

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN  
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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND  
RESEARCH

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SUBJECT: Suicidality in pediatric clinical trials with paroxetine and other  
antidepressant drugs: Follow-up to 9-4-03 consult

Drugs: paroxetine, sertraline, venlafaxine, fluoxetine, fluvoxamine,  
citalopram, nefazodone, mirtazapine, and bupropion

**EXECUTIVE SUMMARY**

This consult is a follow-up to the previous consult on this topic, dated 9-5-03. As described in that consult, GlaxoSmithKline (GSK) performed an analysis of suicidal behaviors in their paroxetine pediatric clinical trial database, and found that there was a statistically significant increase in suicide-related adverse events for paroxetine-treated subjects compared to placebo. The method GSK used for their analysis involved an electronic search of the adverse event data for certain events that might have represented suicidal behaviors, followed by a blinded review of these events to select those that appeared to be probably related to suicide. In July 2003, the Division of Neuropharmacological Drug Products (DNDDP) requested the sponsors of the other antidepressant drugs to replicate GSK's analysis in their own pediatric clinical trial databases. This consult summarizes the results of these analyses for 22 short-term placebo-controlled trials involving 9 different antidepressant drugs.

These trials included a total of 4250 pediatric subjects, 2298 treated with active drug and 1952 treated with placebo. There were 108 patients with suicide-related events (74 on active drug and 34 on placebo); 78 of these adverse events were serious (54 on active drug and 24 on placebo).

Considering individual development programs separately, the data for venlafaxine and paroxetine showed a statistically significant increase in suicide-related events relative to placebo. Additionally, on one measure (the incidence rate difference for serious suicide-related events) the data for citalopram approached statistical significance (p-value = 0.063). The relative risks for suicide related events with two compounds, fluoxetine and mirtazapine, were below one, raising the possibility of a protective effect. However, the mirtazapine relative risk estimate of 0.5 was based on a very small number of events and had very broad confidence intervals. The relative risk

of suicide-related events for fluoxetine was 0.9 (95% confidence limits 0.3-2.3). (For all the other drugs, the relative risk estimates were greater than one, or undefined because of no events on placebo.)

Overall, comparing active drug treatment to placebo, there was an association of suicide-related events (incidence rate difference 0.08/year, p-value = 0.002) and serious suicide-related events (incidence rate difference 0.06/year, p-value = 0.006) with active drug treatment. This association was observed principally in major depressive disorder (MDD) trials, where the relative risk was 1.8 (95% confidence limit 1.2—2.8) and the attributable risk was 0.24/patient year for drug minus 0.14/patient year for placebo, yielding a value of 0.10 per patient-year of exposure to drug (p-value = 0.013). For serious suicide-related events in MDD trials, the relative risk was 1.9 (95% confidence interval 1.2–3.2), and the attributable risk was 0.19/patient year for drug minus 0.10/patient year for placebo, yielding a value of 0.085 events per patient-year of exposure to drug (p-value = 0.015), equivalent to approximately 1 excess serious suicide-related event per 12 years of drug treatment. For non-MDD trials, the data also showed a higher rate of events with active drug treatment, but the attributable risk for serious events was much smaller than for MDD trials (0.01/year), and the data were not statistically significant.

There are a number of limitations to this analysis, the chief among them being that the clinical trial data are limited to short-term use of these drugs. Unfortunately, there are not comparable data available regarding safety and efficacy of long-term use of these drugs in pediatric patients. Also, although there were attempts to standardize the methodology and case definitions among the various sponsors, in practice there may have been differences because each sponsor conducted their own separate analysis.

At the present time, a number of additional steps are under way to enhance the quality of the data for the assessment of this signal. These initiatives include arranging for a blinded review of the clinical trial cases by suicidology experts at Columbia University, requesting additional details on how each sponsor conducted their analysis, and obtaining electronic clinical trial datasets for each study to permit a more sophisticated statistical analysis.

However, while these efforts will yield valuable information, particularly at the level of the data for individual trials and drugs, in my view it is unlikely that the new information will alter the basic finding of an association of suicide-related events and serious suicide-related events with active treatment. This is because of the size of the effect and the statistical significance of the overall finding. Also, it seems less likely that misclassification or failure to identify relevant events would produce a false positive signal; rather, those types of errors tend to weaken a signal. Only systematic bias could be reasonably expected to yield a false positive signal of this magnitude, and that seems unlikely.

**Recommendations:** Given the strength of the association shown by the present data, the clinical importance of the apparent effect (i.e., an estimated excess of one additional serious suicide-related event per 12 patient-years of active treatment), and the fact that the additional analyses are likely to take several more months to complete while considerable numbers of pediatric patients are being exposed to these drugs, I favor an interim risk management plan regarding use of these drugs in the pediatric population. This might be of value to physicians, patients and families who are faced with the need to make a decision regarding pharmacotherapy at the present time. Specifically, I propose a risk management strategy directed at discouraging off-label pediatric use of antidepressant drugs, particularly the use of drugs other than fluoxetine in the treatment of pediatric MDD. Conceivably, this might include discouraging the initiation of treatment of drug-naïve pediatric MDD patients with off-label drugs, in the absence of some over-riding clinical

consideration. (Of course, all such warnings should be made in a manner that emphasizes the fact that the available data apply only to short-term, acute treatment, and that sudden discontinuation of antidepressant treatment, or discontinuation without medical supervision, are unwise.)

I recommend this approach for two reasons. First, of all the drugs with pediatric MDD clinical trial programs, only fluoxetine is approved for pediatric MDD, on the basis of two positive clinical studies (out of two MDD studies conducted). Of course, the failure to demonstrate efficacy in pediatric MDD trials with other antidepressants does not necessarily mean that these other drugs are ineffective in pediatric MDD. Still, for drugs other than fluoxetine, judgement regarding their efficacy in pediatric MDD must remain a matter of speculation until further trials are conducted. Secondly, although the confidence limits are broad, fluoxetine is the drug for which the estimate of the relative risk of suicidal events appears most favorable.

## **BACKGROUND**

This memorandum is in follow-up to our consult to DNDP dated 9-5-03. On May 22 of this year, GlaxoSmithKline submitted an analysis of adverse events related to suicidal behaviors in pediatric trials of paroxetine (Paxil, NDA 20-031). The sponsor performed this analysis by conducting an automated, electronic search of the safety database from their pediatric trials for adverse event terms that would suggest suicidal behaviors. This analysis showed a statistically significant increase in such behaviors with paroxetine treatment, compared to placebo. A previous consult reviewed these data, and also provided a preliminary analysis of data from seven other pediatric development programs for other antidepressant drugs.<sup>2</sup> Overall, there was a statistically significant increase in suicidal adverse events for active drug treatment compared to placebo, similar to the findings from the paroxetine trials. These findings were discussed at a CDER Regulatory Briefing.<sup>3</sup>

However, this preliminary review of pediatric trials with the other antidepressant drugs was limited to a manual search of the reports submitted to FDA. In order to provide a meaningful comparison to the paroxetine findings, the Division of Neuropharmacological Drug Products requested the sponsors of eight other drugs (sertraline, venlafaxine, fluoxetine, fluvoxamine, citalopram, nefazodone, mirtazapine, and bupropion) to conduct a search of their databases similar to the analysis performed by GlaxoSmithKline. All of the 8 sponsors responded to this request within the next few months. The purpose of this memorandum is to summarize the findings reported in those submissions.

With respect to pediatric indications for the antidepressant drugs, clomipramine, fluvoxamine, sertraline and fluoxetine are approved for pediatric obsessive compulsive disorder. (Clomipramine is an older tricyclic compound that was not part of this analysis.) For pediatric major depressive disorder (in children 8 years and up), the only drug approved is fluoxetine. Appendix table 5 presents a summary of the efficacy results from placebo-controlled trials with the aforementioned drugs, along with the regulatory status of the drugs for pediatric use.

## **METHODS**

The sponsors of the aforementioned 8 drugs all received identical information request letters from DNDP dated 7-22-03. The letters asked for the following analyses for all randomized, placebo-

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<sup>2</sup> PID# D030341, 9-4-03.

<sup>3</sup> CDER Regulatory Briefing 9-16-03

controlled trial involving pediatric subjects (the indented text below is reproduced from the letters):

The identification of the following events should be done blinded to treatment to avoid bias. All adverse events occurring within 30 days of the last dose of drug should be included in the search.

“Suicide-related events” should be identified using the following algorithm:

- Any events coded to preferred terms that include the text strings “suic” or “overdos”
- Exclude “accidental overdose” cases
- Regardless of the preferred term to which the verbatim term is mapped, all verbatim terms should be searched for the following text strings: “attempt”, “cut”, “gas”, “hang”, “hung”, “jump”, “mutilat-”, “overdos-”, “self damag-”, “self harm”, “self inflict”, “self injur-”, “shoot”, “slash”, “suic-”
- Any terms identified by this search because the text string was a substring of an unrelated word should be excluded (for example, the text string “cut” might identify the word “acute”)
- In addition to the algorithm above, narratives of all serious adverse events (SAEs) should be reviewed (in a blinded fashion) to identify any additional cases of suicidality or self-harm. In particular, SAEs related to mania and hostility should be examined closely for suicidality or self-harm.
- Any death found to be due to suicide or overdose should be included (if not already identified by the previous search methods).

We are also interested in an analysis of suicide attempts. “Suicide attempts” are a subset of the “suicide-related events” identified above; they should be identified using a blinded hands-on review of the records of all patients identified by the above algorithm as having a “suicide-related event”. For the purposes of this analysis, any case in which the patient exhibited self-injurious behavior should be considered as a suicide attempt. Any case in which the patient’s suicidal ideation did not lead to self-injurious behavior should be excluded from this subset.

Separate analyses should be performed for the group of “suicide-related” events and the group of “suicide attempts”. Both the risk (# of events/# of patients) and the rate (# of events/person-time exposure ) should be presented by treatment group. All treatment groups should be presented, including active controls. If a study has a blinded extension phase, events identified while the patient is in that extension phase should be excluded.

In addition to presenting the overall risks and rates across all indications and within each indication, the following stratified analyses should be performed:

- Child (<12) vs. Adolescent (>= 12).
- On-therapy vs. On-therapy + 30 days.
- Within each indication, data from each trial should be presented separately.

Also requested were detailed clinical data about the patients identified as having suicidal events, in the form of narrative summaries and tabulations.

The analyses submitted by each sponsor are summarized herein. A brief description of the relevant pediatric clinical trials is presented for each drug. Also, Appendix table 3 lists each pediatric subject having a suicide-related event.

Although I reviewed all the narrative summaries of the identified adverse events, I have not reclassified any events myself; the sponsors maintained the blind on treatment when they categorized these events, and this is obviously not possible for me. Instead, I have simply noted the few cases where in my opinion a different classification of the event might reasonably have been made. For a few patients who experienced more than one event of interest, I have chosen to count each patient only once in the analysis, at the time of their first event; their subsequent events are described under “Comments” in appendix table 3. Also described under “Comments” are any other adverse events that were prominently associated with the suicidal events. For a few of the clinical development programs, there were a sufficient number of cases to warrant a discussion of possible contributing clinical factors such as dose and duration of treatment, and I have included those details where appropriate.

Also included is a summary analysis of the clinical trial data, both overall and by drug and indication, with statistical testing. This analysis examines the question of the association of these events with active drug treatment in two ways: by calculation of the attributable risk (more precisely, the incidence rate difference between drug and placebo), as well as the relative risk (i.e., incidence rate ratios for drug:placebo). All statistical calculations were performed with Stata version 7.0 software. (Grateful acknowledgement is made to Dr. Yi Tsong of OPSS for his comments on the statistical methods.)

## RESULTS

Including the previously reviewed data on paroxetine, this analysis comprised a total of 22 randomized, placebo-controlled trials with 9 different antidepressant drugs in the pediatric population. A total of 2298 pediatric subjects were exposed to active drug, for a total of 406.9 patient-years; for placebo, there were 1952 subjects exposed for a total of 347.6 patient-years. (One trial, Study 329 for paroxetine, included an imipramine arm as an active control, in which the rate of suicide-related events was intermediate between paroxetine and placebo at 0.24 per patient-year, but I have omitted those data from this analysis. Also, patient-years of exposure were not available for the single trial with bupropion.)

The sponsors identified a total of 108 patients with suicide-related events in these trials, 74 on active drug and 34 on placebo. There were no completed suicides. All 83 patients with suicide-related events described in the previous consult were included among these 108 patients. Seventy-eight patients had events classified as serious (54 on drug and 24 on placebo), and 75 had events classified as “suicide attempts” under the method described above (with 49 suicide attempts on drug, and 26 on placebo). Appendix Table 1 presents the complete data on the numbers of these events from all 22 clinical trials, and Appendix Table 2 presents the derived rates of these events for each trial. Appendix Figures 1-4 depict graphically the rates enumerated in Appendix table 2, for MDD and non-MDD studies. Note that the placebo rates of events vary considerably from trial to trial, even within the subgroup of MDD studies. With respect to the classification of events, discussion at the 9-16-03 CDER Regulatory Briefing and subsequently has raised questions about the appropriateness of the “suicide attempts” classification, since this category actually includes all types of deliberate self-injury. Accordingly, in the following I have chosen to emphasize the category of serious suicide-related events, rather than the category of suicide attempts, as being perhaps more clinically meaningful. The data for the category “suicide attempt” are included in Appendix Tables 1 and 2 for completeness.

### Overview of each sponsor’s submission.

*Bupropion (Wellbutrin, NDA 18-644, GlaxoSmithKline, submission dated 8-22-03)*

There were no pediatric studies for the indications of major depressive disorder (MDD) or smoking cessation. There was one placebo-controlled pediatric study for the indication of attention deficit hyperactivity disorder (ADHD), as shown below. The requested electronic search of adverse event data revealed no suicide-related events in this study.

| Indication | Protocol | No. of sites | Age range (yrs) | Duration (wks) | N         |         |
|------------|----------|--------------|-----------------|----------------|-----------|---------|
|            |          |              |                 |                | Bupropion | Placebo |
| ADHD       | 75       | 4            | 6-12            | 6              | 71        | 36      |

Thus, there are no available data on pediatric suicidality with bupropion in the relevant patient populations.

