# Assessments of Suicidality in Double-Blind, Placebo-Controlled Trials of Ziprasidone

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***Objective:*** A pooled analysis was conducted to identify possibly suicide-related adverse events in Pfizer-sponsored, phases 2–4, placebo-controlled, double-blind, adult and pediatric completed randomized controlled trials of ziprasidone and to evaluate the risk of suicidality with ziprasidone versus placebo.

***Method:*** The trials included were initiated as early as June 1992, and the cutoff date for selection of the placebo-controlled trials in the Pfizer database was October 2, 2009. The US Food and Drug Administration (FDA)–defined search methodology was used to identify possibly suicide-related adverse events, and the Columbia Classification Algorithm of Suicide Assessment (primary outcome measure) was used to categorize them. The incidences of possibly suicide-related adverse events were calculated for individual classifications and for the predefined combined categories of suicidality (comprising classification codes 1–4) and suicidal behavior (comprising classification codes 1–3), along with the ziprasidone versus placebo relative risks and corresponding 95% CIs. Exact binomial 95% CIs were calculated for the individual treatment group incidences.

***Results:*** Suicidality events were identified in 52 among 5,123 subjects treated with either ziprasidone or placebo in 22 trials. No cases of completed suicide occurred in this analysis. There were no statistically significant differences between ziprasidone and placebo in any of the individual classification categories, combined suicidal behavior category (ziprasidone vs placebo relative risk = 0.67; 95% CI, 0.206–2.201), or combined suicidality risk category (ziprasidone vs placebo relative risk = 0.90; 95% CI, 0.514–1.563).

***Conclusions:*** Results of our analyses, performed in accordance with the FDA-specified search strategy, reveal no significant differences in treatment-emergent suicidality risk in ziprasidone versus placebo subjects treated in controlled clinical trials.

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Suicidality is an inherent risk in many psychiatric disorders, including schizophrenia and bipolar disorder.[1–7] Although antipsychotic drugs represent a mainstay of treatment for both disorders, little is known whether some antipsychotic-treated subjects experience treatment-emergent suicidality (ie, suicidal thoughts and actions). Currently available data on treatment-emergent suicidality associated with use of the first-generation antipsychotics (FGAs) or second-generation antipsychotics (SGAs) in subjects diagnosed with either schizophrenia or bipolar disorder are limited and inconsistent.[8–16] This may be related to methodological obstacles such as the sporadic nature of the suicidality events, inconsistencies in reporting, and different methodology used in the analyses, all of which make magnitude of the suicidality risk emerging during antipsychotic drug treatment difficult to establish.[17]

Until now, there have been several published reports on evaluation of treatment-emergent suicidality through identification of possibly suicide-related adverse events in randomized controlled trials of antidepressants,[18–22] the antiepileptic lamotrigine,[23] the leukotriene receptor antagonist montelukast,[24] or atomoxetine, the nonstimulant medication used in the attention-deficit/hyperactivity disorder treatment.[25] For each medication included in these analyses, the electronic databases for adverse events reported during the double-blind phase of treatment were searched for terms related to suicidality, ie, possibly suicide-related adverse events. Because it was difficult to determine whether events represented a change in condition or resulted from a preexisting condition, all possibly suicide-related adverse events reported during the double-blind phase were included in the analyses. A US Food and Drug Administration (FDA)–developed methodology for identification of possibly suicide-related adverse events was used,[26,27] and events were categorized using the Columbia Classification Algorithm of Suicide Assessment (C-CASA).[28] The resulting incidences of events under either active treatment or placebo were used to calculate estimates of treatment-emergent suicidality risk.

Although antipsychotic drugs represent the mainstay of the treatment of schizophrenia, the relationship with suicidal behavior and treatment-related suicidality remains to be fully elucidated.[17] In the review on effects of antipsychotics on suicidality in schizophrenia, Aguilar and Siris[17] note that the sporadic nature of events and inconsistencies across the various reports make the magnitude of suicidal risk hard to establish. There are a number of reports that assessed the incidence of suicidality in subjects with schizophrenia treated prior to the antipsychotic era versus those treated with antipsychotics.[28–30] Effects of noncompliance[12,31] or drug discontinuation have also been reported.[32] Nevertheless, little is known about treatment-emergent suicidality associated with the usage of antipsychotics. Khan and colleagues[14] analyzed FDA-reviewed data for risperidone, olanzapine, and quetiapine (number of subjects = 10,118). Each of the included trials used the standard exclusion criterion of not enrolling actively suicidal subjects or those posing a serious

suicidal risk. There were no statistically significant differences among the incidences of suicide or suicide attempts calculated on the basis of patient exposure years. Another analysis of the FDA database (number of subjects = 46,575) from the same group[33] found no significant differences in rates of suicide and suicide attempts among subjects assigned to the psychotropics (ie, antipsychotics, antidepressants, and anxiolytics) or placebo as measured by the frequency of completed suicides and suicide attempts. Storosum et al[15] analyzed all double-blind placebo-controlled trials that were part of a registration dossier for the indication schizophrenia submitted to the Medicines Evaluation Board in the Netherlands during the years 1992 through 2002 (ie, since submission of the first atypical antipsychotic to the Medicines Evaluation Board) for committed and attempted suicides (N = 7,152). There were no statistically significant differences between the active compounds versus placebo in the incidences of suicide or suicide attempt. This analysis was based on data from placebo-controlled trials only, with all suicides and attempted suicides occurring in the short-term trials with duration of less than 9 weeks and in hospitalized subjects.

