FDA

Psychopharmacological Drugs

Advisory Committee

19 July 2000

Briefing Document for

ZELDOX® CAPSULES

(Ziprasidone HCl)

EXECUTIVE SUMMARY

Ziprasidone is an atypical antipsychotic that may offer important clinical benefits to the approximately 1%-2% of the population that suffer from the devastating effects of acute and chronic schizophrenia and schizoaffective disorder. This document summarizes safety and efficacy data available for ziprasidone with particular emphasis on ECG findings and other important cardiovascular risk factors.

Ziprasidone Is an Effective and Well-Tolerated Agent for the Short-Term and Long-Term Management of Psychosis.

In short-term (4 to 6 week), double-blind, fixed-dose, placebo-controlled trials ziprasidone was superior to placebo in treating the positive, negative, and depressive symptoms associated with an acute exacerbation of schizophrenia or schizoaffective disorder. In a one-year, double-blind, placebo-controlled maintenance trial, ziprasidone significantly reduced the risk of recurrence of acute exacerbation in hospitalized patients with chronic or subchronic schizophrenia. Ziprasidone was also effective in treating the negative symptoms of schizophrenia.

Ziprasidone was well tolerated in both the short-term and long-term placebo-controlled trials, with a low overall incidence of adverse events. Ziprasidone demonstrated a particularly low liability for movement disorder adverse events as evidenced by a low rate of spontaneous reports and by specific rating scales. Ziprasidone treatment was not associated with any laboratory test abnormalities indicative of clinically relevant toxicity.

Pharmacokinetics of Ziprasidone have been Extensively Studied in Individual Trials as well as in a Large Population Pharmacokinetic Database.

Ziprasidone displays linear pharmacokinetics over the recommended dose range (80 to 160 mg daily) and has a mean half-life of 6.6 hrs. Its relative oral bioavailability is increased by up to 100% in the presence of food. In multiple dose studies, the Cmax typically occurs at approximately 6 hrs after dosing in the fed state, with steady-state attained within 1 to 3 days. Ziprasidone is extensively metabolized by both aldehyde oxidase and P-450 mixed function oxidases (predominantly CYP3A4). One circulating metabolite of ziprasidone, S-methyl-dihydroziprasidone (M9), may contribute to its pharmacologic effects. Co-administration of CYP3A4 inhibitors or inducers with ziprasidone results in limited (~35%) increases/decreases in ziprasidone exposure. No other clinically significant drug-drug interactions have been observed.

The Effect of Ziprasidone on the QTc is Modest and Well Characterized.

In the short-term, double-blind, placebo-controlled trials submitted with the NDA, doses of ziprasidone from 80 to 160 mg daily were associated with a mean

increase in QTc relative to baseline of 5.9 to 9.7 msec (Bazett correction) or 4.4 to 9.3 msec (Baseline correction).

The FDA issued a not-approvable letter for oral ziprasidone in June of 1998, characterizing the decision as a "very close" one. The sponsor was asked to conduct further evaluation of the compound with respect to QT effects.

Study 054 was designed, in consultation with the Agency, to measure the effects, at peak drug exposure after dosing, of ziprasidone, risperidone, olanzapine, quetiapine, thioridazine and haloperidol on the QTc. Electrocardiograms were recorded under fasting conditions and at the time of estimated maximum exposure to each study drug, in the absence and presence of a metabolic inhibitor. QT interval measurements were made using standardized 12-lead ECG methodology. A mean prolongation of QTc was measured for every antipsychotic agent tested, a finding that is consistent with preclinical properties of these agents. Although selected as a comparator in part because it was expected to have no effect on QTc, a relationship between concentration and QTc effect was detected for haloperidol, providing evidence of the capacity of that drug to prolong QTc at a therapeutic dose. The QTc effect of ziprasidone 160 mg was found to be approximately 10 msec greater than the effects of four of the comparative antipsychotics (haloperidol, quetiapine, risperidone and olanzapine) and 10 msec less than the QTc effect of thioridazine 300 mg.

Ziprasidone Demonstrated no Further QTc Prolongation in the Presence of Metabolic Inhibition. The QTc Effect of Ziprasidone Appears to be Limited, as a Function of its Pharmacology and the Stability of its Metabolism, under Observed and Expected Conditions of Use.

The metabolism of ziprasidone is mediated by aldehyde oxidase and by CYP3A4. There are no clinically recognized inhibitors or inducers of aldehyde oxidase. Inhibition of CYP3A4 resulted in an increase in the concentrations of both ziprasidone and its M9 metabolite, S-methyl-dihydroziprasidone, but no further increase in QTc effect. These observations demonstrate that drug interactions with potential to cause alterations of ziprasidone metabolism have not produced an increase in the effect of ziprasidone on QTc. Further support is provided by concentration – QTc data collected in Phase 2/3 clinical trials, and by review of the clinical experience of those individuals with highest concentrations of ziprasidone or its metabolites.

The Ziprasidone Database Showed No Signal of Increased Cardiovascular Risk:

- ***Rare QTc ≥ 500 msec***
- ***No Torsade de Pointes***
- ***Mortality Rate Equal to Background***
- ***Benign Overdose Experience***

There is no general consensus in either the reported literature or among cardiovascular experts that permits identification of a threshold of QTc effect that is clinically significant. The QTc interval is highly variable and is affected by a broad set of both internal and external influences. The precise relationship between cardiac repolarization and the risk of serious adverse cardiac events remains unsettled.

What is certain is that QTc prolongation is of concern because of its potential to induce syncope, torsade de pointes and sudden death. Since the overwhelming majority of reported cases of torsade de pointes are seen in individuals with measured QTc values of 500 msec or greater, a prolongation of QTc to ≥500 msec provides a clinically meaningful measure for purposes of assessing QTc risk.

The ziprasidone database and Study 054 are reassuring with regard to this issue. In the Phase 2/3 development program overall, only 0.06% (2/3095) of patients had a QTc (Bazett) interval ≥500 msec. In Study 054, no ziprasidone-treated patient had a QTc ≥500 msec, despite coadministration of the metabolic inhibitor ketoconazole to patients receiving the highest recommended dose of ziprasidone.

Also meaningful is the lack of excess total mortality, sudden deaths or syncope for ziprasidone patients compared with patients given placebo or other commonly prescribed antipsychotics. In fact, the mortality rate in the ziprasidone group has declined slightly since the NDA was filed and is less than that measured in the placebo group in each reporting category. This has occurred while the number of patients receiving ziprasidone has more than doubled since filing the NDA, and the cumulative patient-years of exposure to ziprasidone has increased nearly three-fold. No episodes of torsade de pointes have been reported among the 4571 patients treated with ziprasidone for a cumulative total of 1733 patient-years exposure. No significant cardiac events were associated with ziprasidone in the ten overdose cases.

The Overall Experience with Terfenadine is Instructive when Considering the Risk of Modest vs. Marked QTc Prolongation

It has been widely quoted that terfenadine causes an approximately 6 msec prolongation of the QTc in the absence of CYP3A4 metabolic inhibition. Further, it is generally believed, based upon data from large epidemiological studies as well

as a marketing experience of over 100 million prescriptions, that terfenadine is safe when administered alone. It is presumed that this understanding underlies the belief that a drug associated with QTc prolongation in the range of 5 to 10 msec is acceptably safe. However, in using this information as a benchmark against which to compare the cardiovascular safety of new agents, it is critical to acknowledge that the QTc prolongation of 6 msec associated with terfenadine represents the ***mean*** over the dosing interval, i.e. QTc effect averaged across the dosing interval. Closer examination of data collected in a clinical trial examining the effect of terfenadine on the QT interval[1] reveals a QTc prolongation of approximately 18 msec occurring one hour after administration of terfenadine 60 mg, in the absence of metabolic inhibition. This observation provides an appropriate context in which to assess the QTc data presented in this submission.

The withdrawal of terfenadine from the market was prompted by safety concerns related to drug interactions. Administration of terfenadine in combination with ketoconazole, a potent inhibitor of CYP3A4, has been reported to cause a QTc prolongation of 82 msec 12 hours after dosing (i.e., at or near trough)[2] and is associated with documented cases of torsade de pointes and sudden death. It is only under circumstances of such drug interactions that terfenadine poses an unacceptably high safety risk.

As documented in this submission the ***mean*** QTc prolongation associated with therapeutic doses of ziprasidone is in the range of 5 to10 msec. When examined at the time of peak serum concentrations, ziprasidone is associated with a QTc prolongation of approximately 15 to 20 msec. These data compare favorably with terfenadine data under conditions in which its safe use has been well established. More importantly, and in striking contrast to terfenadine, the QTc effect of ziprasidone is not altered in the face of CYP3A4 metabolic inhibition. In Study 054, despite an increase in serum ziprasidone and metabolite concentrations during concomitant administration with ketoconazole, no change in QTc was observed compared to ziprasidone when administered alone.

The QTc Effect of Ziprasidone Is Noticeably Less than the QTc Effect of Sertindole

As reported at the Psychopharmacology Advisory Committee in July 1996, sertindole causes a mean QTc increase of 21-30 msec at its recommended dose of 24 mg/day. In contrast, ziprasidone caused a mean QTc increase of <10 msec at the recommended dose of 160 mg/day. Most noticeably, 7-8% of sertindole patients receiving the recommended dose were reported to have one or more QTc values ≥500 msec. Fewer than 0.1% of ziprasidone patients in the Phase 2/3 clinical program had one or more QTc values ≥500 msec. In addition, sertindole is a substrate for CYP3A4 and CYP2D6, properties that led to considerable variability in exposure across a population. Ziprasidone has a demonstrated absence of CYP-450 interaction liability.

In Contrast to other Antipsychotics, Ziprasidone Is Neutral or has Beneficial Effects on the Well-Established Cardiovascular Risk Factors of Increased Body Weight, Serum Lipid Levels and Glucose Tolerance

Beyond demonstrating that the effect of ziprasidone on the QTc has not been associated with clinically significant adverse effects, it was observed that the profile of ziprasidone with regard to the well-established cardiovascular risk factors of body weight, serum lipids, and glucose tolerance differs considerably from a number of other widely used antipsychotics that adversely impact these risk factors.

Ziprasidone can be differentiated from other atypical antipsychotics with respect to its low propensity to cause weight gain and its beneficial effect on serum lipids. Patients with schizophrenia are likely to have a higher Body Mass Index than individuals in the general population,[3] a trend that is aggravated by the tendency of antipsychotic medications to cause weight gain.[4,5] Data from the short-term, double-blind, placebo-controlled trials demonstrated that the incidence of clinically significant weight gain (≥7% of baseline body weight) in ziprasidone-treated patients was lower than that reported for short-term trials with olanzapine, risperidone, or quetiapine. Similarly, in long-term trials, ziprasidone-treated patients had a lower incidence of clinically significant weight gain than risperidone-treated patients. As individuals afflicted with schizophrenia typically require long term antipsychotic treatment, these findings may have implications for patient compliance and significant consequences with respect to the long-term health of these patients.

In addition, literature reports of an association between at least some antipsychotic agents and glucose intolerance have led to increased regulatory scrutiny of these agents. There is no evidence that ziprasidone carries such an association.

The low liability of ziprasidone with respect to weight gain may have significance for patients even beyond the cardiovascular and other health effects. A recent survey conducted by Consumer Health Sciences among members of the National Alliance for the Mentally Ill and the National Mental Health Association, found that body weight gain is both prevalent and distressing, and frequently leads to patient-driven decisions to switch or discontinue medications.

The favorable effect of ziprasidone on serum cholesterol levels is clinically significant and may lead to important long-term health consequences for patients. Data showing a reduction of total cholesterol levels during ziprasidone treatment were first reported in studies in which patients were switched to ziprasidone from other antipsychotics. Study 054 confirmed and extended this finding by showing that ziprasidone produced clinically important decreases from baseline in fasting total cholesterol, LDL cholesterol, and triglycerides, while having no impact on HDL cholesterol. Finally, the favorable effect of ziprasidone on total cholesterol has been demonstrated over 52 weeks of therapy. This property of ziprasidone is unique, and contrasts with the adverse effects of a number of widely used treatment alternatives. Evidence that patients with psychosis are relatively unlikely

to receive the benefit of therapeutic interventions for hyperlipidemia and cardiac ischemia further emphasize the importance of this property of ziprasidone in the long-term health of this patient population.

* * *

Schizophrenia is a devastating, debilitating illness for patients, their families and caregivers, and exposes those afflicted individuals to higher degrees of morbidity and mortality than is seen in the general population. While the current generation of atypical agents represents an improvement over older neuroleptics, some combination of extrapyramidal symptoms, tardive dyskinesia, QTc prolongation, weight gain, hypercholesterolemia, hypertriglyceridemia, hyperprolactinemia, and diabetes attends the use of any single or combination antipsychotic regimen. Clearly, the treatment armamentarium is by no means complete or satisfactory, and individuals suffering from this disease require more, not fewer, options. A definite need exists for newer agents whose pharmacological and side effect profiles differ from, and offer improvements over, those of the currently marketed antipsychotics. Ziprasidone capsules represent such a safe and efficacious treatment option.

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GLOSSARY

Abbreviation	Definition
AEM	Adverse Event Monitoring
BID	Two Times per Day
BMI	Body Mass Index (weight/height^2 expressed as Kg/m^2)
bpm	Beats Per Minute
BPRS(d)	Brief Psychiatric Rating Scale (derived from PANSS)
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CHD	Coronary Heart Disease
CR	[Pfizer] Central Research
CVD	Cardiovascular Disease
ECG	Electrocardiogram
EPS	Extrapyramidal Syndrome
GAF	Global Assessment of Functioning Scale
GDXI	Global Data Exchange International
HDL	High Density Lipoprotein
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
HMR	Hoechst-Marion-Roussel
HR	Heart Rate
IHD	Ischemic Heart Disease
IM	Intramuscular
ISS	Integrated Summary of Safety - NDA
LDL	Low Density Lipoprotein
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Asberg Depression Rating Scale
MI	Myocardial Infarction
MRFIT	Multiple Risk Factor Intervention Trial
NHIS	National Health Interview Survey
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
PANSS	Positive and Negative Syndrome Scale
PBO	Placebo
POCF	Penultimate Observation Carried Forward
PPG	Pfizer Pharmaceuticals Group
PRW	Premier Research Worldwide, now eRT
QT	Time from beginning of QRS complex to end of T wave in an ECG
QTc	QT interval corrected for heart rate; where not otherwise specified, the Bazett correction was used
RR	Time between two consecutive R waves in an ECG
SD	Standard Deviation
SE	Standard Error
SSRI	Selective Serotonin Reuptake Inhibitor
STFDPC	Short-Term, Fixed-Dose, Placebo-Controlled
TdP	Torsade de pointes
USPI	US Package Insert
VLDL	Very Low Density Lipoprotein

A. BACKGROUND

A.1 Schizophrenia

A.1.1 Epidemiology, Morbidity and Mortality

Epidemiological studies have demonstrated that the prevalence of schizophrenia, approximately 1%, is remarkably consistent world-wide.[6,7,8,9] Schizophrenia may be associated with a variable outcome, but the condition tends to run a deteriorating course often with multiple relapses and residual impairment.

The United States, Canada and Western European countries devote roughly 1% of national income to the treatment of mental illness.[10] In the US, the cost of all mental illness has been estimated at US$103.7 billion, of which schizophrenia alone accounts for US$22.7 billion.[11] Patients with schizophrenia occupy 25% of the beds available for all in-patient care and account for 40% of all long-stay hospital days.[12]

Mortality in patients with schizophrenia is substantially higher than that of the general population. Two recent meta-analyses[13,14] reported consistent findings, with mortality ratios of 1.6 and 1.5, respectively.[15] A substantial portion of the excess is attributable to "unnatural" causes, such as suicide and accidental death (including aspiration[14]), which occur at much higher rates in patients with schizophrenia. Nonetheless, 80% of people with schizophrenia die of natural causes, and such causes account for approximately 60% of the excess mortality described in this population. Deaths from cardiovascular, digestive, genitourinary and respiratory disease in the population with schizophrenia are significantly more frequent than expected from their incidence in the general population.[14]

Two unpublished databases provide more information about mortality in schizophrenia (data on file, Pfizer). The Saskatchewan Health Database includes diagnosis and outcome data on one million people, approximately 3.4% of the population of Canada. The study design was a retrospective cohort using longitudinally collected data on individuals diagnosed with schizophrenia between 1994 and March 1999 (N = 3022), and a general population matched by age and sex (1:4) for comparison (N = 12,088). The second database is a United HealthCare retrospective cohort study using longitudinally collected data from 1995 to 1999 on approximately 2000 patients with schizophrenia matched by age, sex and health plan to a general control population. According to both studies, patients with schizophrenia have an increase in all cause mortality, with ratios of 2.7 ($p<0.001$) and 7.2 ($p<0.001$), respectively. Both databases also show a mortality ratio of approximately 2.5 for cardiovascular disease (Table 1).

Table 1. Mortality in Patients with Schizophrenia vs. General Population

	Risk Ratio	95% CI	p-value
Saskatchewan Health Database			
All-Cause	2.69	NA	<0.0001
Sudden Death	3.33	NA	<0.05
Cardiovascular Disease	2.38	NA	<0.0001
Non- Cardiovascular Disease	2.95	NA	<0.0001
Unknown Cause	4.00	NA	<0.01
United HealthCare database			
All-Cause	7.19	3.47, 14.89	<0.001
Non-Suicide	5.14	2.36, 11.17	<0.001
Cardiovascular Disease	2.51	0.42, 15.02	ns

NA: not available.

At least some of the increased risk of "natural" death may be attributed to a higher incidence of underlying medical illness. Diabetes has been reported to be much more prevalent in persons being treated for schizophrenia than in the general population, and the prevalence of hypertension and heart disease appears to be elevated as well.[16] Although the newest generation of antipsychotic drugs may aggravate this trend, it is important to note that these findings are not new. A 1975 survey of eight psychiatric hospitals and nursing homes in Germany describes striking elevations of obesity and diabetes in 1726 psychiatric patients (70% with psychosis), compared to literature controls.[17] The Saskatchewan Health Database shows a relative risk of diabetes of 1.6 ($p<0.01$), and the United HealthCare sample a relative risk of diabetes of 2.7 ($p<0.001$).

Management of these illnesses and cardiovascular risk factors may be made more difficult by the underlying psychosis, placing the patient at even greater risk. Although socioeconomic status may reduce the access of patients with mental illness to health care, observations in groups whose health care is funded by government[17] or insurance[16] suggest that socioeconomic status is not a complete explanation. In a cohort of 1.3 million patients who received (free) any prescription in Ontario Province in 1995, treatment for unrelated comorbid conditions (estrogen replacement, lipid lowering agents, medical arthritis therapy) was consistently less likely to be prescribed to patients with a psychotic disorder than to the general population.[18] Similarly, coronary revascularization procedures are much less likely to be provided to patients with schizophrenia than to the general population, even after adjusting for clinical and other factors.[19] The undertreatment of comorbid medical illness may frustrate strategies to blunt the adverse impact of some antipsychotic agents on body weight and serum lipids. This factor, combined with the already high prevalence of obesity,[3,20] and cigarette and alcohol abuse[21,22] in this population no doubt contribute to the excess mortality described above. The recognition that antipsychotic drug therapies may themselves introduce or exacerbate cardiovascular risk factors further complicates management of this chronic and disabling condition, the manifestations of which

can seriously compromise the ability of the patient to participate in appropriate behavioral and pharmacologic risk factor management.

A.1.2 Therapeutic Options

Broadening of therapeutic options during the last decade has markedly influenced the management of patients with schizophrenia. The traditional antipsychotics such as chlorpromazine and haloperidol, developed in the 1950's, suppress the positive symptoms of schizophrenia via potent blockade of dopamine D2 receptors.[23] However, these traditional antipsychotics are associated with a very high incidence of movement disorders such as Parkinsonism, dystonia and akathisia that are distressing, debilitating and often result in noncompliance.[23,24,25] Long-term exposure to typical neuroleptics is also associated with the development of tardive dyskinesia.[26]

Primary negative symptoms, such as poverty of thought and speech and social withdrawal, mood symptoms such as depression, and cognitive impairment are considered relatively unresponsive to typical antipsychotics.[27,28,29,30,31] Furthermore, typical antipsychotic agents may induce negative symptoms both directly, by inducing movement disorders and/or exacerbating or precipitating depressive symptoms, and indirectly, through the effects of anticholinergic agents required to manage these side-effects.[32,33] The cognitive impairment associated with schizophrenia, particularly deficits in memory and attention, may also be worsened by typical antipsychotics and anticholinergics.[30] Negative symptoms and cognitive impairment are major factors in the very poor function and ultimately poor outcome in many patients with schizophrenia.[34,35] Depression, a common comorbidity, has been linked to the 10% incidence of suicide among patients with schizophrenia.[36,37,38]

Clozapine, the first of the so-called atypical antipsychotics represented a breakthrough in the treatment of schizophrenia in the 1970's. However, a 1% incidence of fatal agranulocytosis resulted in clozapine being withdrawn from the US market until the mid 1980's when it was re-introduced for the treatment of the most severely ill patients, with a requirement for weekly hematological monitoring.[39,40] The superiority of clozapine over typical agents, both in efficacy and side-effect profile[41,42] provided the impetus for the development of several atypical antipsychotics that did not induce blood dyscrasias.

The atypical antipsychotics are so called because they share the pharmacological property of combining D2 antagonism with even more potent antagonism of the serotonin $5HT_{2A}$ receptor.[43] It is the high 5HT2A:D2 receptor binding ratio which is thought by many to confer efficacy in negative symptoms and to substantially reduce the liability for inducing extrapyramidal side-effects, compared with traditional antipsychotics.[44,45,46,47] However, beyond sharing a high 5HT2A:D2 affinity ratio, the recently developed atypical antipsychotics that include risperidone, olanzapine and quetiapine, exhibit considerable diversity in receptor

binding activities, elimination pathways, side-effect profiles and possibly efficacy in negative and mood symptoms and cognitive impairment.[48,49]

Marked differences in the basic pharmacology of these agents have been linked with variations in clinical effects. Alpha-1 receptor antagonism by risperidone and quetiapine necessitates dose titration to clinically effective doses in order to avoid significant orthostatic hypotension.[49,50] Although olanzapine can be initiated at clinically effective doses without titration, potent muscarinic (m_1) receptor antagonism by olanzapine is thought to result in a relatively high incidence of anticholinergic side-effects such as dry mouth and constipation. The antihistaminic activity of olanzapine and quetiapine may be related to increased sedation and has been proposed as a mechanism contributing to increased weight gain.[5] Risperidone has negligible activity on the m_1 receptor.[49] Agonist activity at the $5HT_{1A}$ receptor, a property of clozapine, is thought to be associated with enhanced efficacy in treating negative symptoms and reduced EPS.[49] Risperidone and olanzapine and to a lesser extent quetiapine are $5HT_{2C}$ antagonists, an activity that has been linked with positive symptom suppression.[49,51] Receptor affinity profiles of risperidone, olanzapine and quetiapine are shown in Table 5 in Section B.1.

Evidence from clinical trials and use in clinical practice confirm that there is substantial variation among atypical antipsychotics in their tolerability profiles. Olanzapine is associated with substantial weight gain, with ≥7% increase in body weight being reported by more than half the patients treated in long-term trials,[52] with 30% reporting a gain of 10kg or more.[53,54] Risperidone and quetiapine are also associated with weight gain although to a lesser extent than olanzapine.[4] Risperidone is associated with sustained prolactin elevation,[55] whereas olanzapine and quetiapine are not.

Differences in efficacy among agents are more difficult to define than differences in pharmacologic and side-effect profiles. Well controlled, long-term comparative trials, as well as a substantial body of clinical experience, are needed to substantiate putative differences. To date, only clozapine has convincingly been found to be effective in patients refractory to conventional treatment.[56] Evidence from clinical trials suggests that there may be some variability in the effects of olanzapine, quetiapine and risperidone upon depressive symptoms.[57,58,59] As predicted by variations in pharmacology, evidence of differences among agents in their effects on cognitive function is emerging, and these may manifest as real differences in effects on functional outcome.[60,61]

As these agents are eliminated via metabolism by different P450 isoenzymes, differences in drug interaction potential exist, particularly as polypharmacy is prevalent in the treatment of schizophrenia.[62,63] For example, risperidone and quetiapine are metabolized by the CYP2D6 and CYP3A4 isoenzymes, respectively, giving these two drugs different spectra of potential interactions with other drugs such as antidepressants, including SSRIs, benzodiazepines and other

antipsychotics. Plasma concentrations of olanzapine, a substrate of CYP1A2 may be affected by cigarette smoking and by fluvoxamine (Luvox).[64]

In summary, the introduction of the first antipsychotic drugs in the 1950's represented a significant advance in the treatment of psychotic disorders. The advent of the atypical antipsychotics in the 1990's is revolutionizing the treatment of schizophrenia. Even so, many patients with schizophrenia still function suboptimally on these agents and up to 40% of patients are considered refractory to treatment.[65] Furthermore, antipsychotic therapy continues to be plagued by significant adverse effects. The heterogeneity of the symptoms and course of schizophrenia dictates that there will be substantial variability among patients in their responses to any given treatment, as well as variability within individuals during the course of their illness. Clearly, unmet medical needs still exist. As pharmacotherapy is the cornerstone of the management of schizophrenia, a wide range of therapeutic options is needed if progress is to be made in ultimately improving the outcome.

A.2 Summary of Ziprasidone Clinical Development Program

A.2.1 Duration of Exposure and Demographics

The NDA for oral ziprasidone, submitted in March 1997, contained data on more than 2800 patients and/or normal volunteers who received ziprasidone. Of these 2800 subjects, over 2100 were patients with schizophrenia or schizoaffective disorder who participated in multiple-dose clinical trials. The conditions and duration of treatment with ziprasidone included open-label and double-blind studies, inpatient and outpatient studies, and short-term and longer-term exposure. Clinical investigations of oral ziprasidone have continued subsequent to the March 1997 NDA submission. Data included in this document extend to the 5 February 2000 cut-off date for the most recent Safety Update submitted to the FDA.

The demographics of patients in Phase 2/3 trials included in the NDA and up to 5 February 2000 are summarized in Table 2.

Table 2. Demographic Characteristics, All Oral Phase 2/3 Trials

		Ziprasidone	Haloperidol	Risperidone	Placebo
NDA database to 31 October 1996					
N		2140	407	206	354
Gender					
Male / Female		1540 / 600	273 / 134	146 / 60	267 / 87
Age (yrs)					
Mean		39.6	38.5	38.0	40.2
Range		7 - 82	18 - 82	18 - 75	9 - 76
Cumulative to 5 February 2000					
N		4571*	1071	426*	605
Gender					
Male / Female		3173 / 1377	761 / 310	284 / 134	414 / 191
Age (yrs)					
Mean		39.1	37.2	37.4	40.5
Range		7 - 98	17 - 82	18 - 75	8 - 92
Race:					
Black		671	135	32	97
Caucasian		3201	699	343	448
Other		678	237	43	60
Weight (Kg)					
Males	Mean	79.1	75.3	82.3	78.4
	Range	27 - 163	36 - 149	48 - 159	25 - 133
Females	Mean	71.7	69.5	73.0	70.1
	Range	33 - 164	30 - 151	40 - 127	35 - 118

* includes 21 ziprasidone and 8 risperidone patients with unknown gender and race.

There were 625 patient-years of exposure at the time of the 31 October 1996 data cut-off for the original NDA (Table 3). The most recent Safety Update submitted to the FDA presents exposure and safety data through 5 February 2000, and accounts for a total of 4571 patients who have received oral ziprasidone in Phase 2/3 clinical trials for a total duration of exposure of 1733 patient-years. The treatment experience of patients included in the most recent Final Safety Update is summarized in Table 3. Of the 4571 patients given oral ziprasidone, 991 had received ziprasidone for more than 6 months, 605 for more than one year, and 151 for longer than 2 years.

Table 3. Duration of Exposure to Study Treatment; All Oral Phase 2/3 Trials

	Ziprasidone	Haloperidol	Risperidone	Placebo
NDA database to 31 October 1996				
N	2140	407	206	354
Exposure Duration				
≤6 months	1697	361	132	329
>6-12 months	238	37	40	9
≥1 year	205	9	34	16
Mean (days)	107	77	150	52
Total (patient -years)	625.0	85.9	84.4	50.3
Cumulative to 5 February 2000				
N	4571	1071	426	605
Exposure Duration				
≤6 months	3580	908	273	550
>6 to 12 months	386	72	62	25
>12 to 18 mos	412	58	83	30
>18 to 24 mos.	42	9	2	0
>2 years	151	24	6	0
Mean (days)	138	102	168	55
Total (patient -years)	1732.6	298.6	196.4	91.8

Table 4 summarizes the prevalence of cardiovascular disease reported for patients entering ziprasidone Phase 2/3 trials that have been completed or are ongoing open-label or single-blind trials; 8.4%, 1.7%, and 3.0% of patients who received ziprasidone had a medical history of hypertensive disease, ischemic heart disease or other form of heart disease, respectively.