*Mirtazapine (Remeron, NDA 20-415, Organon, submission dated 8-21-03 and email dated 11-24-03)*

There was only one clinical protocol in the mirtazapine development program, described below; the sponsor conducted two identical studies under that protocol, which were combined for the analysis of safety information.

| Indication | Protocol | No. of sites | Age range (yrs) | Duration (wks) | Dose (mg/day) | N           |         |
|------------|----------|--------------|-----------------|----------------|---------------|-------------|---------|
|            |          |              |                 |                |               | Mirtazapine | Placebo |
| MDD        | 003-045  | 34           | 7-17            | 8              | 15-45         | 170         | 88      |

The electronic search of the adverse events terms in study 003-045 yielded a total of 13 adverse events; these were listed in Organon’s email submission dated 11-24-03. Of these 13 events, 10 were obviously not related to suicidal behaviors and were excluded, leaving 3 cases for further review; one of these cases occurred pre-randomization and so was not part of the analysis. Additionally, a subject who was hospitalized for suicidal ideation was identified from the review of all serious adverse events (subject 0404), yielding a total of 3 cases, summarized in Appendix table 3. Note, however, that Organon excluded one of these events from the analysis: subject 0801, a 9 year old boy receiving mirtazapine treated in the emergency room for an overdose on 4 Depakote tablets. This was not considered a suicide attempt because the boy took the tablets “on a dare.”

*Fluoxetine (Prozac, NDA 18-936, Lilly)*

N.B. The following summary is based primarily upon Lilly’s submission to Health Canada dated 10-7-03, and not their submission to FDA dated 9-2-03, because Lilly discovered an additional fluoxetine-associated event while preparing their Canadian submission. For details, please refer to Lilly's correspondence dated 10-9-03.

There were four clinical trials relevant to this analysis, three in MDD and one in obsessive-compulsive disorder (OCD). Study HCCJ, a pilot study in adolescent depression, was excluded from the sponsor’s Integrated Summary of Safety for the pediatric supplement, but is included in this analysis.

| Indication | Study | No. of sites | Age range (yrs) | Duration (wks) | Dose (mg/day) | N          |     |
|------------|-------|--------------|-----------------|----------------|---------------|------------|-----|
|            |       |              |                 |                |               | Fluoxetine | Pbo |
| OCD        | HCJW  | 22           | 7-18            | 13             | 10-60         | 71         | 32  |
| MDD        | HCJE  | 22           | 8-18            | 19*            | 20            | 109        | 110 |
| MDD        | X065  | 1            | 8-18            | 8              | 20            | 48         | 48  |
| MDD        | HCCJ  | 1            | 12-17           | 6              | 20-60         | 21         | 19  |

\*includes subacute phase (weeks 10-19), during which poorly responding patients could receive a higher dose of double-blind study medication

Lilly’s search for adverse events of interest yielded a total of 220 possibly relevant events. Of these, 176 were considered obviously unrelated to the issue of suicidality and were not reviewed further (a list of these adverse events was provided by email 11-17-03, and I concur with the

sponsor that none of the events involve self-harm). The remaining cases are summarized in the sponsor's table, reproduced below.

**Number of patients in pediatric fluoxetine MDD and OCD trials, by search category (reproduced from sponsor's submission)**

| <b>Patient Category</b>  | <b>Number of Patients</b> |
|--|---------------------------|
| 1) Suicide-related events with suicide attempts (acute/subchronic phases <sup>a</sup> )    | 10                        |
| 2) Suicide-related events with no suicide attempts (acute/subchronic phases <sup>a</sup> ) | 7                         |
| 3) Accidental overdose/death   | 1                         |
| 4) Could be suicide related, but insufficient information                                  | 3                         |
| 5) Suicide-related event prior to treatment phase  | 14                        |
| 6) Suicide-related event during extension phase  | 2                         |
| 7) Suicide-related event that was not treatment emergent                                   | 7                         |

<sup>a</sup> Defined as the acute treatment phases for Studies HCCJ, X065, and HCJW, and the acute and subchronic phases from Study Periods III through V of Study HCJE.

Lilly provided narratives on all the cases listed, in their aforementioned submission to Health Canada and also in their email submission 11-18-03. My own review of these narratives substantiated Lilly's categorization of them.

The 17 events in categories 1 and 2 above were included in the analysis; a listing of these patients appears in appendix table 3.

A few observations can be made regarding the clinical details of these cases. With respect to dose, among the 9 fluoxetine-treated subjects with suicide-related events, the daily dose at the time of event was 20 mg for 7 subjects, 30 mg for one, and 60 mg for one. Median duration of treatment for fluoxetine subjects at the time of their event was 38 days, and the corresponding median for placebo subjects was 33 days. The adolescent age category predominated; children under 12 years of age comprised 43% of the total sample of 458 clinical trial subjects, but only 3 (18%) of the 17 suicide-related events occurred in children, which is not surprising given the relative infrequency of suicidal behavior among children compared to adolescents. Of the 17 suicide-related events, 13 (76.5%) occurred in female subjects, although females comprised only 228 (49.8%) of the 458 subjects.

Regarding the relationship to drug discontinuation, only one of the events (a drug overdose by fluoxetine patient 001-6401 in study HCCJ) occurred during the 30-day follow-up period. This patient was regarded as having discontinued by virtue of being non-compliant with study medication. However, Lilly acknowledged that "events occurring after study completion were not systematically collected," and so some events in the 30-day follow-up period may have been missed.

*Nefazodone (Serzone, NDA 20-152, Bristol Myers Squibb, submission dated 8-21-03)*

The table below provides the details for the two randomized, placebo-controlled pediatric studies with nefazodone.

| Indication | Protocol | No. of sites | Age range (yrs) | Duration (wks) | Dose (mg/day)      | N               |         |
|------------|----------|--------------|-----------------|----------------|--------------------|-----------------|---------|
|            |          |              |                 |                |                    | Nefazodone      | Placebo |
| MDD        | CN104141 | 15           | 12-18           | 8              | 100-600            | 95              | 95      |
| MDD        | CN104187 | 28           | 7-17            | 8              | 100-300 or 200-600 | 184 (both arms) | 94      |

The sponsor performed the requested search and identified two suicide-related events in these trials, both occurring in nefazodone-treated patients (please refer to Appendix table 3). (In addition to these events, the sponsor reported a total of 5 suicide-related events that occurred during open label treatment with nefazodone in follow-up to study 187. However, only the two events during double-blind treatment are relevant for this analysis.)

*Fluvoxamine (Luvox, NDA 21-519, Solvay, submission dated 8-22-03)*

There was one randomized, placebo controlled pediatric trial with fluvoxamine, described in the table below.

| Indication | Protocol | No. of sites | Age range (yrs) | Duration (wks) | Dose (mg/day) | N           |         |
|------------|----------|--------------|-----------------|----------------|---------------|-------------|---------|
|            |          |              |                 |                |               | Fluvoxamine | Placebo |
| OCD        | 114      | 20           | 8-17            | 10             | 50-200        | 57          | 63      |

Solvay's search of the safety dataset for this trial revealed a single suicide-related event in a fluvoxamine-treated patient.

*Sertraline (Zoloft, NDA 19-839, Pfizer, submission dated 9-12-03)*

There were three randomized, placebo-controlled trials in the pediatric population, summarized in the table below. In addition, Pfizer is conducting a pediatric trial in post-traumatic stress disorder, for which the treatment is still blinded. Note that there were two studies for MDD conducted under the same protocol, and these have been combined in this analysis.

| Indication | Protocol  | No. of sites | Age range (yrs) | Duration (wks) | Dose (mg/day) | N          |         |
|------------|-----------|--------------|-----------------|----------------|---------------|------------|---------|
|            |           |              |                 |                |               | Sertraline | Placebo |
| OCD        | 498       | 12           | 6-17            | 12             | 25-200        | 92         | 95      |
| MDD        | 1001/1017 | 51           | 6-17            | 10             | 50-200        | 189        | 184     |

The electronic search of adverse event terms yielded 89 potential events from these trials. Pfizer's blinded review of the 89 cases identified 25 patients with possibly relevant events, and further review of these cases excluded 19 events (mostly associated with accidental injuries). This yielded a total of 9 events occurring among 8 subjects that were considered suicide-related. (My own review of the listing of these 89 events did not disclose any additional events that were obvious omissions.) In addition, Pfizer performed the requested review of all serious adverse events in these trials, yielding one additional case relevant to the analysis (subject 1001-29533-2006, who was hospitalized for suicidal ideation). Thus there were a total of 9 patients with suicide-related events. It should be noted, however, that in their submission Pfizer questioned the clinical relevance of events in two sertraline-treated patients (subject 30506-1076, with self-mutilation, and subject 6193-1022, who was hospitalized for suicidal threats), although they did not exclude these events from their analysis.

Although the number of events was probably too small for any meaningful characterizations, the median age among the 6 sertraline treated patients with events was 10 years, somewhat younger than seen in other development programs. These 6 subjects included 3 males and 3 females; their median dose was 100 mg/day, and all had MDD.

There were no events reported within the 30-day period after discontinuation of study medication, and no events in the OCD trial. Of the nine events, six occurred on drug and three on placebo. Six of the nine events occurred in female subjects. With respect to age, there was a somewhat different pattern from that seen in other clinical trial programs, since four events out of the nine occurred in children rather than adolescents (one event considered a suicide attempt occurred in a 6 year old boy). The duration of treatment among the six sertraline-associated events ranged from 21 to 50 days.

*Citalopram (Celexa, NDA 20-822, Forest, submission dated 8-21-03)*

There were two randomized, controlled clinical trials in the citalopram pediatric development program, summarized below.

| Indication | Protocol  | No. of sites | Age range (yrs) | Duration (wks) | Dose (mg/day) | N          |         |
|------------|-----------|--------------|-----------------|----------------|---------------|------------|---------|
|            |           |              |                 |                |               | Citalopram | Placebo |
| MDD        | CIT-MD-18 | 21 in U.S.   | 7-17            | 8              | 20-40         | 89         | 85      |
| MDD*       | 94404     | 31 in Europe | 13-18           | 12             | 10-40         | 121        | 112     |

\*subjects could be inpatients or outpatients

Note that in addition to these two completed trials, the sponsor is conducting study SCT-MD-15, a randomized, double blind, placebo controlled trial of escitalopram, the s-isomer of citalopram, in children and adolescents with MDD. This trial is still blinded; the total number of subjects planned is 264, and there have been two suicide-related events thus far.

Forest made a couple of departures from the requested methods for the adverse event search. They included an analysis of 8 patients who experienced worsening of depression, but not suicidal thoughts or behaviors; all these patients were treated with placebo. These events were not included in the analysis presented here; the interested reader should refer to their submission for details. Forest also reported that their search of all serious adverse events for events involving suicidality was not performed blind to treatment. (I reviewed the serious adverse events in these two trials myself, and although I was not blind to treatment group either, I did not find any cases that were obvious omissions. However, among the serious adverse events, there were 6 placebo-treated and 2 citalopram-treated patients in study 94404 with psychiatric hospitalizations. These events were not counted in the analysis, however, because suicidality was not specifically documented.)

In addition to the events selected for the analysis, Forest reported that the electronic search identified 11 patients with “false positives” who were excluded.<sup>4</sup> In addition to the electronic search, Forest conducted a manual search of all adverse events and patient narratives from the

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<sup>4</sup> Email dated 11-17-03

two trials, yielding 6 patients with relevant events that were not disclosed in the electronic search. This made a total of 30 patients with events. In addition, one patient who took an extra dose of medication by mistake was considered to have taken an accidental overdose (patient 485 in study 94404); this event was not included in the analysis. Two events occurred prior to randomized treatment, yielding a total of 28 patients for the analysis (please refer to Appendix table 3 for a list of these patients). Note that 27 of the 28 events were classified as suicide attempts. However, Forest indicated in an email dated 11-17-03 that six of the study 94404 patients classified with “suicide attempts” (patients 664, 693, 867, 607, 152, and 713) were so categorized simply because the recorded preferred term was suicide attempt, and not because the event description documented self-injurious behavior.

Four placebo-treated patients and four citalopram-treated patients had events during the 30-day follow-up period after the end of randomized treatment. However, two of these 4 placebo patients also had events during double blind treatment, and so are counted as having events while on-treatment. Note that patient 007 in study 94404 was actually receiving fluoxetine, not citalopram, at the time of the event during the post-study period.

The median age of the 28 patients with events was 16 years; 19 were females and 9 males. Among the 13 patients receiving citalopram at the time of their event, the median dose was 20 mg/day, and the median duration on treatment was 27 days. Forest noted that 11 of the 16 citalopram-treated patients with suicide-related events in study 94404 had a past history of suicidality.

Forest also provided an analysis of scores on the suicidality item of the depression rating scales in the two trials; i.e., the CDRS-R in study CIT-MD-18, and the K-SADS in study 94404. There was a greater improvement on the suicidality item in study CIT-MD-18 with citalopram treatment compared to placebo, and this almost reached statistical significance. However, the mean change from baseline on item IX from the K-SADS in study 94404 was approximately equal between citalopram and placebo.<sup>5</sup>

#### *Paroxetine (Paxil, NDA 20-031, GlaxoSmithKline)*

Please refer to the consult dated 9-5-03 for details regarding the paroxetine pediatric clinical trial data. Subsequently, GSK provided the agency with a copy of their report to the Committee for Proprietary Medicinal Products of the European Agency for the Evaluation of Medicinal Products.<sup>6</sup> Included in this is an analysis of suicide-related events in adult trials with paroxetine that mirrors GSK’s analysis of the pediatric clinical trials. The results of the adult trial analysis show essentially no difference in the rates of suicide-related events between paroxetine and placebo treatment groups, for all studies combined or for the subset of MDD trials. This is in contrast to the previously described pediatric trial data, which showed a statistically significant increase with paroxetine treatment. The sponsor’s tables describing both the adult and the pediatric analyses are reproduced in Appendix Figure 5.