Among the SGAs, clozapine has the strongest level of evidence for antisuicidal effect, established in patients with schizophrenia and high suicidality risk at baseline.[34,35] Clozapine was the first medical treatment approved by the FDA for reducing the risk of suicidal behavior in patients with schizophrenia or schizoaffective illness.[36] However, for the individual SGAs, data regarding possible treatment-emergent suicidality are scarce. Several case reports described emergence of suicidality in patients treated with aripiprazole.[37–40] In a retrospective analysis of patients with schizophrenia followed up for a 5-year period, Barack and colleagues[8] found that exposure to risperidone and olanzapine may confer protection from suicidality in patients with schizophrenia. Olanzapine was associated with a significant reduction on the Montgomery-Asberg Depression Rating Scale suicidal thoughts item versus haloperidol,[10] or a 2.3-fold reduction in the annual suicide attempt rate.[11] Finally, a recent report by Zisook et al[41] used a scalar approach to assess the effects of citalopram augmentation of antipsychotics on treatment-emergent suicidal ideation in middle-aged and older subjects with schizophrenia and subthreshold depressive symptoms, showing that treatment-emergent suicidal ideation was no more common with citalopram than placebo.

In comparison with schizophrenia, even less evidence is available on treatment-emergent suicidality during antipsychotic treatment of bipolar disorder, with no published reports using the possibly suicide-related adverse events identification and C-CASA classification of events. Nevertheless, even this limited evidence is contradictory. Storosum and colleagues[16] analyzed occurrence of suicide and attempted suicide in all placebo-controlled, double-blind, randomized trials of medications for the treatment of acute manic episode and the prevention of manic/depressive episode that were part of a registration dossier submitted to the Medicines Evaluation Board between 1997 and 2003 (number of subjects = 2,511). Although the list of included drugs was not provided, from the time span it can be concluded that data from at least some SGAs were included. No suicides or suicide attempts occurred, indicating no increase in risk of suicide/suicide attempt in subjects with acute manic episode treated with an active drug or placebo. Yerevanian and colleagues[42] found that treatment of bipolar subjects with antipsychotics was associated with an increase in nonlethal suicidal behavior: the nonlethal suicide event rates were 9.4 times greater during antipsychotic monotherapy and 3.5 times greater during mood stabilizer + antipsychotic than during mood stabilizer monotherapy. First- and second-generation antipsychotics were not distinguished. Marangel et al[43] evaluated the impact of pharmacotherapy on prospectively observed suicides and suicide attempts in subjects with bipolar disorder in the Systematic Treatment Enhancement Program for Bipolar Disorder. The results do not indicate a relationship between antipsychotic use and suicide attempts or completions. A scalar approach used in 2 post hoc analyses found a favorable effect of adjunctive olanzapine on suicidality risk in subgroups of subjects with bipolar disorder.[8,44]

High rates of suicide are also present in adolescents with schizophrenia or bipolar disorder.[45,46] However, the literature on the use of atypical antipsychotics in pediatric subjects is still limited, with most of the published data originating from anecdotal case reports and small, open-label trials.[47] The "boxed" warning[26] added to antidepressant labeling in 2005 for the pediatric population together with improvements in the clinical trial methodology and quality of reporting have undoubtedly increased awareness about treatment-emergent suicidality risk with psychotropic medication. Nevertheless, we could not find any published reports specifically addressing treatment-emergent suicidality associated with antipsychotics nor any evaluations of suicidality risk association with antipsychotics based on well-established possibly suicide-related adverse events search methodology and subsequent C-CASA classification.

Treatment-emergent suicidality was not reported during clinical monitoring of antipsychotics' side effects in a pediatric population[48] or in a clinical trial comparing the efficacy and safety of 2 SGAs (olanzapine and risperidone) with an FGA (molindone) in the Treatment of Early Onset Schizophrenia and Schizoaffective Disorder study.[49] However, in a pooled analysis of the overall adolescent olanzapine exposure database (N = 454, mean age = 15.9 years) in bipolar I disorder, 2 subjects (0.4%) attempted suicide and 13 (2.9%) had suicidal ideation.[50]

To our knowledge, no published reports exist that estimate treatment-emergent suicidality risk in subjects treated with antipsychotic drugs in double-blind, placebo-controlled trials using FDA-developed methodology for possibly suicide-related adverse events identification and C-CASA for categorization of events.

The aim of our assessments was to identify possibly suicide-related adverse events in Pfizer-sponsored, phases 2–4, placebo-controlled, double-blind adult and pediatric randomized controlled trials of the SGA ziprasidone, and to


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evaluate the risk of treatment-emergent suicidality with ziprasidone.

## METHOD

This analysis was based on the FDA-developed methodology.[19,26,27] The analyses were performed on possibly suicide-related adverse events retrieved in the search, which included all Pfizer-sponsored, completed, phases 2–4, all-duration, all-indication, randomized, double-blind, placebo-controlled trials of ziprasidone in adult and pediatric populations. In contrast to the FDA analysis of antidepressants[19,26] in which trials with less than 20 subjects per treatment arm or trials with duration longer than 17 weeks were excluded, there were no limits on number of subjects or trial duration for the ziprasidone analyses. Data from prematurely terminated trials were not included.

