within individual programs based on a crude re-analysis of suicidality from the pediatric supplements resulted in a recommendation from our internal regulatory briefing to request patient level data to permit us to conduct a more refined analysis including adjustment for potentially important covariates. Since the summary data provided by the sponors in response to our July 22, 2003 request have confirmed that finding of inconsistency, we are planning on proceeding with this more detailed analysis of the suicidality data from these programs. A standard letter requesting patient level data sets was issued to all sponsors on October 3, 2003. The variable list was expanded several times in subsequent weeks, and the final variable list is included as **Appendix 3**. We have now received all of these data sets from sponsors, and we are in the process of developing an analysis plan to explore for excess risk of suicidality using a statistical model that provides for adjustment of covariates. The numerator events for this analysis will be identified based on the reclassification of patient events by our outside experts. A member of our safety group will make a presentation on the current status of our plans for this analysis at the Feb 2nd meeting.

Update on Most Recent Regulatory Action on Antidepressant Treatment of Pediatric MDD by MHRA

The MHRA (UK) made a public announcement on Dec 10, 2003 indicating that, in addition to its earlier contraindications of paroxetine and venlafaxine in pediatric MDD, it was now contraindicating sertraline, citalopram, and escitalopram as well for this condition. This announcement noted that the risk benefit profile is unassessable for fluvoxamine, and that, in its view, the risk benefit profile is favorable in pediatric MDD only for fluoxetine.

[Note: Nefazodone and bupropion are not approved drug products in the UK. Mirtazapine is an approved product in the UK, however, MHRA has offered no comment on the pediatric data for this drug.]

Summary of Issues That Complicate the Anaylsis of the Pediatric Suicidality Data; Questions for the Committee

In this section, I will first recap the major issues that have complicated our attempts to understand the pediatric suicidality data, and then list the specific issues for which we would like committee feedback to assist us as we move forward in trying to address this concern. We are not asking for votes on any particular questions, but rather, discussion by the committees and any feedback you might have to offer on our current plans for further exploring these data.

Ascertainment for Suicidality

One of the concerns about these studies is the fact that they were not conducted in a manner to fully and adequately assess patients for emergent suicidality. This is apparent in reviewing the descriptive information for the events identified as possibly suggestive of suicidality. These descriptions are frequently sparse and lacking the kind of detail that would ordinarily be useful in assessing whether or not the events might legitimately be considered to represent suicidality. There is, of course, no fix for this problem with regard to these studies. However, one of our outside experts will address the issue of how one might develop guidance for more adequate assessment for emergent suicidality in future studies. We would welcome any advice from the committees on the development of such guidance.

One might reasonably ask why this would be a concern for these studies, since, despite the generally inadequate ascertainment, signals for drug associated suicidality did emerge. In fact, however, one can easily construct possible explanations for biases being introduced by inadequate ascertainment that work either for drug or against drug. Rather than having to speculate about possible bias, it would have been preferable to have included adequate ascertainment in the first place.

Possible Failure to Fully Capture All Events of Potential Interest with Regard to Suicidality

Quite apart from a concern about ascertainment is the issue of the method used to search the database for events of possible interest. GSK had developed an algorithm for searching for potential events representing suicidality in their database, and we proposed a variation of this to other sponsors. However, this is admittedly a compromise. It is still conceivable that certain cases of interest might have been missed by the search methods employed. The only failsafe approach to identifying all possible events of interest would be to have experts blindly evaluate every case report form for the more than 4000 patients who participated in these trials. Since that is not feasible, we welcome advice from the committee on possible modifications to the search strategies used for identifiying cases that might have been missed. Additional searches at this point would further delay the analyses of these data, and so this needs to be taken into consideration. However, if the committees feel there are serious deficiencies in the search

methods employed, it would be helpful to hear about alternative approaches that might be suggested.