#### *Venlafaxine (Effexor and Effexor XR, NDAs 20-151 and 20-699, Wyeth)*

There were four randomized, double blind, placebo-controlled venlafaxine trials in pediatric patients, summarized in the following table. The sponsor also reported that two additional

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<sup>5</sup> NDA 20-822 8-21-03 submission

<sup>6</sup> NDA 20-031 11-7-03 electronic submission

pediatric placebo-controlled trials, one in social anxiety disorder and one in panic disorder, have been completed but are not fully analyzed yet.

| Indication | Protocol | No. of sites | Age range (yrs) | Duration (wks) | Dose* (mg/day) | N           |         |
|------------|----------|--------------|-----------------|----------------|----------------|-------------|---------|
|            |          |              |                 |                |                | Venlafaxine | Placebo |
| MDD        | 382      | 16           | 7-17            | 8 + taper      | 37.5-225       | 80          | 85      |
| MDD        | 394      | 37           | 7-17            | 8 + taper      | 37.5-225       | 102         | 94      |
| GAD**      | 396      | 39           | 6-17            | 8 + taper      | 37.5-225       | 80          | 84      |
| GAD        | 397      | 35           | 6-17            | 8 + taper      | 37.5-225       | 77          | 79      |

\*administered as Effexor XR in all trials; dosage based upon weight of subject, and tapered over  $\leq 2$  weeks following double-blind treatment

\*\*Generalized Anxiety Disorder

Wyeth identified 16 randomized patients with suicide-related events, along with two MDD patients who had events before beginning the study and who were not counted in the analysis. Additionally, one more event was identified through review of adverse event narratives, yielding a total of 17 patients who experienced a total of 20 events of interest. Wyeth counted all 20 events, rather than simply enumerating the number of patients with events.<sup>7</sup> Note that two patients were considered to have had separate events a few days apart (patients 39402-0041 and 39428-1087); after review of the narrative summaries, I have elected to count these instead as single events. A third patient also had two events, patient 38211-012, but these were separated by approximately 3 weeks and I have elected to count only the first event in the analysis that follows. Thus, the analysis shown below is based upon the number of patients with events, rather than the number of events (as in Wyeth’s analysis). The listing in the Appendix provides further details about the patients.

The patient-years of exposure were not provided in the response to the July 2003 letter, since only rates were displayed in that submission; however, the exposures were available from the original pediatric exclusivity supplement. Additionally, in Wyeth’s analysis, the “on-therapy” period does not include the taper period, but only the period of randomized treatment during which patients received their full dose of study medication. Therefore, “on-therapy period + 30 days” does not include a full 30 days from the last dose of study medication, if the patient had a taper following the end of their study treatment. This is slightly different from GlaxoSmithKline’s analysis of the paroxetine pediatric trials, in which the “on-therapy” period included the taper phase, through the last dose of study medication, and the “on-therapy + 30 days” period included a full 30 days from the last dose of study medication.

With respect to classification of events, there were some issues with the “suicide attempts” category. The reason that patient 38205-019 was not counted in the suicide attempt category for taking an overdose was unclear. Also, I was unable to verify Wyeth’s count of 3 suicide attempts on venlafaxine and 2 on placebo in study 382.<sup>8</sup> Instead, I have used the counts from Wyeth’s “Abbreviated Table of Patient Characteristics.”<sup>9</sup>

The median age among the 17 patients with suicide-related events was 13 years. For the 13 venlafaxine-treated patients, at the time of the event the median dose was 112.5 mg/day, and the median duration of treatment was 24 days. Wyeth counted any events occurring within 1 day of

<sup>7</sup> NDA 20-151 submission 8-28-03

<sup>8</sup> Table 3A, NDA 20-151 submission 8-28-03

<sup>9</sup> Table 4A, NDA 20-151 submission 8-28-03

the last full dose of study medication as having occurred on-therapy. Five of the 17 events did not occur on-therapy, 3 with venlafaxine and 2 with placebo.

## Risk estimates

### *Analysis of attributable risk*

Pooling the exposure and event data by drug and by indication provides the results shown in tables 1 and 2. Appendix figure 6 displays these same results graphically. Here, an incidence rate difference greater than zero would indicate a risk associated with active drug versus placebo, while an incidence rate difference less than zero would indicate a protective effect of the drug.

**Table 1.**

| <b>Attributable risks (incidence rate differences) per patient-year for suicide-related events in pediatric trials</b> |  |                                |                |
|--|--|--------------------------------|----------------|
| <b>Trials</b>  | <b>Incidence rate difference, drug minus placebo</b> | <b>95% confidence interval</b> | <b>p-value</b> |
| Citalopram   | 0.14   | -0.16-0.43                     | 0.374          |
| Fluoxetine   | -0.03  | -0.20-0.14                     | 0.737          |
| Fluvoxamine  | 0.11   | -0.10-0.32                     | 0.485          |
| Mirtazapine  | -0.04  | -0.21-0.14                     | 0.691          |
| Nefazodone   | 0.05   | -0.02-0.12                     | 0.367          |
| Paroxetine   | 0.12   | 0.04-0.20                      | 0.005          |
| Sertraline   | 0.06   | -0.05-0.17                     | 0.327          |
| Venlafaxine  | 0.17   | 0.02-0.33                      | 0.029          |
|  |  |                                |                |
| All MDD trials   | 0.10   | 0.02-0.18                      | 0.013          |
| All non-MDD trials   | 0.04   | -0.01-0.09                     | 0.114          |
| All trials   | 0.08   | 0.03-0.14                      | 0.002          |

**Table 2**

| <b>Attributable risks (incidence rate differences) per patient-year for serious suicide-related events in pediatric trials</b> |  |                                |                |
|--|--|--------------------------------|----------------|
| <b>Trials</b>  | <b>Incidence rate difference, drug minus placebo</b> | <b>95% confidence interval</b> | <b>p-value</b> |
| Citalopram   | 0.24   | -0.01-0.48                     | 0.063          |
| Fluoxetine   | -0.02  | -0.18-0.14                     | 0.775          |
| Fluvoxamine  | 0  | -                              | -              |
| Mirtazapine  | 0.04   | -0.04-0.12                     | 0.654          |
| Nefazodone   | 0.03   | -0.02-0.08                     | 0.606          |
| Paroxetine   | 0.08   | 0.01-0.15                      | 0.038          |
| Sertraline   | 0.06   | -0.04-0.16                     | 0.276          |
| Venlafaxine  | 0.06   | -0.07-0.18                     | 0.379          |
|  |  |                                |                |
| All MDD trials   | 0.09   | 0.02-0.15                      | 0.015          |
| All non-MDD trials   | 0.01   | -0.02-0.05                     | 0.498          |
| All trials   | 0.06   | 0.02-0.11                      | 0.006          |

The incidence rate differences by drug for MDD trials alone are shown in Appendix Tables 6 and 7. These data are displayed graphically in Appendix Figure 7.

It can be seen that overall the data are consistent with an increased risk of suicidal events with active drug treatment; the comparison between active treatment and placebo for all trials pooled together is statistically significant (p-value = 0.002 for all suicide-related events, and p-value = 0.006 for serious suicide-related events). For serious suicide-related events in MDD trials, the attributable risk was 0.19/patient year for drug minus 0.10/patient year for placebo, yielding a value of 0.085 events per patient-year of exposure to drug (p-value = 0.015), equivalent to approximately 1 excess serious suicide-related event per 12 years of drug treatment. The observed serious event incidence rate differences are larger in MDD trials (0.085/year) than in trials with OCD, GAD and Social Anxiety Disorder (SAD) (0.014/year).

With respect to individual drugs, the incidence rate differences for all suicide-related events are largest for paroxetine, venlafaxine and citalopram, reaching statistical significance for paroxetine and venlafaxine. For serious suicide-related events, citalopram showed the largest incidence rate difference, which approached statistical significance (p-value = 0.063).

#### *Analysis of relative risk*

In addition to estimating the excess risk attributable to drug, the data can also be analyzed in terms of the relative risk, or more precisely, the ratio of the incidence rates for drug and placebo. Accordingly, Mantel-Haenszel combined incidence rate ratios were calculated, stratified by study. This approach has the advantage of providing stratification by study, while the analysis of excess risk shown above simply involved summing all the relevant data without regard for differences between trials. In addition to calculating the combined incidence rate ratio, the Stata software also tests for homogeneity of the individual study ratios.

The Stata output for the “All trials” category is shown in Appendix table 3. There were two studies by themselves that showed statistically significant rate ratios for suicide-related events, Paroxetine Study 329 and Venlafaxine Study 394. No individual study showed a statistically significant protective effect.

Table 3 below displays the relative risks (more precisely, the incidence rate ratios) for suicide-related events and serious suicide-related events for each of the antidepressant drugs, and for all 21 clinical trials combined. Here placebo is the reference, and thus a value less than one indicates a protective effect of the drug, and a value greater than one a risk associated with drug treatment. For each combined incidence rate ratio calculated, the Mantel-Haenszel chi-square test showed no lack of homogeneity (i.e., indicating that data from the individual studies can be combined statistically).

**Table 3. Combined incidence rate ratios for suicide-related events and serious suicide-related events**

| Drug           | Number of pediatric trials | Incidence rate ratios* (95% confidence interval), by drug |                                |
|----------------|----------------------------|---|--------------------------------|
|                |                            | All suicide-related events                                | Serious suicide-related events |
| Paroxetine     | 5                          | 2.69 (1.20-6.00)  | 2.19 (0.92-5.24)               |
| Sertraline     | 2                          | 2.03 (0.51-8.16)  | 2.52 (0.49-13.01)              |
| Venlafaxine    | 4                          | 3.33 (1.08-10.33)   | 1.80 (0.52-6.20)               |
| Fluoxetine     | 4                          | 0.88 (0.34-2.30)  | 0.88 (0.32-2.44)               |
| Citalopram     | 2                          | 1.41 (0.66-3.00)  | 2.54 (0.91-7.05)               |
| Mirtazapine    | 1                          | 0.53 (0.007-41.45)  | †                              |
| Nefazodone     | 2                          | †   | †                              |
| Fluvoxamine    | 1                          | †   | †                              |
| MDD trials     | 14                         | 1.81 (1.19-2.77)  | 1.95 (1.19-3.21)               |
| Non-MDD trials | 7                          | 2.36 (0.67-8.33)  | 1.31 (0.26-6.72)               |
| All trials     | 21                         | 1.86 (1.25-2.78)  | 1.89 (1.18-3.04)               |

†Ratio undefined due to zero events in placebo group

\*Mantel-Haenszel method

It will be seen that the suicide-related event incidence rate ratios for venlafaxine and paroxetine indicate an association with drug treatment, and that the corresponding confidence intervals exclude one. Overall, the incidence rate ratio of approximately 1.9 for both suicide-related events and the subcategory of serious suicide-related events indicate an association of these events with drug treatment. Put another way, compared to placebo, treatment with active drug increased the rate of suicide-related events by an estimated 85%, and by an estimated 87% for serious suicide-related events. For the subgroup of MDD trials, the incidence rate ratios were also statistically significant, while for non-MDD trials the incidence rate ratio estimates had very wide confidence intervals.

## DISCUSSION AND CONCLUSIONS

In short-term pediatric trials, antidepressant drug treatment is associated with an increase in suicidal adverse events compared to placebo. This finding is seen for both the broad category of any suicide-related event, and the more specific category of serious suicide-related events. The association is more prominent in the MDD trial data, where the relative risk of serious suicide-related events is approximately 1.9. The rate of serious suicide-related events in MDD trials among drug-treated patients was 0.19/patient-year, and was 0.10/patient-year among placebo-treated patients. These rates represent one serious event per 5.4 patient-years for drug, and one serious event per 9.9 patient-years for placebo, yielding an attributable risk of one additional serious suicide-related event per 11.8 patient-years of drug treatment. The finding appears to be statistically robust, inasmuch as the p-value for the incidence rate difference for all suicide-related events across all trials is 0.002.

With respect to individual drugs, the data for paroxetine and venlafaxine show a statistically significant increase in suicide-related events with active treatment in their pediatric development programs. Also, the incidence rate difference for serious suicide-related events with citalopram was close to statistical significance (p-value = 0.063). For fluoxetine and mirtazapine, the point estimates were consistent with a protective effect, but the confidence intervals for mirtazapine were very broad, and even for fluoxetine the confidence interval on the incidence rate ratio includes a relative risk of greater than 2. Put another way, although an increase in suicide-related

events reached statistical significance for two drugs (paroxetine and venlafaxine), for no drug was a protective effect demonstrated at a statistically significant level.

This analysis has several limitations. Most importantly, it is limited to short-term trials only. Conceivably, long-term treatment in patients who have responded positively to a drug might not produce an increased risk, or might even provide a protective effect. In other words, it may not be appropriate to extrapolate a finding of a risk in short-term trials to use of the drug for long-term maintenance treatment, especially if the patients have manifested a clinical response to the drug. Unfortunately, there is very little long-term controlled pediatric trial data for antidepressant drugs that is available for analysis.

Another limitation of this analysis is that although there is evidence of a class effect overall, it is difficult to know to what extent it applies to particular members of the class. Inspection of the confidence intervals for the risk estimates will show that the confidence limits for individual drugs overlap considerably. The existing clinical trial data, moreover, cannot provide a fair comparison between drugs, since the sizes of the clinical development programs and the specific indications studied vary from drug to drug, not to mention the fact that the intrinsic pharmacologic and pharmacokinetic properties of the drugs themselves are different.