Table 4. Prevalence of Cardiovascular Disease at Baseline: All Oral Phase 2/3 Trials (Excepting Ongoing Double-Blind Trials)

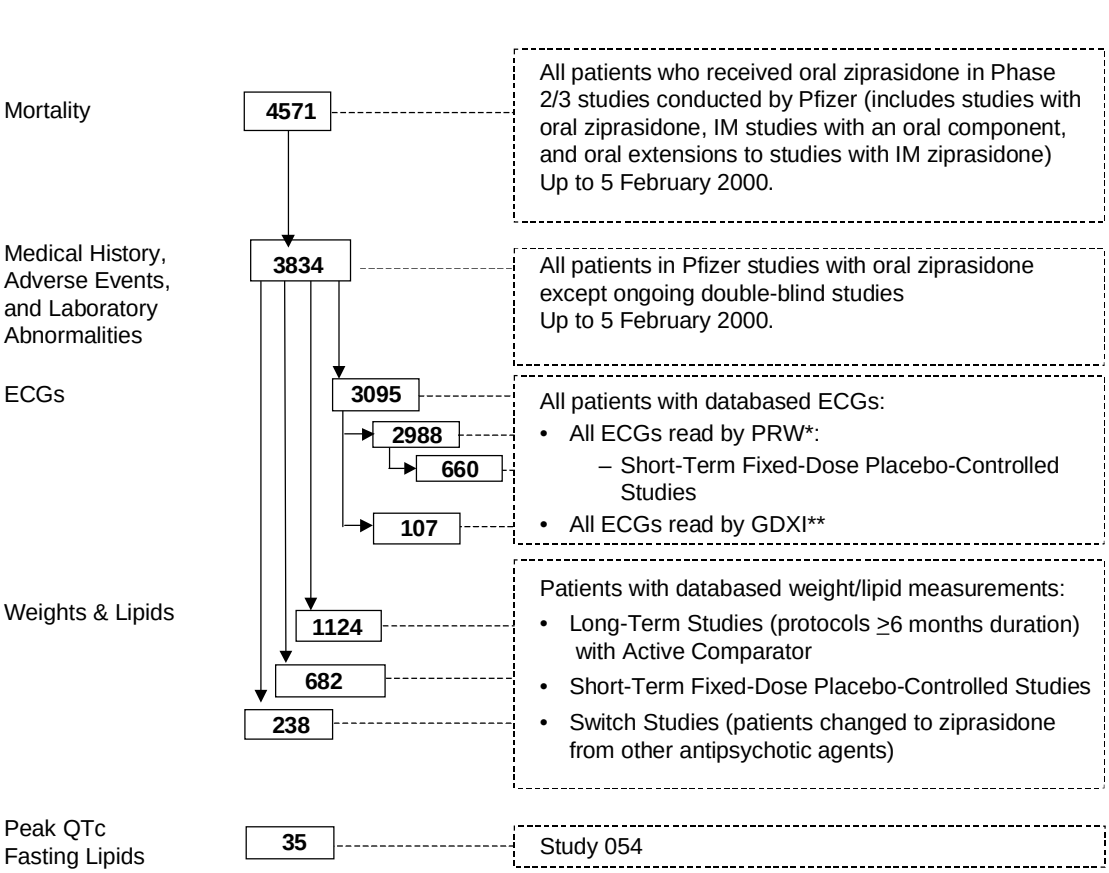
	Ziprasidone	Haloperidol	Risperidone	Placebo
No. Patients entering studies	3834	686	322	506
No. Patients with:				
Hypertensive disease	322 (8.4%)	41 (6.0%)	19 (5.9%)	46 (9.1%)
Ischemic heart disease	65 (1.7%)	9 (1.3%)	3 (0.9%)	14 (2.8%)
Other forms of heart disease	116 (3.0%)	21 (3.1%)	9 (2.8%)	24 (4.7%)

To 5 February 2000.

A.2.2 Data and Analyses Included in this Document

Ziprasidone efficacy and general tolerability data that were presented in the NDA are summarized briefly. The document then focuses on the effects of ziprasidone and other antipsychotic drugs on QTc, the evidence bearing upon the clinical significance of this effect, and the effects of these agents on the important cardiovascular risk factors of body weight, lipids and glucose tolerance. In addition to data from Study 054, observations include all available data in the ziprasidone clinical development program to 5 February 2000.

The following schematic defines the populations of oral ziprasidone-treated patients who contributed data to the additional analyses included in this document:



*PRW: Premier Research Worldwide (now eRT); **GDXI: Global Data Exchange International

The mortality incidence is derived from the Adverse Event Monitoring (AEM) database and is given for the largest possible patient group (N = 4571), i.e., all patients who received oral ziprasidone in Phase 2/3 studies conducted under the auspices of Pfizer Central Research (CR) in North and South America, Europe, South Africa, Australia and in Japan, as well as studies conducted under the auspices of the Pfizer Pharmaceuticals Group (PPG) up to 5 February 2000. Pfizer CR and Pfizer PPG are separate clinical research groups within Pfizer, Inc.

Other analyses presented in this summary document are based on data from all completed studies together with all ongoing open-label or single-blind Phase 2/3 oral ziprasidone trials and oral extensions to trials with intramuscular ziprasidone. These data include all available data in the database up to 5 February 2000.

There are 3834 patients who contributed to this database, which has been searched for the occurrence of specific treatment-emergent adverse events and laboratory test abnormalities. Of the 3834 patients, 3095 have ECGs in the database. These ECGs have all been centrally read; ECGs for the vast majority of patients (N = 2988) were read by Premier Research Worldwide (PRW, now eRT), ECGs for 107 patients in one study (an oral extension to an IM study) were read by Global Data Exchange International (GDXI).

The long-term effects of ziprasidone on body weight are analyzed for the 1124 patients enrolled in Pfizer Central Research protocols of at least 6 months duration and who have baseline and at least one on-treatment weight measurement. Serum cholesterol values were also recorded in the majority of these protocols, allowing the persistence of the effect of ziprasidone on this measure to be examined. Study 054 provided an opportunity to collect blood samples under fasting conditions, allowing complete lipid profiles to be presented together with body weight changes for the patients in this short-term trial. Finally, weight and cholesterol data are analyzed for 238 ziprasidone patients in three studies conducted by the Pfizer Pharmaceuticals Group. These patients received ziprasidone after discontinuing another antipsychotic agent due to insufficient clinical response or unacceptable side effects.

B. CLINICAL PHARMACOLOGY

B.1 Receptor Binding Profile

Oral ziprasidone is the hydrochloride salt of a benzisothiazolylpiperazine. In vitro studies established that ziprasidone is an antagonist at both 5-hydroxytryptamine $5HT_{2A}$ and dopamine D_2-receptors, with an affinity at $5HT_{2A}$ receptors approximately 8-fold greater than that at dopamine D_2-receptors. This receptor binding profile has been confirmed in vivo using positron emission tomography; serum ziprasidone concentrations between 20 and 40 ng/ml were associated with D_2-receptor and $5HT_{2A}$-receptor occupancy greater than 65% and 80%, respectively.

Ziprasidone also possesses a high affinity for $5HT_{1A}$-receptors where it acts as an agonist and at $5HT_{1D}$-receptors where it is an antagonist. Binding at these receptors has been associated with antidepressant ($5HT_{1A}$ and $5HT_{1D}$) and anxiolytic ($5HT_{1A}$) activity.[66] In addition, ziprasidone moderately inhibits the uptake of serotonin and norepinephrine into rat brain synaptosomes. Inhibition of 5HT and norepinephrine uptake has been associated with antidepressant activity. Ziprasidone also acts as an antagonist at $5HT_{2C}$ receptors, a property that may potentially confer antipsychotic activity.[67] Ziprasidone binds with only moderate affinity to H_1-histaminergic receptors and α_1 adrenergic receptors that are associated with sedation and postural hypotension, respectively. Ziprasidone has negligible affinity for the muscarinic-m_1 receptor. Table 5 shows the receptor affinity profile of ziprasidone, compared with those of risperidone, olanzapine, and quetiapine.

Table 5. Relative Receptor Affinities of Ziprasidone, Risperidone, Olanzapine, and Quetiapine

	Ziprasidone	Risperidone	Olanzapine	Quetiapine
D_2	**++++**	**++++**	**++**	**+**
5-HT_{2A}	**+++++**	**+++++**	**++++**	**+**
5-HT_{2C}	**+++++**	**+++++**	**++++**	**+**
5-HT_{1A}	**++++**	**+**	**–**	**+**
5-HT_{1D}*	**++++**	**+**	**+**	**–**
α_1 adrenergic	**++**	**++++**	**++**	**++**
Muscarinic-1 (m_1)	**–**	**–**	**++++**	**++**
Histaminic-1(H_1)	**++**	**++**	**++++**	**++++**
NE/5-HT reuptake inhibition	**++**	**–**	**–**	(**–**5HT),(**+**NE)

Affinity represented as: **+++++** very high, **++++** high, **++** moderate, **+** low, – negligible.
* Bovine binding affinity, all other affinities human.

B.2 Absorption, Distribution, Metabolism, Elimination

Administration of doses in the recommended range of 80 mg to 160 mg daily produced dose-related increases in both C_{max} and the area under the curve (AUC). At these doses, the ratio of highest to lowest AUC among healthy subjects and/or patients ranged from 3 to 7. Since administration of ziprasidone in the fed state enhances its bioavailability (up to a doubling of serum concentrations) and reduces the variability in its absorption, it has been administered with food in all Phase 2/3 clinical trials. The absolute bioavailability of a 20 mg dose of ziprasidone under fed conditions is approximately 60%. C_{max} following multiple oral dosing occurs approximately 6 hours after administration with food.

Following intravenous administration of single doses, ziprasidone has a mean systemic clearance of 7.5 ml/min/kg and a mean apparent volume of distribution of 1.5 L/kg. At steady-state, the mean terminal elimination half-life of ziprasidone is about 6.6 hours following oral dosing. Steady-state serum concentrations of ziprasidone are attained within one to three days following twice daily administration in the fed state.

Ziprasidone is extensively metabolized in humans with less than 1% and 4% being excreted unchanged in urine and feces, respectively. Available *in vitro* data suggest that both aldehyde oxidase mediated reduction (leading to the formation of S-methyl-dihydro ziprasidone [M9]) and P-450 mediated oxidation (formation of ziprasidone sulfoxide [M10] and benzisothiazolyl piperazine [BITP] sulfoxide/sulfone [M2/M1]) play major roles in ziprasidone clearance.

Proposed metabolic pathways for ziprasidone and the major circulating metabolites are illustrated in Figure 1. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP3A4 is responsible for the sulfur oxidation metabolites and CYP3A4 and possibly CYP1A2 are responsible for the N-dealkylation metabolites. The unimodal distribution and limited range (3 to 7-fold) of exposures noted in both healthy subjects and patients are consistent with a lack of CYP2D6 involvement. In addition, the serum concentrations of ziprasidone in one patient in Study 054, who was identified by genetic analysis to be a 2D6 poor metabolizer (see Section E.3.2), were consistent with those of the other subjects studied.

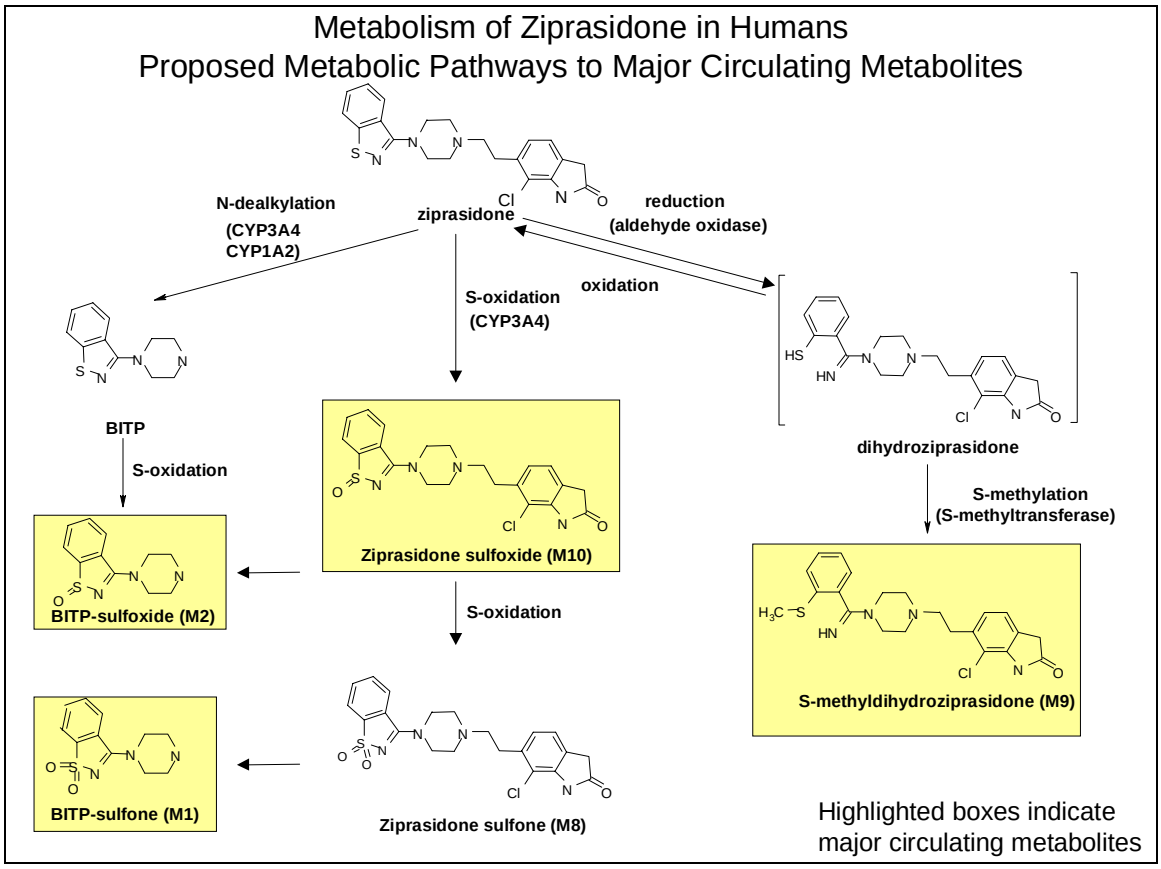


Figure 1. Proposed Metabolic Pathways for Ziprasidone

Three of the four major circulating metabolites of ziprasidone, ziprasidone sulfoxide (M10), and benzisothiazolyl piperazine (BITP) sulfoxide (M2)/sulfone (M1) each possess less than 1% of the binding affinity of ziprasidone at rat brain D_2 and 5-HT_{2A} receptors (more than 100-fold lower affinity). Accordingly, given their much lower affinity for the D_2 and 5-HT_{2A} receptors compared to ziprasidone and that the free serum concentration of these compounds achieved at 160 mg total daily dose is below that of their affinity for these receptor sites, it is unlikely that these metabolites contribute to ziprasidone's antipsychotic effects. The other major metabolite of ziprasidone, S-methyl-dihydroziprasidone (M9), possesses 84- and 62-fold lower affinity than ziprasidone for these two receptor sites. Since the free concentration of M9 in serum at the highest recommended dose of ziprasidone (160 mg/day) at steady state falls within the range of its binding affinity for D_2 and 5-HT_{2A} receptor sites, M9 may contribute to the clinical pharmacology of ziprasidone. Inhibition of ziprasidone metabolism by CYP3A4 would be expected to increase the production of M9 from ziprasidone, by blocking the alternate pathways of metabolism. M10 production and degradation are both mediated by CYP3A4, so that inhibition of that isoenzyme may have less

predictable effects on M10. The effect of ketoconazole, a potent inhibitor of CYP3A4, on ziprasidone metabolism is described below.

B.3 Drug Interactions

Ziprasidone is highly bound to plasma proteins (>99%) and its binding appears to be independent of concentration. The *in vitro* plasma protein binding of ziprasidone was not altered by the presence of two highly bound drugs, warfarin and propranolol, nor did ziprasidone alter the binding of these drugs in human plasma. Consequently, it appears unlikely that ziprasidone will displace other compounds that are highly protein bound.

Because ziprasidone is only partially dependent on CYP3A4 for its elimination, coadministration of a broad spectrum, relatively weak P450 inhibitor (cimetidine - 800 mg/day) had no significant effect on ziprasidone pharmacokinetics. Coadministration of the more potent CYP3A4 inhibitor, ketoconazole (400 mg/day) was associated with a 33% increase in ziprasidone exposure. This magnitude of increase in exposure was consistent with the mean change in ziprasidone concentration of 39% observed at steady state in Study 054 during coadministration of ketoconazole (400 mg/day) to patients receiving ziprasidone at 160 mg daily. In this latter study, the mean serum concentration of M9 increased by 55%, while the mean concentration of M10 increased by 8% following treatment with ketoconazole.

In a separate clinical pharmacology trial, co-treatment with the CYP3A4 inducer, carbamazepine, decreased circulating concentrations of ziprasidone (36% and 27% decreases in AUC_{0-12} and C_{max}, respectively).

There are no clinically recognized inhibitors or inducers of aldehyde oxidase.

Overall, this data suggests that a potential for drug interactions to perturb ziprasidone metabolism sufficiently to increase the effect of ziprasidone or its metabolites on the QTc has not been identified. Examination of QTc – concentration data collected in Study 054 and in Phase 2/3 trials is strongly supportive.

The potency of ziprasidone as an inhibitor of the five major human cytochrome P450 enzymes was determined in vitro. The IC_{50}s were greater than 100 µM for CYP1A2, CYP2C9 and CYP2C19 and the K_i values for CYP2D6 and CYP3A4 were 11 µM and 64 µM, respectively. Thus ziprasidone is not expected to interfere with the metabolic activity of these enzymes, since maximal unbound serum concentrations of ziprasidone at 160 mg daily are very low (~0.5 nM) relative to the concentrations required for inhibition. The failure of coadministered ziprasidone to alter metabolism of dextromethorphan (CYP2D6 substrate) and ethinylestradiol (CYP3A4 substrate) in Phase 1 studies supports this contention.

In addition, Phase 1 studies have demonstrated that ziprasidone does not affect steady-state lithium serum concentrations or the renal clearance of lithium, and that antacids do not affect the oral bioavailability of ziprasidone.

B.4 Special Populations

On average, elderly subjects have serum concentrations of ziprasidone that are 20% higher than in the young. Gender does not affect the pharmacokinetics of ziprasidone. No clinically significant alterations in ziprasidone pharmacokinetics were observed in subjects with renal impairment. Exposure to ziprasidone was 19% and 34% greater in hepatically impaired subjects (Child-Pugh Class A and B, respectively).

B.5 Summary and Conclusions

Ziprasidone is an antagonist at dopamine-D_2 and $5HT_{2A}$ receptors with a $5HT_{2A}/D_2$ receptor affinity ratio of 8:1 in human tissue. In vitro, ziprasidone additionally demonstrates high affinities for the serotonin receptor subtypes $5HT_{1A}$, $5HT_{1D}$, and $5HT_{2C}$. It has modest affinity for serotonin and norepinephrine uptake sites, histamine-H_1 and α_1-adrenergic receptors and a negligible affinity for muscarinic receptors.

Ziprasidone displays linear pharmacokinetics in the recommended dose range (80 to 160 mg daily) and has a mean half-life of 6.6 hrs. The range of ziprasidone exposures in both healthy subjects and patients is 3 to 7-fold at these doses. Food enhances the bioavailability ziprasidone (up to a doubling of serum concentrations) and reduces the variability in its absorption. In multiple dose studies, the C_{max} typically occurs at approximately 6 hrs after dosing in the fed state, with steady-state attained within 1 to 3 days (following twice daily administration in the fed state). Ziprasidone is extensively metabolized by both aldehyde oxidase and P-450 mixed function oxidases. One circulating metabolite of ziprasidone, S-methyl-dihydroziprasidone (M9), may contribute to its pharmacologic effects. Co-administration of CYP3A4 inhibitors or inducers with ziprasidone results in limited (~35%) increases/decreases in ziprasidone exposure.

C. CLINICAL EFFICACY AND GENERAL TOLERABILITY

This section provides a summary of the efficacy and safety of oral ziprasidone in the treatment of acute and chronic schizophrenia and schizoaffective disorder. Schizophrenia is diagnosed by the presence of characteristic symptoms defined by currently accepted diagnostic systems (ICD-10, DSM-IV). In acute schizophrenia, the predominant symptoms include auditory hallucinations, ideas of reference, suspiciousness, flatness of affect, persecutory delusions, thought alienation, and lack of insight. In contrast, chronic schizophrenia is characterized by social withdrawal, underactivity, abnormalities of posture and movement, poverty of thought and speech, emotional blunting, self-neglect and depressive symptoms. Schizophrenia is associated with a variable outcome although the condition tends to run a deteriorating course, often with multiple relapses and residual impairment.

The following summary of data from the oral ziprasidone NDA database supports the claim that ziprasidone is effective in treating both the positive and negative symptoms of schizophrenia (and schizoaffective disorder) and has a favorable side effect profile.

C.1 Efficacy

Four double-blind, short-term (4 to 6 weeks), fixed-dose, placebo-controlled (STFDPC) clinical trials were conducted to investigate the efficacy of ziprasidone in acute exacerbation of schizophrenia and schizoaffective disorder in hospitalized patients (Studies 104, 106, 114, and 115). One of these trials also had an active control arm (haloperidol, Study 115).

A one-year, placebo-controlled, maintenance trial evaluated the efficacy of ziprasidone in the prevention of relapse of schizophrenia (Study 303).

These studies are summarized in Table 6. The results show that:

- Ziprasidone is effective in the treatment of patients experiencing an acute exacerbation of schizophrenia or schizoaffective disorder. Three out of the four STFDPC trials (Studies 106, 114, and 115) confirmed the superior efficacy of ziprasidone (80 mg, 120 mg, and 160 mg daily) over placebo, with statistically significant improvements in the intent-to-treat analysis performed for all primary outcome measures in those studies (except for the BPRS Core Items Score in Study 106, $p = 0.059$).
- Ziprasidone (40 mg to 160 mg daily) significantly reduces the risk of recurrence of acute exacerbation in hospitalized patients with chronic and subchronic schizophrenia (Study 303). The rate of relapse for the duration of the study was lower in the ziprasidone groups than in the placebo group.
- Ziprasidone (40 mg and 160 mg daily) produces statistically significant improvement in primary negative symptoms in patients with predominantly negative symptoms (Study 303). The superior efficacy of ziprasidone,

compared with placebo, in the treatment of the negative symptoms of schizophrenia was further supported by Studies 114 and 115 that showed a statistically significant improvement in PANSS Negative Subscale Score for the 80 mg, 160 mg (Study 114), and 200 mg (Study 115) ziprasidone groups.

Table 6. Oral Ziprasidone Placebo-Controlled Studies: Summary

Study	Description	Duration	Treatment Groups			
			Ziprasidone	N	Comparator	N
104	randomized	4 weeks	10 mg	47	placebo	50
N=200	double-blind		40 mg	55		
	fixed dose		80 mg	48		
106	randomized	4 weeks	40 mg	44	placebo	48
N=139	double-blind		120 mg	47		
	fixed dose					
114	randomized	6 weeks	80 mg	106	placebo	92
N=302	double-blind		160 mg	104		
	fixed dose					
115	randomized	6 weeks	40 mg	87	placebo	83
N=419	double-blind		120 mg	78	haloperidol	85
	fixed dose		200 mg	86	15 mg	
303	randomized	52 weeks	40 mg	76	placebo	75
N=294	double-blind		80 mg	72		
	fixed dose		160 mg	71		

C.1.1 Clinical Rating Scales

The clinical ratings scales used in the studies described in this section are briefly described below:

Positive and Negative Syndrome Scale (PANSS): This scale consists of 30 items, with the total score consisting of the sum of the seven positive items, seven negative items, and 16 general psychopathology items. The PANSS negative subscale score is the sum of the seven negative items. A decrease in PANSS score (Total, Positive, or Negative) reflects improvement in the evaluated items in schizophrenic patients.

PANSS Depression Factor: This scale equals the sum of 5 items derived from the PANNS (anxiety, guilt, depression, somatic concern, and preoccupation).

Brief Psychiatric Rating Scale (BPRS or BPRSd): This scale consists of 18 items with the total score representing the sum of all 18 items while the core items score is the sum of 4 items (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content). A decrease in BPRS score reflects an improvement in the evaluated items in schizophrenic patients. The BPRS may also be derived from the PANSS; it is then designated BPRSd.

Clinical Global Impression Severity (CGI-S) and Improvement (CGI-I): The CGI-S evaluation is a single rating of how mentally ill a skilled rater feels the subject is at the time of evaluation. A decrease in CGI-S score reflects symptomatic improvement in schizophrenic patients. The CGI-I evaluation is a single item reflecting a subject's improvement at baseline compared with screening and improvement at each visit compared with baseline. An increase in CGI-I score reflects symptomatic improvement in schizophrenic patients.

Global Assessment of Functioning Scale (GAF): This instrument considers psychological, social, and occupational functioning on a hypothetical continuum of mental health status. An increase in GAF score reflects symptomatic improvement in schizophrenic patients.

Montgomery-Asberg Depression Rating Scale (MADRS): This scale consisted of ten items assessing symptoms associated with clinical depression.

Based on conversations with the U.S. Food and Drug Administration, PANSS Total and Negative Subscale, BPRSd total and BPRS core items and CGI-S were designated primary efficacy variables in the short-term placebo-controlled trials. PANSS total, PANSS Negative Subscale, CGI-Severity, and GAF scores were used as efficacy measures in the one-year maintenance study (Study 303).

C.1.2 Treatment of Acute Symptoms

Studies 104, 106, 114, and 115 were randomized, double-blind, multicenter, parallel group trials performed in hospitalized patients with a DSM-III-R defined Axis I diagnosis of chronic or subchronic schizophrenia or schizoaffective disorder, in acute exacerbation. This mixed patient population was selected because it was thought to be more representative of a general patient population presenting with acute symptoms of psychosis. A minimum duration of DSM-III-R defined psychiatric diagnosis was specified as an inclusion criterion in each protocol (1 year in Studies 104 and 106; 6 months in Studies 114 and 115). The mean duration of illness exceeded 13 years in all treatment groups in all short-term, fixed-dose, placebo-controlled trials.

In the short-term, fixed-dose, placebo-controlled studies discussed below, a statistical analysis was performed on the change from baseline in BPRS (Studies 104 and 106), BPRSd and PANSS (Studies 114 and 115) and CGI-Severity (all studies) data. These data were analyzed using an analysis of covariance model (ANCOVA), including treatment and center effects. In addition, baseline was used as a covariate. Treatment effects were defined as the adjusted mean change from baseline for the active treatment group mean minus the adjusted mean change from baseline for the placebo group.

Figure 2 shows the estimated treatment effect (with 95% CI) of ziprasidone (10 mg to 200 mg daily) on BPRS (BPRSd) Total score at last visit in the four short-term placebo-controlled trials. The estimated treatment effect of haloperidol (15 mg

daily) in Study 115 has been included for reference. Patients given ziprasidone at doses within the recommended therapeutic range (80 to 160 mg daily) most consistently demonstrated significant improvement in BPRS Total scores compared with placebo.

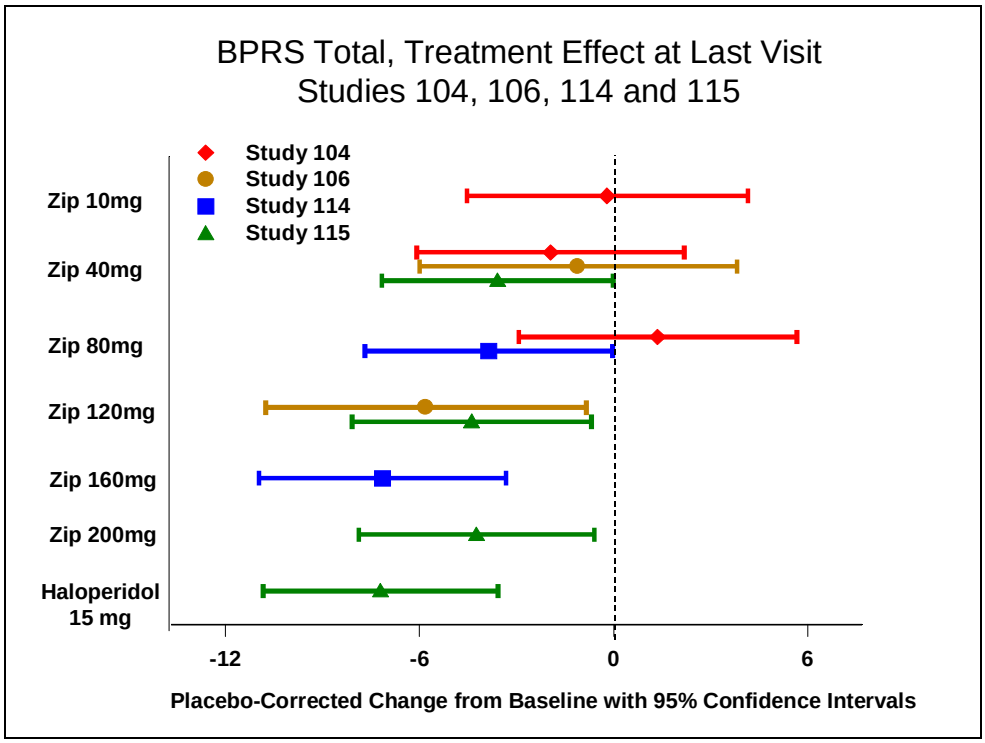


Figure 2. Summary of Estimated Treatment Effects on BPRS Total at Last Visit in Short-Term, Placebo-Controlled Trials

A review of individual studies follows.

Study 104

Study 104 compared the efficacy of three fixed doses of ziprasidone (10 mg, 40 mg, and 80 mg daily) with placebo in a total of 200 patients.

There were no statistically significant differences between any of the ziprasidone treatment groups and placebo in any primary or secondary efficacy endpoints in either the intent-to-treat or evaluable patient groups (Table 7). Given the profile of efficacy across the dose range tested in the Phase 2/3 development program overall, it can be concluded that the 10 mg and 40 mg ziprasidone groups received subtherapeutic or suboptimal doses; thus the lack of statistically significant improvement for these patient groups was not unexpected.