Approaches to Classifying Events into Meaningful Categories for the Purpose of Further Analysis

As noted, an important next step is to decide on categories into which events of interest might be classified, along with operational definitions for such classifications. The approach used by sponsors thus far has been to classify cases first into a crude category of "possibly suicide-related," and then a further subgrouping of that broader group into a "suicide attempt" class. Since we are just now beginning to address this question with our outside experts, we would welcome any advice the committees might have on how to classify these events for the purpose of further analysis.

Patient Level Data Analysis

There will be a brief presentation by a member of our safety group on our plans for the patient level data analysis. Since we are in the preliminary stages of this analysis, this would again be an opportune time to get feedback on how to approach this analysis. In addition, you have seen our list of potential covariates for inclusion in this analysis, and we would welcome any thoughts you might have on this list. If we have left out important covariates, please let us know, since this would be the time to try to gather any additional information that you feel might be helpful in trying to understand these data.

Future Approaches to Trying to Address the Question of What Benefits These Drugs Might Have in Pediatric MDD

As noted earlier, the attempts to demonstrate efficacy in short-term trials for these drugs have not been successful, for the most part. We would welcome your thoughts on how to interpret and understand these largely negative results, and also any thoughts you might have on alternative approaches to demonstrating benefits in this population. An approach often used in expanding information on effectiveness in adult MDD populations is the randomized withdrawal design, in which patients who have responded during open treatment with an antidepressant drug are randomized to either continuation of drug or switch to placebo. The endpoint in these trials is typically time to relapse, and the success rate for these trials is far higher than the roughly 50% success rate in acute trials in adult MDD. We would welcome your thoughts on whether or not this design might be useful in evaluating possible benefits of these drugs in pediatric MDD.

Feedback on Other Relevant Topics

You should not feel limited to providing feedback on the above topics. The purpose of this meeting is to give you interim feedback on where we are at present with our attempts to understand these data, and to gain your insights into how we might proceed. Thus, we would welcome your feedback on other issues as well that you feel are relevant to our continuing evaluation of these data.

Appendix 1		
Summary of Efficacy Results (Primary Outcomes) for Short-Term Placebo-Controlled Pediatric Studies in Major Depressive Disorder		
Drug Program/Study Number	Age Range	Outcome[1] (Drug vs Placebo)
Paroxetine/329	12-18	Negative[2]
Paroxetine/377	13-18	Negative
Paroxetine/701	7-17	Negative
Fluoxetine/HCJE	8-17	Positive
Fluoxetine/X065	8-17	Positive
Sertraline/A050-1001	6-17	Trend
Sertraline/A050-1017	6-17	Negative[3]
Venlafaxine/382	7-17	Negative
Venlafaxine/394	7-17	Negative
Citalopram/CIT-MD-18	7-17	Positive
Citalopram/94404	13-18	Negative
Nefazodone/CN104-141	12-18	Trend
Nefazodone/CN104-187	7-17	Negative
Mirtazapine/003-004/Study 1	7-17	Negative
Mirtazapine/003-004/Study 1	7-17	Negative