A third limitation pertains to the difficulties in standardizing the methodology used by the nine different sponsors. Although all sponsors were given the same set of instructions in the letters issued 7-22-03, there were some discrepancies in how these instructions were applied. For example, Forest (sponsor of citalopram) performed not only the requested electronic search of all adverse event terms, but also a manual search, which yielded cases not found with the electronic search. Also, the 30-day follow-up period was interpreted differently by GSK (paroxetine) and Wyeth (venlafaxine). GSK counted followed-up time for 30 days after the last dose of study medication, and the taper phase was not part of that 30-day period. However, Wyeth began the 30-day period from the last full dose of study medication, so that the period of dosage taper was included in the 30-day follow-up time. Also, Lilly (sponsor of fluoxetine) reported that adverse event data was not consistently collected once patients discontinued their study treatment.

As Appendix figures 1-4 illustrate, there was considerable variability in the rates of these events from trial to trial, even within the same indication. This could be due to differences in the patient population (some trials included children, for example), or to differences in ascertainment of suicide-related events, or to both. This, of course, raises questions about whether it is appropriate to combine the data from different trials. The Mantel-Haenszel chi square test for homogeneity of the rate ratios, however, did not reveal any statistically significant lack of homogeneity.

The increase in suicidal events was most clearly demonstrated in MDD trials. However, events with active drug treatment were more frequent than events with placebo in non-MDD trials, although the numbers are small and the risk estimates are very uncertain. Nonetheless, this leaves open the possibility of a drug-associated risk of such behaviors for non-MDD patients, although at a much lower incidence rate difference than for MDD patients.

With respect to clinical factors that might be contributory, as described in the previous consult, the paroxetine data suggested a possible role for drug withdrawal, but this pattern was not as prominent in the data for other drugs. However, this observation might point to a lack of consistency across development programs with respect to ascertainment of adverse events following the end of double-blind treatment.

The absence of completed suicides in these data is only reassuring to a limited degree. The total drug exposure time in these trials was 407 patient-years. For assessing the rate of a rare event such as completed suicide with active drug treatment, this is a relatively small data set. To illustrate, the upper confidence limit (one sided, 95% level) for the actual rate in the population given an observation of no suicides in 407 patient-years is 1 completed suicide in approximately 136 patient years.

In contrast to the paroxetine pediatric data, the analysis of suicide-related events in adult paroxetine trials, employing methods identical to the corresponding analysis of pediatric trial data, failed to show an increase in the rate of such events with paroxetine treatment relative to placebo. This was despite the fact that the placebo rate for these events was similar between the adult MDD trials (0.10/year) and the pediatric MDD trials (0.13/year). This suggests that adults and pediatric patients may have different responses to paroxetine with respect to suicidality.

Several steps are being taken at the moment to evaluate this signal further. First, a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee will be held 2-2-04 to discuss this issue.<sup>10</sup> Secondly, DNDP has requested electronic data sets from the sponsors of these clinical trials that will permit a more sophisticated statistical analysis. This analysis will permit examination of a number of issues that were beyond the scope of this consult, such as adjustment for a number of relevant covariates and exploration of risk factors such as agitation and relevant family history. Thirdly, DNDP has arranged for a group of suicidology experts at Columbia University to review the clinical narrative summaries for all of the identified cases; this will permit a more sophisticated case classification, particularly with regards to whether the event was a serious suicide attempt, a gesture, or self-mutilation. Fourthly, on 11-24-03 DNDP sent a memo to all the sponsors requesting a more detailed description of the methods each sponsor used to generate the submissions reviewed in this consult, to ensure the highest possible quality of data for review by the Columbia University experts.

One suggestion can be made for the expert group involved in the review of the cases. Because the nature and quality of the case reports received from the sponsors (as listed in Appendix Table 3) vary considerably, it is likely that even experts in classifying suicidal behaviors will have some uncertainty about how to classify some of the case reports. Accordingly, it will be important to reserve a category of indeterminate cases with which to do a sensitivity analysis. The principle here would be to do an analysis including the doubtful cases, and another analysis excluding them, to see if the results are very dependent upon how uncertain cases are classified.

These initiatives should indeed provide higher-quality data for evaluation of this signal. However, in my view, the new analyses are more likely to change the findings for individual studies and drug compounds where the numbers are relatively small, than they are to alter the overall finding of an increase in suicide-related adverse events and serious suicide-related events with active drug treatment compared to placebo. There are, I believe, several reasons for this. First, the aggregate findings are statistically robust (e.g.,  $p$ -value = 0.002). Secondly, the counts of serious suicide-related events are, in my view, less likely to be unstable, because of the methods routinely employed to account for serious adverse events in clinical trials, and the greater amount of clinical information that is often collected about serious adverse events compared to non-serious events. Additionally, to the extent that events have been misclassified or overlooked in the sponsor's searches, this would generally be expected to introduce "noise" that would weaken the signal and produce a false negative, not generate a false positive. Only a systematic bias that

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<sup>10</sup> Federal Register Vol. 68, No. 211 Friday, October 31, 2003

caused events in the placebo group to be missed while events in the drug group were captured would be expected to produce a false positive, and it is difficult to conceive of what could produce such a bias.

As previously noted, fluoxetine is currently the only drug approved for pediatric MDD, although several drugs are approved for pediatric OCD (see Appendix table 5). As shown in that table, all of the four pediatric OCD trials were positive and provided evidence of efficacy for approval of the drugs for pediatric OCD. This is in contrast to the experience with pediatric MDD trials, for which only 3 of the 15 trials have been judged positive, two with fluoxetine and one with citalopram.

In sum, short-term pediatric clinical trials of antidepressant drugs demonstrate an increased rate of suicidal events with active drug compared to placebo.

Recommendations: Given the strength of the association shown by the present data, the clinical importance of the apparent effect (i.e., an estimated excess of one additional serious suicide-related event per 12 patient-years of active treatment), and the fact that the additional analyses are likely to take several more months to complete while considerable numbers of pediatric patients are being exposed to these drugs, I favor an interim risk management plan regarding use of these drugs in the pediatric population. This might be of value to physicians, patients and families who are faced with the need to make a decision regarding pharmacotherapy at the present time. Specifically, I propose a risk management strategy directed at discouraging off-label pediatric use of antidepressant drugs, particularly the use of drugs other than fluoxetine in the treatment of pediatric MDD. Conceivably, this might include discouraging the initiation of treatment of drug-naïve pediatric MDD patients with off-label drugs, in the absence of some over-riding clinical consideration. (Of course, all such warnings should be made in a manner that emphasizes the fact that the available data apply only to short-term, acute treatment, and that sudden discontinuation of antidepressant treatment, or discontinuation without medical supervision, are unwise.)

I recommend this approach for two reasons. First, of all the drugs with pediatric MDD clinical trial programs, only fluoxetine is approved for pediatric MDD, on the basis of two positive clinical studies (out of two MDD studies conducted). Of course, the failure to demonstrate efficacy in pediatric MDD trials with other antidepressants does not necessarily mean that these other drugs are ineffective in pediatric MDD. Still, for drugs other than fluoxetine, judgement regarding their efficacy in pediatric MDD must remain a matter of speculation until further trials are conducted. Secondly, although the confidence limits are broad, fluoxetine is the drug for which the estimate of the relative risk of suicidal events appears most favorable.

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**Appendix Table 1. Summary of pediatric clinical trial data on suicidal adverse events**

| Drug               | Indication               | Study     | Drug        |               |                        |                                |                  | Placebo     |               |                        |                                |                  |
|--------------------|--------------------------|-----------|-------------|---------------|------------------------|--------------------------------|------------------|-------------|---------------|------------------------|--------------------------------|------------------|
|                    |                          |           | N           | Patient-years | Suicide-related events | Serious suicide-related Events | Suicide attempts | N           | Patient-years | Suicide-related events | Serious suicide-related events | Suicide attempts |
| Paroxetine*        | MDD                      | 329†      | 93          | 13            | 8                      | 7                              | 5                | 88          | 13            | 1                      | 1                              | 0                |
|                    | MDD                      | 377       | 181         | 41            | 9                      | 7                              | 8                | 95          | 21            | 4                      | 4                              | 4                |
|                    | MDD                      | 701       | 104         | 16            | 3                      | 3                              | 2                | 102         | 17            | 2                      | 1                              | 1                |
|                    | OCD                      | 704       | 99          | 19            | 1                      | 1                              | 0                | 107         | 22            | 0                      | 0                              | 0                |
|                    | SAD                      | 676       | 165         | 51            | 4                      | 0                              | 1                | 157         | 47            | 0                      | 0                              | 0                |
|                    | <i>Paroxetine Total</i>  |           |             | <i>642</i>    | <i>140</i>             | <i>25</i>                      | <i>18</i>        | <i>16</i>   | <i>549</i>    | <i>120</i>             | <i>7</i>                       | <i>6</i>         |
| Sertraline         | MDD                      | 1001/1017 | 189         | 32.2          | 6                      | 5                              | 3                | 184         | 32.5          | 2                      | 2                              | 2                |
|                    | OCD                      | 498       | 92          | 18.8          | 0                      | 0                              | 0                | 95          | 19.7          | 1                      | 0                              | 0                |
|                    | <i>Sertraline Total</i>  |           |             | <i>281</i>    | <i>51</i>              | <i>6</i>                       | <i>5</i>         | <i>3</i>    | <i>279</i>    | <i>52.2</i>            | <i>3</i>                       | <i>2</i>         |
| Venlafaxine        | MDD                      | 382       | 80          | 11.01         | 5                      | 3                              | 1                | 85          | 11.73         | 3                      | 3                              | 3                |
|                    | MDD                      | 394       | 102         | 15.95         | 7                      | 3                              | 3                | 94          | 15.47         | 0                      | 0                              | 0                |
|                    | GAD                      | 396       | 80          | 13.08         | 0                      | 0                              | 0                | 84          | 13.56         | 0                      | 0                              | 0                |
|                    | GAD                      | 397       | 77          | 11.63         | 1                      | 1                              | 1                | 79          | 11.44         | 1                      | 1                              | 1                |
|                    | <i>Venlafaxine Total</i> |           |             | <i>339</i>    | <i>51.67</i>           | <i>13</i>                      | <i>7</i>         | <i>5</i>    | <i>342</i>    | <i>52.2</i>            | <i>4</i>                       | <i>4</i>         |
| Fluvoxamine        | OCD                      | 114       | 57          | 9.37          | 1                      | 0                              | 0                | 63          | 9.95          | 0                      | 0                              | 0                |
| Mirtazapine        | MDD                      | 003-045   | 170         | 24.05         | 1                      | 1                              | 0                | 88          | 12.7          | 1                      | 0                              | 1                |
| Fluoxetine         | MDD                      | HCJE      | 109         | 31.57         | 4                      | 3                              | 1                | 110         | 27.96         | 4                      | 3                              | 2                |
|                    | MDD                      | HCCJ      | 21          | 2.11          | 1                      | 1                              | 1                | 19          | 2.11          | 1                      | 1                              | 1                |
|                    | MDD                      | X065      | 48          | 6.71          | 2                      | 2                              | 2                | 48          | 5.83          | 2                      | 2                              | 0                |
|                    | OCD                      | HCJW      | 71          | 15.12         | 2                      | 2                              | 2                | 32          | 5.98          | 1                      | 1                              | 1                |
|                    | <i>Fluoxetine Total</i>  |           |             | <i>249</i>    | <i>55.51</i>           | <i>9</i>                       | <i>8</i>         | <i>6</i>    | <i>209</i>    | <i>41.88</i>           | <i>8</i>                       | <i>7</i>         |
| Nefazodone         | MDD                      | 141       | 95          | 13.6          | 1                      | 0                              | 1                | 95          | 12.5          | 0                      | 0                              | 0                |
|                    | MDD                      | 187       | 184         | 25.4          | 1                      | 1                              | 1                | 94          | 12.9          | 0                      | 0                              | 0                |
|                    | <i>Nefazodone Total</i>  |           |             | <i>279</i>    | <i>39</i>              | <i>2</i>                       | <i>1</i>         | <i>2</i>    | <i>189</i>    | <i>25.4</i>            | <i>0</i>                       | <i>0</i>         |
| Citalopram         | MDD                      | CIT-MD-18 | 89          | 12.8          | 1                      | 0                              | 1                | 85          | 12            | 2                      | 0                              | 1                |
|                    | MDD                      | 94404     | 121         | 23.5          | 16                     | 14                             | 16               | 112         | 21.3          | 9                      | 5                              | 9                |
|                    | <i>Citalopram Total</i>  |           |             | <i>210</i>    | <i>36.3</i>            | <i>17</i>                      | <i>14</i>        | <i>17</i>   | <i>197</i>    | <i>33.3</i>            | <i>11</i>                      | <i>5</i>         |
| Bupropion          | ADHD                     | 75        | 71          | **            | 0                      | 0                              | 0                | 36          | **            | 0                      | 0                              | 0                |
| <b>Grand Total</b> |                          |           | <b>2298</b> | <b>406.9</b>  | <b>74</b>              | <b>54</b>                      | <b>49</b>        | <b>1952</b> | <b>347.63</b> | <b>34</b>              | <b>24</b>                      | <b>26</b>        |

\*Paroxetine patient-years of exposure were provided only to the nearest integer \*\*Patient-years of exposure data were not provided †Imipramine arm omitted