Suicidality risk evaluations were performed in the overall and segmented populations as follows: all adult and pediatric trials, all adult trials, all adult trials in schizophrenia, all adult trials in bipolar disorder, all pediatric trials, all pediatric trials in schizophrenia, and all pediatric trials in bipolar disorder. The details of the 22 trials included in these analyses are presented in Table 1.

**Table 1. Overview of Pfizer-Sponsored, Phases 2–4, Completed, Placebo-Controlled, All-Duration, All-Indication, Adult and Pediatric Trials of Ziprasidone**

| | Trial Registration No.[a] | No. of Trials | Ziprasidone, N | Placebo, N |
|---|---|---|---|---|
| Adult trials | | | | |
| Schizophrenia, schizoaffective disorder | | 9 | 1,122 | 471 |
| Bipolar I disorder | NCT00141271, NCT00280566, NCT00282464, NCT00312494, NCT00483548 | 9 | 1,792 | 1,167 |
| Dementia, Alzheimer's disease: primary degenerative dementia or multi-infarct dementia | | 1 | 11 | 12 |
| Subtotal | | 19 | 2,925 | 1,650 |
| Short-term adult trials (duration ≤ 6 wk)[b] | | 14 | 2,426 | 1,390 |
| Long-term adult trials (duration ≥ 40 wk)[b] | | 5 | 499 | 260 |
| Pediatric trials | | | | |
| Schizophrenia | NCT00257192 | 1 | 193 | 90 |
| Acute bipolar mania | NCT00257166 | 1 | 149 | 88 |
| Chronic tic disorder, Tourette's syndrome | | 1 | 16 | 12 |
| Subtotal | | 3 | 358 | 190 |
| Short-term pediatric trials (duration ≤ 8 wk)[b] | | 3 | 358 | 190 |
| Long-term pediatric trials (duration ≥ 40 wk)[b,c] | | 0 | 0 | 0 |
| Total | | 22 | 3,283 | 1,840 |

[a]Some trials took place prior to the time when it was standard to register with clinicaltrials.gov. Studies in which clinicaltrials.gov registration numbers are available are included in the table.
[b]There were no adult or pediatric placebo-controlled trials of ziprasidone with a duration between > 8 weeks and < 40 weeks.
[c]There were no long-term, placebo-controlled pediatric trials of ziprasidone.
Abbreviation: N = number of subjects treated.

The trials included were initiated as early as June 1992, and the cutoff date for selection of the placebo-controlled trials in the Pfizer database was October 2, 2009. The search for possibly suicide-related adverse events included all preferred and verbatim terms of adverse events, serious adverse events, or deaths and was limited to the time window defined by the FDA,[26] ie, the period between the first and last day of double-blind treatment plus 1 day after stopping double-blind treatment.

As little information is consistently and reliably available on subjects after they leave a trial, the FDA concluded that the only information likely to be consistently available would be information about any deaths that may have occurred in subjects after leaving the trial.[26] Thus, for the purpose of exploring the robustness of any suicidality findings, we also performed an additional exploratory analysis that included deaths by any cause by expanding the above time window beyond double-blind treatment plus 1 day to include the period up to 90 days after the discontinuation of double-blind treatment.[26]

The search was based on the following FDA-specified text strings[26] for all adverse events, serious adverse events, or deaths: *accident-*, *attempt*, *burn*, *cut*, *drown*, *gas*, *gun*, *hang*, *hung*, *immolat*, *injur**, *jump*, *monoxide*, *mutilate**, *overdos**, *self-damag**, *self harm*, *self inflict*, *self injur**, *shoot*, *slash*, *suic**, *poison*, *asphyxiation*, *suffocation*, and *firearm*, with a term *laceration* added. Comment fields were not included in the text string search. All possibly suicide-related adverse events identified by this search strategy, and not excluded as false-positives (eg, the text string *gas* was almost always associated with the adverse event flatulence or was part of the word *orgasm* in the adverse event delayed orgasm), had narrative summaries prepared in line with the FDA instructions, ie, providing information (when available) regarding patient ID number, trial number, and treatment group; sex and age; diagnosis; dose at time of event (mg); recent dose change; history of suicidal thoughts/suicide attempt/self-harm; adverse event preferred term; adverse event verbatim term; serious adverse event (yes/on); number of days on drug at the time of event; treatment discontinuation following event (yes/no); death of patient—if yes, elaboration on cause of death; associated treatment-emergent adverse events; concurrent psychosocial stressors; psychiatric comorbidities; concomitant medication; and other pertinent information (eg, family history of psychiatric disorders). The narratives were blinded to treatment assignment and

**Table 2. Incidences of Possibly Suicide-Related Adverse Events and Relative Risks With Corresponding 95% CIs in Pfizer-Sponsored, Phases 2–4, Completed, Placebo-Controlled, All-Duration, All-Indication, Adult and Pediatric Trials of Ziprasidone**

| | Ziprasidone (N = 3,283) | | Placebo (N = 1,840) | | Ziprasidone Versus Placebo | |
|---|---|---|---|---|---|---|
| Code | n (%) | 95% CI[a] | n (%) | 95% CI[a] | Relative Risk | 95% CI[a] |
| 1 (completed suicide) | 0 (0.00) | … | 0 (0.00) | … | … | … |
| 2 (suicide attempt) | 5 (0.15) | 0.05–0.36 | 5 (0.27) | 0.09–0.63 | 0.56 | 0.162–1.933 |
| 3 (preparatory acts toward imminent suicidal behavior) | 1 (0.03) | 0.00–0.17 | 0 (0.00) | 0.00–0.20 | $P > .999$[b] | … |
| 4 (suicidal ideation) | 26 (0.79) | 0.52–1.16 | 15 (0.82) | 0.46–1.34 | 0.97 | 0.516–1.829 |
| Suicidal behavior (codes 1–3)[c] | 6 (0.18) | 0.07–0.40 | 5 (0.27) | 0.09–0.63 | 0.67 | 0.206–2.201 |
| Suicidality (codes 1–4)[d] | 32 (0.97) | 0.67–1.37 | 20 (1.09) | 0.67–1.67 | 0.90 | 0.514–1.563 |

