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Background Package

from

Pfizer Inc

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Psychopharmacological Drugs Advisory Committee

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A. Introduction

Major Depressive Disorder (MDD) in children and adolescents is a critical public health issue for the youth of America. If left untreated, MDD can result in a significant risk of suicidal behavior, and is the third leading cause of death in the pediatric population. Epidemiological studies strongly suggest that usage of SSRIs have resulted in a reduction of the number of suicides in this vulnerable patient population. Moreover, Pfizer's analysis of the placebo-controlled Zoloft® (sertraline hydrochloride) pediatric database (281 Zoloft treated subjects and 279 placebo treated subjects) demonstrates no association between Zoloft usage and an increased risk of suicide and/or suicide related behavior.

B. Major Depressive Disorder in Pediatric Population

B.1 Prevalence, Symptoms and Impact

Major depressive disorder (MDD) occurs in children and adolescents as well as adults. The annual prevalence of depression is estimated to be 2-3% in children aged 8-12 years and slightly higher (4-8%) in youth aged 11 ½ to 18 years (AACAP, 1998) as compared with rates of 6.6% in adults aged 18 and older (Kessler, 2003).

In order to diagnose depression, the Diagnostic and Statistical Manual Version IV with revisions (DSM-IV TR) is used. The diagnostic criteria are similar in children and adolescents to those utilized to diagnose depression in adults, with the exception that DSM notes that children and adolescents may exhibit an irritable mood rather than a depressed mood. In all age groups, suicidal thinking or behavior can be one of the diagnostic criteria, characterized in DSM as "abnormal morbid thoughts of death (not just fear of dying) or suicide".

Clinical and epidemiological studies in children and adolescents have shown that a typical episode of MDD lasts 2-9 months; with a probability of the disease returning of 40% within 2

years and 70% by 5 years, similar to the rates of recurrence that have been reported for adults (Birmaher, 1996). Children and adolescents who suffer from MDD may experience a drop in school performance, family tension/problems, and conflicts with friends.

It is common to see coexisting psychiatric disorders in depressed youth (40% to 90% of the time). The most frequent coexisting disorders are dysthymic disorder (sometimes referred to as minor depression in that these youth display a chronically depressed mood or irritability lasting at least 1 year but do not meet criterion for major depression) and anxiety disorders (both at 30% to 80%), disruptive behavior disorders (10% to 80%), and abuse of alcohol or illicit substances (20% to 30%) (AACAP, 1998).

MDD in the pediatric population is associated with significant risk of suicidal thinking, attempts and even completed suicide. Approximately half of teenagers with MDD attempt suicide at some time during their lives and among children with MDD, there is a 4- to 5-fold higher lifetime risk of suicide attempt, compared with healthy children without depression (Kovacs, 1993; Rao, 1993). Kovacs et al (1993) noted similar results in a study of outpatient youths with MDD. They noted that, at study entry, 66% of subjects acknowledged a history of suicidal ideation, and 9% had already made at least one suicide attempt. The rate of suicide attempts in this study reached 24% by age 17. Important comorbid risk factors for suicide attempts included conduct and/or substance-abuse disorders.

B.2 Treatment Options

The American Academy of Child and Adolescent Psychiatry recommends, for first-line acute treatment of MDD in children and adolescents, psychotherapy, treatment with a selective serotonin reuptake inhibitor (SSRI), or both combined, depending on the patient, the patient's circumstances, and the severity of disease (AACAP, 1998).

Psychotherapy may take the form of individual, group, or family therapy; cognitive behavioral therapy, interpersonal-, problem-solving, or play therapy. There are few placebo-controlled studies with psychotherapy. Cognitive-behavioral therapy has been shown to work in small studies, but does not appear to be as effective for more severe illness. Treatment studies

comparing psychotherapy, medication or their combination are needed and are beginning to be conducted, and presented.