**Appendix Table 2. Rates of suicidal adverse events, per patient-year, in pediatric clinical trials**

| Drug        | Indication | Study     | Drug          |                                |  |                          | Placebo       |                                |  |                          |
|-------------|------------|-----------|---------------|--------------------------------|--|--------------------------|---------------|--------------------------------|--|--------------------------|
|             |            |           | Patient-years | Rate of Suicide-related events | Rate of Serious suicide-related Events | Rate of Suicide attempts | Patient-years | Rate of Suicide-related events | Rate of Serious suicide-related events | Rate of Suicide attempts |
| Paroxetine  | MDD        | 329       | 13            | 0.62                           | 0.54                                   | 0.38                     | 13            | 0.08                           | 0.00                                   | 0.08                     |
|             | MDD        | 377       | 41            | 0.22                           | 0.17                                   | 0.20                     | 21            | 0.19                           | 0.19                                   | 0.19                     |
|             | MDD        | 701       | 16            | 0.19                           | 0.19                                   | 0.13                     | 17            | 0.12                           | 0.06                                   | 0.06                     |
|             | OCD        | 704       | 19            | 0.05                           | 0.05                                   | 0.00                     | 22            | 0.00                           | 0.00                                   | 0.00                     |
|             | SAD        | 676       | 51            | 0.08                           | 0.00                                   | 0.02                     | 47            | 0.00                           | 0.00                                   | 0.00                     |
| Sertraline  | MDD        | 1001/1017 | 32.2          | 0.19                           | 0.16                                   | 0.09                     | 32.5          | 0.06                           | 0.06                                   | 0.06                     |
|             | OCD        | 498       | 18.8          | 0.00                           | 0.00                                   | 0.00                     | 19.7          | 0.05                           | 0.00                                   | 0.00                     |
| Venlafaxine | MDD        | 382       | 11.01         | 0.45                           | 0.27                                   | 0.09                     | 11.73         | 0.26                           | 0.26                                   | 0.26                     |
|             | MDD        | 394       | 15.95         | 0.44                           | 0.19                                   | 0.19                     | 15.47         | 0.00                           | 0.00                                   | 0.00                     |
|             | GAD        | 396       | 13.08         | 0.00                           | 0.00                                   | 0.00                     | 13.56         | 0.00                           | 0.00                                   | 0.00                     |
|             | GAD        | 397       | 11.63         | 0.09                           | 0.09                                   | 0.09                     | 11.44         | 0.09                           | 0.09                                   | 0.09                     |
| Fluvoxamine | OCD        | 114       | 9.37          | 0.11                           | 0.00                                   | 0.00                     | 9.95          | 0.00                           | 0.00                                   | 0.00                     |
| Mirtazapine | MDD        | 003-045   | 24.05         | 0.04                           | 0.04                                   | 0.00                     | 12.7          | 0.08                           | 0.08                                   | 0.00                     |
| Fluoxetine  | MDD        | HCJE      | 31.57         | 0.13                           | 0.10                                   | 0.03                     | 27.96         | 0.14                           | 0.07                                   | 0.11                     |
|             | MDD        | HCCJ      | 2.11          | 0.47                           | 0.47                                   | 0.47                     | 2.11          | 0.47                           | 0.47                                   | 0.47                     |
|             | MDD        | X065      | 6.71          | 0.30                           | 0.30                                   | 0.30                     | 5.83          | 0.34                           | 0.34                                   | 0.00                     |
|             | OCD        | HCJW      | 15.12         | 0.13                           | 0.13                                   | 0.13                     | 5.98          | 0.17                           | 0.17                                   | 0.17                     |
| Nefazodone  | MDD        | 141       | 13.6          | 0.07                           | 0.00                                   | 0.07                     | 12.5          | 0.00                           | 0.00                                   | 0.00                     |
|             | MDD        | 187       | 25.4          | 0.04                           | 0.04                                   | 0.04                     | 12.9          | 0.00                           | 0.00                                   | 0.00                     |
| Citalopram  | MDD        | CIT-MD-18 | 12.8          | 0.08                           | 0.00                                   | 0.08                     | 12            | 0.17                           | 0.08                                   | 0.00                     |
|             | MDD        | 94404     | 23.5          | 0.68                           | 0.60                                   | 0.68                     | 21.3          | 0.42                           | 0.42                                   | 0.23                     |
| Total       |            |           | 406.9         | 0.18                           | 0.13                                   | 0.12                     | 347.63        | 0.10                           | 0.07                                   | 0.07                     |

**Appendix Table 3. Listing of all patients with suicide-related events in pediatric antidepressant drug trials.**

**MIRTAZAPINE**

| Study   | Indication | Patient ID | Age Sex | Treatment   | Dose (mg/day) at time of event | Duration (days) | Event                                 | Serious (y/n) | Comments                   |
|---------|------------|------------|---------|-------------|--------------------------------|-----------------|---------------------------------------|---------------|----------------------------|
| 003-045 | MDD        | 0404       | 15 M    | Mirtazapine | 15                             | 7               | Hospitalization for suicidal ideation | Y             |                            |
| 003-045 | MDD        | 0801       | 9 M     | Mirtazapine | 45                             | 52              | Depakote overdose "on a dare"         | Y             | <i>Excluded by sponsor</i> |
| 003-045 | MDD        | 1603       | 12 F    | Placebo     | -                              | 56              | Self inflicted cuts                   | N             |                            |

**FLUOXETINE**

| Study | Indication | Patient ID | Age Sex | Treatment  | Dose (mg/day) at time of event | Duration (days) | Event  | Serious (y/n) | Comments  |
|-------|------------|------------|---------|------------|--------------------------------|-----------------|--|---------------|---|
| HCCJ  | MDD        | 001/6401   | 17 F    | Fluoxetine | 30                             | 40              | Overdose, details unknown; discontinued from trial     | y             | Patient poorly compliant with study drug                                |
| HCCJ  | MDD        | 001-6408   | 13 M    | Placebo    | -                              | 33              | Overdose of aspirin                                    | y             |   |
| HCJE  | MDD        | 008-0806   | 15 M    | Placebo    | -                              | 37              | Hospitalized for suicidal ideation and self-mutilation | y             |   |
| HCJE  | MDD        | 008/0804   | 15 F    | Placebo    | -                              | 60              | Overdose on study medication                           | y             |   |
| HCJE  | MDD        | 009-0901   | 15 F    | Fluoxetine | 60                             | 101             | Self-mutilation  | n             |   |
| HCJW  | OCD        | 006-0609   | 15 F    | Placebo    | -                              | 71              | Self-injurious behavior                                | Y             | No details provided   |
| HCJW  | OCD        | 013-1300   | 12 F    | Fluoxetine | 20                             | 25              | Tylenol overdose                                       | Y             | Hospitalized  |
| HCJW  | OCD        | 018-1811   | 7 F     | Fluoxetine | 20                             | 60              | Self-destructive cutting                               | y             |   |
| X065  | MDD        | 001-2051   | 16 F    | Fluoxetine | 20                             | 14              | Multiple drug overdose                                 | Y             | Other adverse events included manic reaction                            |
| X065  | MDD        | 001-2163   | 17 F    | Fluoxetine | 20                             | 12              | Overdose on unknown pills                              | Y             | No psychiatric family history, no previous attempts                     |
| HCJE  | MDD        | 004-0419   | 13 F    | Fluoxetine | 20                             | 67              | Hospitalized for suicidal ideation                     | Y             |   |
| HCJE  | MDD        | 022-2216   | 15 F    | Fluoxetine | 20                             | 38              | Suicidal ideation                                      | Y             |   |
| HCJE  | MDD        | 003-0302   | 17 F    | Fluoxetine | 20                             | 32              | Suicidal thoughts                                      | y             |   |
| HCJE  | MDD        | 019-1901   | 11 F    | Placebo    | -                              | ?               | "wanting to die"                                       | N             |   |
| HCJE  | MDD        | 022-2203   | 9 M     | Placebo    | -                              | 9               | Suicidal ideation, intermittent                        | Y             | Displayed self-injurious behavior during later extension phase of trial |
| X065  | MDD        | 001-2052   | 16 M    | Placebo    | -                              | 33              | Suicidal ideation X 1 day (not hospitalized)           | Y             | Considered serious  |
| X065  | MDD        | 001-2087   | 14 F    | Placebo    | -                              | 6               | Hospitalized for suicidal ideation                     | y             |   |

## NEFAZODONE

| Study | Indication | Patient ID | Age Sex | Treatment  | Dose (mg/day) at time of event | Duration        | Event                                      | Serious (y/n) | Comments     |
|-------|------------|------------|---------|------------|--------------------------------|-----------------|--|---------------|--------------|
| 141   | MDD        | 3-1065     | 12 M    | Nefazodone | 600                            | 38              | Self mutilation (superficial cutting)      | n             |              |
| 187   | MDD        | 18-322     | 13 F    | Nefazodone | 0                              | 4 days post d/c | Overdose on 14 tablets of study medication | y             | Hospitalized |

## FLUVOXAMINE

| Study     | Indication | Patient ID | Age Sex | Treatment   | Dose (mg/day) at time of event | Duration (days) | Event             | Serious (y/n) | Comments  |
|-----------|------------|------------|---------|-------------|--------------------------------|-----------------|-------------------|---------------|---|
| RH1140201 | OCD        | 65815      | 15 M    | Fluvoxamine | 200                            | 36              | Suicidal ideation | N             | Self-mutilation during open label extension phase |

## SERTRALINE

| Study | Indication | Patient ID | Age Sex | Treatment  | Dose (mg/day) at time of event | Duration (days) | Event  | Serious (y/n) | Comments  |
|-------|------------|------------|---------|------------|--------------------------------|-----------------|--|---------------|---|
| 498   | OCD        | 90N0242-19 | 12 F    | Placebo    | -                              | 12              | Suicidal ideation                                  | N             |   |
| 1001  | MDD        | 29533-2006 | 12 M    | Sertraline | 100                            | 49              | Suicidal ideation                                  | y             | Hospitalized  |
| 1001  | MDD        | 29534-1089 | 10 F    | Sertraline | 100                            | 35              | Suicidal ideation                                  | Y             | Hospitalized  |
| 1001  | MDD        | 30506-1076 | 9 F     | Sertraline | 100                            | 37              | Self mutilation                                    | n             | Second episode of self mutilation on day 46         |
| 1001  | MDD        | 6193-1022  | 10 M    | Sertraline | 100                            | 21              | Suicidal ideation                                  | Y             | Hospitalized. Also had mild agitation.              |
| 1017  | MDD        | 29384-4022 | 16 F    | Sertraline | 150                            | 50              | Multidrug overdose                                 | Y             | Also noted to have restlessness                     |
| 1017  | MDD        | 30627-3095 | 6 M     | Sertraline | 100                            | 34              | Threatened to jump from vehicle, suicidal ideation | Y             | Hospitalized; also experienced agitation            |
| 1017  | MDD        | 31940-4329 | 17 F    | Placebo    | -                              | 9               | Attempted self-immolation                          | Y             | Minor burn wounds. Subject later denied suicidality |
| 1017  | MDD        | 31942-4321 | 15 F    | Placebo    | -                              | 63              | Attempted suicide by hanging                       | Y             | Second suicide attempt by overdose on day 66        |

CITALOPRAM

| Study     | Indication | Pt ID | Age Sex | Treatment  | Dose (mg/day) at time of event | Duration (days) | Event  | Serious (y/n) | Comments   |
|-----------|------------|-------|---------|------------|--------------------------------|-----------------|--|---------------|--|
| CIT-MD-18 | MDD        | 193   | 9 M     | Citalopram | 20                             | 37              | Cut self with knife  | N             | Agitation reported on previous day   |
| CIT-MD-18 | MDD        | 137   | 10 M    | Placebo    | -                              | 31              | Attempted to hang self (but not designated as a serious event)                 | N             | Personality disorder; 24 days post-tx had another suicide-related event                                |
| CIT-MD-18 | MDD        | 519   | 12 F    | Placebo    | -                              | 41              | Severe suicidal tendency (no details)  | N             |  |
| 94404     | MDD        | 007   | 15 M    | Citalopram | -                              | 25 days post tx | Multiple drug overdose   | Y             | <i>Patient had received fluoxetine X 25 days since completing trial</i>                                |
| 94404     | MDD        | 009   | 17 F    | Citalopram | 20                             | 15              | Hospitalized for suicidality; overdose on naproxen on day 6 of hospitalization | Y             |  |
| 94404     | MDD        | 121   | 18 F    | Citalopram | -                              | 12 days post tx | Overdose of chlorzaxone  | Y             | Patient had been discontinued from study on day 8 because of abnl clinical laboratories                |
| 94404     | MDD        | 148   | 17 F    | Citalopram | 20                             | 47              | Overdose of 4-6 citalopram tablets   | Y             | Made a second overdose later in trial  |
| 94404     | MDD        | 426   | 14 F    | Citalopram | 20                             | 70              | Overdose on 11 paracetamol tablets; denied suicidal intent                     | Y             | Event coded as medication error  |
| 94404     | MDD        | 573   | 14 F    | Citalopram | 20                             | 88              | Intentional ingestion of cigarettes  | Y             | Subject was an inpatient at screening  |
| 94404     | MDD        | 575   | 14 F    | Citalopram | 20                             | 55              | Suicidal ideation, cut arm   | Y             | Subject was an inpatient at screening  |
| 94404     | MDD        | 664   | 15 M    | Citalopram | 20                             | 10              | Re-hospitalized for suicidality  | Y             | Subject was an inpatient at screening  |
| 94404     | MDD        | 713   | 16 M    | Citalopram | 30                             | 27              | Re-hospitalized for suicidality  | N             | Subject was an inpatient at screening. No explanation for why this was not designated a serious event. |
| 94404     | MDD        | 715   | 17 F    | Citalopram | 20                             | 14              | Hospitalized for suicidality, cut wrists, denied suicidal intent               | Y             |  |
| 94404     | MDD        | 729   | 16 M    | Citalopram | 10                             | 63              | Ingested 15 caffeine pills plus alcohol  | N             | Event coded as medication error  |
| 94404     | MDD        | 761   | 13 M    | Citalopram | -                              | 1 day post tx   | Hospitalized for suicidality, event designated as a suicide attempt            | Y             | Also developed agitation, mood lability  |
| 94404     | MDD        | 776   | 17 F    | Citalopram | -                              | 1 day post tx   | Multiple drug overdose; only dose of study medication was the previous day     | Y             | Subject was an inpatient at screening. Also experienced anxiety  |
| 94404     | MDD        | 867   | 17 F    | Citalopram | 30                             | 20              | Hospitalization due to suicidal thoughts                                       | Y             | Also experienced anxiety   |
| 94404     | MDD        | 874   | 17 f    | Citalopram | 20                             | 13              | Overdose   | Y             | Patient cut her wrist 4 days after overdose  |
| 94404     | MDD        | 884   | 16 F    | Citalopram | 20                             | 16              | Hospitalized after overdose on diazepam (9 tablets)                            | Y             | On day 22, re-hospitalized for suicidality, and on day 81, another overdose                            |
| 94404     | MDD        | 071   | 16 F    | Placebo    | -                              | 16              | Hospitalized after self-inflicted wrist laceration                             | Y             | Re-hospitalized for suicidality on day 36  |
| 94404     | MDD        | 152   | 14 F    | Placebo    | -                              | 8 days post tx  | Hospitalized for suicidality   | Y             | Treated with citalopram after hospitalization  |
| 94404     | MDD        | 412   | 18 F    | Placebo    | -                              | 1 day post tx   | Overdose on mother's medication  | Y             | Also receiving oxazepam for anxiety  |

| Study | Indication | Pt ID | Age Sex | Treatment | Dose (mg/day) at time of event | Duration (days) | Event   | Serious (y/n) | Comments  |
|-------|------------|-------|---------|-----------|--------------------------------|-----------------|---|---------------|---|
| 94404 | MDD        | 605   | 13 M    | Placebo   | -                              | 35              | Self mutilation (forearm)                             | N             |   |
| 94404 | MDD        | 607   | 17 M    | Placebo   | -                              | 62              | Suicidal ideation and tension, treated with lorazepam | N             | Inpatient at screening.   |
| 94404 | MDD        | 691   | 17 F    | Placebo   | -                              | 29              | Self mutilation (palms)                               | N             |   |
| 94404 | MDD        | 693   | 16 F    | Placebo   | -                              | 2               | Hospitalized for suicidal ideation                    | Y             | Later in trial had self-inflicted scratches on arm. After completing trial, started citalopram and was re-hospitalized for suicidal ideation 8 days later |
| 94404 | MDD        | 787   | 13 F    | Placebo   | -                              | 29              | Self-mutilation                                       | N             |   |
| 94404 | MDD        | 871   | 17 F    | Placebo   | -                              | 25              | Overdose on 8 tablets of tolfenamic acid              | Y             |   |