[a]Exact binomial 95% CIs are used for treatment group percentages.
[b]*P* value from Fisher exact test comparing incidence of ziprasidone versus placebo (relative risk could not be calculated).
[c]The secondary outcome was suicidal behavior (outcomes 1, 2, or 3 as per Posner et al,[28] also called preparatory actions or worse).
[d]The primary outcome was suicidality (outcomes 1, 2, 3, or 4 above as per Posner et al,[28] also called suicidal ideation or worse or suicidal behavior and ideation).
Abbreviations: N = number of subjects treated, n = number of subjects having an event.

details that might bias the assessment and classification. If a subject had more than 1 possibly suicide-related adverse event, all were included in the narrative.

The completed, blinded narratives were sent to the Center for Suicide Risk Assessment, Department of Psychiatry, Columbia University, New York, New York for an independent review. The classification of each possibly suicide-related adverse event was performed through application of the C-CASA,[28] the primary outcome measure. The C-CASA[28] classifications of possibly suicide-related adverse events are as follows: 1 = completed suicide; 2 = suicide attempt; 3 = preparatory acts toward imminent suicidal behavior; 4 = suicidal ideation; 5 = self-injurious behavior, intent unknown; 6 = not enough information (fatal); 7 = self-injurious behavior, no suicidal intent; 8 = other—accident, psychiatric, medical; and 9 = not enough information (nonfatal).

If a subject had more than 1 possibly suicide-related adverse event, the most severe event was retained and included in the analysis (eg, completed suicide > suicide attempt > suicidal ideation) as per Posner et al.[28] Subsequent to classification, treatment allocations were unblinded and assigned to each case.

### Statistical Analysis

The incidences of possibly suicide-related adverse events in the ziprasidone and placebo groups were calculated for each classification code for the predefined primary outcome suicidality (comprising classification codes 1, 2, 3, or 4; also known as suicidal ideation or worse, or suicidal behavior and ideation) and for the secondary outcome suicidal behavior (comprising classification codes 1–3, also known as preparatory actions or worse).[19,26] The incidences of possibly suicide-related adverse events with ziprasidone versus placebo were compared using relative risks and corresponding 95% CIs. In our analysis, suicidality risk evaluations are presented for the individual categories 1–4 and the primary and secondary outcomes. Fisher exact test (2-sided) was used to compare incidences when relative risk was undefined using a .05 level of significance. Exact binomial 95% CIs were calculated for the individual treatment-group incidences.

For the relative risk, confidence intervals that exclude the value of 1 indicated a statistically significant difference between the incidences in the ziprasidone and placebo treatment groups. In contrast to the FDA analysis, clinical trials with no events were included in these analyses, allowing for increased precision of point estimates. Analyses were performed using SAS version 8.2 and 9.1 (SAS Institute Inc, Cary, North Carolina).

As a sensitivity analysis, risk differences between ziprasidone and placebo were estimated using a Mantel-Haenszel approach,[51] which is a generalization to risk differences of the Mantel-Haenszel odds ratio method. A common risk difference (ziprasidone minus placebo) across trials (including trials with no events) was estimated using a weighted mean method, with which the weight of a given trial was a function of the number of subjects in the trial. In addition, risk differences were estimated by using the DerSimonian-Laird[52] approach with which the weight of a given trial is a function of the inverse variance estimated using a random effects model. The confidence intervals (95%) for the common risk differences were obtained using a normal approximation to the binomial distribution. In order to avoid individual trial variances being equal to 0, a 0.5 continuity correction was applied to empty cells for trials in which neither treatment arm had events. In addition, a separate analysis was performed using exact methods for estimating a common odds ratio (ziprasidone/placebo) across trials. This approach makes use of trials in which at least 1 event occurred in either treatment arm; trials with no events were not included. The exact methods were applied with the software StatXact 5 for SAS, using the PROC STRATIFY procedure. Homogeneity of odds ratios was verified by a Zelen test, which is the exact equivalent of the Breslow-Day asymptotic test. "Mid-p adjusted" 95% exact confidence intervals were calculated for the common odds ratio.

## RESULTS

### Adult and Pediatric Trials Combined

The overall analysis was based on a total of 22 adult and pediatric placebo-controlled trials, with 5,123 treated subjects (Table 2).