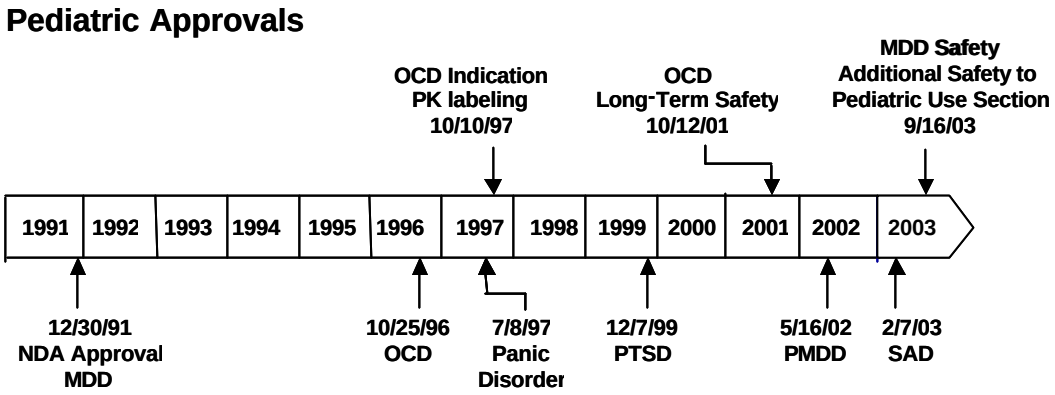
Prior to the widespread use of SSRIs, tricyclic antidepressants (TCAs) were the most commonly used pharmacotherapy for MDD. Although tricyclic antidepressants (TCAs) have been shown to effect some improvement in small open studies in children, more rigorous placebo-controlled studies failed to demonstrate that TCAs were more effective than placebo for the treatment of MDD in children and adolescents. TCAs also pose certain safety risks in children, specifically cardiac arrhythmias, and a potential lethality in overdose. The high degree of acceptance of SSRIs for the treatment of MDD in adults, together with their low incidence of side effects, easy once-a-day administration, and safety when taken in overdose made it natural that physicians, faced with the need to treat patients suffering from MDD would prescribe these in younger patients also, even if off-label. Fluoxetine is currently the only SSRI is indicated for the treatment of depression in childhood. The Zoloft label contains safety and efficacy information with respect to the use of Zoloft in pediatric OCD (acute and long-term), and safety information derived from the pediatric MDD program.

Several epidemiological studies address rates of suicide following the introduction of SSRIs in adults (Hall *et al*, 2003 [patients ranged in age upward from 15 years]; Isaacson *et al*, 2000) and adolescents (Olfson *et al*, 2003). In each of these studies, a negative correlation was noted between usage of SSRIs and suicide rates and the correlation coefficients noted by Hall *et al* were quite strong (men, $r=-0.91$, $p<0.01$; women, $r=-0.76$, $p<0.05$). Olfson *et al* specifically assessed the rates of suicide in adolescents in a large managed care database and found a risk reduction for suicide of 0.23/100,000 population per year with a 1% increase in antidepressant usage.

C. Zoloft Pediatric Utilization Data

Figure 1 below shows the chronology of Zoloft regulatory approvals in the United States, from initial approval for adult Major Depressive Disorder (MDD) in late 1991 and launch in 1992, through the present.

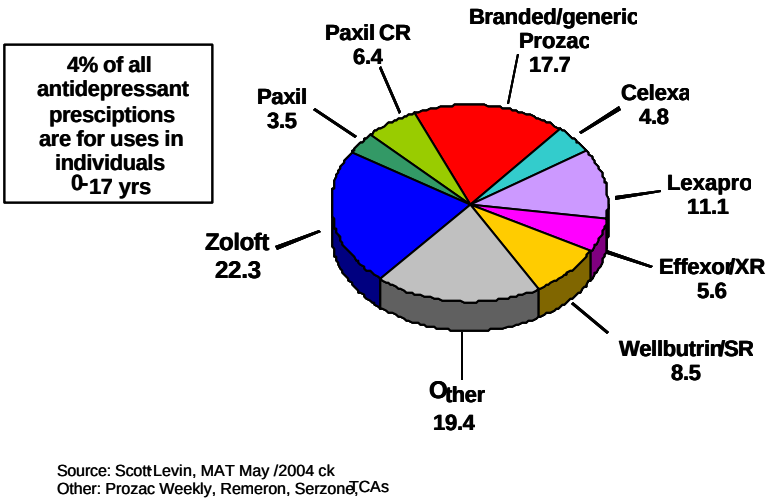
Figure 1. Zoloft Approvals: Adult and Pediatric Indications