PAROXETINE (Sources: 6-16-03 submission and Excel spreadsheet courtesy of Dr. Judith Racoosin, Division of Neuropharmacological Drug Products)

| Study | Indication | Pt ID       | A<br>G<br>e | S<br>E<br>x | Treatment  | Dose (mg/day) at time of event | Duration (days) | Event  | Serious (y/n) | Comments   |
|-------|------------|-------------|-------------|-------------|------------|--------------------------------|-----------------|--|---------------|--|
| 329   | MDD        | 32900300313 | 18          | M           | Paroxetine | 20                             | 11              | Command hallucinations, self mutilation                                      | Y             | Hospitalized   |
| 329   | MDD        | 32900400015 | 16          | F           | Paroxetine | 20                             | 31              | Mild self mutilation   | N             |  |
| 329   | MDD        | 32900600038 | 15          | F           | Paroxetine | 20                             | 57              | Multiple drug overdose   | Y             |  |
| 329   | MDD        | 32900200245 | 14          | F           | Paroxetine | 20                             | 13              | Acetaminophen overdose (27-28 capsules)                                      | Y             | Treated in emergency room and released   |
| 329   | MDD        | 32900500250 | 15          | F           | Paroxetine | 30                             | 28              | Overcompliance (by 124%) with study medication                               | Y             | Coded as "overdose intentional." (Same patient subsequently overdosed on 20 capsules of study medication during continuation treatment.) |
| 329   | MDD        | 32900100065 | 14          | M           | Paroxetine | 20                             | 13              | Angry outburst (with destruction of property) followed by suicidal thoughts  | Y             |  |
| 329   | MDD        | 32900500333 | 16          | F           | Paroxetine | 20                             | +4 post study   | Hospitalized for severe suicidal ideation                                    | Y             |  |
| 329   | MDD        | 32900200106 | 15          | F           | Paroxetine | 40                             | 51              | Combative with mother, threatened suicide                                    | Y             | Hospitalized   |
| 377   | MDD        | 37701100061 | 17          | F           | Paroxetine | 40                             | 75              | Overdose (28 tablets of study medication)                                    | Y             | Hospitalized   |
| 377   | MDD        | 37702400158 | 14          | F           | Paroxetine | 30                             | 86              | Slapping herself in the face (automutilation)                                | N             |  |
| 377   | MDD        | 37702300172 | 16          | M           | Paroxetine | 30                             | 38              | Overdose on 5 gm paracetamol plus 600 mg aspirin                             | N             | Considered a non-serious event by investigator   |
| 377   | MDD        | 37703000181 | 18          | F           | Paroxetine | 40                             | 56              | Hostility, depression, writing suicide notes; possible drug abuse (cannabis) | Y             | Hospitalized   |
| 377   | MDD        | 37700900225 | 17          | F           | Paroxetine | 20                             | 78              | Overdose on study medication   | Y             | Hospitalized   |
| 377   | MDD        | 37704200310 | 15          | F           | Paroxetine | 20                             | 23              | Self-inflicted wrist lacerations, superficial                                | Y             |  |

| Study | Indication | Pt ID       | Age | Sex | Treatment  | Dose (mg/day) at time of event | Duration (days) | Event   | Serious (y/n) | Comments                                    |
|-------|------------|-------------|-----|-----|------------|--------------------------------|-----------------|---|---------------|---|
| 377   | MDD        | 37705300508 | 14  | F   | Paroxetine | 20                             | 54              | Cut left wrist after arguing with mother                                  | Y             |   |
| 377   | MDD        | 37704200315 | 15  | F   | Paroxetine | 20                             | +4 post study   | Overdose on 5 acetaminophen pills and two other pills, agitation, anxiety | Y             | Hospitalized                                |
| 377   | MDD        | 37704900479 | 17  | M   | Paroxetine | 40                             | +2 post study   | Suicidal ideation, irritability   | Y             | Hospitalized                                |
| 676   | SAD        | 67601124283 | 15  | M   | Paroxetine | 30                             | +1 post study   | Vague suicidal ideation   | N             |   |
| 676   | SAD        | 67601424376 | 13  | F   | Paroxetine | 40                             | 34              | Worsening panic attacks, suicidal ideation                                | N             |   |
| 676   | SAD        | 67610024705 | 16  | F   | Paroxetine | 20                             | 43              | Self-inflicted scratch on wrist   | N             |   |
| 676   | SAD        | 67610124629 | 14  | F   | Paroxetine | 40                             | 99              | Threatened suicide when brother hospitalized                              | N             |   |
| 701   | MDD        | 70116325718 | 16  | F   | Paroxetine | 50                             | 41              | Patient reported taking an overdose of 100 paroxetine tablets             | Y             | Overdose not confirmed by urine drug screen |
| 701   | MDD        | 70118025639 | 15  | F   | Paroxetine | 30                             | +2 post study   | Cut arms, overdose on acetaminophen                                       | Y             | Required ICU admission                      |
| 701   | MDD        | 70118327620 | 11  | F   | Paroxetine | 20                             | +4 post study   | Threatened to hang self   | Y             | Hospitalized                                |
| 704   | OCD        | 70403325513 | 15  | M   | Paroxetine | 40                             | 25              | Hospitalization due to suicidal thoughts                                  | Y             |   |
| 329   | MDD        | 32900100123 | 16  | F   | Placebo    | -                              | 45              | Worsening depression, suicidal thoughts                                   | Y             |   |
| 377   | MDD        | 37700500231 | 14  | F   | Placebo    | -                              | 31              | Overdose of study medication and chlorazepate                             | Y             |   |
| 377   | MDD        | 37701000068 | 14  | F   | Placebo    | -                              | 83              | Overdose on 21 alprazolam tablets   | Y             | Hospitalized                                |
| 377   | MDD        | 37702900024 | 17  | F   | Placebo    | -                              | 29              | Tried to kill herself with scissors                                       | Y             | Details not provided                        |
| 377   | MDD        | 37704100294 | 14  | F   | Placebo    | -                              | 84              | Overdose on 10 gm of acetaminophen  | Y             | Hospitalized                                |
| 701   | MDD        | 70115425768 | 13  | M   | Placebo    | -                              | 5               | Wrecked parent's car and became suicidal                                  | Y             | Hospitalized                                |
| 701   | MDD        | 70118327617 | 12  | F   | Placebo    | -                              | 3               | Mild self-mutilation of arms  | N             |   |

#### VENLAFAXINE

| Study | Indication | Pt ID     | Age | Sex | Treatment      | Dose (mg/day) | Duration (days) | Event                                      | Serious (y/n) | Comments   |
|-------|------------|-----------|-----|-----|----------------|---------------|-----------------|--|---------------|--|
| 382   | MDD        | 38202-036 | 13  | F   | Placebo        | -             | +18 post tx     | Angry, kicked a cabinet                    | Y             | Resulted in ER visit                                       |
| 382   | MDD        | 38204-023 | 11  | F   | venlafaxine ER | 112.5         | 21              | Suicidal ideation                          | N             |  |
| 382   | MDD        | 38205-008 | 12  | M   | venlafaxine ER | 75            | 29              | Suicidal ideation, auditory hallucinations | Y             | Hospitalized   |
| 382   | MDD        | 38205-019 | 8   | F   | venlafaxine ER | NA            | 13              | Overdose on venlafaxine 300 mg             | Y             | Hospitalized   |
| 382   | MDD        | 38207-008 | 12  | M   | Placebo        | -             | +17 post tx     | Suicidal ideation, scratching on arms      | Y             | Hospitalized   |
| 382   | MDD        | 38207-023 | 14  | F   | Placebo        | -             | 3               | Overdose on study medication (~8 capsules) | Y             | Treated at ER and released                                 |
| 382   | MDD        | 38209-020 | 13  | F   | venlafaxine ER | 37.5          | 13              | Suicidal ideation with plan to overdose    | Y             | Hospitalized   |
| 382   | MDD        | 38211-012 | 10  | F   | venlafaxine ER | 112.5         | 23              | Mild self-injurious behavior               | N             | On day 43 of trial, hospitalized for swallowing aftershave |

|     |     |            |    |   |                |      |            |  |   |   |
|-----|-----|------------|----|---|----------------|------|------------|--|---|---|
| 394 | MDD | 39402-0041 | 7  | M | venlafaxine ER | 75   | 25 and 29  | Suicidal ideation, plan to stab self                                     | Y | Hospitalized (considered 2 events by sponsor)                               |
| 394 | MDD | 39404-0126 | 14 | M | venlafaxine ER | 75   | 15         | Suicidal and homicidal ideation  | Y | Hospitalized  |
| 394 | MDD | 39411-0405 | 14 | F | venlafaxine ER | 150  | 51         | Cut arm in context of family discord                                     | N | Treated at ER and released  |
| 394 | MDD | 39420-0769 | 13 | M | venlafaxine ER | 225  | 36         | Mild suicidal ideation   | N |   |
| 394 | MDD | 39428-1087 | 16 | M | venlafaxine ER | 150  | 47 and 50  | Rage attack, suicidal, homicidal   | Y | Hospitalized; drug screen positive for PCP (considered 2 events by sponsor) |
| 394 | MDD | 39435-1366 | 17 | F | venlafaxine ER | 37.5 | 5          | Mild self-mutilation   | N |   |
| 394 | MDD | 39440-1561 | 12 | F | venlafaxine ER | -    | +6 post tx | Overdose on study medication (17 capsules)                               | N | Treated at ER and released. Not considered a serious event                  |
| 397 | GAD | 39701-0012 | 17 | F | Placebo        | -    | 15         | Overdose of 18 Excedrin PM tablets following fight with boyfriend        | Y | Hospitalized  |
| 397 | GAD | 39710-0361 | 10 | M | venlafaxine ER | -    | +3 post tx | Suicidal (wrapped cord around neck), agitated, and physically aggressive | Y | Hospitalized  |

BUPROPION No cases



Appendix table 4. Stata outputs for calculation of combined incidence rate ratios

Category: Suicide-related events

| Study        | IRR      | [95% Conf. Interval] |          | M-H Weight |         |
|--------------|----------|----------------------|----------|------------|---------|
| 003-045      | .5281385 | .0067291             | 41.45135 | .6543909   | (exact) |
| 1001/1017    | 3.028078 | .5414406             | 30.67137 | .9953421   | (exact) |
| 114          | .        | .0272237             | .        | 0          | (exact) |
| 141          | .        | .0235638             | .        | 0          | (exact) |
| 187          | .        | .0130205             | .        | 0          | (exact) |
| 329          | 8        | 1.072641             | 354.959  | .5         | (exact) |
| 377          | 1.152439 | .3216551             | 5.121634 | 2.645161   | (exact) |
| 382          | 1.775317 | .3454063             | 11.43182 | 1.452651   | (exact) |
| 394          | .        | 1.39804              | .        | 0          | (exact) |
| 396          | .        | .                    | .        | 0          | (exact) |
| 397          | .9837456 | .0125341             | 77.21001 | .5040969   | (exact) |
| 498          | 0        | 0                    | 40.8801  | .4882943   | (exact) |
| 676          | .        | .6083716             | .        | 0          | (exact) |
| 701          | 1.59375  | .1825649             | 19.08565 | .969697    | (exact) |
| 704          | .        | .0296822             | .        | 0          | (exact) |
| 94404        | 1.611357 | .6704749             | 4.137106 | 4.720969   | (exact) |
| CIT-MD-18    | .46875   | .0079441             | 9.004248 | 1.032258   | (exact) |
| HCCJ         | 1        | .0127412             | 78.48575 | .5         | (exact) |
| HCJE         | .8856201 | .1649537             | 4.754807 | 2.121318   | (exact) |
| HCJW         | .7910853 | .0411829             | 46.67882 | .7165671   | (exact) |
| X065         | .8689261 | .0629945             | 11.98569 | 1.070133   | (exact) |
| Crude        | 1.859448 | 1.223071             | 2.879198 |            | (exact) |
| M-H combined | 1.863115 | 1.246773             | 2.784147 |            |         |