There were no suicides in the overall patient population. The absolute number of suicidality events was low across both treatment groups (ziprasidone-treated subjects: 32/3,283; placebo-treated subjects: 20/1,840), yielding a relative risk of 0.90 (95% CI, 0.514–1.563). There

**Table 3. Incidences of Possibly Suicide-Related Adverse Events and Relative Risks With Corresponding 95% CIs in Pfizer-Sponsored, Phases 2–4, Completed, Placebo-Controlled, All-Duration, Adult Trials of Ziprasidone in Schizophrenia and Bipolar Disorder**

| | Ziprasidone (N = 2,925) | | Placebo (N = 1,650) | | Ziprasidone vs Placebo | |
|---|---|---|---|---|---|---|
| Code | n (%) | 95% CI[a] | n (%) | 95% CI[a] | Relative Risk | 95% CI[a] |
| All adult trials | | | | | | |
| 1 (completed suicide) | 0 (0.00) | … | 0 (0.00) | … | … | … |
| 2 (suicide attempt) | 3 (0.10) | 0.02–0.30 | 4 (0.24) | 0.07–0.62 | 0.42 | 0.095–1.888 |
| 3 (preparatory acts toward imminent suicidal behavior) | 1 (0.03) | 0.00–0.19 | 0 (0.00) | 0.00–0.22 | $P > .999$[d] | … |
| 4 (suicidal ideation) | 21 (0.72) | 0.45–1.10 | 11 (0.67) | 0.33–1.19 | 1.08 | 0.521–2.228 |
| Suicidal behavior (codes 1–3)[b] | 4 (0.14) | 0.04–0.35 | 4 (0.24) | 0.07–0.62 | 0.56 | 0.141–2.253 |
| Suicidality (codes 1–4)[c] | 25 (0.85) | 0.55–1.26 | 15 (0.91) | 0.51–1.49 | 0.94 | 0.497–1.778 |
| All adult trials in schizophrenia | | | | | | |
| | Ziprasidone (N = 1,122) | | Placebo (N = 471) | | | |
| 1 (completed suicide) | 0 (0.00) | … | 0 (0.00) | … | … | … |
| 2 (suicide attempt) | 2 (0.18) | 0.01–0.64 | 2 (0.42) | 0.05–1.53 | 0.42 | 0.059–2.971 |
| 3 (preparatory acts toward imminent suicidal behavior) | 1 (0.09) | 0.00–0.50 | 0 (0.00) | 0.00–0.78 | $P > .999$[d] | … |
| 4 (suicidal ideation) | 8 (0.71) | 0.31–1.40 | 0 (0.00) | 0.00–0.78 | $P = .114$[d] | … |
| Suicidal behavior (codes 1–3)[b] | 3 (0.27) | 0.06–0.78 | 2 (0.42) | 0.05–1.53 | 0.63 | 0.106–3.756 |
| Suicidality (codes 1–4)[c] | 11 (0.98) | 0.49–1.75 | 2 (0.42) | 0.05–1.53 | 2.31 | 0.514–10.376 |
| All adult trials in bipolar disorder | | | | | | |
| | Ziprasidone (N = 1,792) | | Placebo (N = 1,167) | | | |
| 1 (completed suicide) | 0 (0.00) | … | 0 (0.00) | … | … | … |
| 2 (suicide attempt) | 1 (0.06) | 0.00–0.31 | 2 (0.17) | 0.02–0.62 | 0.33 | 0.030–3.587 |
| 3 (preparatory acts toward imminent suicidal behavior) | 0 (0.00) | … | 0 (0.00) | … | … | … |
| 4 (suicidal ideation) | 13 (0.73) | 0.39–1.24 | 11 (0.94) | 0.47–1.68 | 0.77 | 0.346–1.712 |
| Suicidal behavior (codes 1–3)[b] | 1 (0.06) | 0.00–0.31 | 2 (0.17) | 0.02–0.62 | 0.33 | 0.030–3.587 |
| Suicidality (codes 1–4)[c] | 14 (0.78) | 0.43–1.31 | 13 (1.11) | 0.59–1.90 | 0.70 | 0.331–1.487 |

[a]Exact binomial 95% CIs are used for treatment group percentages.
[b]The secondary outcome was suicidal behavior (outcomes 1, 2, or 3 as per Posner et al,[28] also called preparatory actions or worse).
[c]The primary outcome was suicidality (outcomes 1, 2, 3, or 4 above as per Posner et al,[28] also called suicidal ideation or worse or suicidal behavior and ideation).
[d]*P* value from Fisher exact test comparing incidence of ziprasidone versus placebo (relative risk could not be calculated).
Abbreviations: N = number of subjects treated, n = number of subjects having an event.

were no statistically significant differences in risk between ziprasidone- and placebo-treated subjects in any of the individual classification codes or in the primary or secondary outcome (Table 2).

In the additional exploratory analysis, which included deaths by any cause occurring in the period up to 90 days after completion of double-blind treatment, a total of 2 completed suicides occurred in the combined adult and pediatric population. One case was reported in a ziprasidone-treated adult (1/3,283 [0.03%]; 95% CI, 0.00–0.17) and 1 in a placebo-treated adult (1/1,840 [0.05%]; 95% CI, 0.00–0.30) yielding a relative risk of 0.56 (95% CI, 0.035–8.955). The first suicide occurred in a subject with mixed bipolar disorder and a history of alcohol abuse who was randomized to treatment with ziprasidone.[53] On day 1 of treatment, the subject experienced moderate restlessness considered related to study drug. Ziprasidone was discontinued because of this event, with the last dose administered on day 9. Topiramate was started on day 11, followed by sertraline and quetiapine on day 12. The subject reported suicidal ideation after ziprasidone discontinuation and committed suicide on day 17, the day of discharge (9 days after the last dose of ziprasidone). The investigator attributed the suicide to the disease under study. The second suicide occurred in a subject with a diagnosis of chronic paranoid schizophrenia (acute episode). Seven days after completing 32-day dosing with placebo, the subject committed suicide. This event was not considered study drug related by the investigator.