NDA: New Drug Application
MDD: Major Depressive Disorder
OCD: Obsessive-Compulsive Disorder
PTSD: Posttraumatic Stress Disorder
PMDD: Premenstrual Dysphoric Disorder
SAD: Social Anxiety Disorder

Since its launch into the US marketplace in January 1992, approximately 250 million prescriptions for Zoloft have been written, accounting for over 13 billion patient days of therapy. Approximately 465,000 prescriptions were written for Zoloft in the pediatric population in 2003, which accounted for 1.4% of total Zoloft prescriptions in 2003.

Figure 2. Distribution of Antidepressant Use in the Pediatric Market



Source: Scott Levin, MAT May /2004 ck
Other: Prozac Weekly, Remeron, Serzone, TCAs

D. Overview of Zoloft Placebo-controlled Studies in the Pediatric Population

Pfizer has conducted three, double-blind, placebo-controlled studies in the pediatric population. A fourth study in the PTSD pediatric population is currently ongoing. Table 1 provides an overview of the placebo-controlled pediatric studies.

Table 1. Summary of Placebo-Controlled Pediatric Studies Conducted with Zoloft

Study	Study Design	Indication	No. of Patients		Age Range
			Zoloft	Placebo	
Studies in Obsessive Compulsive Disorder (OCD)					
R-0498	DB, 12-wk, flex-dose (25-200mg)	OCD	N=92	n=95	6-17 yrs
Studies in Major Depressive Disorder (MDD)					
A0501001	DB, 10-wk, flex-dose (25-200mg)	MDD	N=97	n=91	6-17 yrs
A0501017	DB, 10-wk, flex-dose (25-200mg)	MDD	N=92	n=93	6-17 yrs
Ongoing Study					
A0501061*	DB, 10-wk, flex-dose (25-200mg)	PTSD	n=80 [projected]	n=80 [projected]	6-17 yrs

* A total of 70 patients have been enrolled to date.

D.1 Placebo-controlled Pediatric Studies in Obsessive Compulsive Disorder

Study R-0498: This was a double-blind study to evaluate the safety and efficacy of Zoloft compared to placebo in children (6-12 years) and adolescents (13-17 years) with obsessive compulsive disorder over 12 weeks of treatment. A total of 187 patients were enrolled, 92 randomized to Zoloft treatment and 95 randomized to placebo treatment. The randomization was stratified by age so there would be an even distribution of children and adolescents in the Zoloft and placebo groups. The starting dose was 25 mg for children and 50 mg for adolescents and, in the absence of dose-limiting adverse events, the doses were increased in 25 mg increments for children and 50 mg increments for adolescents to a maximum of 200 mg/day.

D.2 Placebo-controlled Pediatric Studies in Major Depressive Disorder

Studies A0501001 and A0501017: In order to comply with the requirements of a Written Request, two identical, 10-week, flexible-dose, placebo-controlled, multicenter studies of Zoloft in children and adolescents with MDD were conducted. Study A0501001 was conducted from December 1999 to May 2001 and Study A0501017 was conducted from February 2000 to March 2001.

Study A0501001 enrolled 188 patients and Study A0501017 enrolled 185 patients. Patients were required to have a current episode of MDD. As is typical in studies assessing efficacy of MDD, subjects who previously attempted suicide or who would pose a serious suicidal or homicidal risk were excluded from the studies. Patients entering the trial were evaluated for two weeks (screening period) and, if all entry criteria were met, they were randomly assigned to receive Zoloft or matching placebo in a double-blind manner. In both studies randomization was stratified to ensure that an equal number of children and adolescents were included. For the first 3 days of dosing, patients received 25 mg/day of study drug, followed by an increase to 50 mg/day, thought to be the minimum effective dose, for the remainder of the first two weeks. Thereafter, at the discretion of the investigator and in the absence of any dose limiting side effects, a patient's dose could be increased by 50 mg/day every two weeks to a maximum of 200 mg/day. Doses could be decreased by 50 mg/day every week for tolerability issues. The Children's Depression Rating Scale-Revised (CDRS-R) was chosen as the primary endpoint

measure for depressive symptoms because it was the emerging standard outcome measure in the field, even though there were at the time few studies that had used it in the public record.