Table 7. Statistical Summary for Primary Efficacy Variables; Study 104

Treatment Group (ITT)		BPRS Total Score	BPRS Core Items Score	CGI-Severity
Ziprasidone	Estimated Treatment Effect	-0.204	0.282	0.325
10 mg	95% CI	(-4.549, 4.141)	(-1.408, 1.973)	(-0.034, 0.684)
N=44‡	p value*	0.926	0.742	0.076
Ziprasidone	Estimated Treatment Effect	-1.946	-0.258	0.039
40 mg	95% CI	(-6.079, 2.187)	(-1.863, 1.347)	(-0.308, 0.385)
N=55	p value*	0.354	0.751	0.827
Ziprasidone	Estimated Treatment Effect	1.355	0.873	0.216
80 mg	95% CI	(-2.943, 5.654)	(-0.787, 2.533)	(-0.140, 0.572)
N=47	p value*	0.535	0.301	0.233

‡N = 46 for CGI-Severity
* versus placebo

Additionally, between 28% and 44% of patients in each group were discontinued during the first two weeks of treatment, with the highest rate (44%) of discontinuation being in the 80 mg group. These discontinuations did not arise from poor toleration of treatment (of 21 discontinuations in the first 14 days, 10 were for insufficient clinical response, 9 for protocol violation or withdrawn consent), but may at least in part explain the failure to demonstrate efficacy in this four-week trial.

Study 106

Study 106 compared the efficacy of two fixed doses of ziprasidone (40 mg and 120 mg daily) with placebo in a total of 139 patients. In the intent-to-treat last observation carried forward (LOCF) analysis, the 120 mg ziprasidone group demonstrated statistically significant superiority in two out of three primary efficacy variables (BPRS Total and CGI-Severity) compared with placebo. The third primary efficacy variable, the BPRS Core Items Score, showed numerical advantage that approached statistical significance (Table 8).

Table 8. Statistical Summary for Primary Efficacy Variables; Study 106

Treatment Group (ITT)		BPRS Total Score	BPRS Core Items Score	CGI-Severity
Ziprasidone	Estimated Treatment Effect	-1.102	-0.365	-0.254
40 mg	95% CI	(-6.006, 3.801)	(-2.097, 1.366)	(-0.651, 0.144)
N=43	p value*	0.657	0.677	0.209
Ziprasidone	Estimated Treatment Effect	-5.812	-1.682	-0.421
120 mg	95% CI	(-10.765, -0.860)	(-3.428, 0.064)	(-0.819, -0.022)
N=41‡	p value*	0.022	0.059	0.039

‡N=42 for CGI-Severity
* versus placebo

Study 114

Study 114 compared the efficacy of two fixed doses of ziprasidone (80 mg and 160 mg daily) with placebo in a total of 302 patients. Both doses showed statistically significant superiority to placebo in all 5 primary efficacy outcome measures (PANSS Total, PANSS Negative Subscale, BPRSd Total and Core Items, and CGI-Severity) in the intent-to-treat LOCF analysis, with improvement being numerically greater in the 160 mg dose group. Estimated treatment effects for PANSS Total, BPRSd Total and Core Items, and CGI-Severity are shown below (Table 9). Results of the PANSS Negative Subscale are discussed in Section C.1.4.

Table 9. Statistical Summary for Primary Efficacy Variables; Study 114

Treatment Group (ITT)		PANSS Total	BPRSd Total Score	BPRSd Core Items Score	CGI-Severity
Ziprasidone	Est. Treatment Effect	-6.661	-3.875	-1.345	-0.314
80 mg	95% CI	(-13.258, -0.065)	(-7.701, -0.049)	(-2.625, -0.065)	(-0.596, -0.031)
N=104	p value*	0.048	0.047	0.040	0.030
Ziprasidone	Est. Treatment Effect	-12.452	-7.152	-2.466	-0.600
160 mg	95% CI	(-19.048, -5.855)	(-10.972, -3.333)	(-3.746, -1.186)	(-0.884, -0.316)
N=103	p value*	<0.001	<0.001	<0.001	<0.001

* versus placebo

In contrast to the experience at 80 mg in Study 104, only 20% of patients randomized to that dose in Study 114 discontinued from the trial during the first two weeks of treatment.

Study 115

Study 115 compared the efficacy of three fixed doses of ziprasidone (40 mg, 120 mg, and 200 mg daily) and haloperidol (15 mg daily) with placebo in a total of 419 patients. In the intent-to-treat LOCF analysis, all three ziprasidone dose groups as well as the haloperidol group demonstrated statistically significant improvement in PANSS Total, BPRSd Total and Core Items, and CGI-Severity scores, compared with placebo (Table 10). The 200 mg dose group additionally demonstrated statistically significant improvement in the PANSS Negative Subscale Score. (Results of the PANSS Negative Subscale are discussed further in Section C.1.4.) A 15 mg dose of haloperidol produced statistically significant improvement in all five primary efficacy variables.

Results in the ziprasidone-treated patients were consistent with those reported in Studies 106 and 114.

Table 10. Statistical Summary for Primary Efficacy Variables; Study 115

Treatment Group (ITT)		PANSS Total	BPRSd Total Score	BPRSd Core Items Score	CGI-Severity
Ziprasidone	Est. Treatment Effect	-6.774	-3.588	-1.396	-0.330
40 mg	95% CI	(-12.930, -0.618)	(-7.163, -0.013)	(-2.682, -0.110)	(-0.628, -0.033)
N=86	p value*	0.031	0.049	0.034	0.030
Ziprasidone	Est. Treatment Effect	-8.232	-4.390	-1.351	-0.331
120 mg	95% CI	(-14.590, -1.873)	(-8.090, -0.690)	(-2.678, -0.024)	(-0.638, -0.024)
N=76	p value*	0.011	0.020	0.046	0.035
Ziprasidone	Est. Treatment Effect	-8.009	-4.242	-1.736	-0.427
200 mg	95% CI	(-14.279, -1.739)	(-7.884, -0.599)	(-3.042, -0.430)	(-0.728, -0.125)
N=82‡	p value*	0.012	0.023	0.009	0.006
Haloperidol	Est. Treatment Effect	-13.841	-7.215	-3.159	-0.745
15 mg	95% CI	(-20.075, -7.607)	(-10.835, -3.594)	(-4.460, -1.857)	(-1.045,-0.445)
N = 82‡	p value*	<0.001	<0.001	<0.001	<0.001

‡N = 83 for CGI-Severity
* versus placebo

In Study 115, a dose-response analysis was defined as the primary statistical analysis. This analysis, which included placebo, demonstrated a statistically significant dose-response relationship for all primary efficacy variables. No consistent dose-response relationship was observed across ziprasidone treatment groups when the placebo group was excluded from the analysis.

Efficacy by Age, Gender and Race

Analysis of the effects of age, gender, and race on data pooled from Studies 104, 106, 114, and 115 showed no statistically significant treatment interaction effects for any of the efficacy variables tested. The number of elderly patients (aged 65 years or over) and the number of patients in certain racial groups (e.g., Asian patients) was small, so that definitive conclusions regarding efficacy in these populations could not be made.

C.1.3 Prevention of Relapse

The importance of neuroleptic therapy in the prevention of relapse in chronic schizophrenia has been well documented.[68 69 70 71 72] Virtually all chronic schizophrenic patients not treated with some form of antipsychotic drug will relapse within three years.[73]

Study 303, a one-year, double-blind, placebo-controlled study, was conducted specifically to assess the use of ziprasidone in this highly important aspect of the management of schizophrenic patients.

A total of 293 patients with a DSM-III-R Axis I diagnosis of chronic or subchronic schizophrenia were randomized and had post-baseline efficacy assessments. Patients were to have been currently hospitalized for a period of not less than two

months, with a score of 5 (markedly ill) or less in CGI-Severity at baseline. The primary efficacy variable of the study was the time to relapse. Relapse was prospectively defined as either:

- a score of 6 (much worse) or greater in CGI-Improvement;
- a score of 6 (severe) or greater in either PANSS Items P7 (hostility) or G8 (uncooperativeness) on two successive days.

Patients meeting these criteria were immediately withdrawn from the study and were considered to have relapsed. Careful monitoring of patients was assured as patients were either in hospital or (if clinically stable) in sheltered accommodation with continuous medical or nursing supervision.

Baseline characteristics included numerous previous psychiatric hospitalizations (mean: 9.9) and evidence of severe disease, as expressed particularly by the high PANSS Negative Symptom Subscale Scores (mean: 25.1) and low GAF scores (mean: 47.9) at baseline. Patients entered the study receiving maintenance treatment with other antipsychotics. The risk of relapse increased by week in all treatment groups. The relapse rate, based on a survival analysis of time to relapse, was statistically significantly lower in all ziprasidone groups compared with placebo (Figure 3). Similarly, the probability of relapse was lower in the ziprasidone groups than in the placebo group at each treatment week (Table 11).

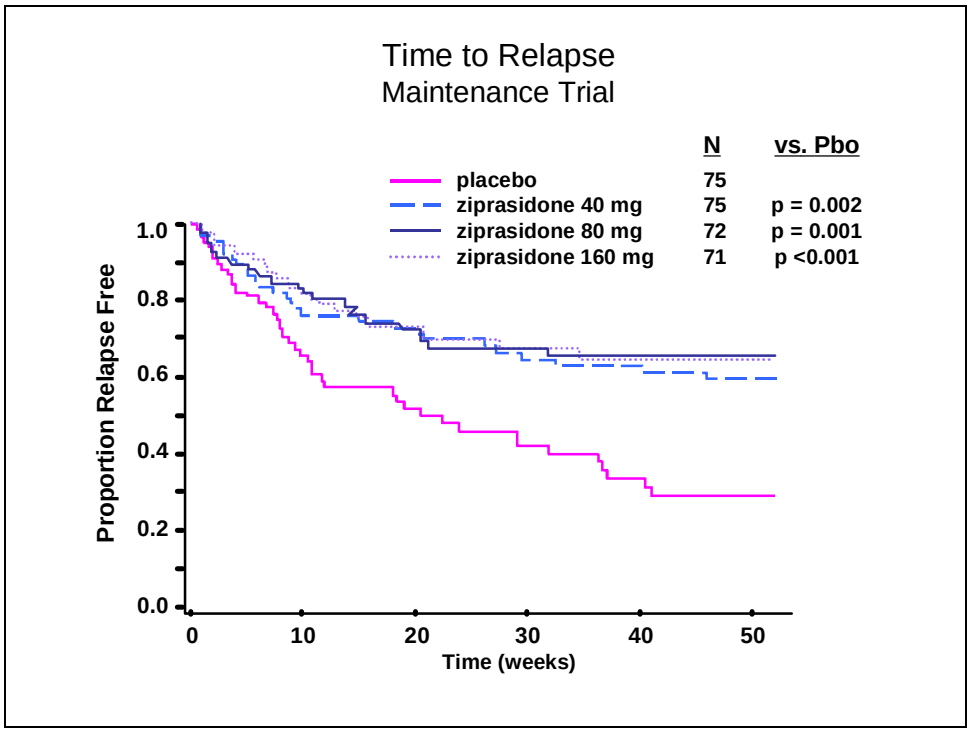


Figure 3. Time to Relapse - Kaplan-Meier Curve; Study 303

Table 11. Cumulative Probability of Relapse by Treatment Week; Study 303

Treatment Groups (ITT)	N	Probability of Relapse			
		Week 16	Week 28	Week 40	Week 52
Ziprasidone 40 mg	75	0.26	0.34	0.37	0.41
Ziprasidone 80 mg	72	0.27	0.33	0.35	0.35
Ziprasidone 160 mg	71	0.24	0.32	0.36	0.36
Placebo	75	0.43	0.55	0.67	0.71

* based on Kaplan-Meier product-limit method

Only 6% (7/117) compared with 35% (8/23) of placebo-treated patients who were participating in Study 303 at Week 28 experienced a relapse over the next six months of treatment. These findings illustrate both the protracted nature of the increase in risk of relapse following cessation of neuroleptic treatment and the efficacy of ziprasidone in preventing relapse over the long term.

Additional efficacy variables in this study included the PANSS Total and Negative Subscale, CGI-Severity, and the GAF Scale. In intent-to-treat LOCF analyses, the three ziprasidone dose groups (individually and pooled) demonstrated statistically significant improvement in these efficacy measures compared with placebo. Estimated treatment effects for PANSS Total, CGI-Severity, and GAF are summarized in Table 12.

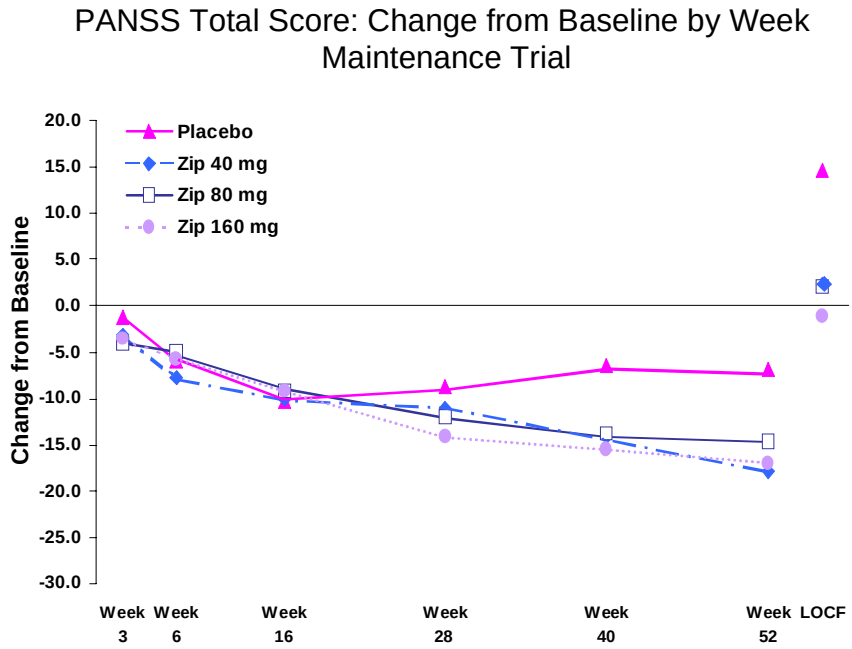
Table 12. Statistical Summary for Additional Efficacy Variables; Study 303

Treatment Group (ITT)		PANSS Total	CGI-Severity	GAF
ziprasidone 40 mg N=75	Estimated Treatment Effect (95%CI)	-12.689 (-19.883, -5.496)	-0.591 (-0.952, -0.230)	6.914 (2.326, 11.502)
	p value*	0.001	0.001	0.003
ziprasidone 80 mg N=72	Estimated Treatment Effect (95%CI)	-11.571 (-18.790, -4.352)	-0.761 (-1.125, -0.398)	7.902 (3.288, 12.516)
	p value*	0.002	<0.001	0.001
ziprasidone 160 mg N=71	Estimated Treatment Effect (95%CI)	-15.575 (-22.795, -8.354)	-0.744 (-1.106, -0.382)	8.342 (3.727, 12.957)
	p value*	<0.001	<0.001	<0.001

* versus placebo

The improvement in PANSS Total Score for patients remaining in the study at each time point (Observed Cases) is shown in Figure 4. In contrast to the patients given placebo, patients taking ziprasidone continued to show improvement in PANSS Total Scores after Week 16.

Changes in the PANSS Negative Subscale Scores are discussed in Section C.1.4.



	Number of Subjects/Treatment Group by Week							
Treatment Group (ITT)	BL	Wk3	Wk6	Wk16	Wk28	Wk40	Wk52	Last
Ziprasidone 40 mg	75	67	60	48	40	38	35	75
Ziprasidone 80 mg	72	66	58	47	36	33	33	72
Ziprasidone 160 mg	71	68	66	50	42	36	34	71
Placebo	75	70	56	31	23	16	14	75

Figure 4. Change in PANSS Total Score by Week; Study 303, Observed Cases

In conclusion, Study 303 demonstrated the statistically significant superiority of three fixed doses (40 mg, 80 mg, and 160 mg) of ziprasidone, compared with placebo, in the prevention of recurrence of acute exacerbation in patients with a DSM-III-R Axis I diagnosis of chronic or subchronic schizophrenia. The probability of relapse between 6 months and one year was particularly low and patients who remained on ziprasidone showed continued improvement in symptoms over the duration of the study.

C.1.4 Treatment of Negative Symptoms of Psychosis

The negative symptoms of flat affect, poverty of speech, cognitive impairment, anhedonia and anergia, are frequent concomitants of schizophrenia. Not all of the features are specific to the negative syndrome, but the symptom cluster and, in particular, the core symptoms of flat affect and poverty of speech, are particularly associated with schizophrenia.[74] Although not invariant, these symptoms are

much more stable over time than other symptoms[75,76] and are a source of considerable morbidity and impairment in social functioning.

Studies to investigate efficacy of antipsychotic agents in the negative syndrome of schizophrenia are often difficult to interpret given the many confounding factors that must be understood and, optimally, controlled. These include the secondary effects of positive symptoms, extrapyramidal symptoms associated with use of a neuroleptic comparator, the unwanted effects of other drugs, and co-existing depressive symptoms.

In the LOCF analysis, ziprasidone treatment groups showed statistically significant improvement in efficacy variables, including the PANSS Negative Subscale, compared with placebo. Compared with placebo, the 40 mg and 160 mg groups demonstrated a statistically significant improvement in negative symptoms in a prospectively-defined analysis of patients with predominantly negative symptoms (i.e., patients having a baseline score of at least 21 on the PANSS Negative Subscale and a Positive Subscale Score of at least six points lower than the Negative Subscale Score). There was a trend towards improvement in the 80 mg group (Table 13).

Table 13. Statistical Summary for PANSS Negative Scores; Study 303

Treatment Group (ITT)		PANSS Negative Score			
		All Patients		Predominantly Negative Symptom Subgroup	
ziprasidone 40 mg	Estimated Treatment Effect (95% CI)	N=75	-3.444 (-5.192, -1.697)	N=41	-3.267 (-5.698, -0.835)
	p value*		<0.001		0.009
ziprasidone 80 mg	Estimated Treatment Effect (95% CI)	N=72	-2.272 (-4.030, -0.513)	N=35	-2.280 (-4.773, 0.213)
	p value*		0.012		0.073
ziprasidone 160 mg	Estimated Treatment Effect (95% CI)	N=71	-3.967 (-5.717, -2.216)	N=42	-3.829 (-6.193, -1.465)
	p value*		<0.001		0.002

* versus placebo

Study 303 was a uniquely designed trial of one year duration in a population of patients with relatively stable positive symptoms and significant negative symptomatology. Intention-to-treat last observation carried forward (ITT LOCF) analysis of efficacy rating scales is a common method of dealing with missing data. However, ITT LOCF analysis, by carrying forward the last observation of prematurely withdrawn subjects (including those withdrawn due to acute exacerbation of symptoms), may not provide a clear indication of symptom change while patients are relatively stable i.e. free from acute exacerbation. Since negative symptoms may increase during acute exacerbation, the LOCF analysis may overstate the intensity of negative symptoms predominant during the pre-exacerbation time period. The longer the trial, the greater the importance of this time period, particularly in view of the unfortunate tendency of even treated patients to relapse over time.

Additional analyses of these efficacy variables were therefore undertaken to elucidate the effects of ziprasidone on negative symptoms. As EPS in the ziprasidone groups was similar to placebo and depressive symptoms at baseline appeared low in all treatment groups (five item PANSS-Depression Factor means at baseline ranged from 11.6 to 12.5), these factors were considered unlikely to confound the negative symptoms assessment. To minimize the confounding effects of acute psychosis on negative symptoms, a comparison of mean changes in PANSS negative subscale was performed when patients were clinically stable. In this analysis, termed penultimate observation carried forward analysis (POCF), for patients who had withdrawn from the study, the observation at the assessment before withdrawal was included in the analysis. Although all groups showed an initial improvement, only the ziprasidone groups demonstrated continued improvement in PANSS Total scores for the duration of the study (Figure 5).

Figure 6 confirms the characterization of the placebo-treated group as being relatively stable, suggesting that the improvement in negative symptoms was primary, i.e. could not be accounted for by the treatment of symptoms associated with impending relapse. This was supported by the prolonged time course of the treatment effect and the contrast over this time provided by a stable placebo-treated population of patients with schizophrenia, eliminating any consideration of extrapyramidal symptoms as a confounding factor in the comparator group.

This analysis suggests that ziprasidone provides significant improvement in symptoms of schizophrenia over time in addition to preventing relapse, a finding that could not be drawn from examination of the LOCF analysis alone.

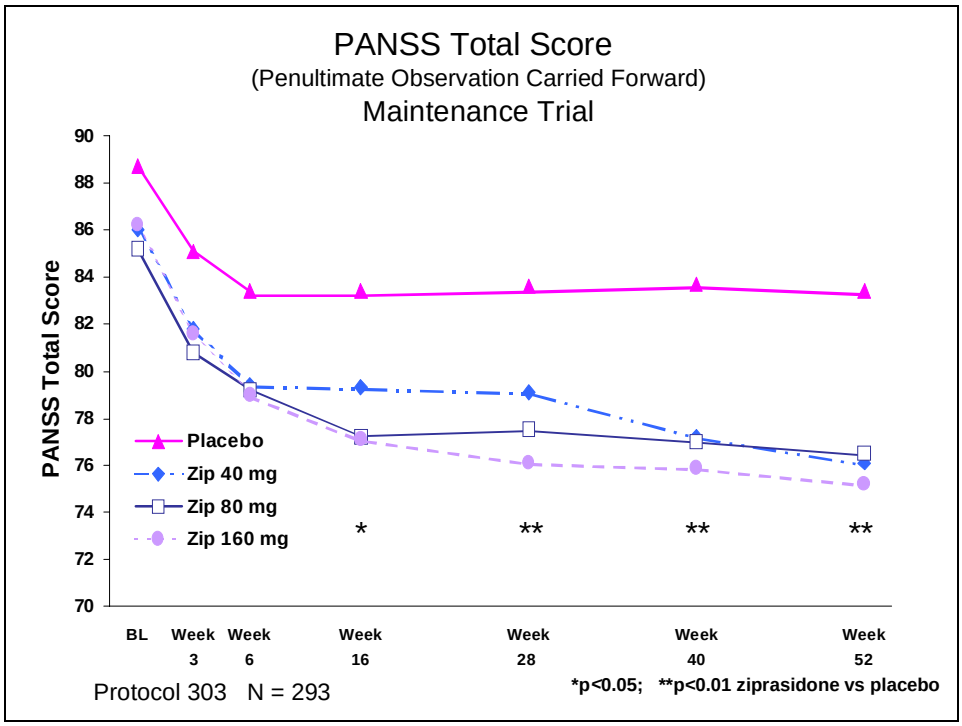


Figure 5. Change in PANSS Total Score - Excluding Assessment at Time of Discontinuation; Study 303

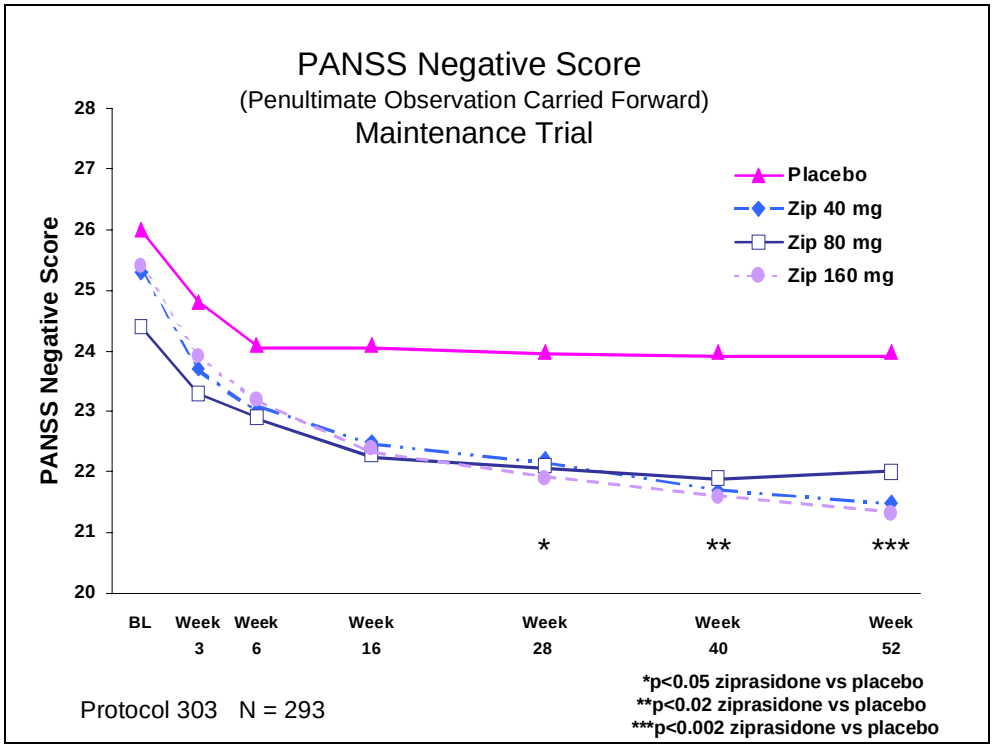


Figure 6. Change in PANSS Negative Subscale - Excluding Assessment at Time of Discontinuation; Study 303

As mentioned in Section C.1.2, the effect of ziprasidone on negative symptoms was also assessed in Studies 114 and 115. The mean baseline PANSS Negative scores of ziprasidone-treated patients in Studies 114 and 115 were 24.8 and 22.9, respectively, compared with 27.8 for the predominantly negative symptoms subgroup in Study 303. PANSS Negative data from Studies 114 and 115 are summarized below (Table 14).

Table 14. Statistical Summaries for PANSS Negative Scores; Studies 114 and 115

Treatment Group (ITT)		PANSS Negative Subscale
Study 114		
Ziprasidone 80 mg	Est. Treatment Effect (95%CI)	-2.030 (-3.786, -0.274)
N=104	p value*	0.024
Ziprasidone 160 mg	Est. Treatment Effect (95%CI)	-3.094 (-4.849, -1.339)
N=103	p value*	0.001
Study 115		
Ziprasidone 40 mg	Est. Treatment Effect (95%CI)	-1.439 (-3.261, 0.383)
N=86	p value*	0.121
Ziprasidone 120 mg	Est. Treatment Effect (95%CI)	-1.745 (-3.630, 0.139)
N=76	p value*	0.069
Ziprasidone 200 mg	Est. Treatment Effect (95%CI)	-2.201(-4.048, -0.355)
N=82	p value*	0.020
Haloperidol 15 mg	Est. Treatment Effect (95%CI)	-2.533 (-4.384, -0.681)
N=82	p value*	0.008

The improvement was statistically significant at doses of 80 mg and 160 mg in Study 114 and at 200 mg in Study 115. In Study 115, patients given a 15 mg daily dose of haloperidol also showed a statistically significant improvement in negative symptoms. The six week duration of these studies and the coincident improvement in positive symptoms in a population being treated for an acute exacerbation of psychosis limit the interpretation of these effects. Nonetheless these findings were supportive of Study 303.

The analyses of negative symptoms presented above indicate that ziprasidone is effective in reducing negative symptoms in acutely ill patients and in stable patients with chronic schizophrenia.

C.2 Treatment of Depressive Symptoms Associated with Psychosis

Depressive symptoms occur in 25% to 50% of patients with schizophrenia. Depression is a core symptom of the illness and is not only closely linked to the high rate of suicide (10%[36]) among patients with schizophrenia, but is also associated with an increased risk of relapse and poor functional outcome.

The Montgomery-Asberg Depression Rating Scale (MADRS) was used in Studies 114 and 115 to assess depressive symptoms. Analyses were carried out for All Patients who received study drug and had a post-Baseline efficacy

measure, for patients with clinically significant depressive symptoms at baseline (total score ≥14, equal to the median score at baseline in Study 114, and prospectively identified for analysis of Study 115), and for patients whose primary diagnosis was Schizoaffective Disorder. Neither study was prospectively powered to demonstrate efficacy in the MADRS analyses.

The analysis of MADRS Total Scores in All Patients showed a numerical improvement in all ziprasidone groups compared with placebo. In Study 115, the improvement in MADRS scores in the three ziprasidone dose groups (40 mg, 120 mg, and 200 mg) was statistically significant compared with placebo; the patients who received haloperidol at 15 mg daily also demonstrated a statistically significant improvement in total MADRS scores in this study. No statistically significant improvement was seen in this analysis in Study 114 (Figure 7).

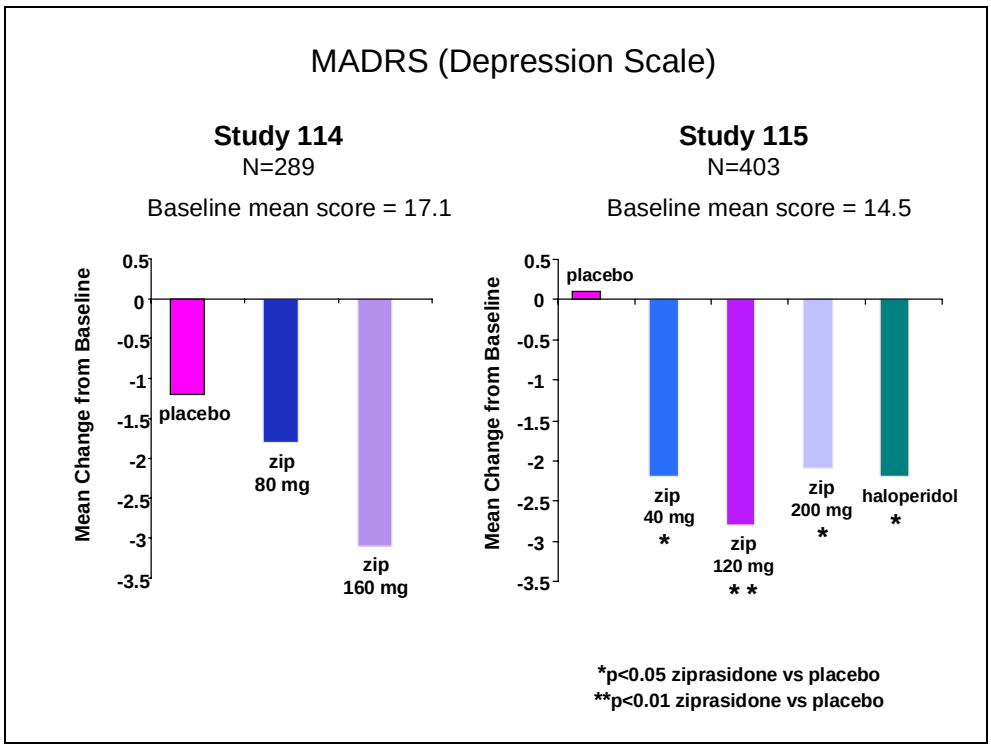


Figure 7. Studies 114 and 115: Change in Montgomery-Asberg Depression Rating Scale

In the prospectively-defined subgroup analysis of patients with baseline MADRS Scores of at least 14 (mean total baseline score of 22) in Study 115, the 120 mg ziprasidone group (but not the 40 mg or 200 mg ziprasidone groups or the haloperidol group) demonstrated statistically significant improvement (p = 0.018) in MADRS scores compared with placebo. This analysis also demonstrated statistically significant improvement in Study 114 for the 160 mg dose (p = 0.011).