### Adult Trials

In the analysis of all adult trials, which were based on a total of 19 placebo-controlled trials with 4,575 treated subjects included (Table 3), the relative risk for suicidality was 0.94 (95% CI, 0.497–1.778). Respective relative risks for suicidality in the adult schizophrenia and bipolar disorder trials were 2.31 (95% CI, 0.514–10.376) and 0.70 (95% CI, 0.331–1.487). In all 3 analyses of adult subjects, the absolute number of suicidality events was low across both treatment groups, with no statistically significant differences in risk between ziprasidone- and placebo-treated subjects in any of the individual classification codes primary or secondary outcomes (Table 3). In the exploratory analysis, there were 2 cases of completed suicide, yielding a relative risk of 0.56 (95% CI, 0.035–9.013). Details about the 2 cases are given in the Adult and Pediatric Trials Combined section of this article.

**Table 4. Incidences of Possibly Suicide-Related Adverse Events and Relative Risks With Corresponding 95% CIs in Pfizer-Sponsored, Phases 2–4, Completed, Placebo-Controlled, All-Duration, Pediatric Trials of Ziprasidone in Schizophrenia and Bipolar Disorder**

| | Ziprasidone (N = 358) | | Placebo (N = 190) | | Relative | |
|---|---|---|---|---|---|---|
| Code | n (%) | 95% CI[a] | n (%) | 95% CI[a] | Risk | 95% CI[a] |
| All pediatric trials (subjects 7–17 years of age) | | | | | | |
| 1 (completed suicide) | 0 (0.00) | … | 0 (0.00) | … | … | … |
| 2 (suicide attempt) | 2 (0.56) | 0.07–2.00 | 1 (0.53) | 0.01–2.90 | 1.06 | 0.097–11.631 |
| 3 (preparatory acts toward imminent suicidal behavior) | 0 (0.00) | … | 0 (0.00) | … | … | … |
| 4 (suicidal ideation) | 5 (1.40) | 0.46–3.23 | 4 (2.11) | 0.58–5.30 | 0.66 | 0.180–2.442 |
| Suicidal behavior (codes 1–3)[b] | 2 (0.56) | 0.07–2.00 | 1 (0.53) | 0.01–2.90 | 1.06 | 0.097–11.631 |
| Suicidality (codes 1–4)[c] | 7 (1.96) | 0.79–3.99 | 5 (2.63) | 0.86–6.03 | 0.74 | 0.239–2.310 |
| All pediatric trials in schizophrenia (subjects 13–17 years of age) | | | | | | |
| | Ziprasidone (N = 193) | | Placebo (N = 90) | | | |
| 1 (completed suicide) | 0 (0.00) | … | 0 (0.00) | … | … | … |
| 2 (suicide attempt) | 1 (0.52) | 0.01–2.85 | 0 (0.00) | 0.00–4.02 | $P > .999$[d] | … |
| 3 (preparatory acts toward imminent suicidal behavior) | 0 (0.00) | … | 0 (0.00) | … | … | … |
| 4 (suicidal ideation) | 2 (1.04) | 0.13–3.69 | 1 (1.11) | 0.04–6.04 | 0.93 | 0.086–10.152 |
| Suicidal behavior (codes 1–3)[b] | 1 (0.52) | 0.01–2.85 | 0 (0.0) | 0.00–4.02 | $P > .999$[d] | … |
| Suicidality (codes 1–4)[c] | 3 (1.55) | 0.32–4.48 | 1 (1.11) | 0.03–6.04 | 1.40 | 0.148–13.264 |
| All pediatric trials in bipolar disorder (subjects 10–17 years of age) | | | | | | |
| | Ziprasidone (N = 149) | | Placebo (N = 88) | | | |
| 1 (completed suicide) | 0 (0.00) | … | 0 (0.00) | … | … | … |
| 2 (suicide attempt) | 1 (0.67) | 0.02–3.68 | 1 (1.14) | 0.03–6.17 | 0.59 | 0.037–9.324 |
| 3 (preparatory acts toward imminent suicidal behavior) | 0 (0.00) | … | 0 (0.00) | … | … | … |
| 4 (suicidal ideation) | 3 (2.01) | 0.42–5.77 | 3 (3.41) | 0.71–9.64 | 0.59 | 0.122–2.863 |
| Suicidal behavior (codes 1–3)[b] | 1 (0.67) | 0.02–3.68 | 1 (1.14) | 0.03–6.17 | 0.59 | 0.037–9.324 |
| Suicidality (codes 1–4)[c] | 4 (2.68) | 0.74–6.73 | 4 (4.55) | 1.25–11.23 | 0.59 | 0.151–2.303 |

[a]Exact binomial 95% CIs are used for treatment group percentages.
[b]The secondary outcome was suicidal behavior (outcomes 1, 2, or 3 as per Posner et al,[28] also called preparatory actions or worse).
[c]The primary outcome was suicidality (outcomes 1, 2, 3, or 4 above as per Posner et al,[28] also called suicidal ideation or worse or suicidal behavior and ideation).
[d]*P* value from Fisher exact test comparing incidence of ziprasidone versus placebo (relative risk could not be calculated).
Abbreviations: N = number of subjects treated, n = number of subjects having an event.