An important element in the design of any clinical trial is the estimation of the number of patients to be included. As in any sampling situation, the larger the sample the greater the confidence one can have that an observed effect accurately reflects the true effect. In a very uniform and homogeneous group one can expect that a smaller sample will be representative, whereas, if the whole group is diverse and has greater variability a larger sample is required. In order to get a good estimate of the number of patients needed, statisticians look at the data from previous similar trials to get information regarding what values might be due to random variability between patients and what values represent a true effect. The sample sizes for Studies A0501001 and A0501017 were calculated based on data from a small (n=48 per treatment group) single-center study of fluoxetine in children and adolescents with MDD published by Dr. Graham Emslie, the only published placebo-controlled study of an SSRI utilizing the CDRS-R at the time. Based on the available estimates of treatment effect using the CDRS-R scale, it was estimated that 160 subjects (80 per treatment group and age stratum) would be required to provide 88% likelihood that an observed effect would represent the true effect.

There was at that time no published multicenter trial that had used the CDRS-R rating scale to demonstrate efficacy, and hence no data to provide information regarding any additional variability between subjects and between sites that might be expected in a larger, multicenter trial. To address the concern that the random variability in such a study might be greater than in a small well-placebo-controlled single site study, a plan was generated to make the two studies identical and, at a point half-way through the studies, to re-do the sample size calculations using the real-time data from the ongoing studies. When this predefined and protocol-specified blinded evaluation of the variability in the individual studies was performed, it was clear that the original sample size estimate based on the single-center experience with the CDRS-R was a substantial underestimate for the multicenter setting. Indeed, the variability in the studies was approximately three-fold higher than the expected value that had been built into the original sample size calculation. It was clear that the two individual study datasets would need to be combined. Analyzed together, the two studies would provide a sample size that was large

enough to ensure that the result would be true and accurate to a 90% level of confidence. Statistical analysis plans for the double-blind studies and a statistical analysis plan for the combined analysis of the two studies were all finalized on May 5, 2000, well before completion of subject enrollment for the studies. The primary analysis for all three study reports (two individual and one combined) was the mean adjusted change from baseline to endpoint (Last Observation Carried Forward [LOCF]) for the CDRS-R total score in the intent- to- treat (ITT) population. All analyses were conducted in accordance with the statistical analysis plan.

E. Evaluation of Suicide-Related Behavior in Placebo-controlled Zoloft Pediatric Studies

There were no completed suicides in the placebo-controlled pediatric trials with Zoloft. A comprehensive evaluation conducted by Pfizer of the Zoloft placebo-controlled trials shows that the risk of suicide related behavior in children and adolescents treated with Zoloft in clinical trials of MDD is no greater than that with placebo.

E.1 Suicide Attempts

Table 2 summarizes the incidence of suicide attempts in the placebo-controlled Zoloft pediatric trials. In the MDD program, in Study A0501017, two patients in the Zoloft-treated group and two patients in the placebo-treated group were classified as having made a suicide attempt. One patient in the placebo-treated group attempted suicide twice. In the attempts with high lethality, one subject was taking Zoloft (subject 5010-4022: multi-drug overdose) and two subjects were taking placebo (subject 5062-4321: 2 attempts, attempted hanging and drug overdose; subject 5061-4329: attempted self-immolation). There were no suicide attempts in the OCD program.

Table 2. Incidence of suicide attempts in Zoloft placebo-controlled pediatric studies

Diagnosis	Sertraline		Placebo		Sertraline-Placebo	
	n / N	Incidence % [95% CI][1]	n / N	Incidence % [95% CI][1]	p-value[2]	Difference [95% CI][3]
MDD	2 / 189	1.1% [0.1 – 3.8%]	2 / 184*	1.1% [0.1 – 3.9%]	1.000	-0.03% [-2.1 – 2.1%]
OCD	0 / 92	0% [-]	0 / 95	0% [-]	1.000	0% [0]

[1]exact binomial confidence bounds.
[2]Fisher's exact test.
[3]95% confidence intervals based on normal approximation
*there were 3 attempts in 2 subjects on placebo, when expressed as events incidence is 1.6% [0.3 – 4.7%]

E.2 Suicidal Ideation

Table 3 summarizes the incidence of suicide ideation in the Zoloft pediatric placebo-controlled trials. Three cases of suicide ideation were reported in MDD study A0501001, and one in the OCD program, none of which were deemed by the investigator to be related to study drug.