1   Positive ($p \leq 0.05$); Negative ($p > 0.10$); Trend ($0.05 < p \leq 0.10$)

2   Keller, et al, 2001; positive on most secondary endpoints

3   Wagner, et al, 2003; positive on pooling of 2 studies

	"Possibly Suicide-Related"			**"Suicide Attempts"**		
Drug/Study Number	**Drug**	**Placebo**	**Risk Ratio**	**Drug**	**Placebo**	**Risk Ratio**
Paroxetine/329	**6.5%**	**1.1%**	**5.9**	**5.4%**	**0**	**--**
Paroxetine/377	**3.9%**	**4.2%**	**0.9**	**3.9%**	**4.2%**	**0.9**
Paroxetine/701	**1.0%**	**1.0%**	**1.0**	**1.0%**	**1.0%**	**1.0**
Fluoxetine/HCCJ	**0**	**5.3%**	**--**	**0**	**5.3%**	**--**
Fluoxetine/HCJE	**3.7%**	**3.6%**	**1.0**	**0.9%**	**1.8%**	**0.5**
Fluoxetine/X065	**4.2%**	**4.2%**	**1.0**	**4.2%**	**0**	**--**
Sertraline/A050-1001	**4.1%**	**0**	**--**	**1.0%**	**0**	**--**
Sertraline/A050-1017	**2.2%**	**2.2%**	**1.0**	**2.2%**	**2.2%**	**1.0**
Venlafaxine/382	**6.25%**	**1.18%**	**5.3**	**2.50%**	**1.18%**	**2.1**
Venlafaxine/394	**7.84%**	**0**	**--**	**1.96%**	**0**	**--**
Citalopram/CIT-MD-18	**1%**	**2%**	**0.5**	**1%**	**1%**	**1.0**
Citalopram/94404	**13%**	**8%**	**1.6**	**13%**	**8%**	**1.6**
Nefazodone/CN104-141	**1.1%**	**0**	**--**	**1.1%**	**0**	**--**
Nefazodone/CN104-187	**0.5%**	**0**	**--**	**0.5%**	**0**	**--**
Mirtazapine/003-045	**0.59%**	**1.14%**	**0.5**	**0**	**1.14**	**--**

Appendix 2
Risk (%) and Risk Ratio for Events Classified as "Possibly Suicide-Related" and "Suicide Attempts"
in Pediatric Studies of Major Depressive Disorder
[All subjects; On-Therapy Data]

Appendix 3

[Note: This was the final variable list submitted to sponsors (10-28-03) as an update to the original request for patient level data sets send 10-3-03]

We would appreciate your adding these variables to the previously requested dataset.

HXPSHOSP: This is a Y/N variable indicating that the subject had a history of psychiatric hospitalization prior to entering the RCT.

SCALESUI: The score of the suicide item for the primary scale used to rate baseline severity of depression. As part of your response to this data request, please include the range and meaning of the scores for the suicide item.

Clarifications of 10/27/03 updated request:

- Please note that the description of the variable HXSUIATT referred to history of suicide attempts. The description should be corrected to read "attempt" (see table below). In other words, to qualify for a "yes" on that variable, a subject need only have had one suicide attempt (not multiple).

- "." Will be added as a response option for missing data for the psychiatric history variables

- In the variable "HXNONCOM", "erratic" compliance is defined as not taking the study drug as prescribed.

The changes described above are highlighted in the following table.

Variable name	Length	Type	Description	Coding notes
TRIAL	NS	Character	Trial ID	No missing values are allowed in this variable.
CTPID	NS	Character	Patient ID within each trial.	No missing values are allowed in this variable
UNIQUEID	NS	Character	A unique ID for every patient	It should incorporate both the trial ID and the patient ID within each trial. No missing values are allowed in this variable.
DIAG	NS	Character	Condition for which patient was being treated (e.g., dementia-related psychosis or schizophrenia).	Should be one of the diagnoses listed for the corresponding trial in the "Controlled Trial File". No missing values are allowed in this variable.
DIAGCAT	3	Numeric	Diagnosis category	1= major depressive disorder 2= obsessive compulsive disorder 3= social anxiety disorder 4= other anxiety disorder
AGE	3	Numeric	Age of patient in years	. = Missing.
AGECAT	3	Numeric	Categories of age	1= AGE < 12 2= AGE >= 12 . = Missing