### Pediatric Trials

This analysis included 3 placebo-controlled trials, with 548 ziprasidone- and placebo-treated subjects aged 7–17 years (Table 4). There were no completed suicides in the pediatric trials in the time window initially defined by the FDA or in the exploratory analysis. Suicidality was identified in a total of 12 subjects (relative risk = 0.74; 95% CI, 0.239–2.310). The relative risk for suicidality in the pediatric schizophrenia trial (N = 283) was 1.40 (95% CI, 0.148–13.264) and, in the bipolar disorder trial (N = 237), was 0.59 (95% CI, 0.151–2.303). In all 3 analyses of pediatric subjects, the absolute number of suicidality events was low across both treatment groups, with no statistically significant differences in treatment-emergent suicidality risk between ziprasidone- and placebo-treated subjects in any of the individual classification codes or in the primary or secondary outcomes (Table 4).

### Sensitivity Analysis

The results using the Mantel-Haenszel and DerSimonian-Laird risk difference approaches and the exact methods for the common odds ratio are shown in Table 5 for adult and pediatric trials combined for events using the period between the first and last day of double-blind treatment plus 1 day after stopping double-blind treatment. All the confidence intervals for risk differences include the value of 0, indicating that ziprasidone and placebo are not significantly different with respect to the risk of suicidality. Furthermore, when exact methods were applied, in all instances in which the common odds ratio was estimable, the confidence interval included the value of 1, indicating once more that there is no statistically significant difference between ziprasidone and placebo. Furthermore, results obtained in the sensitivity analysis of all adult and all pediatric trials separately (data not shown) fully concur with the above results. In addition, the above results were also seen when the extended time window between the first day and the last day of double-blind treatment plus 90 days after stopping double-blind treatment was used (results not shown).

## DISCUSSION

To our knowledge, these analyses are the first to report results of treatment-emergent suicidality risk evaluations in placebo-controlled trials of an antipsychotic across different indications and patient populations that are based on a possibly suicide-related adverse event–identified[26] and subsequently C-CASA–classified[28] events. All results (ie, in the overall population, across schizophrenia or bipolar disorder indications, as well as in adult and pediatric populations) are consistent in showing no significant difference in suicidality risk in ziprasidone versus placebo subjects treated in controlled clinical trials. These results were further confirmed in the sensitivity analyses.

Because any published reports using at least similar methodology are currently lacking, it is difficult to compare our results with other reports available in the public domain. Khan et al[14,33] or Storosum et al[15] did not use possibly suicide-related adverse events search methodology or C-CASA classification. In particular, Khan and colleagues'[14,33] results are difficult to compare with ours, since their incidences were based on calculations using patient exposure years. Nevertheless, similar to the results in Storsum et al,[15] in our analysis of adult subjects with schizophrenia, which was based on a smaller sample, there were no statistically significant differences between ziprasidone and placebo in the incidences of suicide (ziprasidone, 0.00% vs placebo,

Table 5. Risk Differences and Exact Odds Ratios for Possibly Suicide-Related Adverse Events With Corresponding 95% CIs in Pfizer-Sponsored, Phases 2–4, Completed, Placebo-Controlled, Adult and Pediatric Trials of Ziprasidone

| Code | Ziprasidone (N = 3,283), n (%) | Placebo (N = 1,840), n (%) | Unadjusted Risk Difference[a] | 95% CI | Mantel-Haenszel–Adjusted Risk Difference[a] | 95% CI | DerSimonian-Laird–Adjusted Risk Difference[a] | 95% CI | Exact OR | 95% CI, Mid-p Corrected |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 (completed suicide) | 0 (0.00) | 0 (0.00) | −0.0026 | −0.0066 to 0.0014 | −0.0026 | −0.0068 to 0.0016 | −0.0017 | −0.0052 to 0.0018 | Nonestimable | |
| 2 (suicide attempt) | 5 (0.15) | 5 (0.27) | −0.0031 | −0.0075 to 0.0014 | −0.0033 | −0.0079 to 0.0014 | −0.0023 | −0.0063 to 0.0018 | 0.47 | 0.1260 to 1.7623 |
| 3 (preparatory acts toward imminent suicidal behavior) | 1 (0.03) | 0 (0.00) | −0.0025 | −0.0065 to 0.0016 | −0.0025 | −0.0067 to 0.0017 | −0.0017 | −0.0052 to 0.0018 | Nonestimable | |
| 4 (suicidal ideation) | 26 (0.79) | 15 (0.82) | −0.0035 | −0.0095 to 0.0025 | −0.0023 | −0.0083 to 0.0037 | −0.0002 | −0.0051 to 0.0047 | 1.15 | 0.6031 to 2.2570 |
| Suicidal behavior (codes 1–3)[b] | 6 (0.18) | 5 (0.27) | −0.0029 | −0.0074 to 0.0016 | −0.0031 | −0.0078 to 0.0015 | −0.0022 | −0.0063 to 0.0019 | 0.55 | 0.1590 to 1.9676 |
| Suicidality (codes 1–4)[c] | 32 (0.97) | 20 (1.09) | −0.0035 | −0.0100 to 0.0029 | −0.0027 | −0.0092 to 0.0038 | −0.0008 | −0.0063 to 0.0047 | 0.98 | 0.5543 to 1.7646 |

[a]0.5 has been added to the cells with 0 frequencies in calculations of risk differences and 95% CIs.
[b]The secondary outcome was suicidal behavior (outcomes 1, 2, or 3 as per Posner et al,[28] also called preparatory actions or worse).
[c]The primary outcome was suicidality (outcomes 1, 2, 3, or 4 above as per Posner et al,[28] also called suicidal ideation or worse or suicidal behavior and ideation).
Abbreviations: N = number of subjects treated, n = number of subjects having an event.