Patients with schizoaffective disorder represented 23% of the total study population in Study 114 and 31% in Study 115. In Study 115, schizoaffective patients in the 40 mg, 120 mg, and 200 mg ziprasidone groups (but not the haloperidol group) demonstrated statistically significant improvement ($p = 0.003$, $p = 0.019$ and $p = 0.033$, respectively) in MADRS scores compared with placebo. Results of a comparable analysis in Study 114 were not statistically significant.

Meta-analysis of the results of Studies 114 and 115 provide additional support for the efficacy of ziprasidone in the treatment of depressive symptoms. In the meta-analysis of MADRS Total Scores in all intent-to-treat patients, the combined ziprasidone doses in the range 80 mg to 160 mg demonstrated statistically significant superiority over placebo ($p = 0.004$). The analyses of MADRS Total Scores in intent-to-treat patients with baseline scores ≥14 were also statistically significantly superior to placebo for combined doses in the range from 80 mg to 160 mg ($p = 0.034$).

These data provide evidence that ziprasidone effectively treats depressive symptoms associated with acute psychosis.

C.3 Safety

Adverse experience data were routinely recorded throughout the ziprasidone clinical trial program, capturing both spontaneously reported adverse events at each trial visit and serious adverse events reported throughout the trial as they were reported by the investigator. In addition, special rating instruments were used to assess the occurrence of extrapyramidal signs and symptoms.

The following section summarizes the adverse event (AE) incidence presented in the NDA for placebo-controlled trials. Specifically, data are presented from:

Studies 106, 114, 115 and 104: short-term (4 and 6 weeks), fixed-dose, placebo-controlled (STFDPC) trials in patients with acute exacerbation of schizophrenia or schizoaffective disorder.

Study 303: a one-year maintenance trial in patients with chronic or subchronic schizophrenia.

The results showed that:

- Ziprasidone was well tolerated by adult patients. The overall incidence of AEs was comparable in patients receiving ziprasidone or placebo in both short-term and long-term, fixed-dose, placebo-controlled trials.
- In STFDPC Phase 2/3 trials, the most frequently reported AEs in ziprasidone-treated patients were those affecting the nervous system. Among AEs reported more frequently by ziprasidone-treated than placebo-treated patients, the most prevalent in the short-term trials was somnolence and the most prevalent in the maintenance study was insomnia.

- Ziprasidone had a very low liability for inducing movement disorders, including extrapyramidal syndrome, as evidenced by spontaneous adverse event reports, specific rating scales, and concomitant drug therapy for extrapyramidal syndrome.
- Ziprasidone treatment was not associated with any laboratory test abnormalities indicative of clinically relevant toxicity.
- Ziprasidone treatment was associated with a low incidence of discontinuations due to adverse events and laboratory test abnormalities.
- Ziprasidone had a low propensity to cause prolactin elevations and, when they occurred, the increases in prolactin levels were generally transient.

C.3.1 Discontinuations

C.3.1.1 Short-Term, Fixed-Dose, Placebo-Controlled Trials

In the STFDPC clinical trials, 4.1% (29/702) of ziprasidone-treated patients and 2.2% (6/273) of placebo-treated patients were discontinued due to all causality, treatment-emergent adverse events; 8.2% (7/85) of patients receiving haloperidol were discontinued for treatment-emergent adverse events. Discontinuations due to laboratory test abnormalities were rare (0.6% (4/702) in the ziprasidone group, none in the placebo and haloperidol groups).

Ziprasidone-treated patients were most commonly discontinued due to adverse events affecting the nervous system [10 patients (1.4%) compared with 2 (0.7%) in the placebo group and 7 (8.2%) in the haloperidol group]. Among the 702 ziprasidone-treated patients in these trials there were only two adverse event categories that led to discontinuation of more than 2 patients:

Rash: 7 ziprasidone-treated patients were discontinued due to rash (rash, 5 patients; maculopapular rash, 2 patients); the overall incidence of all types of rash in the short-term placebo-controlled trials was 5.0% for ziprasidone compared with 4.0% for placebo. The incidence of rash was 4.5% for ziprasidone, 3.4% for placebo, and 2.0% for haloperidol for all Phase 2/3 trials included in the NDA. Most patients continued treatment with resolution of the rash. Review of the case histories of ziprasidone-treated patients discontinuing any Phase 2/3 trial because of rash (rash, 14 patients; maculopapular rash, 2 patients; vesiculobullous rash, 1 patient) revealed no other evidence of significant systemic illness and no incidence of clinically significant hypereosinophilia. The incidence of rash remains approximately 1% greater in ziprasidone-treated patients than in placebo-treated patients; as of 5 February 2000, incidences were 4.5% for ziprasidone, 3.4% for placebo, and 2.3% for haloperidol.

Nausea: 3 ziprasidone-treated and one placebo-treated patient were discontinued due to nausea (incidence equal at 0.4%); the overall incidence of nausea in the STFDPC trials was 9.5% for ziprasidone (no significant dose-relationship), 7.0% for placebo, and 9.4% for haloperidol. The incidence of nausea in all Phase 2/3 studies in the NDA was 10.3% for ziprasidone and 5.4% for haloperidol and for placebo. As of 5 February 2000, the incidence of nausea in all Phase 2/3 trials was 11.9% for the ziprasidone group, 5.3% for placebo, and 6.7% for haloperidol.

C.3.1.2 Long-Term Maintenance Trial

In the one-year maintenance trial, Study 303, approximately 9% of ziprasidone-treated patients and 15% of placebo-treated patients were discontinued due to all causality, treatment-emergent adverse events (Table 15), most commonly movement disorders. Discontinuations for laboratory abnormalities occurred with similar frequency in ziprasidone- and placebo-treated patients.

Table 15. Discontinuations in a One-Year Maintenance Trial; Study 303

	Ziprasidone	Placebo
Number of Patients	219	75
Patients Discontinued for:		
Adverse Events	19(8.7%)	11(14.7%)
Laboratory Abnormalities	3(1.4%)	1(1.3%)

C.3.2 Incidence of Treatment-Emergent Adverse Events

The overall incidence of all causality, treatment-emergent adverse events in ziprasidone-treated patients did not exceed that in placebo-treated patients in the short-term trials (79.6% ziprasidone vs. 79.9% placebo) and maintenance Study 303 (73.1% ziprasidone vs. 77.3% placebo).

C.3.2.1 Short-Term, Fixed-Dose, Placebo-Controlled Trials

Table 16 shows adverse events that occurred with an incidence of at least 5% in the ziprasidone group and with greater frequency in ziprasidone-treated patients than in placebo-treated patients in STFDPC trials. The proportion of haloperidol-treated patients who experienced these same adverse events is shown for reference.

Table 16. Incidence of Treatment-Emergent Adverse Events (≥5% and More Frequent on Ziprasidone than on Placebo) in Short-Term, Fixed-Dose, Placebo-Controlled Trials

	Incidence of Adverse Events (%)		
	Ziprasidone	Placebo	Haloperidol
Number of Patients	702	273	85
Mean Duration of Treatment	28.4 days	24.6 days	31.5 days
%Patients with:			
Somnolence*	14.4	6.6	23.5
Nausea	9.5	7.0	9.4
Constipation	9.3	8.4	7.1
Akathisia	8.4	7.0	28.2
Dyspepsia	8.1	7.0	15.3
Dizziness	7.8	5.9	9.4
Respiratory Disorder*	7.7	3.3	8.2

*p <0.05 vs. placebo

Somnolence was the only treatment-emergent adverse event with an incidence more than 5% higher in ziprasidone-treated patients than in placebo-treated patients. Cases of somnolence were generally mild or moderate in severity and led to the discontinuation of only 2 patients.

The incidences of treatment-emergent extrapyramidal syndrome (EPS) and akathisia observed in ziprasidone-treated patients were higher than or comparable to those observed in placebo-treated patients (4.7% and 8.4% vs. 1.1% and 7.0%, respectively) but were substantially lower than those observed in the haloperidol group (15 mg daily) in Study 115 (14.1% and 28.2%), respectively. Furthermore, most cases of EPS and akathisia that did occur were mild or moderate and necessitated the discontinuation of just one patient and 2 patients, respectively. The relationship between ziprasidone and movement disorders is discussed in Section C.3.3.

Incidence of Adverse Events Typically Associated with Antipsychotic Drugs

The incidence of certain adverse events associated with neuroleptics and some of the newer antipsychotic drugs was low in ziprasidone-treated patients (Table 17). Impotence, abnormal ejaculation and other manifestations of male sexual dysfunction were less frequent in ziprasidone-treated than in placebo-treated patients. Postural hypotension and dystonia were only slightly more frequent with ziprasidone than placebo. By comparison, patients given haloperidol (Study 115) demonstrated a higher overall incidence of these adverse events than patients in either of the other two groups.

Table 17. Incidence of Treatment-Emergent Adverse Events Typically Associated with Antipsychotic Drug Treatment in Short-Term, Fixed-Dose, Placebo-Controlled Trials

	Ziprasidone	Placebo	Haloperidol
Number of Patients	702	273	85
Mean Duration of Treatment	28.4 days	24.6 days	31.5 days
%Patients with:			
Abnormal ejaculation	0.0	0.4	0.0
Impotence	0.3	0.4	1.2
Other male sexual dysfunction	0.0	0.4	0.0
Postural hypotension	1.3	0.4	2.4
Weight gain	0.4	0.4	1.2
Dystonia	4.0	2.2	11.8
Tardive dyskinesia	0.4	0.7	1.2

C.3.2.2 Long-Term Maintenance Trial

Treatment-emergent adverse events that occurred with an incidence of at least 5% in the ziprasidone group and with greater frequency than in the placebo group in the one-year maintenance trial, Study 303, are shown in Table 18.

Table 18. Incidence of Treatment-Emergent Adverse Events (≥5% and More Frequent on Ziprasidone than on Placebo) in a One-Year Maintenance Trial; Study 303

	Incidence of Adverse Events (%)	
	Ziprasidone	Placebo
Number of Patients	219	75
Mean Duration of Treatment	218.3 days	138.9 days
%Patients with:		
Insomnia	35.6	32.0
Akathisia	9.6	5.3
Hallucinations	9.1	5.3
Depression	8.2	5.3
Headache	6.8	5.3
Hostility	6.8	5.3
Diarrhea	6.8	4.0
Rash	5.9	1.3
Asthenia*	5.5	0.0
Vomiting	5.0	4.0

*p <0.05 vs. placebo

The majority of treatment-emergent adverse events in both the ziprasidone and placebo groups were mild or moderate in severity and disappeared with continued treatment.

C.3.3 Extrapyramidal Effects of Treatment

Movement disorders were assessed using the Simpson-Angus and Barnes Akathisia rating scales; there were no statistically significant differences between the ziprasidone and placebo groups in mean decreases from baseline to endpoint in either movement disorder scale (Table 19).

Table 19. Change in Movement Disorder Rating Scores from Baseline to Endpoint in Short-Term, Fixed-Dose, Placebo-Controlled Trials

	Ziprasidone	Placebo	Haloperidol	p-value (zip vs. pbo)
Simpson-Angus				
Number of Patients	686	264	83	
Mean Change in Score (SD)	-0.33 (2.51)	-0.34 (2.69)	1.12 (3.81)	0.934
Barnes Akathisia				
Number of Patients	691	267	83	
Mean Change in Score (SD)	-0.02 (0.88)	-0.11 (0.92)	0.31 (1.2)	0.156

Figure 8 shows the mean change in Simpson-Angus and Barnes Akathisia scores by modal ziprasidone dose. The mean change from baseline to final assessment in Simpson-Angus scores ranged from –0.66 to –0.05 in the ziprasidone dose groups compared with –0.34 in the placebo group and 1.12 in the haloperidol

group. The mean change from baseline to final assessment in Barnes Akathisia scores ranged from –0.08 to 0.06 in the ziprasidone dose groups compared with –0.11 in the placebo group and 0.31 in the haloperidol group. There was no statistically significant dose-response relationship across the ziprasidone dose levels.

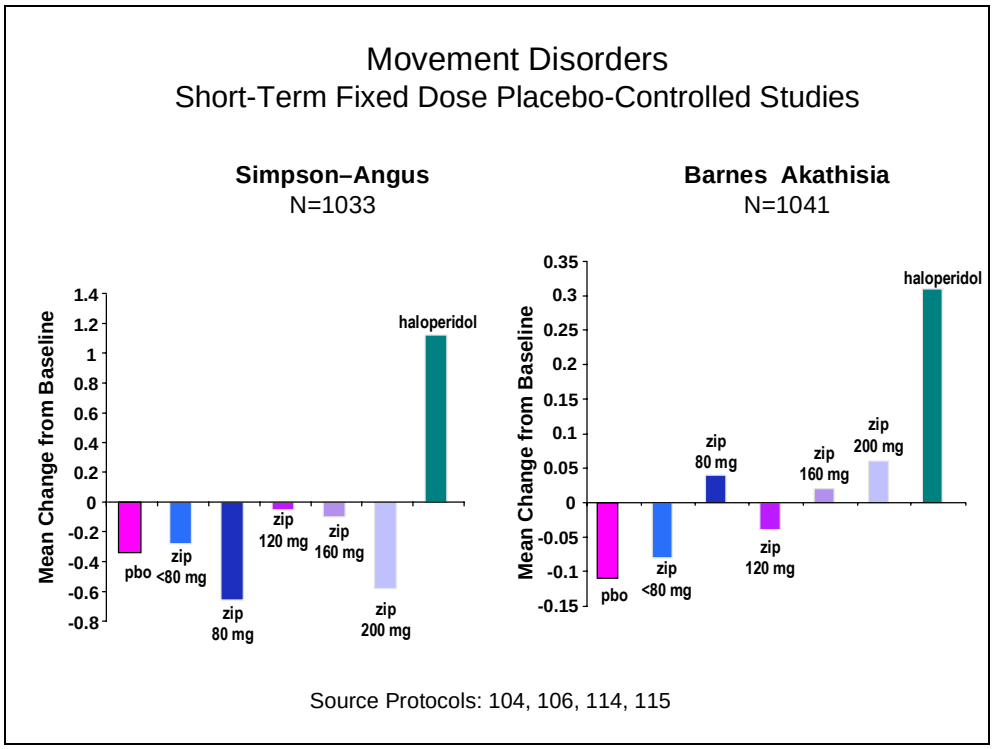


Figure 8. Mean Change from Baseline in Movement Disorder Scores in Short-Term, Fixed-Dose, Placebo-Controlled Trials

Further evidence for ziprasidone's low liability for EPS may be seen in the low usage of benztropine and ß-blockers commonly prescribed for the treatment of EPS and akathisia. Pooled data from the short-term, fixed-dose, placebo-controlled trials showed that similar proportions of ziprasidone-treated (all doses combined) and placebo-treated patients required benztropine at some time during a study (22.4% and 18.3%, respectively); comparable results were obtained for ß-blocker usage (7.1% and 6.2%, respectively). The proportion of ziprasidone-treated patients using benztropine increased from an average of 19% for daily doses up to 120 mg and 25% at the 160 mg daily dose to 41.9% at the 200 mg daily dose; 6.4% of ziprasidone-treated patients taking up to 120 mg daily used a ß-blocker compared with 9.6% taking a daily dose of 160 mg and 8.1% at the 200 mg daily dose. In contrast, 50.6% of patients in the haloperidol group required benztropine and 18.8% required a ß-blocker at some time during a study.

In Study 303, the mean changes from baseline to last observation for the Simpson-Angus scale ranged from -2.0 to -2.6 for the 3 ziprasidone doses compared with -1.7 in the placebo group. The Barnes Akathisia results were comparable to those observed in the short-term trials.

There were no apparent effects of age, gender, or race upon movement disorder rating scale measures among patients receiving ziprasidone.

C.3.4 Laboratory Safety Tests

Laboratory data were routinely captured throughout the ziprasidone clinical trial program. In general, randomly drawn (i.e., non-fasting) laboratory safety tests were performed at baseline, during the study and/or at the end of treatment.

Selected laboratory test data from the NDA safety database and from the database as of 5 February 2000 are shown below (Table 20). The incidence of elevated liver enzyme levels (SGOT, SGPT, alkaline phosphatase) among ziprasidone-treated patients as of 5 February 2000 was comparable to that reported in the NDA. For both the NDA and 5 February 2000 databases, the incidence of clinically significant elevations in random glucose, cholesterol, and triglycerides among ziprasidone-treated patients was comparable to, or less than, those given an active comparator, with the exception of random cholesterol in the short-term, placebo-controlled NDA trials. There was no evidence of elevated eosinophil levels in any of the active treatment groups compared with placebo and no evidence that ziprasidone was associated with blood dyscrasias.

Table 20. Incidence of Clinically Significant Laboratory Test Abnormalities in the Ziprasidone Phase 2/3 Clinical Program

	Ziprasidone		Placebo		Haloperidol		Risperidone	
Laboratory Test	N*	n (%)**	N	n (%)	N	n (%)	N	n (%)
NDA Database (STFDPC Trials only)								
SGOT (AST) (>3xULN)	685	2 (0.3)	261	0	84	0		NA
SGPT (ALT) (>3xULN)	684	8 (1.2)	261	1 (0.4)	84	0		NA
Alk Phos (>3xULN)	685	0	261	0	84	0		NA
Random Glucose								
>1.2xULN	684	57 (8.3)	261	20 (7.7)	83	12 (14.5)		NA
<0.6xLLN	684	3 (0.4)	261	0	83	0		NA
Cholesterol (>1.2xULN)	685	16 (2.3)	261	0	83	1 (1.2)		NA
Triglycerides (>1.2xULN)	684	85 (12.4)	261	17 (6.5)	83	16 (19.3)		NA
Eosinophils (≥10%)	683	21 (3.1)	261	3 (1.1)	83	0		NA
Cumulative to 5 February 2000								
SGOT (AST) (>3xULN)	3500	20 (0.6)	463	3 (0.6)	662	2 (0.3)	301	2 (0.7)
SGPT (ALT) (>3xULN)	3496	40 (1.1)	463	2 (0.4)	662	6 (0.9)	301	0
Alk Phos (>3xULN)	3491	2 (0.06)	463	0	653	1 (0.2)	301	0
Random Glucose								
>1.2xULN	2362	352 (14.9)	393	48 (12.2)	282	46 (16.3)	134	20 (14.9)
<0.6xLLN	2362	14 (0.6)	393	0	282	2 (0.7)	134	1 (0.8)
Cholesterol (>1.2xULN)	2478	333 (13.4)	331	48 (14.5)	309	59 (19.0)	162	49 (30.2)
Triglycerides (>1.2xULN)	2262	545 (24.1)	331	53 (16.0)	309	75 (24.3)	162	61 (37.6)
Thyroxine (T4)								
>1.2xULN	1033	14 (1.4)	111	1 (0.9)	127	1 (0.8)	16	1 (6.2)
<0.8xLLN	1033	4 (0.4)	111	0	127	2 (1.6)	16	0
TSH								
>1.2xULN	1039	26 (2.5)	110	0	129	5 (3.9)	17	0
<0.8xLLN	1039	75 (7.2)	110	6 (5.4)	129	4 (3.1)	17	1 (5.9)
Eosinophils (≥10%)	3388	108 (3.2)	459	15 (3.3)	605	13 (2.2)	300	11 (3.7)

*N = number of patients evaluated.
**n(%) = number (%) of patients with laboratory test abnormality
NT = not tested; NA = not applicable

Like other drugs that possess significant D_2 receptor antagonist properties, ziprasidone has the potential to elevate serum prolactin. The incidence of prolactin >22 ng/ml (>1.1xULN) in the one-year maintenance trial was 17.3% for

ziprasidone compared to 4.3% for placebo. Further information about the effects of ziprasidone on prolactin levels may be obtained by examining data from all Phase 2/3 oral dosing studies in the NDA database (Table 21). Although the incidence of clinically significant prolactin elevation in ziprasidone patients was higher than in placebo patients, it was markedly lower than that observed in the haloperidol or risperidone comparator groups. Moreover, the degree of prolactin elevation in both males and females, as evidenced by the mean post baseline concentration, was lower with ziprasidone than with haloperidol or risperidone. In fact, for males, the mean serum prolactin concentrations in ziprasidone-treated and placebo-treated patients were similar.

The low incidence of persistent prolactin elevation (defined as >35 ng/ml for males and >50 ng/ml for females on more than one post baseline measurement) in ziprasidone-treated patients indicated that prolactin elevation is a transient phenomenon. These data confirm the relatively low incidence of significant elevation, and suggest that significant attenuation of ziprasidone's prolactin-stimulating effect takes place in both genders, leaving the great majority of patients without a clinically significant elevation.

Table 21. Incidence of Prolactin Elevation in All Oral Phase 2/3 Trials (NDA Database)

	Ziprasidone	Placebo	Haloperidol	Risperidone
Incidence of Prolactin >1.1xULN (All patients)	n/N (%) 148/741 (20)	n/N (%) 3/75 (4)	n/N (%) 45/98 (46)	n/N (%) 105/118 (89)
Mean Prolactin ng/ml*				
Males	9.7 (N=610)	7.6 (N=60)	17.1 (N=80)	34.0 (N=79)
Females	18.2 (N=213)	8.6 (N=15)	40.1 (N=33)	89.2 (N=35)
Elevated at least once				
Males >35 ng/ml	40/610 (6.6)	1/60 (1.7)	9/80 (11.3)	40/79 (50.6)
Females >50 ng/ml	18/213 (8.5)	0/15 (0)	9/33 (27.3)	27/35 (77.1)
Elevated more than once**				
Males >35 ng/ml	7/421 (1.7)	0/47 (0)	2/50 (4.0)	16/50 (32.0)
Females >50 ng/ml	5/143 (3.5)	0/11 (0)	4/19 (21.1)	19/26 (73.1)

* Group means of individual patient means using all post-baseline prolactin values.
** Denominator includes only patients who had more than one post baseline measurement.

In conclusion, there is no evidence from either the NDA or the 5 February 2000 safety databases that ziprasidone treatment is associated with any laboratory test abnormality indicative of clinically relevant toxicity.

C.4 Summary and Conclusions

Data from four placebo-controlled clinical trials indicated that ziprasidone is an effective agent in the short-term and long-term management of psychosis. One 4-week study (Study 106) and two 6-week studies (Studies 114 and 115)

demonstrated the effectiveness of ziprasidone in the treatment of an acute exacerbation of psychosis. One 52-week study (Study 303) demonstrated that ziprasidone significantly reduced the risk of relapse in hospitalized individuals with chronic schizophrenia. Across studies, ziprasidone effectively ameliorated the positive, negative, and depressive symptoms associated with psychosis. There was no statistically significant relationship between therapeutic response and age, gender, or race.

Ziprasidone was exceptionally well tolerated in adult patients in both short-term and long-term placebo-controlled trials. The overall incidence of adverse events was comparable to placebo and there was a relatively low liability for movement disorder adverse events. Ziprasidone treatment was not associated with any laboratory test abnormalities indicative of clinically relevant toxicity. Its prolactin-stimulating effect was modest and appeared to be transient.

Thus, oral ziprasidone was shown to be an efficacious and well-tolerated treatment for both acute and long-term treatment of schizophrenia and schizoaffective disorder.

D. EFFECT ON THE QT INTERVAL: PRECLINICAL STUDIES

Electrophysiologic studies with ziprasidone, its four major circulating metabolites and several atypical antipsychotic drugs were conducted in vitro using AT-1 cells and/or canine isolated Purkinje fibers. The effects of drugs on ion channels expressed in these preparations can often provide some insight into the ionic basis that could underlie ECG effects in the clinic.

D.1 Effects of Antipsychotics on the Delayed Rectifier Potassium Current, I_{Kr}, in AT-1 cells

Prolongation of the QTc interval may be attributable to blockade of the rapidly activating component of the delayed rectifier potassium current, I_{Kr}. I_{Kr} is associated with an ion channel that has been identified in cardiac myocytes across a variety of species including man.[77,78,79]

To determine whether ziprasidone affects ion flux through this K^+ channel, Dr. D.M. Roden (Vanderbilt University) evaluated the I_{Kr} blocking potency of ziprasidone in mouse atrial tumor (AT-1) cells. This study compared the effects of ziprasidone, ziprasidone sulfoxide (M10), risperidone, olanzapine, and the positive control, d-sotalol, on I_{Kr}. When tested at concentrations ranging from 10nM to 3.2 µM (see Table 22 and Table 23), ziprasidone (10 nM), the metabolite, ziprasidone sulfoxide M10 (0.32 µM), risperidone (0.1 µM), and olanzapine (0.32 µM) appeared to block I_{Kr} by 10% (olanzapine) to 27% (ziprasidone sulfoxide) in AT-1 cells, while the vehicle used produced a mean block of 5.1%±13 (SE). Increasing the concentration by 10-fold, ziprasidone, ziprasidone sulfoxide M10, and olanzapine did not achieve 50% block. However, IC_{50}s of ~0.8 µM and ~30 µM were estimated for risperidone and d-sotalol, respectively. The concentrations of d-sotalol that were active in this study were consistent with those observed in previous studies[80] and with the plasma levels of free drug achieved following therapeutic doses in man.[81]

Table 22. Test Concentrations of Antipsychotics and d-Sotalol Used in In Vitro Electrophysiological Studies

Drug	% Free in Plasma	Clinical Dose mg/day	C_{free} @ Clinical Dose ng/ml (nM)	*In Vitro* Test Concentration (nM)	Multiple Above Free Plasma Concentration
Sotalol	100	320	2,000 (7,342nM)	1,000 10,000 100,000	0.14 1.4 14
Ziprasidone	0.1	160	0.202 (0.49nM)	10 32 100	20 65 204
Benzisothiazolylpiperazine (BITP) sulfone (M1)	20.4	n/a	(87nM)	320 1,000 3,200	3.7 12 37
Benzisothiazolyl piperazine (BITP) sulfoxide (M2)	16.1	n/a	(69nM)	320 1,000 3,200	4.6 14 46
S-methyl-dihydro ziprasidone (M9)	32	n/a	24 (56nM)	320 1,000 3,200	5.7 18 57
Ziprasidone Sulfoxide (M10)	7.5	n/a	3.8 (8.9nM)	320 1,000 3,200	36 112 360
Risperidone	10	8	3.3 (8.1nM)	100 320 1,000	12 40 123
Olanzapine	7	20	3.2 (10.1nM)	320 1,000 3,200	32 99 317

Cmax and free plasma for
Ziprasidone: Ziprasidone NDA; M1, M2, M9, and M10: Pfizer Inc, data on file, 1998 and 2000.
Sotalol: Hanyok, 1993.[2] Olanzapine: extrapolated from FDA Review Documents.[82]
Risperidone: extrapolated from Sommers, 1997[83] Grant & Fitton 1994.[84]

Table 23. Inhibition of I_{Kr} by Atypical Antipsychotics and d-Sotalol

	Mean % Decrease in I_{Kr} ± SE	
	Low Concentration	High Concentration
D-Sotalol 10, 100µM	22.3±4.7	75.3±2.7
Ziprasidone 10, 100nM	15.5±3.4	25.2±5.9
Ziprasidone Sulfoxide (M10) 0.32, 3.2µM	26.8±9.4	28.1±3.1
Risperidone 0.1, 1µM	23.3±5.6	57.7±1.1
Olanzapine 0.32, 3.2µM	9.6±0.8	20.8±2.2
Vehicle 1% Acidified DMSO	5.1±13	

In addition, Crumb and colleagues[85] have demonstrated that typical as well as atypical antipsychotics can, in a concentration-dependent manner, inhibit I_{Kr} in a human cell line (HEK-293 cells; Figure 9). In Crumb's study, the atypical antipsychotics ziprasidone, risperidone, and olanzapine were approximately equipotent in their ability to block I_{Kr}; the IC_{50}s of these antipsychotics were 152, 163, and 181 nM, respectively. At other human cardiac ion channels known to be important in modulating cardiac conduction and repolarization (the sodium current, I_{Na+}, transient outward potassium current, I_{to}, sustained current, I_{sus} and another inwardly rectifying potassium current, I_{K1}), ziprasidone, risperidone, and olanzapine did not achieve 50% blockade at concentrations of at least 10 µM, suggesting no clinically relevant activity at these sites.