Test of homogeneity (M-H) chi2(13) = 7.67 Pr>chi2 = 0.8642

Category: Serious suicide-related events

| Study        | IRR      | [95% Conf. Interval] |          | M-H Weight |         |
|--------------|----------|----------------------|----------|------------|---------|
| 003-045      | .        | .0135386             | .        | 0          | (exact) |
| 1001/1017    | 2.523398 | .4131554             | 26.50048 | .9953421   | (exact) |
| 114          | .        | .                    | .        | 0          | (exact) |
| 141          | .        | .                    | .        | 0          | (exact) |
| 187          | .        | .0130205             | .        | 0          | (exact) |
| 329          | 7        | .8993189             | 315.599  | .5         | (exact) |
| 377          | .8963415 | .2278526             | 4.175488 | 2.645161   | (exact) |
| 382          | 1.06519  | .1426495             | 7.953972 | 1.452651   | (exact) |
| 394          | .        | .4008445             | .        | 0          | (exact) |
| 396          | .        | .                    | .        | 0          | (exact) |
| 397          | .9837456 | .0125341             | 77.21001 | .5040969   | (exact) |
| 498          | .        | .                    | .        | 0          | (exact) |
| 676          | .        | .                    | .        | 0          | (exact) |
| 701          | 3.1875   | .2559633             | 167.3341 | .4848485   | (exact) |
| 704          | .        | .0296822             | .        | 0          | (exact) |
| 94404        | 2.537888 | .8637632             | 9.002482 | 2.62276    | (exact) |
| CIT-MD-18    | .        | .                    | .        | 0          | (exact) |
| HCCJ         | 1        | .0127412             | 78.48575 | .5         | (exact) |
| HCJE         | .8856201 | .1186016             | 6.613087 | 1.590989   | (exact) |
| HCJW         | .7910853 | .0411829             | 46.67882 | .7165671   | (exact) |
| X065         | .8689261 | .0629945             | 11.98569 | 1.070133   | (exact) |
| Crude        | 1.922267 | 1.168124             | 3.25143  |            | (exact) |
| M-H combined | 1.890265 | 1.175603             | 3.039376 |            |         |

Test of homogeneity (M-H) chi2(10) = 6.44 Pr>chi2 = 0.7768

**Appendix table 5. Summary of efficacy findings from eight pediatric antidepressant development programs**

| Drug        | Indication | Approval status for pediatric use* | Study     | N    |         | Efficacy results on primary variable                                |
|-------------|------------|------------------------------------|-----------|------|---------|---|
|             |            |                                    |           | Drug | Placebo |   |
| Paroxetine  | MDD        | NA                                 | 329       | 93   | 88      | Failed (but + on secondary variables)                               |
|             |            |                                    | 377       | 181  | 95      | Failed  |
|             |            |                                    | 701       | 104  | 102     | Failed  |
|             | OCD        | AE                                 | 704       | 99   | 107     | +   |
|             | SAD        | Not submitted                      | 676       | 165  | 157     | ? (not submitted)   |
| Sertraline  | MDD        | NA                                 | 1001/1017 | 189  | 184     | Two studies under same protocol, both failed (but + if data pooled) |
|             | OCD        | AP                                 | 498       | 92   | 95      | +   |
| Venlafaxine | MDD        | NA                                 | 382       | 80   | 85      | Failed  |
|             |            |                                    | 394       | 102  | 94      | Failed  |
|             | GAD        | NA                                 | 396       | 80   | 84      | Failed, by a small margin (p=0.09)                                  |
|             |            |                                    | 397       | 77   | 79      | +   |
| Fluvoxamine | OCD        | AP                                 | 114       | 57   | 63      | +   |
| Mirtazapine | MDD        | NA                                 | 003-045   | 170  | 88      | Two studies under this protocol, both failed                        |
| Fluoxetine  | MDD        | AP                                 | HCJE      | 109  | 110     | +   |
|             |            |                                    | X065      | 48   | 48      | +   |
|             | OCD        | AP                                 | HCJW      | 71   | 32      | +   |
| Nefazodone  | MDD        | NA                                 | 141       | 102  | 99      | Failed, by a small margin (p=0.08)                                  |
|             |            |                                    | 187       | 184  | 94      | Failed  |
| Citalopram  | MDD        | NA                                 | CIT-MD-18 | 89   | 85      | +   |
|             |            |                                    | 94404     | 121  | 112     | Failed  |

\* NA not approvable, AE approvable, AP approved

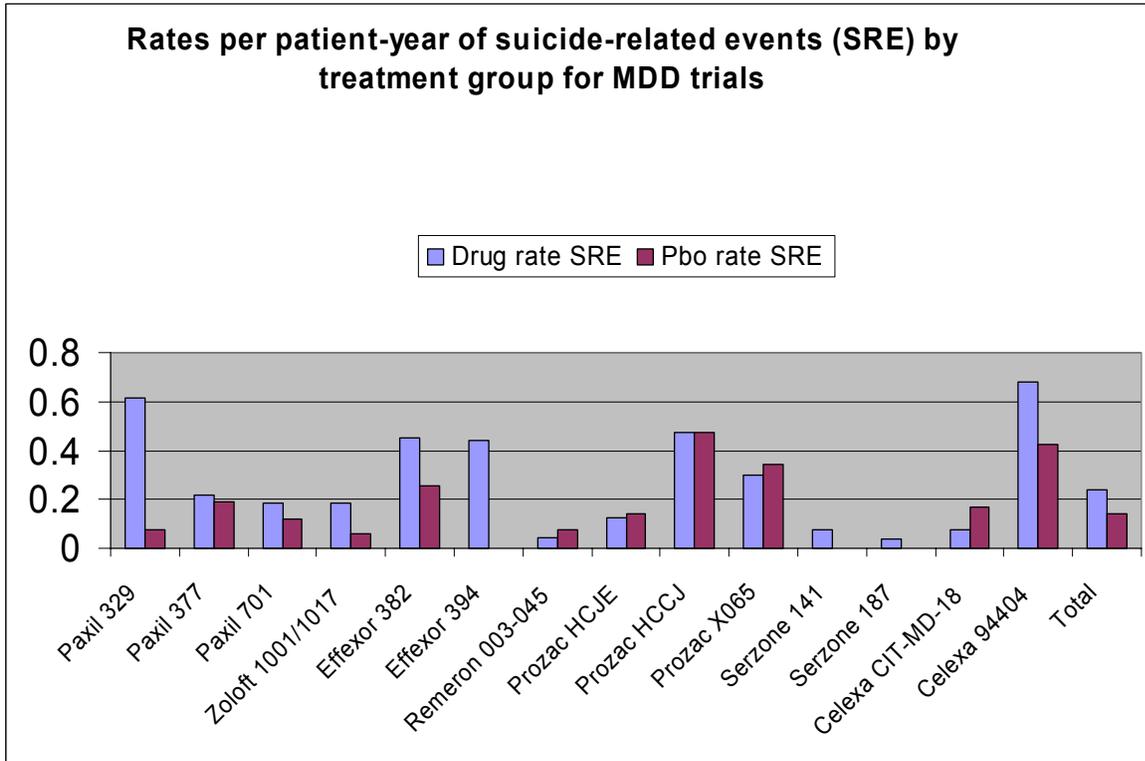
**Appendix Table 6.**

| <b>Attributable risks (incidence rate differences) per patient-year for suicide-related events in pediatric MDD trials</b> |  |                                |                |
|--|--|--------------------------------|----------------|
| <b>Drug</b>  | <b>Incidence rate difference, drug minus placebo</b> | <b>95% confidence interval</b> | <b>p-value</b> |
| <b>Citalopram</b>  | <b>0.14</b>  | <b>-0.16-0.43</b>              | <b>0.374</b>   |
| <b>Fluoxetine</b>  | <b>-0.02</b>   | <b>-0.21-0.17</b>              | <b>0.829</b>   |
| <b>Mirtazapine</b>   | <b>-0.04</b>   | <b>-0.21-0.14</b>              | <b>0.691</b>   |
| <b>Nefazodone</b>  | <b>0.05</b>  | <b>-0.02-0.12</b>              | <b>0.367</b>   |
| <b>Paroxetine</b>  | <b>0.15</b>  | <b>-0.01-0.31</b>              | <b>0.088</b>   |
| <b>Sertraline</b>  | <b>0.12</b>  | <b>-0.05-0.30</b>              | <b>0.176</b>   |
| <b>Venlafaxine</b>   | <b>0.33</b>  | <b>0.05-0.62</b>               | <b>0.020</b>   |
| <b>All MDD trials</b>  | <b>0.10</b>  | <b>0.02-0.18</b>               | <b>0.013</b>   |

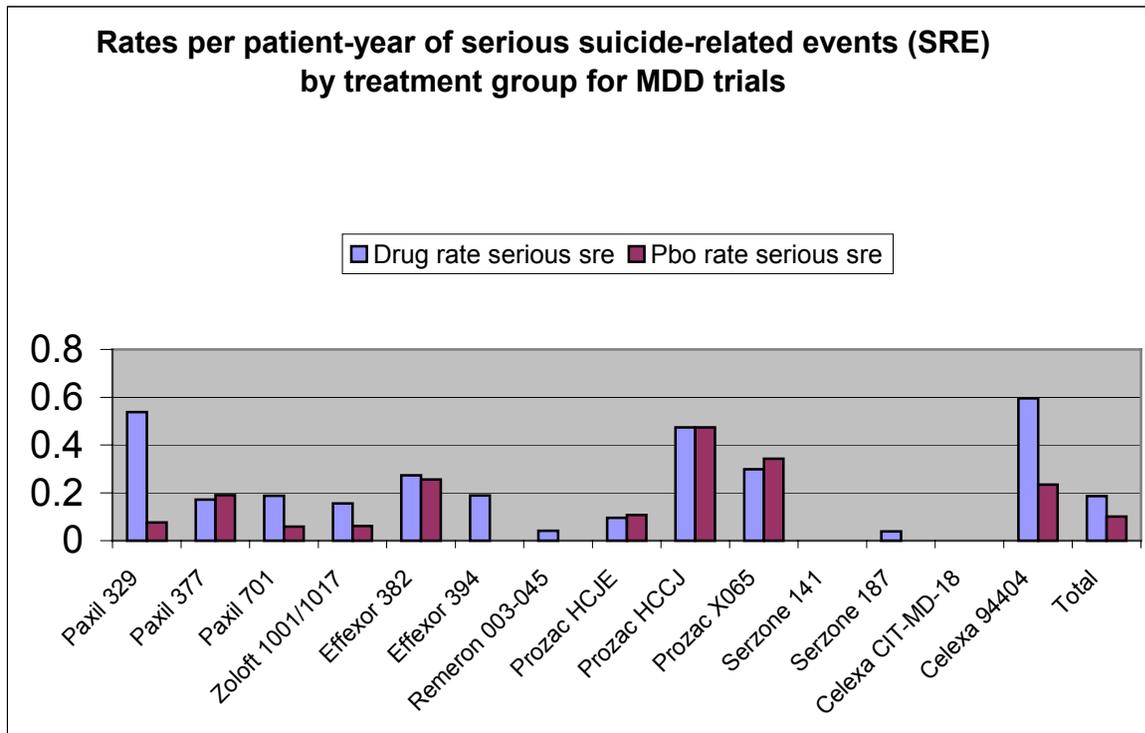
**Appendix Table 7.**

| <b>Attributable risks (incidence rate differences) per patient-year for serious suicide-related events in pediatric MDD trials</b> |  |                                |                |
|--|--|--------------------------------|----------------|
| <b>Drug</b>  | <b>Incidence rate difference, drug minus placebo</b> | <b>95% confidence interval</b> | <b>p-value</b> |
| <b>Citalopram</b>  | <b>0.24</b>  | <b>-0.01-0.48</b>              | <b>0.063</b>   |
| <b>Fluoxetine</b>  | <b>-0.02</b>   | <b>-0.20-0.16</b>              | <b>0.842</b>   |
| <b>Mirtazapine</b>   | <b>0.04</b>  | <b>-0.04-0.12</b>              | <b>0.654</b>   |
| <b>Nefazodone</b>  | <b>0.03</b>  | <b>-0.02-0.08</b>              | <b>0.606</b>   |
| <b>Paroxetine</b>  | <b>0.13</b>  | <b>-0.02-0.27</b>              | <b>0.121</b>   |
| <b>Sertraline</b>  | <b>0.09</b>  | <b>-0.07-0.25</b>              | <b>0.284</b>   |
| <b>Venlafaxine</b>   | <b>0.11</b>  | <b>-0.11-0.33</b>              | <b>0.337</b>   |
| <b>All MDD trials</b>  | <b>0.09</b>  | <b>0.02-0.15</b>               | <b>0.015</b>   |

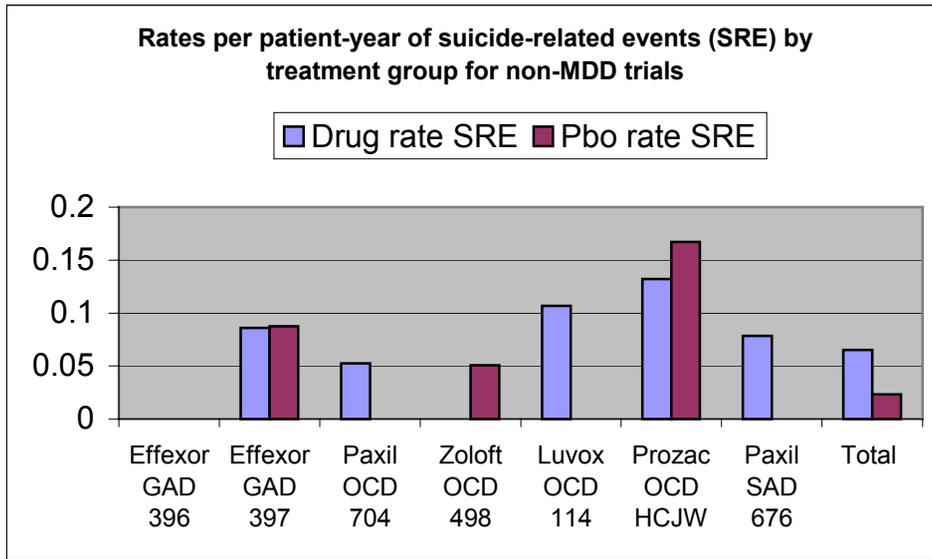
Appendix Figure 1.