Table 3. Incidence of suicidal ideation in Zoloft placebo-controlled pediatric studies

Diagnosis	Sertraline		Placebo		Sertraline-Placebo	
	n / N	Incidence % [95% CI][1]	n / N	Incidence % [95% CI][1]	p-value[2]	Difference [95% CI][3]
MDD	3 / 189	1.6% [0.3 – 4.6%]	0 / 184	0.0% [–%]	0.2481	1.6% [-0.2 – 3.4%]
OCD	0 / 92	0% [-]	1 / 95	1.1% [0.03 – 5.7%]	1.000	-1.1% [-3.2 – 1.1%]

[1]exact binomial confidence bounds.
[2]Fisher's exact test.
[3]95% confidence intervals based on normal approximation

E.3 Event Classification Issues

Classification by investigators of behaviors exhibited by children and adolescents in a clinical program is inherently subjective. This is particularly the case with potential suicide related behaviors. As described in the study report narratives (see section F, individual patient narratives) some of the cases involving Zoloft-treated subjects may have been inappropriately classified by the investigator. With respect to suicide attempts, subject 5049-3095 made no clear attempt; rather, the child expressed intent in the midst of an argument with his mother two weeks after his grandmother had attempted suicide. With respect to cases of suicidal ideation, for

subject 5028-1022, the emergency room attending physician (not the study investigator) treating the subject saw no evidence of suicide related behavior.

F. Individual Patient Narratives

Subject ID (study)	Narrative
90N0242-19 (90CE21-0498) Placebo treatment	The subject is a 12 year old female with a principal diagnosis of obsessive compulsive disorder and secondary diagnoses of social anxiety disorder and attention deficit hyperactivity disorder randomized to double blind placebo treatment. The subject had the adverse event of suicidal ideation on day 12. At screening, the subject was administered a Hamilton Depression Rating Scale in order to exclude subjects with significant MDD. The subject's score was 7 without any suicidal ideation. It was noted that prior to entering the trial the patient had not responded to either fluoxetine or clomipramine. Physical exam and labs were unremarkable except for mild thyromegaly and low normal T4. The subject did not receive any concomitant medication during the study. At screening baseline, the subject's CYBOCS was 26. Prior to the event, on day 8 of the study, the subject had a CYBOCS score of 21 and a CGI-S score of 6 (severely ill). On day 12 of blinded treatment, the patient experienced 2 days of mild suicidal ideation which did not require any action. In the investigator's judgement, the AE was due to the subject's frustration with recurrent OCD symptoms. The patient subsequently continued her participation until week 6 of the study. No clinical improvement was noted on placebo.
5026-2006 (A0501001)	The subject is a 12 year old male with a diagnosis of MDD, recurrent, with current episode that began 3 months prior to study entry randomized to double blind sertraline. The subject also has a past history of suicidal ideation. The subject experienced the AE of suicidal ideation on day 49 on a dose of sertraline 100mg. His medical history was significant for congenital ventricular septal defect, physical exam and lab evaluation was otherwise unremarkable. At baseline, the subject's CDRS-R score was 53, with an irritability item score of 3 and suicidal ideation item score of 2. His CGI-S score was 5 (markedly ill). On day 42, the subject's CDRS-R total score was 62, and his irritability item score was 6 and the suicidal ideation item score was 1. The