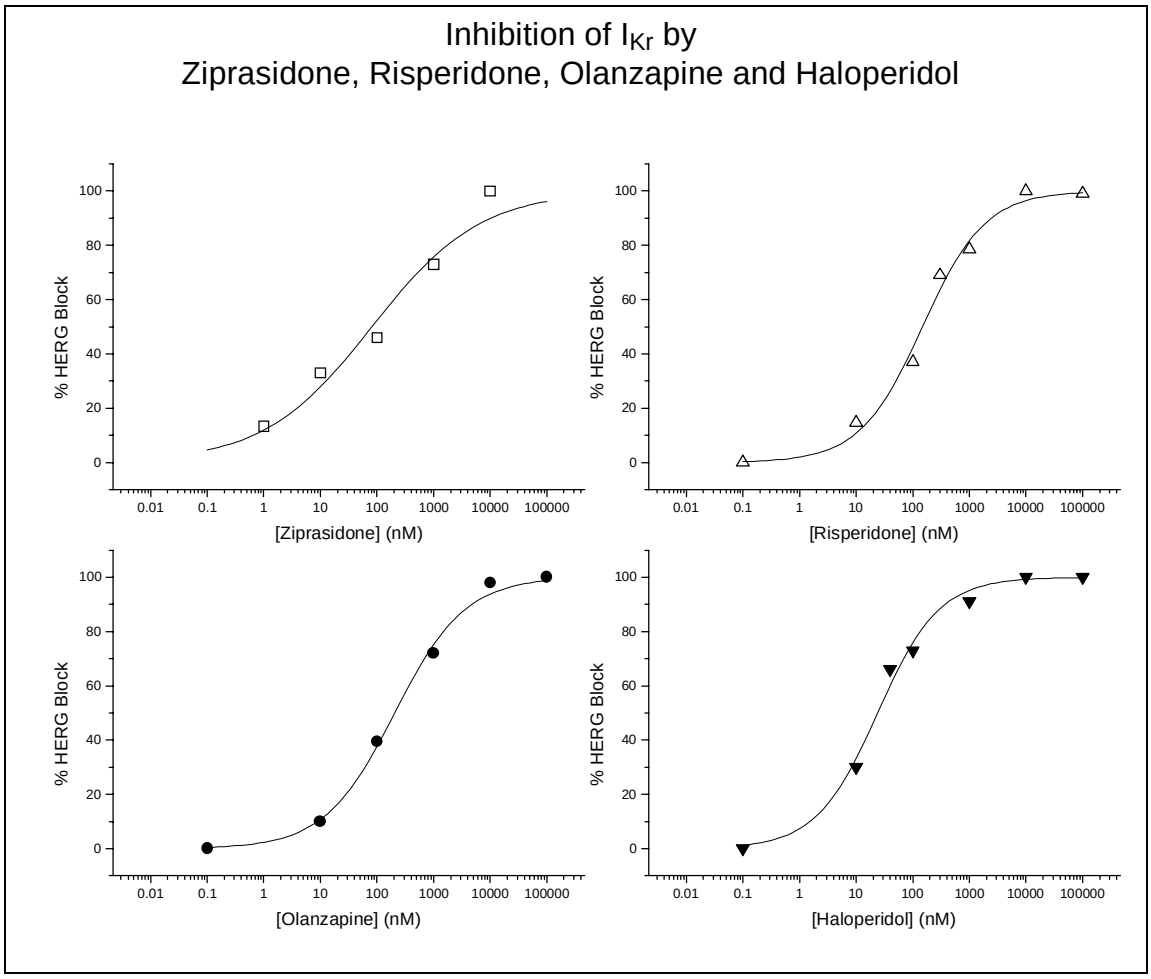


Figure 9. Effects of antipsychotics on HERG current expressed in a human cell line (HEK-293). Adapted from Crumb *et al.,* 1999.[85]

D.2 Effects of Antipsychotics on Canine Purkinje Fibers

The effects on membrane potential, action potential amplitude, and rate of depolarization of ziprasidone, the 4 major circulating metabolites of ziprasidone , risperidone, olanzapine, and d-sotalol, a positive control, were examined in canine isolated Purkinje fibers using standard electrophysiological techniques.

There were no significant effects of ziprasidone, any of the ziprasidone metabolites, d-sotalol, risperidone, or olanzapine on the membrane potential, action potential amplitude, or the rate of depolarization at any concentration tested compared with vehicle. Furthermore, the effects of ziprasidone, the ziprasidone metabolite M10, risperidone, olanzapine, and d-sotalol on action potential duration at 90% repolarization ($APD_{90;}$ Figure 10) were consistent with their effects on I_{Kr} in

as much as the rank order of potency was similar to that determined for these agents in AT-1 cells.

Neither ziprasidone, the ziprasidone metabolites M1 and M2, nor olanzapine had any statistically significant effect on APD_{90}. Ziprasidone metabolite M10 at 3,200 nM significantly increased APD_{90} by 14.7 ± 1.3% compared with pre-treatment control values while M9 significantly increased APD_{90} by 24.0 ± 3.7% and 51.7 ± 7.1% at 1,000 and 3,200nM, respectively. Risperidone also produced a concentration-related prolongation of the action potential duration significantly increasing the duration by 26.1 ± 3.8% and 57.3 ± 11.0% at 320 and 1,000nM, respectively. The positive control, d-sotalol, produced a robust concentration-dependent prolongation of APD_{90} in canine Purkinje fibers.

D.3 Summary and Conclusions

Studies in AT-1 cells showed that ziprasidone and ziprasidone sulfoxide (M10) at concentrations 200-fold and 360-fold higher than their respective free plasma concentrations achieved at the highest recommended clinical dose (160 mg/day) at steady state, reduced the delayed rectifier potassium current, I_{Kr}, by 25.2% and 28.1% respectively. Ziprasidone was not unique among the atypical antipsychotic drugs as an I_{Kr} blocker. Indeed, independent studies by Drs. Roden and Crumb comparing a number of atypical antipsychotics, including ziprasidone, olanzapine, and risperidone, in different model systems concluded that all are I_{Kr} blockers. Since the atypical antipsychotics did not achieve 50% blockade at other human cardiac currents important in cardiac conduction and repolarization (I_{Na+}, I_{to}, I_{sus} and I_{K1}) at concentrations of at least 10 µM, these data would suggest that these agents are all capable of prolonging the QTc in humans. Findings in canine Purkinje fiber are consistent with this interpretation, and suggest that ziprasidone metabolite M9 may play a role as well.

Ziprasidone and its M9 and M10 metabolites have been measured in Study 054 and in a number of individuals who participated in Phase 2/3 trials.

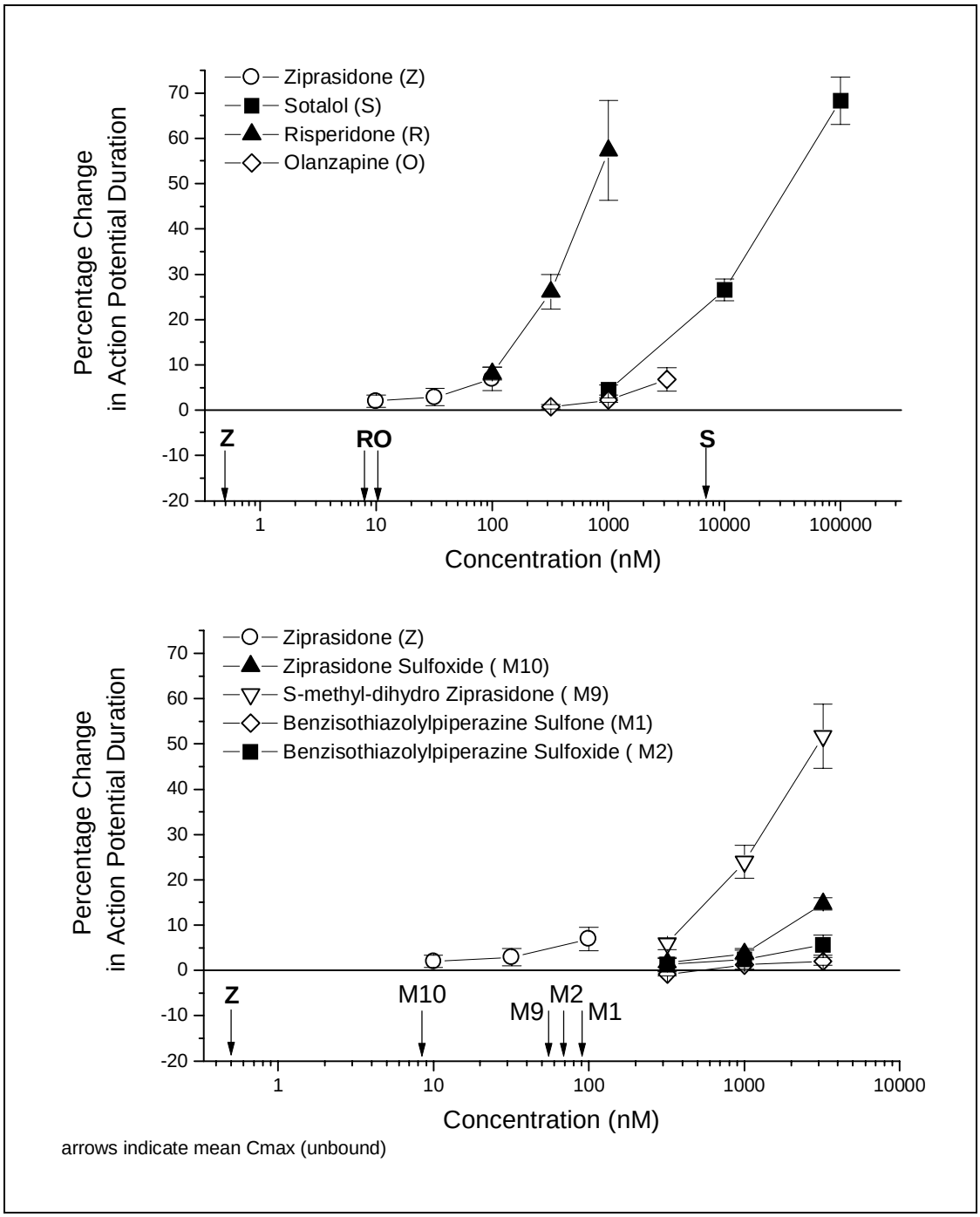


Figure 10. Effects of Antipsychotics and Metabolites of Ziprasidone on Action Potential Duration in Canine Isolated Purkinje Fibers

E. EFFECT ON THE QT INTERVAL: CLINICAL TRIALS

The effect of ziprasidone on the QTc has been well-characterized and appears to be limited, as a function of it's pharmacology and the stability of its metabolism under observed and expected conditions of use. The increase in the QTc is modest as evidenced by an extremely low incidence of QTc values exceeding 500 msec.

Calculation of the QTc interval throughout the ziprasidone clinical development program was based on Bazett's formula. Bazett's correction provides a value that represents the QT interval normalized for a heart rate of 60 bpm and is the formula that has been most commonly used in clinical trials and reported in the literature. However, the Bazett formula has been criticized for "overcorrecting" QT when heart rate exceeds 60 beats per minute, and "undercorrecting" at heart rates below 60 beats per minute. At the request of the Agency, much of the QTc data in this submission has been calculated using both the Bazett correction formula and a population-derived correction formula. For Study 054, the correction formula [$QTc = QT/RR^{0.35}$] will also be used to calculate the QTc results of that trial. A second correction formula [$QTc = QT/RR^{0.38}$] has been derived from baseline ECG data in the Phase 2/3 population overall, and will be presented along with Bazett QTc for all QTc measures from that population, or from subsets of that population (e.g. short term fixed dose trials; individuals taking concomitant medications of interest), with the sole exception of Study 054.

Published reports of QTc data which are quoted in this document have typically provided only Bazett – derived measures.

In the clinical trial program, centrally-read ECGs from all Phase 2/3 studies in the oral ziprasidone clinical program that were included in the ziprasidone NDA demonstrated a mean QTc prolongation of 2.86 msec when compared with screening and 3.59 msec when compared with baseline when the Bazett correction was applied. Using the correction formula derived from the Phase 2/3 population, the corresponding values for the mean QTc prolongation are 2.32 msec when compared with screening and 3.03 msec when compared with baseline. Data on QTc changes observed in clinical trials with other atypical antipsychotic agents are reported in publicly available regulatory review documents, in which only the Bazett formula was applied. Comparisons of ECG measurements across different drugs and clinical trials are, however, problematic since the ECGs are typically not recorded in a uniform manner with respect to washout of previous treatment, time of maximum drug concentration, number of QT measurements and other sources of variability. Consequently, Study 054 was conducted to measure the effects of ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol on the QT interval under standardized conditions in the absence and presence of an appropriate metabolic inhibitor(s) for each agent.

The following section presents a review of the effect of ziprasidone on the QTc, as observed in Study 054 and all completed and ongoing (except double-blind) studies with oral ziprasidone that were reported through 5 February 2000.

In summary:

- As of 5 February 2000, a QTc ≥500 msec was recorded for 2/3095 (0.06%) ziprasidone-treated patients compared with 1/440 (0.23%) patients taking placebo (Bazett correction) or just 1/3095 (0.03%) ziprasidone-treated patients compared with no patients taking placebo (Baseline correction).
- ECG measurements obtained in short term (4-6 week) trials conducted in hospitalized patients who were receiving fixed doses of ziprasidone (80 to 160 mg daily) revealed a modest prolongation in QTc at the final observation:

5.9 to 9.7 msec	Bazett correction
4.4 to 9.3 msec	Baseline correction

- In Study 054, the rank ordering of increase in QTc (from greatest to least effect) was thioridazine, ziprasidone, quetiapine, risperidone, olanzapine, and haloperidol using the Bazett formula; the effect of haloperidol is greater than that of quetiapine when calculated using the Baseline correction formula.
- Ziprasidone produced no further increase in QTc when administered in the presence of the metabolic inhibitor, ketoconazole.

The QTc values from the ziprasidone database that are presented in this section were all derived from centrally read ECGs. Any ECGs in the oral ziprasidone program that were not originally centrally read were subsequently reinterpreted by Premier Research Worldwide (PRW) except those for 107 patients in an oral extension to an intramuscular ziprasidone study, whose ECGs were centrally read by Global Data Exchange International (GDXI).

E.1 Methodological and Analytical Issues

E.1.1 Sources of Variability in QTc Measurements

The ability to detect a measurable change in QTc is limited by the methodology applied in a clinical trial and the extent of spontaneous variability in the QT interval.

Multiple sources of variability in ECG measurements can exist in clinical trials. For example, there is typically no special effort made in the majority of trials to maintain a consistent relationship between the timing of ECG recordings and the time of peak drug exposure. Inconsistencies within and across studies may be introduced by differences in methodology used to record and measure the QT interval. Choice of ECG lead and difficulty in defining the end of the T wave may

both introduce variability. Manual measurement may not correlate well with automated measurement.[86]

Another source of variability in clinical trials is the choice of the reference ECG (baseline). The ziprasidone NDA short-term, fixed-dose, placebo-controlled (STFDPC) trials required, by protocol, two pre-randomization ECGs - one at screening and one at baseline, separated by a 4 to 7 day placebo washout period. Table 24 shows, for the same group of patients, the change from each of these pre-drug measurements to the final QTc value. There was a consistent reduction in QTc between screening and baseline, possibly due to washout of previous antipsychotic medication that may have been producing prolongation. Hence the timing of the reference measurement (screening or baseline) has an impact on the apparent magnitude of the drug effect. This underscores the limitations of comparing data from different trials and different clinical programs where the specifics of the baseline ECG measurement may not always be reported.

Table 24. Comparison of QTc Change to Final Measurement from Screening and from Baseline; Short-Term Fixed-Dose Placebo-Controlled Trials

Modal		Change from Screening (msec)			Change from Baseline (msec)		
Daily Dose	N	Screen	Final	Mean Δ	Baseline	Final	Mean Δ
Bazett Correction							
PBO	147	400.1	396.6	-3.6	398.7	396.6	-2.2
Ziprasidone							
<80mg	85	398.4	398.8	0.4	397.4	398.8	1.4
80mg	87	401.1	406.0	4.9	398.8	406.0	7.1
120mg	68	402.7	406.1	3.4	398.0	406.1	8.1
160mg	93	400.2	404.7	4.4	395.6	404.7	9.1
≥200mg	65	402.2	407.6	5.5	400.8	407.6	6.9
Haloperidol	65	400.7	396.1	-4.6	398.2	396.1	-2.2
Baseline Correction							
PBO	147	388.4	384.8	-3.6	386.2	384.8	-1.4
Ziprasidone							
<80mg	85	388.7	387.7	-1.0	387.7	387.7	-0.0
80mg	87	389.2	392.7	3.5	386.6	392.7	6.0
120mg	68	390.3	393.6	3.3	386.5	393.6	7.0
160mg	93	388.3	393.5	5.2	384.5	393.5	9.0
≥200mg	65	391.9	395.5	3.6	388.3	395.5	7.2
Haloperidol	65	388.6	385.3	-3.2	387.1	385.3	-1.7

Only patients with a screening, baseline, and final QTc value are included in this table; where screening = prior to Day –1 and baseline = Day 0 (first day of study treatment) or Day –1.

The interpretation of drug effects is further complicated by the fact that the mean changes of interest are small relative to the inherent inter- and intra-patient variability in QT measurements.

Figure 11 provides an illustration of the variability across a population, specifically the 2775 patients enrolled in ziprasidone Phase 2/3 clinical trials who had baseline ECG recordings read by PRW. In this group, the mean = median QTc was 401 msec (SD: 25 msec), with a range of 314 to 494 msec.

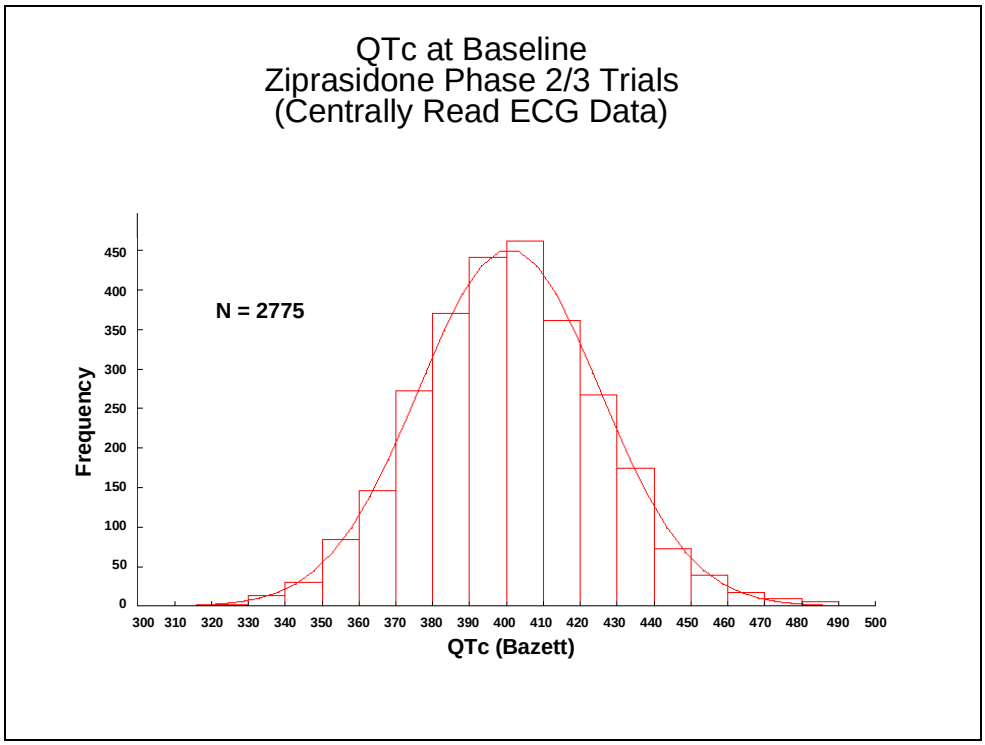


Figure 11. Distribution of Baseline QTc Values for Patients Entering Ziprasidone Phase 2/3 Clinical Trials

Contributors to this variability include gender and BMI. While an association between QTc prolongation and obesity has been identified,[87] the correlation between QTc and BMI has not been extensively described. The ziprasidone Phase 2/3 database demonstrates an increase in QTc in association with a BMI >27, a finding that was subsequently independently confirmed by the Framingham investigators. Both populations demonstrate as well the increase in QTc observed in females relative to males (Figure 12).

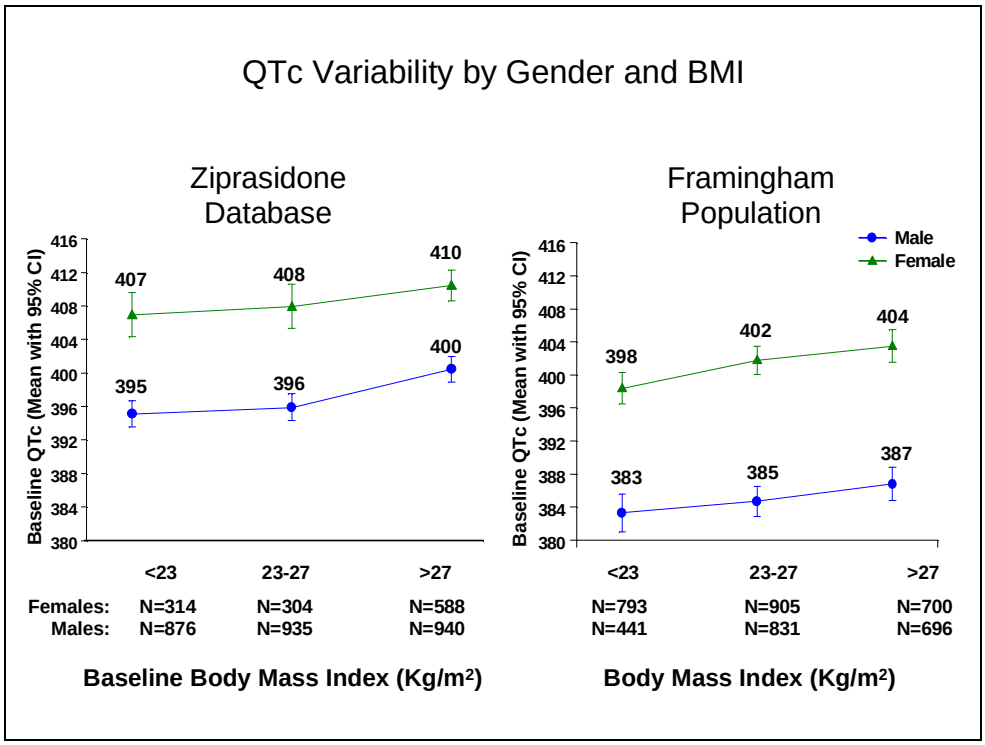


Figure 12. QTc (Bazett) Variability by Gender and Body Mass Index; Ziprasidone Database and Framingham Population

Spontaneous QTc variability within individuals has been noted as well, with mean ranges of 66 to 95 msec described, depending upon experimental conditions (Table 25). In addition to diurnal patterns, postprandial QTc prolongation provides another source of variability, with mean (N = 11) increases of 16 to 23 msec reported during the 60 minutes following a meal.[88]

Table 25. Spontaneous Intra-Individual QTc Variability

N	Mean Intra-Individual Range (msec)	QTc >500 msec	Mean Age (yrs)	Measures per Subject	Method	Source
20	76 ± 19	1/20	40	44 / 24 hrs	Holter	Morganroth *et al.*[89]
56	66 ± 15	NA	58	40 / 5 days	12-lead	Pratt *et al.*[90]
21	95 ± 20	6/21	57	288 / 24 hrs	Holter	Molnar *et al.*[91]

In sum, there are many sources of variability that make it difficult to interpret changes in QTc obtained from clinical trials within and across clinical development programs. Estimates of QTc change need to be qualified with descriptions of the conditions of post-drug measurement and reference measurement (baseline vs. screening).

E.1.2 Correction of QT Interval for Heart Rate

An important determinant of QT interval duration is the heart rate at which it was measured. One option for expressing this dependence is to describe both measures, e.g. "QT interval 420 msec at heart rate of 50 beats per minute." Instead however, the measured QT interval is "corrected" for the heart rate at which it is measured, by application of a mathematical correction formula. At least seventeen (17) formulas have been published for this purpose, all intended to provide a measure of the duration of ventricular repolarization independent of heart rate. Selection of the "best" formula is controversial, and it is widely recognized that no formula accomplishes the ideal. Bazett[92] and Fridericia[93] advocated a log-linear correction for heart rate ($QTc = QT*RR^{-k}$, with k = 0.5 or 0.33, respectively) based upon the observed QT:RR relationship in their sample populations. The FDA has calculated a log-linear correction with k = 0.37 (correspondence from Dr. R. Katz, 13 September 1999), based upon a review of data acquired across a number of psychotropic development programs. Similarly, at the request of the Agency, the QT-RR relationships measured at Baseline in Study 054 (k = 0.35), or in Phase 2/3 trials (k = 0.38) have been employed in this document to calculate QTc.

The exercise of correcting the QT interval for heart rate should be carried out with several caveats in mind. The implicit assumption that the QT:RR relationship is constant before and after administration of drug is challenged when the compound(s) under evaluation affect both the QT (ventricular repolarization) and the RR (heart rate) intervals as measured by ECG. A positive or negative chronotropic effect not only shifts on-drug observations to a different range of heart rates but also raises the possibility that the drug itself may alter the QT-RR relationship. Additionally, the physiologic adjustment in repolarization that occurs as the heart rate changes is not instantaneous, as correction formulas assume.[94] Thus, correction of the QT for HR may conceal important information, such as the kinetics of QT interval adaptation to a change in HR.

Finally, when examining a drug effect, an independent contribution of heart rate to clinical outcome is not accounted for by any heart rate correction of the QT interval. Tachycardia has been identified as an independent risk factor for cardiac death.[95]

E.2 Effect of Ziprasidone on the QTc: Short-Term, Fixed Dose, Placebo-Controlled Trials

The NDA included a subset of clinical trials, which were conducted entirely in hospitalized patients who were randomized to fixed doses of ziprasidone, placebo, or haloperidol. ECGs were obtained at random times of day, on protocol-specified pre- and post-randomization days. In an analysis of QTc change from baseline to final visit, the mean increase in QTc at daily doses between 80 mg and $\geq$200 mg ranged from 5.9 to 9.7 msec (Bazett correction) or 4.4 to 9.3 msec (Baseline

correction) (Table 26). Increasing the dose beyond 160 mg did not lead to a further prolongation of QTc.

Table 26. QTc Mean Change from Baseline to Last Observation; Short-Term Fixed-Dose Placebo-Controlled Trials

Modal Daily Dose	N	Baseline (msec) Mean ± SD	Final (msec) Mean ± SD	Change (msec) Mean ± SD
Bazett Correction				
PBO	250	399.0 ± 22.4	396.5 ± 22.6	-2.6 ± 21.2
Ziprasidone				
<80mg	230	396.9 ± 20.9	397.5 ± 21.8	0.6 ± 21.4
80mg	138	397.6 ± 20.1	403.4 ± 18.7	5.9 ± 17.8
120mg	111	398.0 ± 21.9	405.7 ± 18.7	7.7 ± 17.9
160mg	100	394.6 ± 22.4	404.3 ± 23.0	9.7 ± 19.3
≥200mg	77	402.7 ± 24.1	409.1 ± 25.0	6.4 ± 20.8
Haloperidol	76	400.2 ± 22.4	398.6 ± 19.3	-1.6 ± 22.2
Baseline Correction				
PBO	250	386.0 ± 19.8	384.1 ± 19.1	-1.9 ± 18.0
Ziprasidone				
<80mg	230	386.0 ± 17.9	385.3 ± 18.6	-0.8 ± 16.0
80mg	138	385.6 ± 17.5	390.0 ± 16.7	4.4 ± 14.9
120mg	111	386.2 ± 21.1	393.8 ± 18.4	7.5 ± 17.0
160mg	100	383.7 ± 19.7	393.0 ± 19.4	9.3 ± 16.1
≥200mg	77	390.3 ± 20.1	396.7 ± 22.1	6.4 ± 17.7
Haloperidol	76	389.2 ± 19.0	387.1 ± 16.5	-2.1 ± 17.0

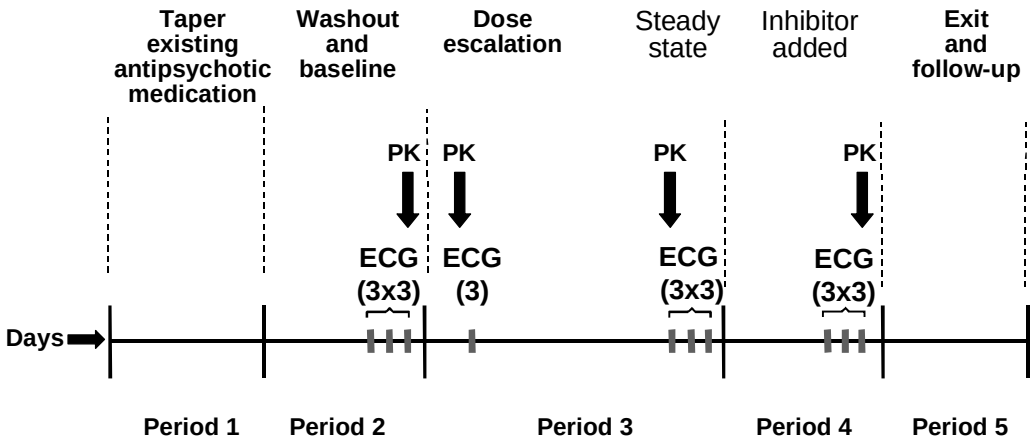
E.3 Study 054

E.3.1 Study Design

Study 054 was an open-label, parallel-group study in patients with schizophrenia to assess the effect of oral doses of ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol on the QT interval. The times of ECG measurements were estimated to correspond with the mean Tmax ± 30 to 60 min for each study drug. ECGs and blood samples for pharmacokinetic analysis were obtained at baseline, during dose escalation, and at steady state (in the absence and presence of a metabolic inhibitor). All ECGs were manually read in a blinded fashion by a central reader (Premier Research Worldwide). Bazett's correction was specified in the protocol, but by request of the Division of Neuropharmacological Drug Products, a correction formula derived from the population ECG data at baseline has also been used to calculate QTc. Other safety assessments (adverse events, clinical laboratory tests, vital signs) were made at intervals throughout the study; efficacy was not assessed.