GENDER	3	Numeric	Patient gender	1= Female 2= Male . = Missing
RACE	3	Numeric	Race	1= White Caucasian 2= African-American 3= Hispanic 4= Asian 5= Other . = Missing
BMI	3	Numeric	Body mass index	Calculated as weight in kg/(height in meters)^2 . = Missing
SET	3	Numeric	Setting at randomization	1= Inpatient 2= Outpatient . = Missing
LOC	3	Numeric	Location of trial center	1= North America 2= Non-north America . = Missing
HXSUIATT	3	Numeric	The subject had a history of suicide attempt prior to entering the RCT	0=No 1=Yes . = Missing
HXSUIID	3	Numeric	The subject had a history of suicidal ideation prior to entering the RCT	0=No 1=Yes . = Missing
HXPSHOSP	3	Numeric	The subject had a history of psychiatric hospitalization prior to entering the RCT	0=No 1=Yes . = Missing
HXSUBAB	3	Numeric	The subject had a history of substance abuse prior to entering the RCT	0=No 1=Yes . = Missing
HXHOST	3	Numeric	The subject had a history of hostility or aggressive behavior prior to entering the RCT	0=No 1=Yes . = Missing
HXIRRAG	3	Numeric	The subject had a history of irritability or agitation prior to entering the RCT	0=No 1=Yes . = Missing
RANTX	NS	Character	Name of post-randomization treatment assignment	"Your drug name", "Placebo", or the name of the active control drug No missing values are allowed in this variable.
RANTXCAT	3	Numeric	Category of the drug	1=SSRI 2=non-SSRI 3=placebo
DOSE	3	Numeric	Dose of the post-randomization investigational treatment; If a flexible dose scheme was used, then report the modal dose. If there were multiple modal doses, select the maximal modal dose	0=Placebo . = Missing
DFRAN	10	Date	Date of first dose of	Use date format: MM

			randomized treatment	/DD/YYYY, e.g. 3/4/2000 . = Missing
DLRAN	10	Date	Date of last dose of randomized treatment	Use date format: MM /DD/YYYY e.g. 6/14/2000 . = Missing
EXPOSURE	3	Numeric	Number of days of exposure to randomized treatment	Should represent the difference between "DFRAN" and "DLRAN". [DLRAN-DFRAN]+1 . = Missing
HXNONCOM	3	Numeric	There is some evidence in the subject's medical record or case report form that the subject had a history of erratic compliance with the study medication during the RCT	0=No 1=Yes
RCTYEARS	12	Numeric	Exposure in years	=Exposure/365.25 . = Missing
SEVSCALE[2]	3	Numeric	Primary scale used to rate baseline severity of depression	1=HAM-D 2=CDRS-R 3=K-SADS-L 4=Kutcher 5=Other 6= NA (if not measured)
BASESEV	3	Numeric	Baseline severity score	. = Missing
HAMD17	3	Numeric	Score on HAM-D 17 if performed (or adapted from HAM-D 21)	. = Missing
SCALESUI	3	Numeric	The score of the suicide item for the primary scale used to rate baseline severity of depression	. = Missing
DURATION [Add DURACAT variable if duration of illness was recorded as a categorical variable]	3	Numeric	Duration of illness prior to randomization in months	. = Missing
SUIEVENT	3	Numeric	A suicide-related event as defined in July 2003 submission occurred during the RCT	0= No 1=Yes
SUIATT	3	Numeric	A suicide attempt as defined in July 2003 submission occurred during the RCT [Suicide attempt is a subset of suicide-related event]	0=No 1=Yes

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[2] HAM-D – Hamilton Depression Scale; CDRS =Children's Depression Rating Scale-Revised ; K-SADS-L = 9 item depression subscale of the Schedule for Affective Disorders and Schizophrenia for School Age Children-Lifetime version ; Kutcher = Kutcher Adolescent Depression Rating Scale

EVENTDC	3	Numeric	The first suicide-related event occurred following discontinuation	0=No 1=Yes
DAYEVENT	3	Numeric	The number of days to the first suicide-related event counting from the day of the first dose. Counting from the first day of drug should occur even if the event occurred after the patient discontinued the drug.	. = Missing or patient did not have an event
TEAEAG	3	Numeric	A treatment-emergent adverse event coded to the preferred term agitation occurred during the RCT	0=No 1=Yes
TEAEHOST	3	Numeric	A treatment-emergent adverse event coded to the preferred term hostility occurred during the RCT	0=No 1=Yes
SOURCE	4	Character	First 4 letters of your drug name	

NS=not specified.

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cc:
HFD-120/TLaughren/RKatz/JRacoosin/PDavid
HFD-040/RTemple
HFD-020/JJenkins

DOC: PDAC_Memo_Feb2004_TL02.doc