	sertraline dose was increased at this visit to 100mg. Over the next 8 days prior to the AE of suicidal ideation, he forgot to take his medication on days 44, 47, and 49. On day 49, the subject experienced worsening symptoms of major depression and expressed suicidal ideation. Because the subject could not contract for safety, the investigator decided to hospitalize the subject. The subject was withdrawn from the study. The event was considered resolved on 25 July 2000, 13 days after the AE was reported. In the investigator's opinion, the event was due to the major depression.
5027-1089 (A0501001)	The subject is a 10 year old female with a primary diagnosis of MDD, single episode of 8 months duration, and secondary diagnoses of separation anxiety disorder, GAD, and panic disorder of 2 years duration randomized to double blind sertraline. The subject experienced suicidal ideation with plan on day 35. At the time, the subject was taking 100 mg of sertraline. The patient was not on any concomitant medications immediately before or during the onset of the suicidal ideation. Her medical history, physical exam, and lab evaluation were unremarkable except for migraine headaches and overweight. Her baseline CDRS-R total score was 72, with an irritability item score of 7 and suicidal ideation item score of 1, and CGI-S rating of 4. On day 28 of study treatment, the subject's CDRS-R total score was 30, with irritability item score of 4 and suicidal ideation item score of 1. On day 35, the subject experienced suicidal ideation with plan. Reportedly, the subject held a kitchen knife to her neck while alone but did not cut herself and the event was not witnessed. At her next scheduled visit, on day 42, the subject reported the suicidal ideation described above, and she was hospitalized and withdrawn from the study. The event was considered resolved 7 days later and she was discharged from the hospital in improved condition. The investigator attributed the cause to the depression. The subject had been on stable sertraline dosing of 100 mg for 13 days prior to the adverse event.
5028-1022 (A0501001)	The subject is a 10 year old male with diagnosis of major depression, single episode of 9 months duration randomized to double blind sertraline who experienced the adverse event (AE) of suicidal ideation on day 21 of the study while receiving 100 mg of sertraline. The subject also had a secondary diagnosis of ADHD for the past 3 years. At baseline, the CDRS-R total score was 82 with an irritability item score of 6 and suicidal ideation item score of 4. The subject was determined to be markedly ill (CGI-S =5). The baseline physical exam and laboratory evaluation was unremarkable. The patient received no concomitant

	medications during the trial. On day 3, the patient experienced an AE of mild psychomotor agitation while on sertraline 25mg which in the investigator's judgement was due to study drug. The AE resolved on day 31. At his scheduled visit on day 18, the patient had a CDRS-R score of 74, and irritability score was 4, suicidal ideation was 2. He then received an increase of sertraline to 2 tabs a day (100 mg) on day 19. On day 21, the patient experienced the adverse event of suicidal ideation of moderate intensity which led to the patient being withdrawn from the study and hospitalized. Apparently, he was involved in an argument with his teacher and he made a comment suggestive to the teacher suggestive of suicidality. The school social worker was not immediately available to assess the child so EMS was called and the subject was hospitalized. His attending physician saw no evidence of suicidality and he was discharged from the hospital 5 days later. In the investigator's judgement, the AE was not due to study drug and the causality was school altercation.
5010-4022 (A0501017)	The subject is a 16 year old female with MDD single episode of 3 years duration who received double blind sertraline. The subject had an AE of suicide attempt on day 50. The dose of sertraline at AE onset was 150 mg. Her medical history, physical exam and lab evaluation were unremarkable. Concomitant medications taken during the study included fexofenadine and ibuprofen. At baseline, her CDRS-R total score was 66, with irritability item score of 7, and suicidal ideation item score of 1. On day 24, the subject had an AE of physical restlessness of moderate severity which did not resolve. No action was taken, and the investigator attributed this AE to study drug which had been increased to 100 mg 9 days before. The visit on day 44 was unremarkable – her CDRS-R score was 44, irritability and suicidal ideation item scores were both 1. On day 50, the subject attempted suicide by multidrug overdose including ibuprofen, acetaminophen, naprosyn, aspirin, and dimenhydrinate of indeterminate quantities. The patient was withdrawn from the study, sertraline was discontinued and the subject was hospitalized, given gastric lavage, and admitted for 2 days. At the time of the suicide attempt, the patient had been taking sertraline 150 mg a day and had been at that dose since day 30. The causality for the attempt was identified as disease under study. Prior to the attempt, the subject was involved in a family argument regarding school attendance.
5049-3095 (A0501017)	The subject is a 6 year old male with MDD single episode of 2 yrs duration who received double blind sertraline treatment. On day 34, the subject attempted suicide.