The sample size of the study was based upon within- and between-patient variances from historical data derived from healthy male placebo-treated patients. Twenty-five patients per group allowed a 95% confidence interval to be constructed having a width of ±7msec. Completers were designated the primary cohort for ECG and pharmacokinetic analyses to ensure that the QTc calculated before and after the metabolic inhibitor would be derived from the same patients.

The study was comprised of five periods, in addition to a screening visit, as illustrated below.



During Period 1, each patient's antipsychotic medication was tapered to the lowest possible dose over about 7 days. Patients were randomized one day prior to the start of Period 2 (day –5). During Period 2, patients received placebo once daily for 5 days (days –4 to 0) at a dosing time that remained fixed for the remainder of the study. Baseline ECG measurements were obtained on the last 3 days of Period 2 at timepoints surrounding the mean Tmax of the agent to which the patient had been assigned.

During Period 3, study drug was administered in open-label fashion. The dose ranges used for each antipsychotic were as follows: ziprasidone, 20 to 80 mg BID; risperidone, 1 to 8 mg BID; olanzapine, 5 to 20 mg QD; quetiapine, 25 to 375 mg BID; thioridazine, 25 to 150 mg BID; and haloperidol, 2 to15 mg QD. For each of the atypical antipsychotics, the highest dose was that recommended in the US Package Insert. For risperidone only, a second dose (6 to 8 mg/day), in the range of what is commonly prescribed in practice, was also evaluated. Clinically relevant doses were chosen for haloperidol and thioridazine. Based on observations from previous clinical trials, the effect of haloperidol on QTc was expected to be small or nonexistent, while thioridazine was expected to have the greatest effect on QTc among the drugs tested.

The duration and dosing schedule in Period 3 were unique for each agent due to differences in tolerability, pharmacokinetics, and the time required to reach steady-state exposure (see details in Table 27).

Study Drug	Period 3 Study Days	Top Dose (mg/day)	Mean Tmax (hr)	ECG Times (hr post-dose)
Ziprasidone	1 – 10	160	6	5, 6, 7
Risperidone	1 – 18	16 (6 - 8)	1	0.5, 1, 2
Olanzapine	1 – 13	20	6	5, 6, 7
Quetiapine	1 – 12	750	1.5	1, 1.5, 2.5
Thioridazine	1 – 10	300	3	2, 3, 4
Haloperidol	1 – 12	15	5	4, 5, 6

QTc measured at mean Tmax ± 0.5-1 hr on day 2 of Period 3 and on 3 steady-state days at top dose (risperidone was also evaluated at 6 - 8 mg/day on days 5 - 7). ECGs were measured in triplicate for each Tmax, on three consecutive days at steady-state.

During Period 4, a cytochrome P450 (CYP) inhibitor was co-administered with the highest dose of antipsychotic drug obtained in Period 3. ECGs were collected at the same time of day relative to the morning dose as in Periods 2 and 3. On the last day of Period 4, study drug(s) were administered only in the morning. A pharmacokinetic sample was obtained immediately after the second ECG on the last day of the period. The schedule of administration of metabolic inhibitor for each study drug was as follows:

Study Drug	Cytochrome P450 Pathway	Inhibitor	Period 4 Study Days
Ziprasidone	CYP3A4	Ketoconazole (200mg BID)	11 – 15
Risperidone	CYP2D6	Paroxetine (20 mg QD AM)	19 – 25
Olanzapine	CYP1A2	Fluvoxamine (50mg→100mg QD AM)	14 – 20
Quetiapine	CYP3A4	Ketoconazole (200mg BID)	13 – 17
Thioridazine	CYP2D6	Paroxetine (20mg QD AM)	11 – 16
Haloperidol	CYP3A4, CYP2D6	Paroxetine/Ketoconazole (20 mg QD AM/200 mg BID)	13 – 18

QTc was measured at mean Tmax ± 0.5-1 hr (triplicate) in the presence of CYP inhibitor on the last 3 days of treatment.

Ketoconazole coadministration with ziprasidone would be expected to inhibit CYP3A4 – mediated oxidation, and shift a greater proportion of ziprasidone metabolism toward the production of M9 (see Sections B and D).

Exit procedures, including withdrawal of study medication, safety assessment, and the reinstitution of neuroleptic therapy, were carried out in Period 5.

Table 27. Study 054 Dosing Schedule

Study Day	Group 1: Ziprasidone 160 mg/day		Group 2: Risperidone 16 mg/day		Group 3: Olanzapine 20 mg/day		Group 4: Quetiapine 750 mg/day		Group 5: Thioridazine 300 mg/day		Group 6: Haloperidol 15 mg/day	
Screen	--	ECG, CHEM	--	ECG, CHEM	--	ECG, CHEM	--	ECG, CHEM		ECG, CHEM	--	ECG, CHEM
-11 to -5	Tapering		Tapering		Tapering		Tapering		Tapering		Tapering	
-4 to 0[a]	Washout	ECG[b], CHEM[c]	Washout	ECG[b], CHEM[c]	Washout	ECG[b], CHEM[c]	Washout	ECG[b], CHEM[c]	Washout	ECG[b],CHEM[c]	Washout	ECG[b], CHEM[c]
	DOSE mg BID		DOSE mg BID		DOSE mg QD		DOSE mg BID		DOSE mg BID		DOSE mg QD	
1	20		1		5		25		25		2	
2	20	PK,ECG	2	PK,ECG	5	PK,ECG	50	PK,ECG	50	PK,ECG	4	PK,ECG
3	40		2		10		100		75		4	
4	40		3		15		150		100		10	
5	60		3	PK,ECG	20		200		150		10	
6	80		4	ECG	20		250		150		10	
7	80		4	ECG	20		300		150		15	
8	80	ECG,PK,CHEM	5		20		375		150	ECG,PK,CHEM	15	
9	80	ECG	6		20		375		150	ECG	15	
10	80	ECG	6		20		375	ECG,PK,CHEM	150	ECG	15	ECG,PK,CHEM
11	80 + K		8		20	ECG,PK,CHEM	375	ECG	150 + P		15	ECG
12	80 + K		8		20	ECG	375	ECG	150 + P		15	ECG
13	80 + K	ECG	8		20	ECG	375 + K		150 + P		15 + K,P	
14	80 + K	ECG	8		20 + F		375 + K		150 + P	ECG	15 + K,P	
15	80 + K	ECG,PK, CHEM	8		20 + F		375 + K	ECG	150 + P	ECG	15 + K,P	
16	inpatient	ECG, CHEM[d]	8	ECG,PK,CHEM	20 + F		375 + K	ECG	150 + P	ECG,PK,CHEM	15 + K,P	ECG
17	inpatient		8	ECG	20 + F		375 + K	ECG,PK, CHEM	inpatient	ECG,CHEM[d]	15 + K,P	ECG
18	inpatient		8	ECG	20 + F	ECG	inpatient	ECG, CHEM[d]	inpatient		15 + K,P	ECG,PK,CHEM
19	D & FU		8 + P		20 + F	ECG	inpatient		inpatient		inpatient	ECG,CHEM[d]
20			8 + P		20 + F	ECG,PK,CH	inpatient		D & FU		inpatient	
21			8 + P		inpatient	ECG, CHEM[d]	D & FU				inpatient	
22			8 + P		inpatient						D & FU	
23			8 + P	ECG	inpatient							
24			8 + P	ECG	D & FU							
25			8 + P	ECG,PK,CH								
26			inpatient	ECG, CHEM[d]								
27			inpatient									
28			inpatient									
29			D & FU									

a = No neuroleptic medication allowed. b = Days -2, -1, 0; c = Day 0 d = ECG and safety labs in period 5 done prior to the initiation of outpatient antipsychotic therapy.
P = Paroxetine ; F = Fluvoxamine; K = Ketoconazole; D & FU = discharge and follow up

E.3.2 Results

A total of 164 patients completed the trial. The estimated variability in the QT measurements was consistent with the initial assumptions used to estimate sample size.

E.3.2.1 Change in QTc and Drug Concentration

The mean increases in QTc (calculated with the Bazett correction and the 054 population-derived Baseline correction) in the absence and presence of a metabolic inhibitor are given for each compound in Table 28 and illustrated in Figure 13. The numbers of patients with categorical increases in QTc (Bazett and Baseline corrections) are similarly summarized in Table 29. Mean drug concentrations for ziprasidone, its metabolites M9 and M10, and each of the comparator drugs in the absence and presence of inhibitor are shown in Table 30.

Steady State, Metabolic Inhibitor Absent - Period 3

Consistent with preclinical evidence that many antipsychotic agents, including the more recently introduced atypical compounds, block IKr^{85} (see Section D.1), a mean change greater than zero was measured in association with each of the antipsychotic agents studied.

Steady State, Metabolic Inhibitor Present - Period 4

Compared with steady-state concentrations in Period 3, mean serum concentrations of ziprasidone increased by 39%, M9 by 55% and M10 by 8%, while plasma concentrations of risperidone, olanzapine, quetiapine, and haloperidol increased by >50% in the presence of a metabolic inhibitor). Following the co-administration of the metabolic inhibitor, a further prolongation in QTc was not evident in the ziprasidone group (Figure 13).

[Note: Through retrospective genotyping, one CYP2D6 poor metabolizer was identified in the ziprasidone group. Ziprasidone concentrations for this individual (162 ng/ml at steady state and 233 ng/ml in the presence of metabolic inhibitor) very closely approximated the means for the Completers cohort (N = 31; mean ziprasidone concentrations of 171 ng/ml at steady state and 224 ng/ml in the presence of metabolic inhibitor; see Table 30). These data are consistent with preclinical and clinical evidence that CYP2D6 is not an important metabolic pathway for ziprasidone, even in the presence of CYP3A4 inhibition. Average QTc changes (Bazett correction) for this individual were 12.3 msec on Day 2, 7.3 msec at steady state, and 25 msec in the presence of metabolic inhibitor.

Table 28. QTc Change from Baseline; Study 054

	Ziprasidone *N = 31/31	Risperidone *N = 25/20	Olanzapine *N = 24/24	Quetiapine *N = 27/27	Thioridazine *N = 30/30	Haloperidol *N = 27/20
Bazett Correction						
Baseline						
Mean (msec)	402.1	396.3	397.9	398.0	395.9	394.7
(95% CI)	(393.4, 410.8)	(389.6, 403.0)	(389.7, 406.1)	(390.9, 405.1)	(388.5, 403.3)	(386.1, 403.4)
Period 3: Steady-State (except days 5-7 for Risperidone)						
Mean Δ (msec)	20.3	11.6	6.8	14.5	35.6	4.7
(95% CI)	(14.2, 26.4)	(7.4, 15.8)	(0.8, 12.7)	(9.5, 19.5)	(30.5, 40.7)	(-2.0, 11.3)
% Δ	5.2	2.9	1.8	3.7	9.1	1.2
(95% CI)	(3.6, 6.8)	(1.9, 4.0)	(0.2, 3.3)	(2.4, 5.0)	(7.7,10.4)	(-0.5, 2.9)
Period 3: Steady-State for Risperidone						
Mean Δ (msec)		9.1				
(95% CI)		(1.9,16.2)				
% Δ		2.4				
(95% CI)		(0.5, 4.2)				
Period 4: Inhibitor Present						
Mean Δ (msec)	20.0	3.2	5.3	19.7	28.0	8.9
(95% CI)	(13.7, 26.2)	(-4.7, 11.1)	(-0.1, 10.7)	(14.3, 25.0)	(21.6, 34.5)	(1.9, 15.9)
% Δ	5.1	0.9	1.4	5.0	7.2	2.4
(95% CI)	(3.5, 6.8)	(-1.2, 2.9)	(0, 2.8)	(3.6, 6.3)	(5.5, 8.9)	(0.6, 4.2)
Baseline Correction						
Baseline						
Mean (msec)	389.4	387.7	387.6	386.8	388.2	383.3
(95% CI)	(383.0, 395.9)	(381.6, 393.8)	(380.1, 395.1)	(379.8, 393.9)	(382.2, 394.2)	(377.4, 389.2)
Period 3: Steady-State (except days 5-7 for Risperidone)						
Mean Δ (msec)	15.9	3.9	1.7	5.7	30.1	7.1
(95% CI)	(10.6, 21.2)	(0.3, 7.5)	(-3.8, 7.1)	(1.8, 9.7)	(24.8, 35.5)	(1.8, 12.4)
% Δ	4.2	1.0	0.5	1.5	7.8	1.9
(95% CI)	(2.8, 5.5)	(0.1, 1.9)	(-0.9, 1.9)	(0.5, 2.5)	(6.4, 9.2)	(0.5, 3.3)
Period 3: Steady-State for Risperidone						
Mean Δ (msec)		3.6				
(95% CI)		(-3.0, 10.2)				
% Δ		1.0				
(95% CI)		(-0.7, 2.7)				
Period 4: Inhibitor Present						
Mean Δ (msec)	16.6	2.6	3.0	8.0	29.6	13.3
(95% CI)	(10.6, 22.6)	(-4.7, 9.8)	(-2.0, 8.0)	(3.2, 12.7)	(23.4, 35.8)	(7.6, 19.1)
% Δ	4.4	0.7	0.8	2.1	7.7	3.5
(95% CI)	(2.8, 6.0)	(-1.2, 2.6)	(-0.4, 2.1)	(0.8, 3.3)	(6.0, 9.3)	(2.0, 5.1)

*N = Number of patients (completers) included in Period 3/Period 4 analyses.

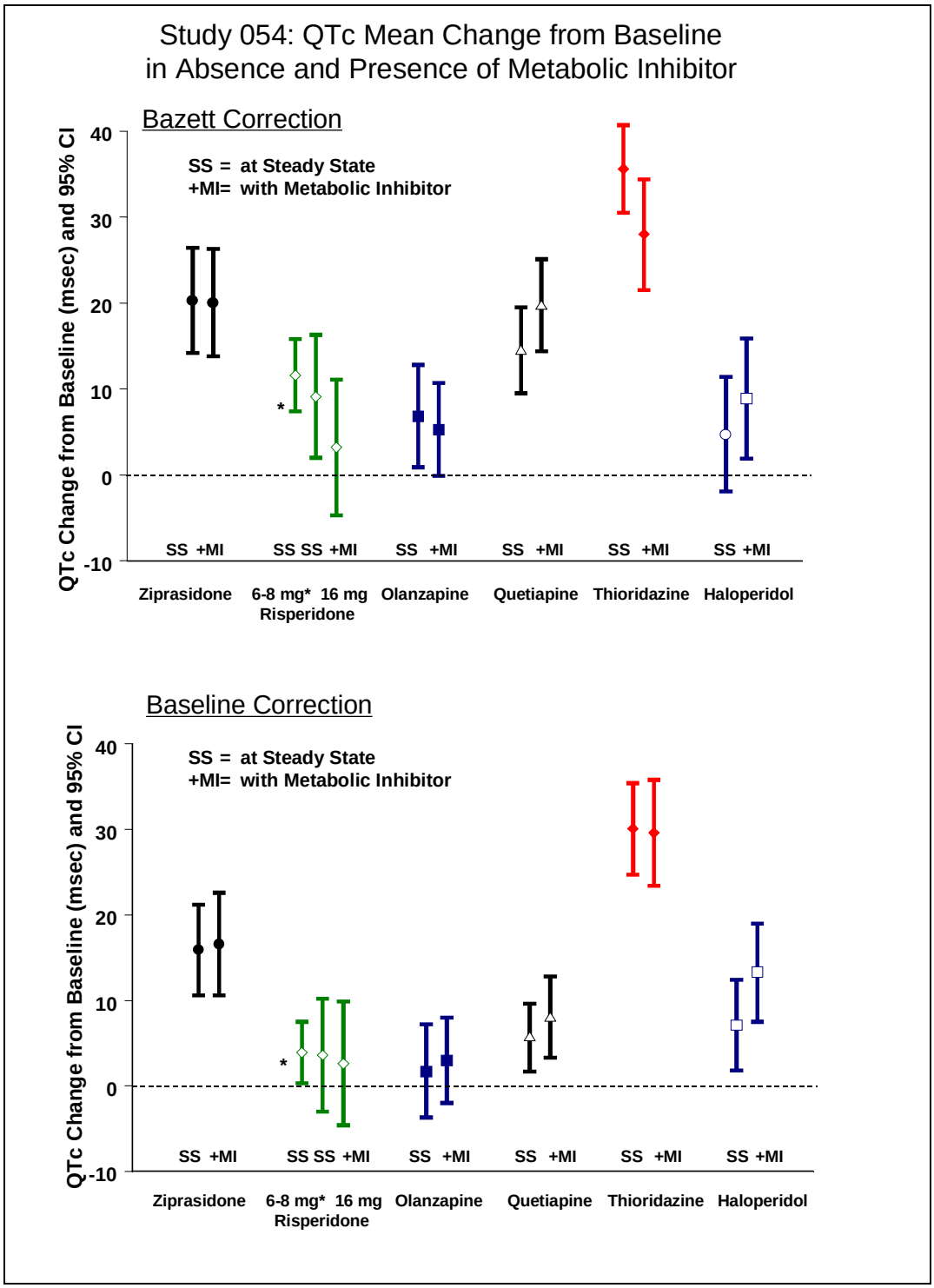


Figure 13. Mean QTc Change from Baseline in the Absence and Presence of Metabolic Inhibitor; Study 054

Table 29. Incidence of Categorical Increases in QTc; Study 054

	Number of Patients in Periods 3 and 4 Meeting Categorical Criteria											
	Ziprasidone		Risperidone days 5-7 / steady-state		Olanzapine		Quetiapine		Thioridazine		Haloperidol	
	Per3	Per4	Per3	Per4	Per3	Per4	Per3	Per4	Per3	Per4	Per3	Per4
Bazett Correction												
N*	24	24	24/24	20	23	23	25	25	29	29	24	18
≥ 450 msec§	8	7	5/3	0	1	1	3	5	14	9	2	2
N**	31	31	25/25	20	24	24	27	27	30	30	27	20
≥ 480	1	1	1/0	0	0	0	0	0	0	1	0	0
≥ 500	0	0	0/0	0	0	0	0	0	0	0	0	0
with ΔQTc:												
≥ 30 msec	20	24	11/12	8	8	8	14	18	29	27	11	9
≥ 60 msec	7	3	2/1	0	1	0	3	4	9	6	1	0
≥ 75 msec	1	1	0/0	0	0	0	0	0	3	4	0	0
Baseline Correction												
N*	31	31	25/25	20	24	24	26	26	30	30	27	20
≥ 450 msec§	2	3	0/0	0	0	0	0	0	6	7	0	0
N**	31	31	25/25	20	24	24	27	27	30	30	27	20
≥ 480	0	0	0/0	0	0	0	0	0	0	0	0	0
≥ 500	0	0	0/0	0	0	0	0	0	0	0	0	0
with ΔQTc:												
≥ 30 msec	16	20	4/5	6	4	5	6	10	25	25	10	11
≥ 60 msec	2	2	0/0	0	0	0	0	0	5	7	0	0
≥ 75 msec	0	0	0/0	0	0	0	0	0	1	3	0	0

Data for patients who completed the study.
§ Excludes patients with baseline readings at this level.
* Number of patients in Periods 3 and 4 with QTc <450 msec at baseline.
** All patients with QTc measurements.

The relative magnitude of the effect maintained the same rank ordering of treatments, whether the measure of comparison was mean change or categorical count. Sample size for the study was based on a confidence interval approach, specifically to provide 95% confidence intervals of approximately 7 msec around the mean changes. No other endpoints, such as incidence rates based on different categorical thresholds, were subjected to any sample size calculation. Thus, the study was not intended to provide precise estimates of the frequency of these events, which is in part dependent upon the number of measurements made. Figure 14 and Figure 15 illustrate the variability around the observed incidence rates for thresholds of 450 msec and 30 msec increase from baseline, respectively.

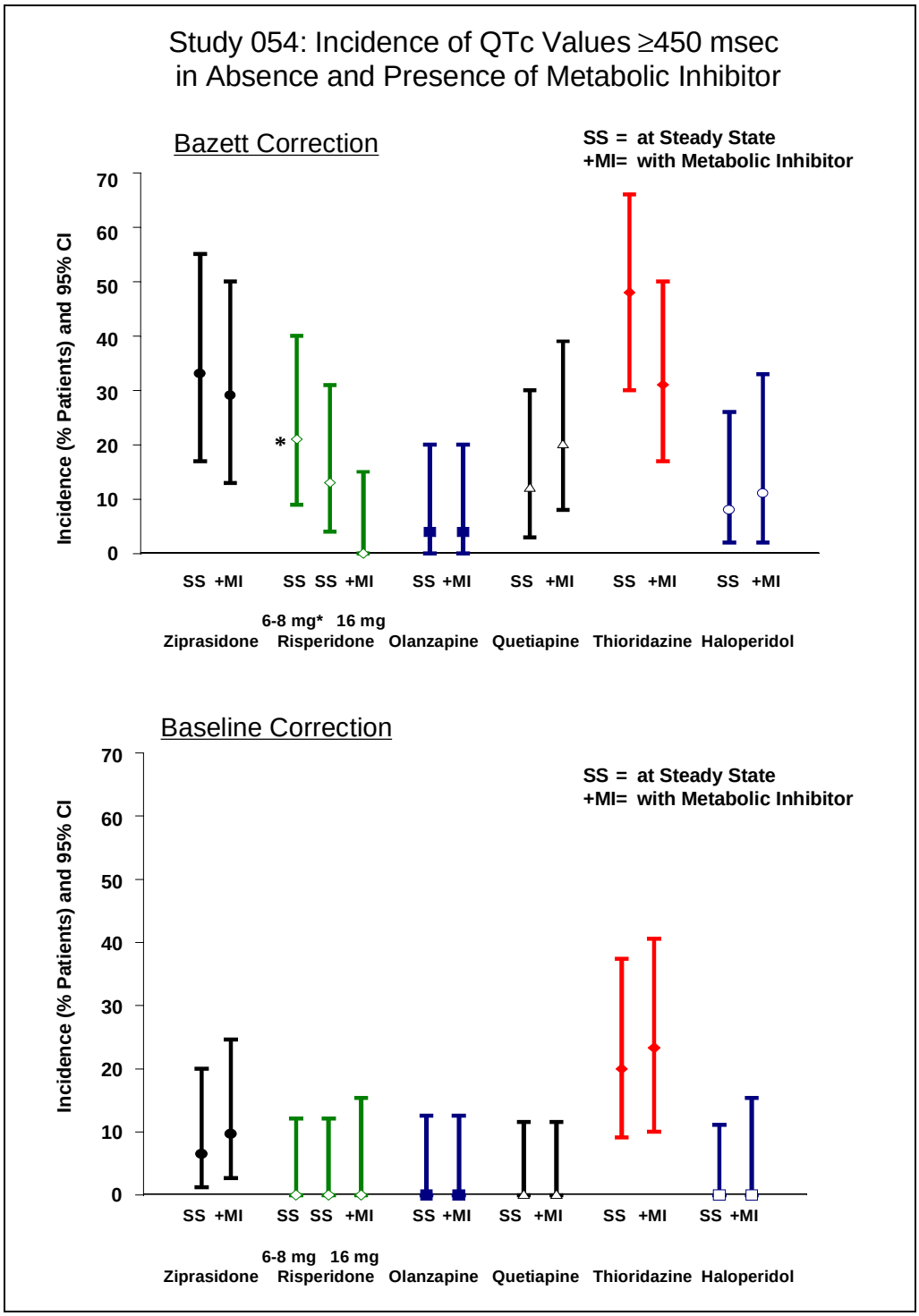


Figure 14. Incidence of QTc Increases ≥450 msec at Steady State and with Metabolic Inhibitor; Study 054

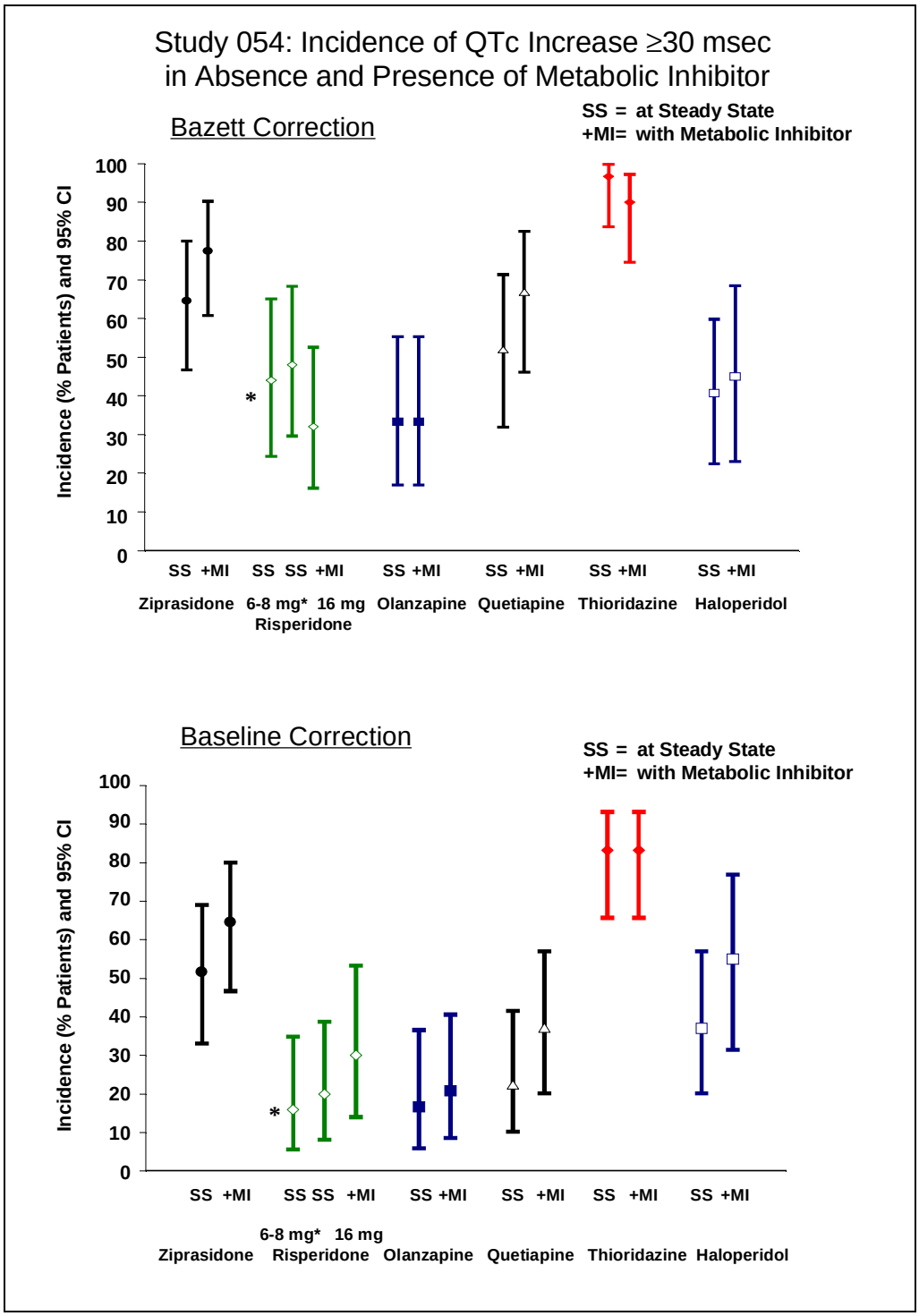


Figure 15. Incidence of QTc Increases ≥30 msec at Steady State and with Metabolic Inhibitor; Study 054

Table 30. Mean Drug Concentrations at Expected Tmax in the Absence/Presence of Metabolic Inhibitor; Study 054

	Mean (CV, %) Drug* Concentrations (ng/ml) at Expected Mean Tmax		
	Ziprasidone N=31	Ziprasidone M9 N=30†	Ziprasidone M10 N=30†
Day 2 of Period 3	49 (41)	8.3 (38)	15.0 (63)
Period 3 Steady-State	171 (34)	74.5 (32)	50.3 (51)
Period 4 Inhibitor Present	224 (35)	110.0 (30)	51.6 (59)
Ratio Periods 4/3**	1.39 (40)	1.55 (34)	1.08 (41)

	Risperidone N=20	Olanzapine N=23	Quetiapine N=26	Thioridazine N=31	Haloperidol N=26
Day 2 of Period 3	14.8 (61)	9.2 (54)	175 (48)	215 (43)	2.1 (91)
Day 5 of Period 3	24.8 (67)	NA	NA	NA	
Period 3 Steady-State	58.7 (79)	55.1 (39)	1280 (61)	765 (46)	16.3 (95)
Period 4 Inhibitor Present	124.0 (48)	84.5 (27)	3740 (43)	799 (50)	26.3 (76)
Ratio Periods 4/3**	2.47 (35)	1.77 (45)	4.03 (70)	1.04 (20)	1.94 (50)

Data for patients who completed the study.
*Serum was analyzed for ziprasidone and its metabolites, plasma was analyzed for all others.
** Metabolic inhibitor present in Period 4/metabolic inhibitor absent in Period 3
† Means based on 30 subjects for whom complete metabolite data sets were available.
NA = Not Applicable.

E.3.2.2 Application of Different Correction Factors

In addition to providing unique data concerning the effect of six antipsychotic drugs on the QTc interval, Study 054 measured the effects of these agents upon the heart rate. The Bazett formula was prospectively declared in the protocol to be used to calculate the QTc interval in this study. However, in view of the variable effects upon heart rate of the compounds tested, the absolute and relative magnitudes of the QTc effects can be modified according to the formula selected.