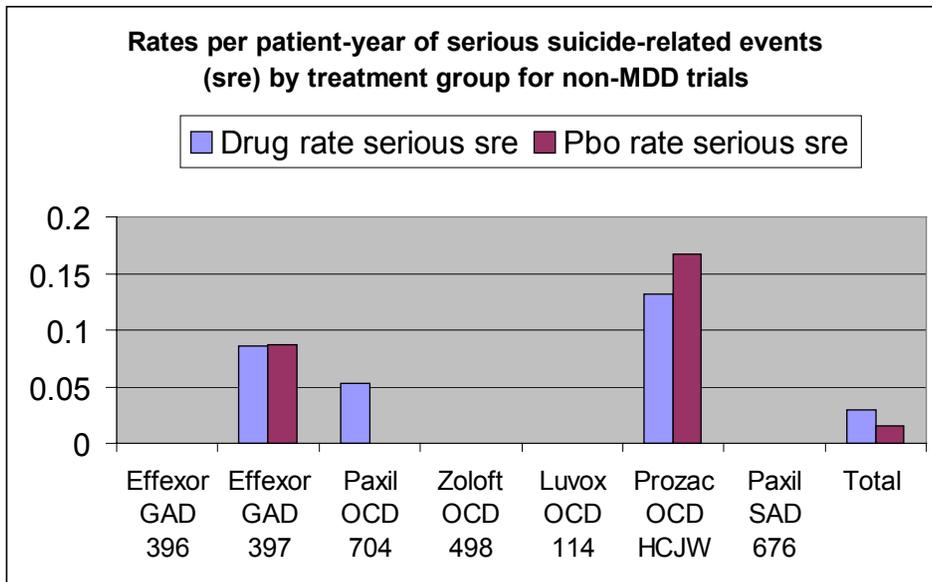
Appendix Figure 2.



Appendix Figure 3.



Appendix Figure 4.



## Appendix Figure 5 (reproduced from the sponsor's submission)

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**Table 2.9 Incidence and Incidence Density for Possibly Suicide-Related Events by Treatment Group and Indication Paediatric Placebo Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy**

| Indication |         | Paroxetine    | Placebo      | Odds Ratio (95% CI) | P value |
|------------|---------|---------------|--------------|---------------------|---------|
| Overall    | n/N (%) | 25/738 (3.4%) | 8/647 (1.2%) | 2.80 (1.25 , 6.25)  | 0.012   |
|            | PYE     | 176           | 149          |                     |         |
|            | n/PYE   | 0.14          | 0.05         |                     |         |
| Depression | n/N (%) | 20/378 (5.3%) | 8/285 (2.8%) | 1.93 (0.84 , 4.46)  | 0.12    |
|            | PYE     | 85            | 61           |                     |         |
|            | n/PYE   | 0.24          | 0.13         |                     |         |
| OCD        | n/N (%) | 1/195 (0.5%)  | 0/205 (0.0%) |                     | 0.49    |
|            | PYE     | 41            | 41           |                     |         |
|            | n/PYE   | 0.02          | 0.00         |                     |         |
| SAD        | n/N (%) | 4/165 (2.4%)  | 0/157 (0.0%) |                     | 0.12    |
|            | PYE     | 51            | 46           |                     |         |
|            | n/PYE   | 0.08          | 0.00         |                     |         |

Data Source: [Appendix 2B, Table 2.56](#)

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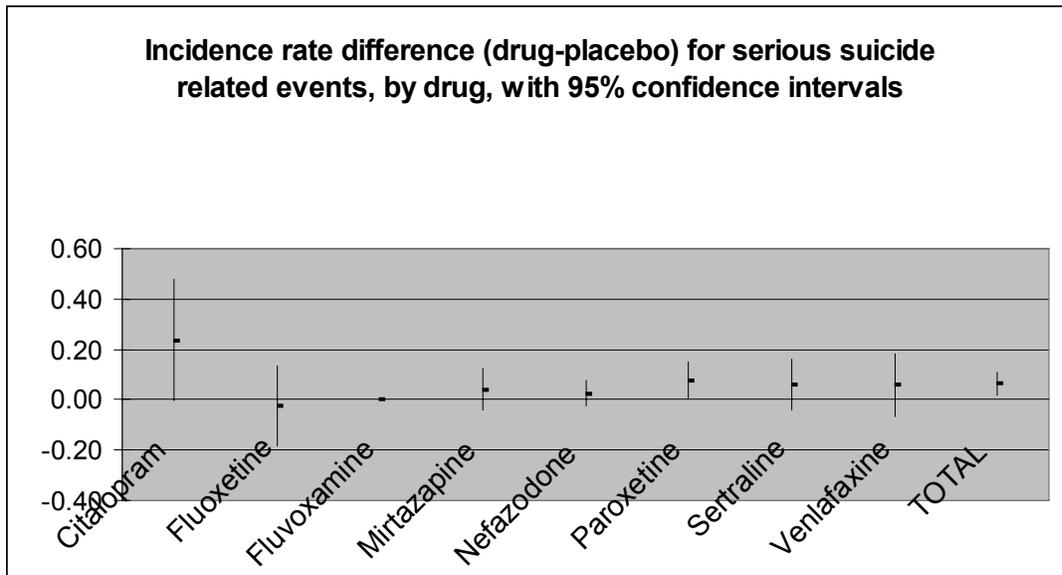
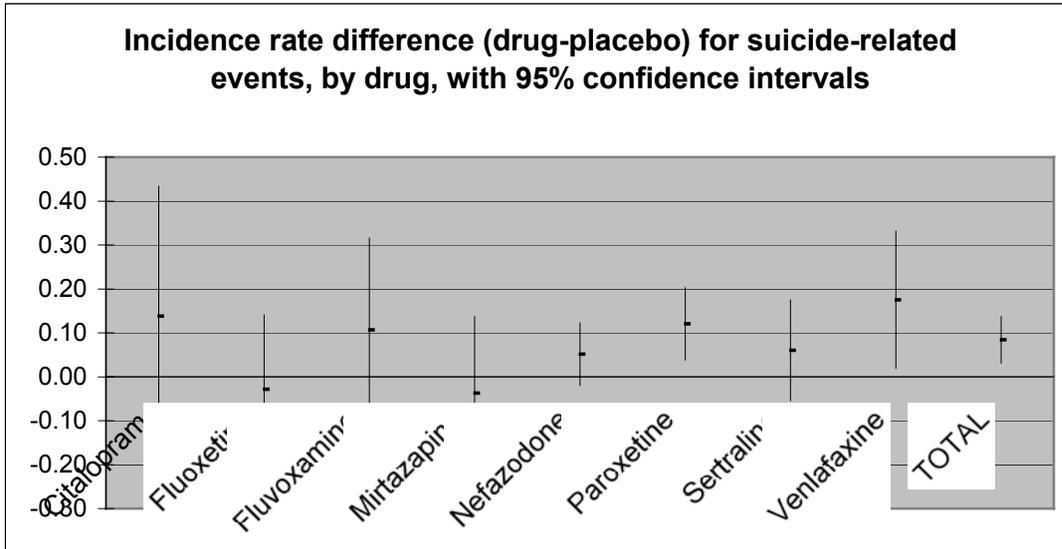
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**Table 2.5 Incidence and Incidence Density for Possibly Suicide-Related Events by Treatment Group and Indication Adult Placebo Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy**

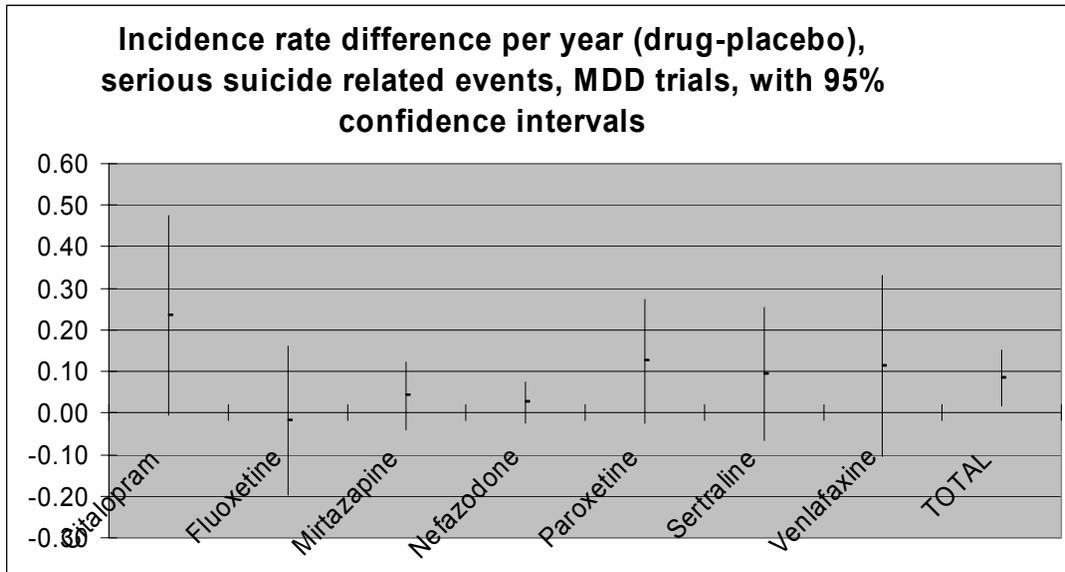
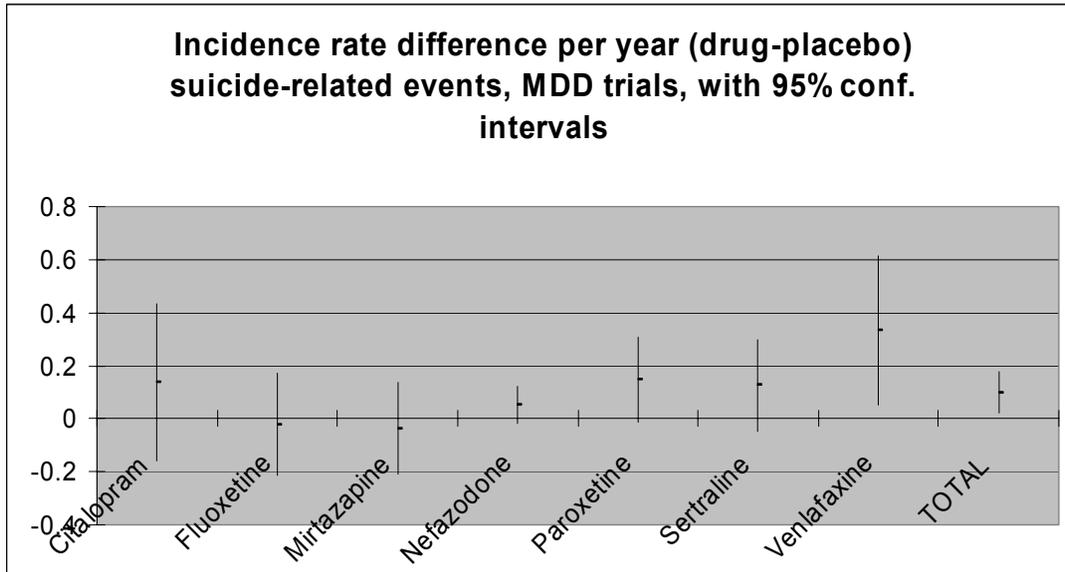
| Indication |         | Paroxetine     | Placebo        | Odds Ratio (95% CI) | P value |
|------------|---------|----------------|----------------|---------------------|---------|
| Overall    | n/N (%) | 92/8481 (1.1%) | 63/5808 (1.1%) | 1.00 (0.72 , 1.38)  | 1.00    |
|            | PYE     | 1916           | 1313           |                     |         |
|            | n/PYE   | 0.05           | 0.05           |                     |         |
| Depression | n/N (%) | 74/3421 (2.2%) | 44/2117 (2.1%) | 1.04 (0.71 , 1.52)  | 0.92    |
|            | PYE     | 671            | 428            |                     |         |
|            | n/PYE   | 0.11           | 0.10           |                     |         |
| GAD        | n/N (%) | 2/1182 (0.2%)  | 2/985 (0.2%)   | 0.83 (0.12 , 5.92)  | 1.00    |
|            | PYE     | 259            | 211            |                     |         |
|            | n/PYE   | 0.01           | 0.01           |                     |         |
| OCD        | n/N (%) | 3/542 (0.6%)   | 4/265 (1.5%)   | 0.36 (0.08 , 1.63)  | 0.23    |
|            | PYE     | 141            | 61             |                     |         |
|            | n/PYE   | 0.02           | 0.07           |                     |         |
| PMDD       | n/N (%) | 0/760 (0.0%)   | 0/379 (0.0%)   |                     |         |
|            | PYE     | 208            | 102            |                     |         |
|            | n/PYE   | 0.00           | 0.00           |                     |         |
| PTSD       | n/N (%) | 7/786 (0.9%)   | 6/598 (1.0%)   | 0.89 (0.30 , 2.65)  | 1.00    |
|            | PYE     | 174            | 138            |                     |         |
|            | n/PYE   | 0.04           | 0.04           |                     |         |
| Panic      | n/N (%) | 3/920 (0.3%)   | 4/780 (0.5%)   | 0.63 (0.14 , 2.84)  | 0.71    |
|            | PYE     | 237            | 186            |                     |         |
|            | n/PYE   | 0.01           | 0.02           |                     |         |
| SAD        | n/N (%) | 3/870 (0.3%)   | 3/684 (0.4%)   | 0.79 (0.16 , 3.90)  | 1.00    |
|            | PYE     | 225            | 187            |                     |         |
|            | n/PYE   | 0.01           | 0.02           |                     |         |

Data Source: [Appendix 2B, Table 2.02](#)

Appendix Figure 6.



Appendix Figure 7.



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/s/  
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