	The dose of sertraline at AE onset was 100 mg. His medical history and physical exam was unremarkable. The subject did not receive any concomitant medications immediately before or during the AE. At baseline, the subject's CDRS-R total score was 58, the irritability item score was 7 and suicidal ideation item score was 3, and judged to be moderately ill (CGI-S =4). On day 16, the subject had an AE of severe agitation which did not resolve. The subject had just increased his dose to 100mg on the prior day. There was no action taken by the investigator and the AE was attributed to study drug. On day 29, the subject's CDRS-R total score was 42 with an irritability item score of 3 and suicidal ideation item score of 4. Of note, at this study visit was an elevated increase of WBC and neutrophil count that was not noted at baseline, possibly indicating latent infection. On day 34, the subject threatened to jump from a moving vehicle stating that he wanted to kill himself. Later that same evening, he expressed suicidal ideation and was hospitalized. The subinvestigator attributed this AE to the study drug and coded the event as a suicide attempt. The study drug was discontinued and the subject was hospitalized for 7 days. Events that may have affected the subject were: 1) his grandmother attempted suicide 2 weeks earlier and 2) his mother informed him that he was going to be withdrawn from the study and that he was to start psychotherapy. In the A0501017 study report, submitted to the Agency on 14 December 2001, the sponsor disputed the attribution to study drug, for the reasons listed, and continues to dispute this attribution.
5061-4329 (A0501017) Placebo treatment	The subject is a 17 year old female with MDD, single episode of 4 months duration randomized to placebo treatment. The subject had an AE of suicide attempt on day 9. Her medical history was significant for treated GI worm infestation one month prior to screening. Before and during the time of the AE, the subject was not receiving any concomitant medications. At baseline, her CDRS-R total score was 45 with irritability and suicidal ideation item scores rated as 1. Her CGI-S rating was 4. At day 8, the subject's CDRS-R total score was 45 with irritability and suicidal ideation item scores of 1. On day 9, the subject attempted suicide by immolation. Her siblings doused the flames immediately. She was left with burns on her abdomen and left shoulder. The subject admitted she was angry with her parents for going away. The subject then subsequently admitted that she acted impulsively and had not intended to kill herself. The subject's parents did not report this event until day 15 because they thought that the subject's burns were minor. It was reported

	that she received burn treatment consisting of tetanus toxoid, silver sulphadiazine and paracetamol. Placebo was permanently discontinued on day 15 due to insufficient clinical response. At the time of the attempt, the subject was taking one placebo tab per day. The AE causality was judged to be MDD.
5062-4321 (A0501017) Placebo treatment	The subject is a 15 year old female with diagnosis of MDD, single episode with 6 months duration and secondary diagnosis of trichotillomania also of 6 months duration who was randomized to double blind placebo treatment. The subject had two separate adverse events of suicide attempt on day 63 and day 66 which were revealed to the investigator at the last study visit (end of week 10). Her past medical history was unremarkable. Her physical exam was notable for sparse hair over the posterior aspect of her scalp. At baseline, her lab examination was significant for low hemoglobin, hematocrit, and MCV consistent with mild iron deficiency anemia which did not correct at the final visit. The subject did not receive any concomitant medications during the trial. Her baseline CDRS-R total score was 72, with an irritability item score of 6 and suicidal ideation item score of 4. The CGI-S rating was 5. On day 59 of the study, the subject's CDRS-R total score was 69, with an irritability item score was 5 and suicidal ideation item score of 3. Her CGI-I score was 4, indicating no change from baseline. On day 63, she tried to hang herself and was prevented from doing so by her family. On day 66, the subject took 32 tablets of study drug (placebo) in another attempt. She suffered no side effects following this event but was hospitalized for suicidal ideation. The suicidal ideation resolved 9 days after hospitalization, but she remained an inpatient for social reasons. Prior to these attempts, the subject was receiving 4 placebo tablets for at least 16 days, but may have been hoarding the tablets. In the opinion of the investigator, these events were due to the disease under study. The subject was considered to have completed study treatment as she completed the final study visit on the same day and prior to hospitalization.