The Bazett, Fridericia, Hodges, and Framingham formulas**,** as well as a log-linear and a linear formula based upon QT:RR modeling of the Study 054 population at baseline, and a log-linear formula described by the FDA, applied to Period 3 data, are presented in Table 31. It can be seen that the difference in QTc duration between these formulas is dependent upon the correction applied for heart rate, and the chronotropic property of the compound. The QTc effects of compounds associated with an increase in heart rate (the four atypical drugs and thioridazine) are maximal with the Bazett formula, while the QTc effect associated with a heart rate-lowering drug (haloperidol) is minimal with the Bazett calculation. Among the atypicals, the departure from Bazett measurements is greatest for quetiapine (associated with an 11.2 bpm mean increase in heart rate) and least for

ziprasidone (4.6 bpm). As a result, the effect of haloperidol is less than the effects of quetiapine, risperidone, and olanzapine using the Bazett formula, but greater than the effects of those three agents when QTc is calculated using several of the alternate formulas presented. Haloperidol produces the smallest change in QTc when calculated using Bazett's correction, due to its negative chronotropic effect. Thioridazine is measured to have the greatest effect regardless of the formula applied.

Table 31. Effect of Different Correction Factors on Mean QTc Change from Baseline; Study 054 Period 3 (Inhibitor Absent)

	Ziprasidone	Risperidone 6-8mg/16mg	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QT Interval (msec)	6.8	-12.1/-8.0	-8.9	-12.2	18.7	12.5
Heart Rate (bpm)	4.6	9.5/6.4	6.5	11.2	5.7	-2.9
Log-linear QT Corrections ($QT*RR^{-k}$)						
Bazett (k=0.5)	20.3	11.6/9.1	6.8	14.5	35.6	4.7
FDA-Proposed (k=0.37)	16.5	4.9/4.3	2.3	6.9	30.8	6.8
Baseline 054 Data (k=0.35^)	15.9	3.9/3.6	1.7	5.7	30.1	7.1
Fridericia (k=0.33)	15.5	3.1/3.0	1.1	4.8	29.6	7.3
Linear QT Corrections (QT+k(1000-RR))						
Hodges (QT+1.75(HR-60)	14.9	4.5/3.3	2.5	7.5	28.7	7.4
Framingham (k=0.154)	14.9	3.6/3.7	1.6	4.4	28.5	6.1
Baseline 054 Data (k=0.148^)	14.6	3.0/3.3	1.2	3.8	28.1	6.3

Data for patients who completed the study.
^ Derived from regression on baseline data from Study 054.

When the various correction formulas are applied to Period 4 data of Study 054 (Table 32), the rank ordering remains generally unchanged with the exception of the increase in magnitude of effect associated with haloperidol.

Table 32. Effect of Different Correction Factors on Mean QTc Change from Baseline; Study 054 Period 4 (Inhibitor Present)

	Ziprasidone	Risperidone 16mg	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QT Interval (msec)	10.0	1.1	-1.8	-15.8	33.3	22.5
Heart Rate (bpm)	3.6	0.5	3.0	15.1	-2.1	-5.7
Log-linear QT Corrections ($QT*RR^{-k}$)						
Bazett (k=0.5)	20.0	3.2	5.3	19.7	28.0	8.9
FDA-Proposed (k=0.37)	17.0	2.7	3.3	9.5	29.3	12.8
Baseline 054 Data (k=0.35^)	16.6	2.6	3.0	8.0	29.6	13.3
Fridericia (k=0.33)	16.3	2.5	2.8	6.7	29.7	13.8
Linear QT Corrections (QT+k(1000-RR))						
Hodges (QT+1.75(HR-60)	16.3	2.0	3.4	10.6	29.6	12.5
Framingham (k=0.154)	15.5	2.5	2.8	5.9	28.6	12.8
Baseline 054 Data (k=0.148^)	15.3	2.4	2.6	5.1	28.8	13.1

Data for patients who completed the study.
^ Derived from regression on baseline data from Study 054.

E.3.2.3 Correlation between Changes in QTc and Haloperidol Concentration

The QTc effect of oral haloperidol has been measured in clinical trials conducted within the development programs of a number of recently approved antipsychotic agents, including ziprasidone (Table 26). This clinical trial data generally does not reveal haloperidol to have an effect on QTc. However, a correlation between change in QTc and change in haloperidol concentration measured in Study 054 was calculated using the Spearman correlation coefficient, which uses the ranks of the variables. The analysis was done using all data from Day 2, Period 3 (steady state) and Period 4 (steady state with metabolic inhibitor). The correlation between change in QTc (Baseline correction) and haloperidol concentration is 0.36, and is highly significant ($p = 0.008$). (Pearson correlation, a parametric form of the Spearman correlation using the actual data values, also shows a statistically significant correlation between change in QTc and change in haloperidol concentration.) These data, presented graphically in Figure 16, are consistent

with preclinical data (Figure 9), and provide evidence that haloperidol can prolong the QTc when administered orally at a therapeutic dose of 15 mg.

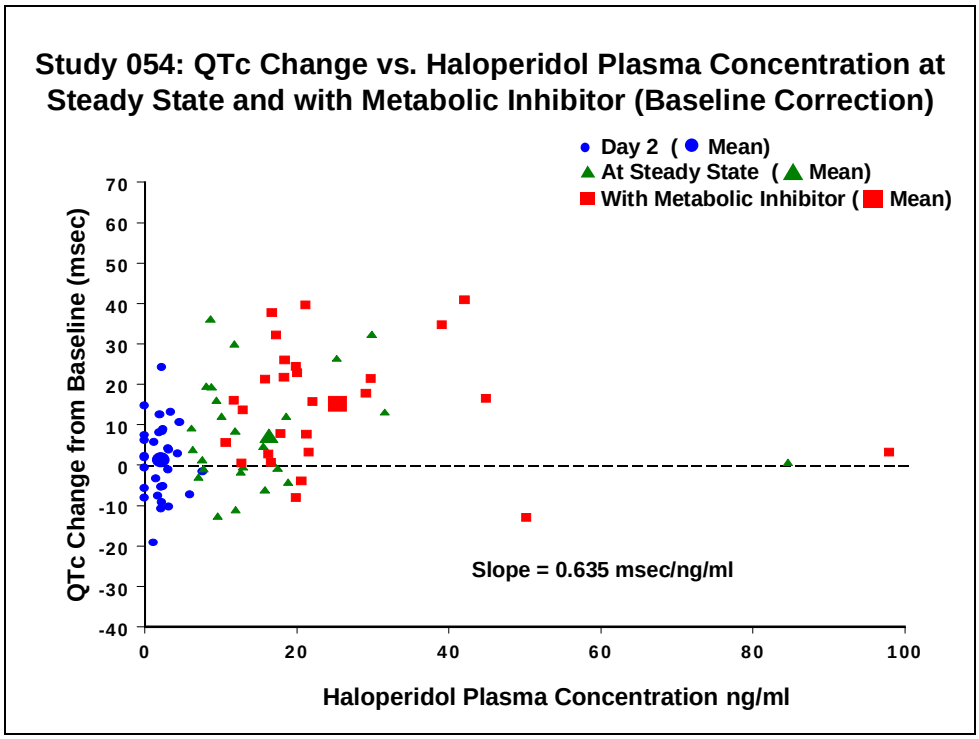


Figure 16. Individual Mean QTc Changes from Baseline vs. Haloperidol Concentration; Study 054

E.3.3 Drug Exposure Summary: Study 054 and Phase 2/3 Outliers

Patients in Study 054 received ziprasidone at a dose of 160 mg daily, and attained serum concentrations that were consistent with observations in Phase 1 trials. Steady-state Cmax (i.e. serum ziprasidone concentration at 6 hours post-dose) in these patients in Period 3 (prior to CYP3A4 inhibition) is comparable to that observed in healthy subjects at the same dose level in Phase 1 Study 043 (mean concentration 171 ng/ml in Study 054 vs. 184 ng/ml in Study 043). Coadministration of the CYP3A4 inhibitor ketoconazole in Period 4 of Study 054 led to a mean increase in exposure of 39%. The degree of this increase is also comparable to mean change in overall exposure of 34% observed in Phase 1 ketoconazole interaction Study 050. In Period 4 of Study 054, i.e., during the period of metabolic inhibition by ketoconazole, the maximum serum concentration of ziprasidone observed in any individual was 380 ng/ml. The maximum serum concentrations of the ziprasidone metabolites M9 and M10 observed in any individual were 178 ng/ml and 155 ng/ml, respectively. A comparison of these exposures to the Phase 2/3 experience is provided below.

Ziprasidone

Data from 23 ziprasidone clinical trials have been included in the Population Pharmacokinetic database. Of the patients enrolled in these trials, 3014 contributed 9994 serum concentration data points with valid dose and sample collection dates and times. The mean (± SD) ziprasidone serum concentration from this dataset is 70 ± 79 ng/ml; range: 1 to 955 ng/ml.

Of these 9994 samples, there were 67 samples from 61 patients with serum ziprasidone concentrations greater than 380 ng/ml, the maximum observed in Period 4 of Study 054. Twenty-four of the 67 samples (36%) were from individuals receiving more than the highest recommended dose of ziprasidone (160 mg/day).

Of the 9994 samples, 2435 ziprasidone concentrations from 1359 individuals were measured within 1 hour of a QTc measurement. Twelve of these were from individuals with serum concentrations >380 ng/ml, including the individual with the highest recorded ziprasidone level (955 ng/ml). The QTc values for the nine patients with serum concentrations >400 ng/ml are indicated on the right side of the vertical axis of Figure 17, a plot of QTc change from baseline versus ziprasidone concentration.

A review of the 12 individuals with ziprasidone serum concentrations greater than 380 ng/ml, reveals no pattern of concomitant medication use, adverse clinical events or ECG change to suggest increased risk.

Ziprasidone Metabolites M9 and M10

In addition to the ziprasidone serum concentration levels, 756 subjects contributed 2234 serum samples that were assayed for concentrations of the S-methyldihydro-ziprasidone (M9) and ziprasidone sulfoxide (M10) metabolites of ziprasidone. The mean (± SD) M9 concentration in this dataset is 52.1 ± 38.2 ng/ml; range: <0.040 to 306 ng/ml, excluding an apparent outlier at 4880 ng/ml. The mean (± SD) M10 concentration in this dataset is 26.7 ± 31.3 ng/ml; range: <0.40 to 489 ng/ml.

Of the 2234 samples, there were 17 samples with serum M9 concentrations greater than 178 ng/ml (the highest concentration observed in Period 4 of Study 054). In addition, there were 12 samples with serum M10 concentrations greater than 155 ng/ml (the highest concentration observed in Period 4 of Study 054).

Of the 2234 serum samples assayed for metabolites, 742 and 739 concentrations for M9 and M10, respectively, from 354 individuals were measured within 1 hour of a QTc measurement and these are shown in Figure 18 and Figure 19, respectively. Seven of these serum concentrations of M9 exceeded 178 ng/ml, including the individual with the highest recorded M9 level (4880 ng/ml). Five of these serum concentrations of M10 exceeded 155 ng/ml, including the sample with the highest recorded M10 level (489 ng/ml). The QTc values for patients with serum concentrations >230 ng/ml are indicated on the right sides of the vertical axes of Figures 18 and 19.

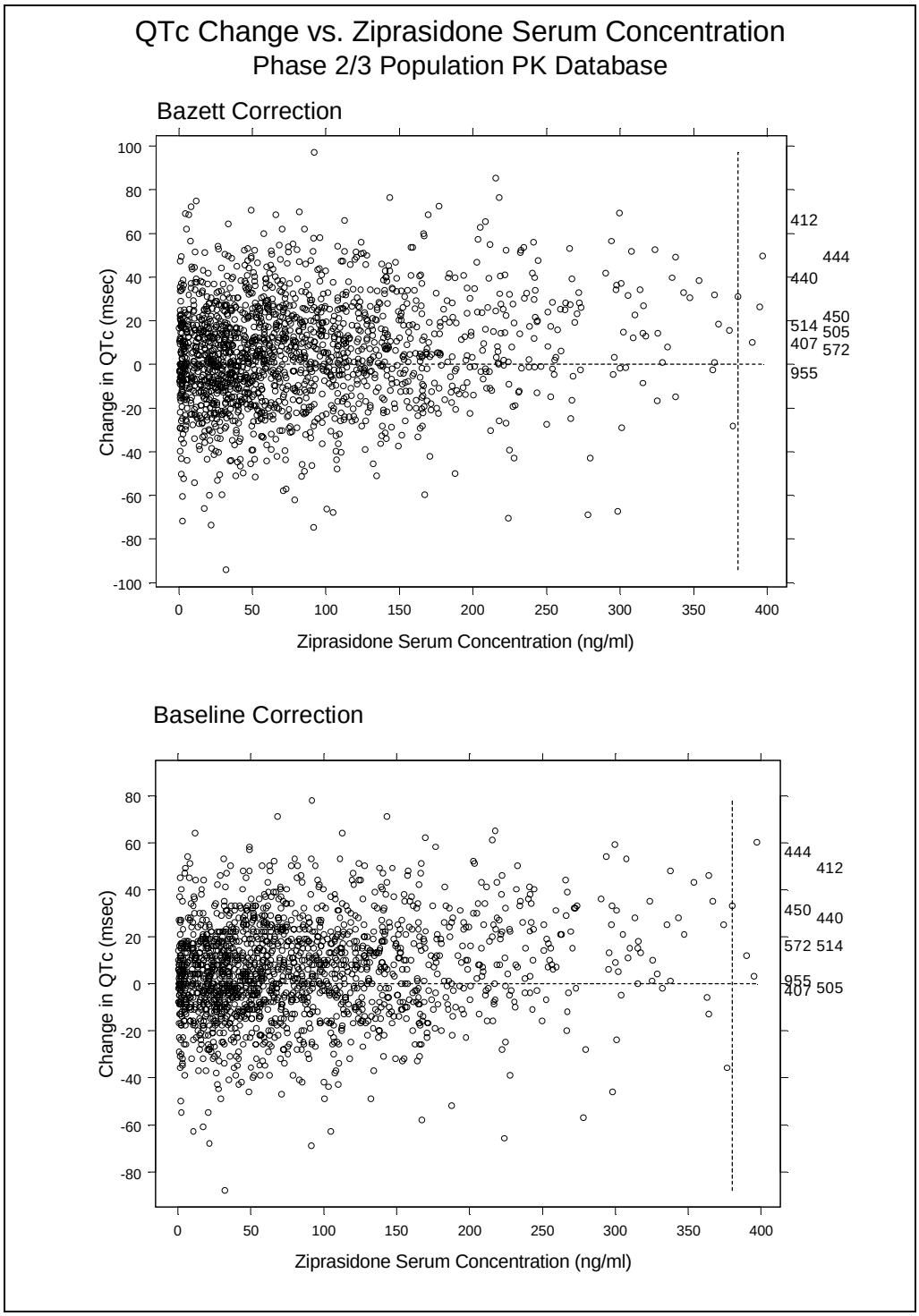


Figure 17. QTc Change from Baseline vs. Ziprasidone Serum Concentration for Samples Collected within 1 Hour of an ECG Measurement

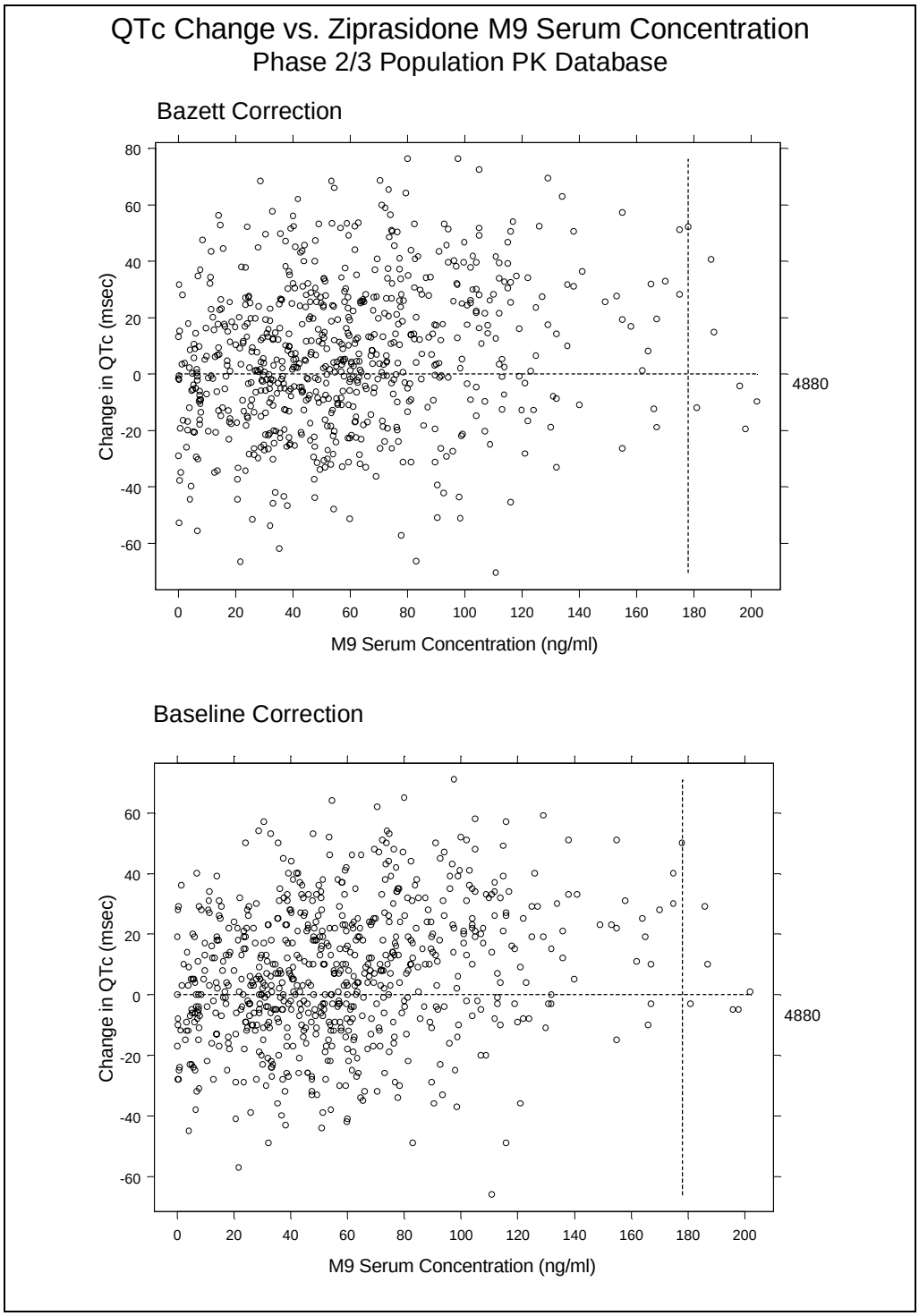


Figure 18. QTc Change from Baseline vs. Ziprasidone M9 Serum Concentration for Samples Collected within 1 Hour of an ECG Measurement

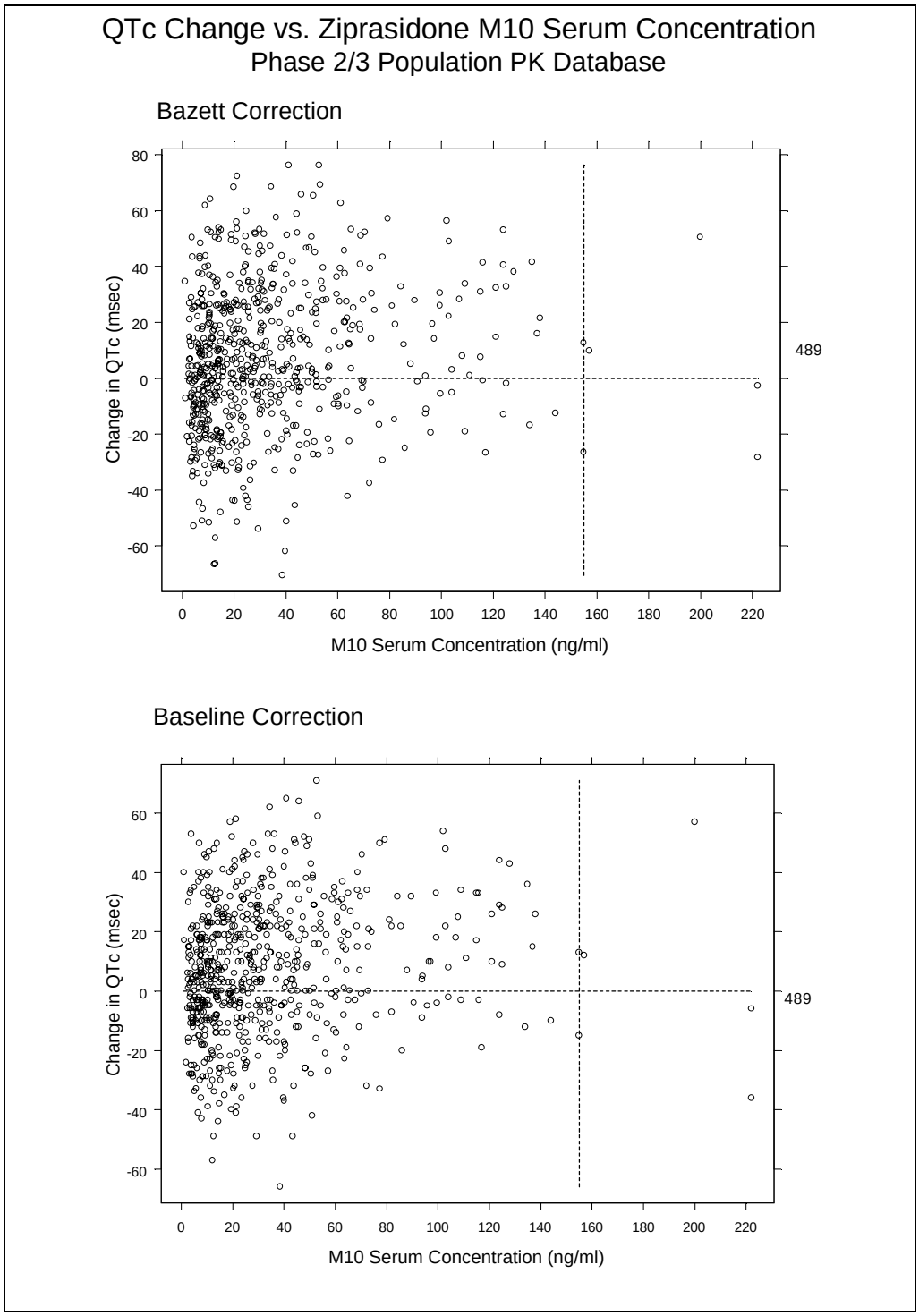


Figure 19. QTc Change from Baseline vs. Ziprasidone M10 Serum Concentration for Samples Collected within 1 Hour of an ECG Measurement

Although individual QTc – concentration data points are reassuring, particularly at the extreme end of the observed concentration ranges (e.g., QTc change of -3 msec [Bazett correction], and 2 msec [Baseline correction] at a ziprasidone concentration of 955 ng/ml; QTc change of -3 msec [Bazett correction], and -6 msec [Baseline correction] at an M9 concentration of 4880 ng/ml; and 11 msec [Bazett correction], and -2 msec [Baseline correction] at an M10 concentration of 489 ng/ml), an apparent linear QTc – concentration relationship can be identified (Table 33) which explains 5.6%, 8.9%, and 6.0% of the variability in the observed data (Bazett correction) for ziprasidone, M9 and M10, respectively, or 6.8%, 13.0%, 7.9% (Baseline correction). It is important to note that the validity of a linear relationship at the extremes of the observed concentration ranges is limited by the paucity of data at these concentrations. This would appear to be a function of the pharmacology of ziprasidone, and the stability of its metabolism under observed and expected conditions of use.

Table 33. Linear Regression of QTc Change from Baseline with Ziprasidone, M9 and M10 Concentrations; Phase 2/3 Population PK Database

	Ziprasidone	Ziprasidone M9	Ziprasidone M10
Bazett Correction			
Slope msec/ng/ml	0.0520	0.113	0.207
% Variability explained	5.6%	8.9%	6.0%
p-value	<0.0001	<0.0001	<0.0001
Baseline Correction			
Slope msec/ng/ml	0.0514	0.120	0.217
% Variability explained	6.8%	13.0%	7.9%
p-value	<0.0001	<0.0001	<0.0001

E.4 Effect of Ziprasidone on QTc: Phase 2/3 Database

In order to fully characterize the effect of ziprasidone on the QTc in the treated patient populations, a review of the incidence of "clinically significant" prolongations is presented. While it is generally accepted that the risk of TdP appears to emerge with QTc measures in excess of 550 msec, or 500 msec,[96] there is not a universally accepted definition of "clinically significant." Therefore, the incidence of changes or absolute QTc measures crossing various thresholds is presented.

E.4.1 Incidence of QTc ≥500 msec

The ziprasidone clinical program has included extensive ECG monitoring, and as of 5 February 2000, Pfizer had on hand 7876 on-treatment ECGs from 3095 patients who received oral ziprasidone in completed or ongoing open-label or single-blind Phase 2/3 trials, either in the oral ziprasidone development program or in oral extensions of trials of the intramuscular formulation. Among these 7876

ECGs, only 3 tracings (0.04%) showed a QTc of ≥500 msec, using the Bazett correction. This compares with 1/809 placebo tracings (0.12%) with a QTc of ≥500 msec. Two of the three ziprasidone ECGs ≥500 msec were recorded for one patient on the same day. Consequently the patient incidence of QTc ≥500 msec on oral ziprasidone (or within 6 days of last dose) is 2/3095 (0.06%), compared with a placebo incidence of 1/440 (0.23%). Details of the two ziprasidone patients with a Bazett QTc ≥500 msec are shown below.

If the Baseline correction formula is used, the QTc values for patient 117-648-0267 and for the placebo-treated patient do not exceed 500 msec, giving a patient incidence of QTc ≥500 msec of 1/3095 (0.03%) on ziprasidone.

Details of the two oral ziprasidone patients with a Bazett QTc ≥500 msec (QTc values obtained with the Baseline correction are given in parentheses):

- 117-648-0267 was a 39 year-old male who discontinued treatment for a QTc of 503 (498) msec on Day 7 of ziprasidone treatment (80 mg/day). The patient had a history of prolonged QTc, and screening and baseline QTc were 489 (486) and 466 (466) msec, respectively. Follow-up QTcs 3 days and 6 days later were 486 (481) msec and 461 (452) msec, respectively.
- 301-311-0977 was a 28 year-old cachectic female, weighing 42 Kg, who was discontinued from ziprasidone (120 mg/day) on Day 57 of the study due to insufficient clinical response. The end of study ECG was obtained after the morning 60 mg dose of ziprasidone; the QTc at that time was 391 (394) msec. Ziprasidone was discontinued at this time. The patient then received 200 mg thioridazine in the afternoon and subsequently had two consecutive ECGs with QTc readings of 518 (523) and 593 (600) msec. She died approximately 34 hours later, after having received a total of 600 mg of thioridazine. The autopsy diagnosis was myocardosis.

E.4.2 Categorical Increases in Phase 2/3 Clinical Trials

Table 34 shows the categorization of maximum QTc values and QTc increases from baseline in the oral ziprasidone Phase 2/3 trials up to 5 February 2000; these data were centrally read by PRW. The incidences of moderate to marked QTc prolongation, whether defined as absolute QTc values of ≥500 msec, or increases of ≥75 msec or ≥25% from baseline, were comparable in the ziprasidone and placebo groups. Depending on the correction formula used, a QTc ≥500 msec was recorded for two ziprasidone-treated patients and one patient on placebo (Bazett correction) or just one ziprasidone-treated patient (Baseline correction). Ziprasidone-treated patients with QTc >500msec are described above in Section E.4.1.

Table 34. Incidence of Categorical QTc Increases; Phase 2/3 Oral Ziprasidone Trials and Oral Extensions to IM Trials (PRW Central Reader)

	Ziprasidone		Haloperidol		Risperidone		Placebo	
Bazett Correction								
N*	2988		541		260		440	
Incidence	n	%	n	%	n	%	n	%
QTc ≥450 msec	171	5.7	13	2.4	11	4.2	11	2.5
QTc ≥480 msec	10	0.3	1	0.2	0	0	1	0.2
QTc ≥500 msec	2	0.1	0	0	0	0	1	0.2
N**	2775		523		237		434	
Increase from Baseline:	n	%	n	%	n	%	n	%
≥30 msec	610	22.0	63	12.0	40	16.9	54	12.4
≥60 msec	71	2.6	5	1.0	2	0.8	5	1.2
≥75 msec	13	0.5	3	0.6	1	0.4	2	0.5
≥15%	97	3.5	9	1.7	4	1.7	5	1.2
≥25%	5	0.2	0	0	0	0	2	0.5
Baseline QTc (msec)								
Median	400.5		401.7		400.5		399.7	
Range	314-494		320-461		321-517		321-507	
Baseline Correction								
N*	2988		541		260		440	
Incidence	n	%	n	%	n	%	n	%
QTc ≥450 msec	36	1.2	5	0.9	2	0.8	2	0.5
QTc ≥480 msec	3	0.1	0	0	0	0	0	0
QTc ≥500 msec	1	0.0	0	0	0	0	0	0
N**	2775		523		237		434	
Increase from Baseline:	n	%	n	%	n	%	n	%
≥30 msec	422	15.2	48	9.2	28	11.8	31	7.1
≥60 msec	28	1.0	2	0.4	0	0	3	0.7
≥75 msec	8	0.3	1	0.2	0	0	2	0.5
≥15%	45	1.6	5	1.0	1	0.4	7	1.6
≥25%	2	0.1	0	0	0	0	1	0.2
Baseline QTc (msec)								
Median	388.8		388.3		388.8		386.2	
Range	305 - 482		324 - 452		326 - 495		314 - 489	

All data to 5 February 2000.
Excludes patients in one study whose ECGs were centrally read by GDXI (N for ziprasidone = 107).
*N = all patients with post baseline ECG. **N = patients with both baseline and post-baseline ECG.