0.00%) or suicide attempt (ziprasidone, 0.18% vs placebo, 0.42%; relative risk = 0.42; 95% CI, 0.059–2.971).

There were several limitations to our analysis. Given the size of the sample (3,283 ziprasidone-treated subjects and 1,840 placebo-treated subjects) and the calculated C-CASA suicidality incidence of approximately 1% in each group, there would be an 80% probability of detecting an increase of 1%, a doubling of the incidence. If the actual incidences were lower, the sample would be too small to have sufficient power to detect an increase in the event incidences.

Although both schizophrenia and bipolar disorder are associated with high suicide rates,[1–7] no completed suicides occurred during the trials included in our analysis. Several factors may have contributed to the absence of completed suicides and low rates of other possibly suicide-related adverse events observed. Our analysis was based on data from participants in controlled clinical trials and not from patients in everyday clinical practice. Active suicidality is a standard exclusion criterion in clinical trials, including those in schizophrenia and bipolar disorder. In addition, the trials involved regular visits to psychiatrists and frequent assessments, which could have contributed to a nonspecific therapeutic effect or possibly to an early detection of potential suicidality and subsequent timely intervention. Given the limitations (ie, number of subjects, post hoc identification of possibly suicide-related adverse events, exclusion of subjects with baseline suicidality from individual trials included in the analysis, and rareness of events), the risk estimates could have been underestimated.

Furthermore, evaluation of treatment-emergent suicidality risk was based on reported adverse events in clinical trials, which are inevitably associated with varying quality.[28] The same remarks were also the basis for criticism of the C-CASA classification system of suicidality.[54–56] However, C-CASA is based on a systematic search and categorization of events occurring during the trial, does not rely on the presence of specific preincluded scales, and, thus, has broad applicability across different types of trials. Despite its shortcomings, it appears that the C-CASA classification system provides a currently acceptable method for retrospective identification of treatment-emergent suicidality and suicidal behavior.[22] Nevertheless, it should be kept in mind that our data were retrospectively collected from clinical trials assessing the efficacy and safety of ziprasidone and not prospectively assessing suicidality during treatment with ziprasidone. Prospectively and systematically assessed treatment-emergent suicidality using specifically designed tools—one of which is the Columbia Suicide Severity Rating Scale (C-SSRS)[57]—would provide more accurate information. The proposed *DSM-5* revisions include 2 new scales (1 for adolescents and 1 for adults) for assessing individuals' risk factors for committing suicide.[58] While the current version of *DSM* includes thoughts of suicide as a symptom of some mental disorders, the proposed suicide risk assessment techniques[58] have been designed to be applied to anyone receiving an evaluation for a mental disorder, regardless of diagnosis, thus helping clinicians identify those at risk for suicide. In



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addition, because of the focus on the question of how best to assess suicidality in future trials, on September 8, 2010, the FDA's Division of Psychiatry Products issued its draft guidance[59] recommending that, for all products that fall under the purview of the Division of Psychiatry Products, prospective assessment of suicidality should be included in clinical development. This requirement pertains to all clinical protocols for any psychiatric condition, as well as neurologic drugs with central nervous system activity irrespective of the indication, throughout every phase of development and at each assessment. An acceptable instrument for suicidality assessment would be C-SSRS[57] or one that maps to the C-CASA[28] categories.

Inclusion of both adult and pediatric trials into our analysis may be a concern since those are 2 distinct populations from both a clinical and regulatory point of view. The suicide risk for adolescents or young adults with schizophrenia is 3 times higher than that for adult subjects with schizophrenia, with the first 2 years of the disease being especially dangerous,[4] while high rates of suicide are present in adolescents with bipolar disorder.[46] Thus, performing an overall analysis for the total patient population (ie, adult and pediatric population combined) provides full insight into effects ziprasidone could have had across all populations at risk, while separate analyses in adult and pediatric populations again demonstrate lack of significant risk of treatment-emergent suicidality in ziprasidone- versus placebo-treated subjects. However, our results in pediatric subjects should be interpreted with caution due to a limited number of trials (3) included in the analysis, limited sample size (N = 548), low rates of reported events, and wide confidence intervals.

We felt it is clinically and statistically prudent to include trials with no events into our analysis. Clinically, the lack of events within the clinical trial is informative, as the diseases studied (ie, schizophrenia and bipolar disorder) involved populations at increased risk for suicide and related behaviors.[22] Furthermore, exclusion may result in a diminished precision of point estimates and, more importantly, an exaggeration of risk that is introduced by ascertainment bias, as well as a tendency to inflate the risk estimate for active treatments.[22]

In conclusion, the results of a retrospective C-CASA classification of possibly suicide-related adverse events from Pfizer's ziprasidone placebo-controlled adult and pediatric trials' database reveal no significant differences in treatment-emergent suicidality risk in subjects treated with ziprasidone versus placebo in controlled clinical trials. Since February 2009, all clinical trials for products developed under the FDA Division of Psychiatry Products must prospectively and systematically monitor the occurrence and emergence of suicidality[59] through consistent methods of ascertainment.[28,57] Results of trials using this prospective assessment approach will help elucidate the relationship between treatment-emergent suicidality and pharmacologic treatments and contribute to improved identification and management of suicidality in clinical practice.

***Drug names:*** aripiprazole (Abilify), atomoxetine (Strattera and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), molindone (Moban), montelukast (Singulair), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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