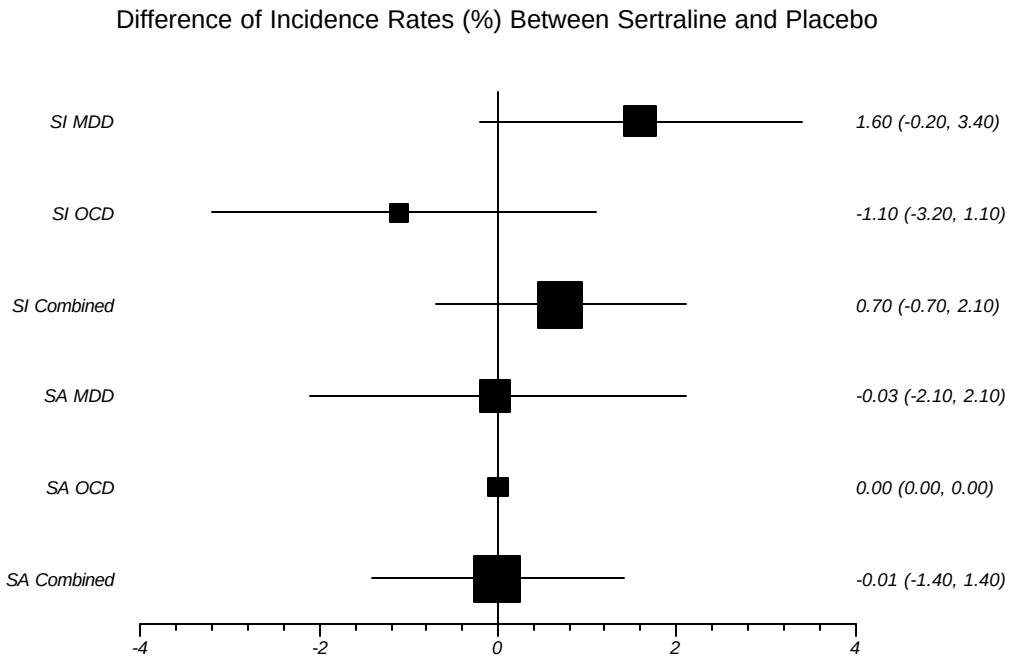
G. Analysis and Conclusion

Because there were relatively few events of suicide related behavior in the Zoloft pediatric placebo-controlled trials, non-statistical inspection of the numbers and derived arithmetic ratios may be prone to subject variability. Therefore, statistical evaluations were conducted to

determine whether the observed results were more likely to occur by chance or a drug-related event.

Figure 3 below summarizes the incidence of suicidal behavior (suicidal ideations and attempts, respectively) in the placebo-controlled pediatric studies. As can be seen from both number of subjects and number of events, the 95% confidence intervals overlap in each instance and the 95% confidence interval of the difference between treatment groups includes zero in all cases, demonstrating that there is no statistical difference detected between treatment groups in terms of suicide related behavior. Further proof of this is derived from Fisher's exact test in all instances – none of the derived p values suggest a statistically significant difference between treatment groups.

Figure 3. Suicidal Ideation and Suicide Attempts: Point Estimate and 95% Confidence Intervals of Difference between Sertraline and Placebo



Abbreviations: SA = suicide attempt; SI = suicidal ideation

Square symbol size is representative of and proportional to study sample size.

These statistical analyses do not demonstrate an association between Zoloft treatment and suicide related behavior. Despite the relatively low statistical power, the analysis is appropriate to demonstrate that the observed difference in incidence of events falls within the range that arises by chance in this population who are at an inherent risk of suicide related behavior.

The narratives illustrate that there are confounding factors which need to be taken into account when examining or attempting analysis of suicidal behavior. These can include, but are not limited to, presence or absence of comorbidities such as anxiety disorders or attention deficit disorder, personal history of suicidal behavior in the past, family history of suicide attempts, MDD, or bipolar disorder, situational precipitants, age and other confounds.

The safety analysis of clinical study data from the use of Zoloft in the treatment of pediatric patients (<18 years of age) with MDD (or with OCD) does not support a clear causal association between Zoloft and suicidal behavior. In the placebo-controlled clinical studies, there was only one relevant event for which a causal relationship with Zoloft had been reported by the investigator. However, a critical evaluation of this case as well as the remaining non-related cases does not detect any signal or establish any pattern that would suggest a causal relationship with Zoloft.

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