E.4.3 Effect of Concomitant Medications

The effect of concomitant medication on the QTc has been investigated by identifying ziprasidone-treated patients in Phase 2/3 clinical trials who had an ECG recorded while receiving medications that had the potential to interfere with ziprasidone metabolism or directly affect cardiac repolarization. ECGs recorded during treatment with selected concomitant medications or within 10 days following final concomitant medication dose were examined (Table 35).

Coadministration of any of these medications did not increase the magnitude of QTc prolongation. Applying the Bazett correction factor, mean changes range from -8.4 and -4.2 msec with coadministered ketoconazole (N = 5) and drugs used for hyperlipidemia (N = 37), respectively, to +4.4 and +7.5 msec with coadministered carbamazepine (N = 24) and cimetidine (N = 20), respectively. When the Baseline correction factor is used, mean changes range from -5.8 and -4.4 msec with coadministered ketoconazole (N = 5) and tricyclic antidepressants (N = 27), respectively, to +5.6 and +7.8 msec with coadministered SSRI antidepressants (N = 56) and cimetidine (N = 20), respectively. There was no evidence of clinically meaningful drug interactions, consistent with the results of Study 054 and the ziprasidone clinical pharmacology trial database.

Table 35. QTc Changes in Ziprasidone-Treated Patients Receiving Selected Concomitant Medications; Phase 2/3 Trials

Concomitant Therapy		Baseline QTc (msec)		Mean QTc Change^ on Concomitant Medication (msec)	
	N*	Mean	± SD	Change	± SD
Bazett Correction					
Tricyclic antidepressants	27	411.1	± 19.6	-3.7	± 29.2
SSRI antidepressants	56	407.3	± 23.6	3.4	± 21.2
Calcium Channel Blockers	74	411.2	± 26.8	1.8	± 19.2
Beta-Adrenoceptor Blocking Drugs	177	403.7	± 23.2	1.7	± 20.9
Angiotensin-Converting Enzyme Inhibitors	51	413.8	± 28.4	-2.4	± 27.0
Benzodiazepine Anxiolytic	1585	401.9	± 24.3	3.8	± 22.8
Diuretics	46	411.0	± 24.8	0.5	± 19.5
Drugs Used in the Treatment of Hyperlipidemia	37	402.3	± 27.9	-4.2	± 33.2
Ketoconazole	5	405.9	± 28.6	-8.4	± 12.8
Erythromycin	20	408.0	± 22.1	4.0	± 18.8
Verapamil	13	403.0	± 31.2	4.3	± 23.1
Diphenhydramine	142	402.2	± 25.5	4.3	± 22.3
Cimetidine	20	407.2	± 29.9	7.5	± 26.8
Antiepileptics	156	402.2	± 22.7	3.2	± 21.9
Carbamazepine	24	395.0	± 16.8	4.4	± 17.8
Baseline Correction					
Tricyclic antidepressants	27	396.1	± 15.5	-4.4	± 27.1
SSRI antidepressants	56	396.4	± 21.6	5.6	± 17.7
Calcium Channel Blockers	74	400.1	± 26.4	1.3	± 18.0
Beta-Adrenoceptor Blocking Drugs	177	393.3	± 22.0	3.1	± 17.6
Angiotensin-Converting Enzyme Inhibitors	51	399.2	± 26.2	-0.5	± 23.0
Benzodiazepine Anxiolytic	1585	390.3	± 21.7	3.2	± 19.1
Diuretics	46	397.7	± 22.7	3.4	± 17.4
Drugs Used in the Treatment of Hyperlipidemia	37	390.8	± 26.1	-2.3	± 31.3
Ketoconazole	5	393.5	± 26.2	-5.8	± 8.9
Erythromycin	20	394.3	± 19.9	3.4	± 18.9
Verapamil	13	395.0	± 30.9	3.3	± 23.6
Diphenhydramine	142	390.2	± 22.5	4.2	± 18.0
Cimetidine	20	397.1	± 27.4	7.8	± 20.1
Antiepileptics	156	389.6	± 20.6	3.5	± 17.7
Carbamazepine	24	383.1	± 14.4	3.4	± 15.7

^ Change from baseline to mean value on concomitant medication; to 5 February 2000.
* Patients who had baseline ECG and ECG on or within 10 days after concomitant medication.

E.5 Comparison with Terfenadine QTc Effect

The effect of ziprasidone 80 mg BID on the QTc is similar to that of terfenadine 60 mg BID, in the absence of metabolic inhibition. In the presence of metabolic inhibition, the QTc effect of ziprasidone remains unchanged, while the QTc effect of terfenadine markedly increases. This comparison predicts a favorable clinical profile for ziprasidone 80 mg BID.

- Clinical experience with terfenadine suggests that widespread use of this agent, in the absence of CYP3A4 inhibition, was not associated with increased risk of fatal arrhythmia.[97,98]
- Numerous published reports describe a mean QTc prolongation of approximately 6 msec (Bazett) in association with terfenadine at a dose of 60 mg BID, in the absence of CYP3A4 inhibition. This would compare with a mean prolongation of 9.7 msec with ziprasidone at maximum recommended dose.
- Examination of data from a double-blind, crossover, dose-response study with terfenadine indicates mean peak values at estimated Tmax to be approximately 18 msec (Bazett). This may be compared with a mean peak prolongation of 16 (Baseline correction) to 20 (Bazett) msec observed for ziprasidone in Study 054; or 18 msec for terfenadine vs. 15 msec for ziprasidone if the linear Framingham correction is applied (a baseline correction formula for the terfenadine population has not been calculated; however, terfenadine has a negligible effect on heart rate in this trial, so that Framingham and Bazett calculations produce essentially equivalent QTc changes).
- Following metabolic inhibition using ketoconazole, the QTc prolongation associated with terfenadine has been reported to be 82 msec,[99] in contrast, coadministration of ketoconazole with ziprasidone (with resulting 39% increase in exposure) is associated with no further increase of the QTc effect.

In 1996, Pratt *et al.*[90] reported on the QTc effects of terfenadine from a double-blind dose-response trial sponsored by Hoechst-Marion-Roussel (HMR). In that double-blind, four-period crossover trial, mean changes in QTc of 6 msec and 12 msec were measured in 28 normal volunteers (mean age 57 years) and 28 individuals with a history of heart disease (mean age 60 years), respectively.

A baseline was established prior to each treatment period, and steady-state measures were obtained on dosing day 5 (see Figure 20 for trial design).

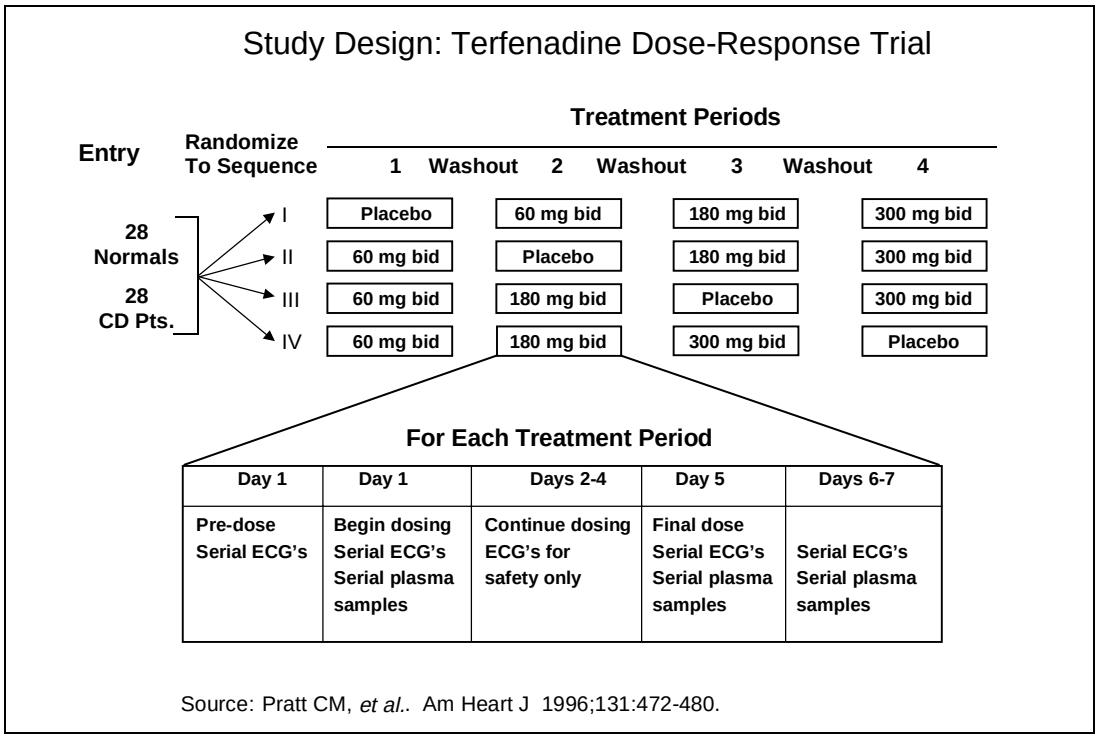


Figure 20. Study Design; Double-Blind Dose-Response Trial of QTc Effects of Terfenadine

The 1996 publication presented analyses of QTc change across pooled timepoints. Through the original investigators, these data have been made available to Pfizer by Hoechst-Marion-Roussel (HMR), allowing an analysis of QTc change at each time point.

Figure 21 shows the mean QTc (Bazett) measured at baseline in normal volunteers. It is important to point out that subjects were provided breakfast during the baseline periods, but not during the dosing periods. The two peaks in QTc which appear rather consistently in each treatment group at baseline may reflect this post-prandial effect. The AM peak is lost on Days 1 and 5, when subjects were not provided with breakfast; however, the effect of the noon meal on the QTc remains evident at steady-state, and may obscure drug effect in the afternoon post-prandial period. There is little evidence for an effect of terfenadine on the first day of dosing, but by the time of steady-state, a dose-related effect is suggested.

Figure 22 displays QTc (Bazett) change from baseline, again reflecting the loss of post-prandial effect in the morning (so that the post-breakfast increase at baseline is reflected as a negative change) at Day 1, while the suggestion of dose-response is again evident on Day 5.

Figure 23 shows placebo-corrected QTc (Bazett) change from baseline. This permits correction for the post-prandial effect, which is shared by the placebo group, and reveals a mean post-dose increase of approximately 18 msec in the 60 mg BID group. The timing of this peak effect - approximately 0.5 to 2 hours post-dose - suggests that it may be due to a transient effect of the parent compound, or combination of parent compound and a less-active metabolite, which is cleared rapidly from plasma.

Figure 24 shows the same placebo-corrected QTc change from baseline as is presented in Figure 23 but with QTc calculated according to the Framingham correction formula. As noted in Section E.3.2.2 of this document, the peak effect of ziprasidone upon the QTc interval, calculated by the Framingham formula, is 14.9 msec in Study 054, somewhat less than that seen with terfenadine 60 mg BID in this trial.

QTc Changes Associated with Terfenadine -- QTc (Bazett Correction) Change by Time of Day

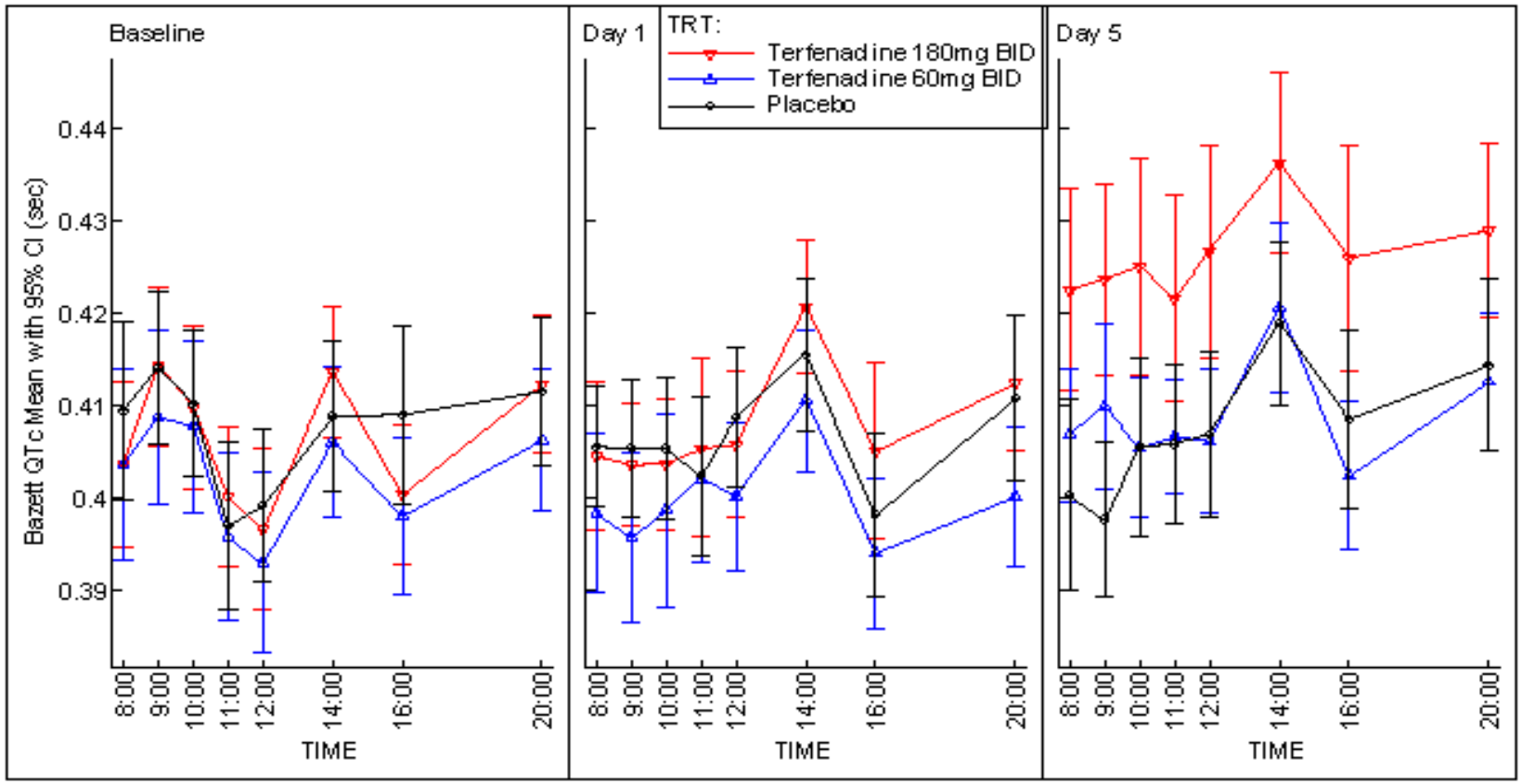
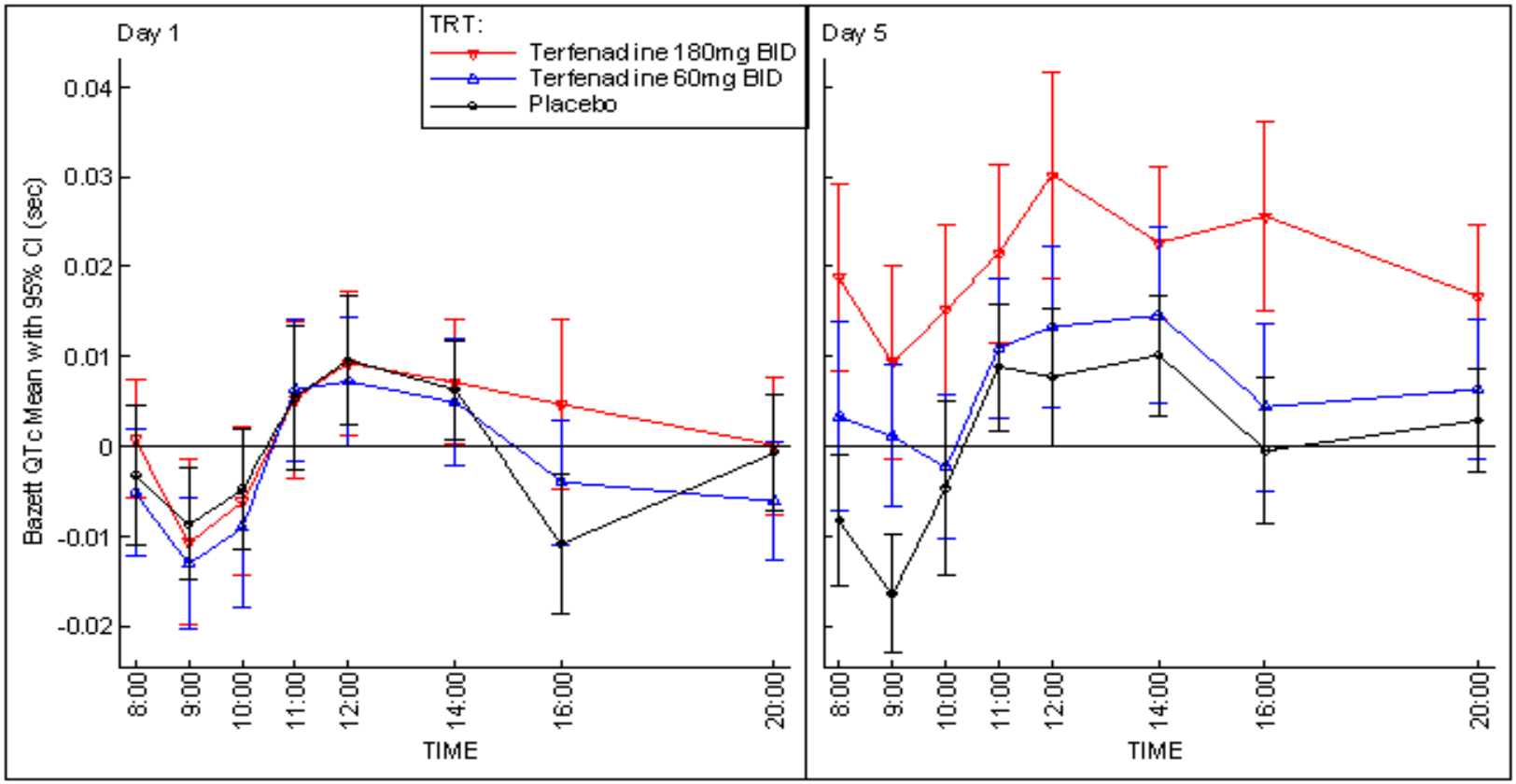


Figure 21. Mean QTc (Bazett Correction) by Time of Day in Normal Subjects Receiving Terfenadine or Placebo; HMR Data

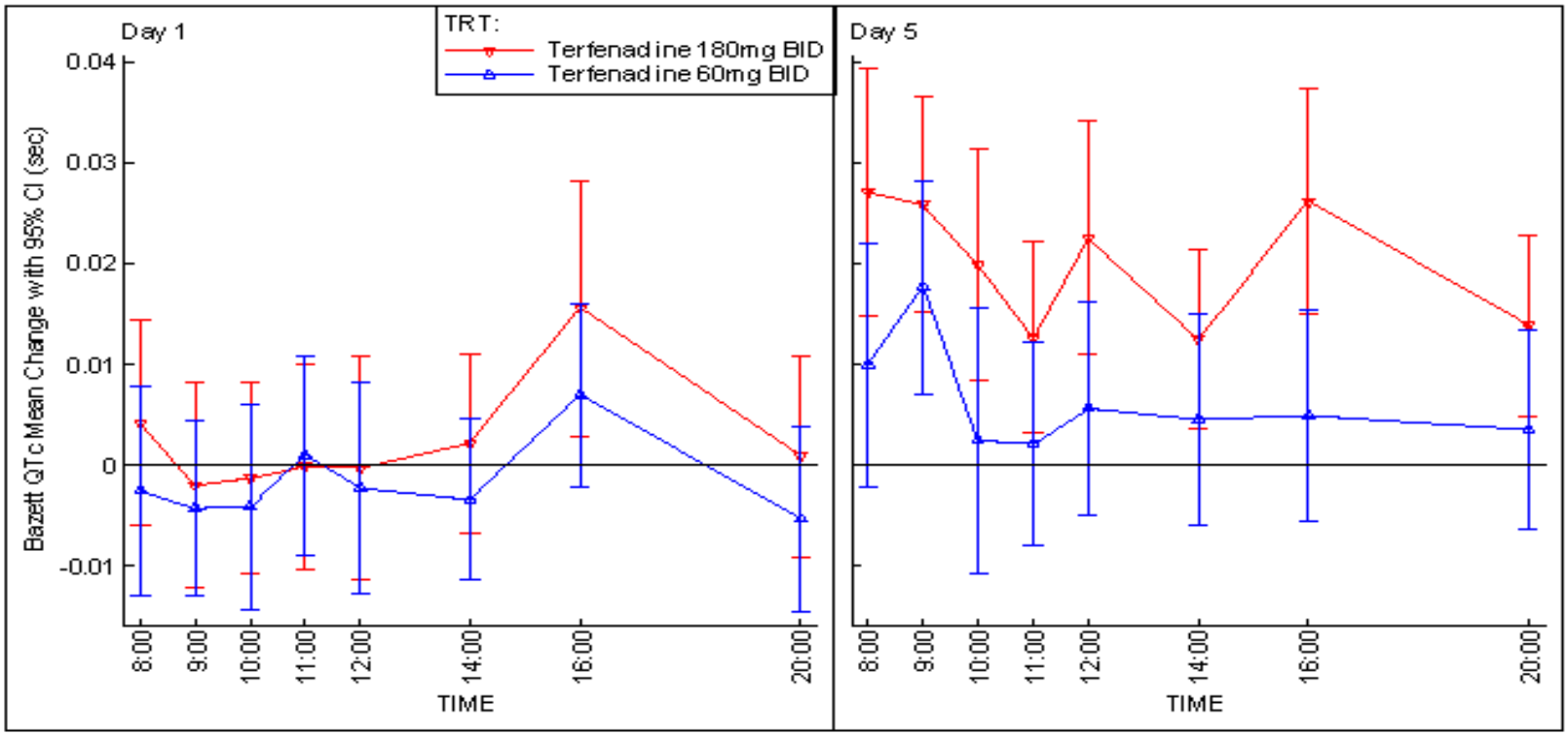
QTc Changes Associated with Terfenadine -- QTc (Bazett Correction) Change from Baseline by Time of Day



For each subject post-baseline QTcs were matched with the corresponding baseline QTc at each hour of the day to create time-matched differences. These differences were then summarized across subjects within population and treatment groups.

Figure 22. Mean QTc (Bazett Correction) Change from Baseline by Time of Day in Normal Subjects Receiving Terfenadine or Placebo; HMR Data

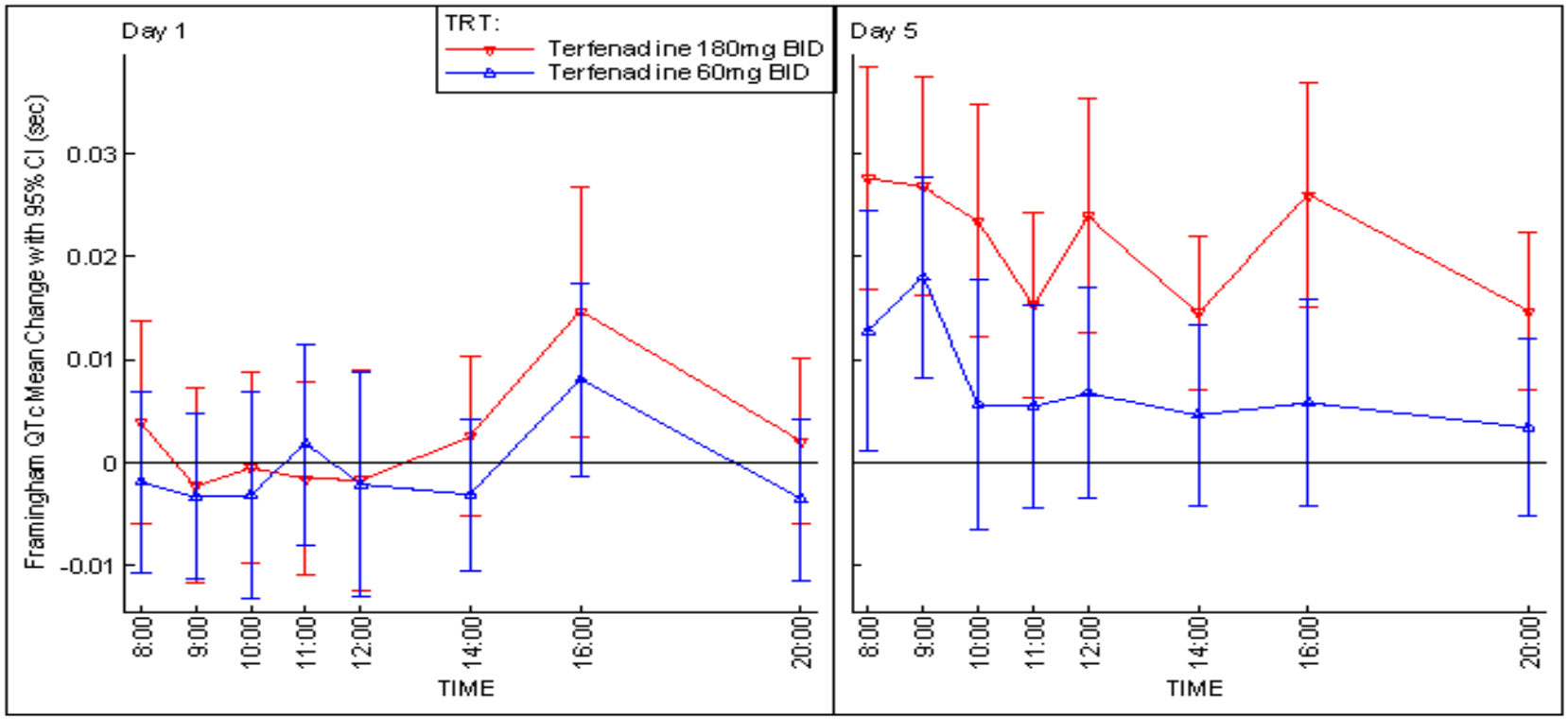
QTc Changes Associated with Terfenadine
Placebo-Corrected QTc (Bazett Correction) Change from Baseline by Time of Day



For each subject post-dose QTcs were matched with the corresponding baseline QTc at each hour of the day to create time-matched differences. Placebo time-matched difference at each hour was then subtracted from the corresponding time-matched difference for each subject to form a placebo-corrected time-matched difference. These differences were then summarized across subjects within the population and treatment groups.

Figure 23. Mean Placebo-Corrected QTc (Bazett Correction) Change from Baseline by Time of Day in Normal Subjects Receiving Terfenadine; HMR Data

QTc Changes Associated with Terfenadine
Placebo-Corrected QTc (Framingham Correction) Change from Baseline by Time of Day



For each subject post-dose QTcs were matched with the corresponding baseline QTc at each hour of the day to create time-matched differences. Placebo time-matched difference at each hour was then subtracted from the corresponding time-matched difference for each subject to form a placebo-corrected time-matched difference. These differences were then summarized across subjects within the population and treatment groups

Figure 24. Mean Placebo-Corrected QTc (Framingham Correction) Change from Baseline by Time of Day in Normal Subjects Receiving Terfenadine; HMR Data.

Overall therefore, the results of this trial show that terfenadine, 60 mg BID for 5 days, is associated with an average increase in QTc of approximately 6 msec (Bazett correction; or 8 msec Framingham correction), using ECG data collected across the dosing interval. A peak effect has been measured during the first two hours post-dose of approximately 18 msec (Bazett or Framingham corrections). For comparison, ziprasidone, at a dose of 80 mg BID, was found to be associated with an increase of <10 msec when ECGs were obtained throughout the dosing cycle (STFDPC trials, conducted in hospitalized patients). The peak effect of ziprasidone, measured near the time of Cmax following administration of ziprasidone 80 mg BID for 5 days in Study 054 (period 3 completers) was 20 msec, or 15 msec when calculated with the Bazett or Framingham corrections, and 16 msec when calculated with the Study 054 Baseline correction.

Importantly, while the QTc effects of terfenadine 60 mg BID and ziprasidone 80 mg BID appear to be similar when administered in the absence of metabolic (CYP3A4) inhibition, there is a marked difference in the behavior of terfenadine and ziprasidone in the presence of metabolic inhibition. The combination of ziprasidone and ketoconazole (200 mg BID) has been studied in Study 054. Consistent with the Phase 2/3 data, the effect of ziprasidone on the QTc interval appears stable. This is in marked contrast with the 82 msec increase in QTc which was measured at expected trough (twelve hours after terfenadine dosing) in a study of ketoconazole and terfenadine coadministration.[99] This effect was considered to be responsible for the reports of sudden death which led to the withdrawal of terfenadine from the market in the United States and elsewhere. These data are summarized in Table 36 and illustrated in Figure 25.

The clinical experience with terfenadine 60 mg BID administered in the absence of metabolic inhibition was favorable when examined in large, prescription – based population studies.[97,98] Examinations of clinical experience with >180,000 terfenadine prescriptions in a medical database[97] and nearly 20,000 terfenadine prescriptions in the Harvard Community Health Plan,[98] both concluded that there was no evidence of increased risk of QTc-related events in the absence of metabolic inhibition.

Table 36. Summary of QTc Changes Associated with Ziprasidone and Terfenadine in the Absence and Presence of Metabolic Inhibitor

	Mean QTc Change (msec) ± SE			
	Metabolic Inhibitor Absent		Metabolic Inhibitor# Present	
	Non-Peak Measurement	At Peak Plasma Concentration	Non-Peak Measurement	At Peak Plasma Concentration
Bazett Correction				
Terfenadine 60mg BID	6 ± 3*	18 ± 5**	82 ± 18***	NA
Ziprasidone 80mg BID	10 ± 2^	20 ± 3^^	NA	20 ± 3^^
Framingham Linear Correction				
Terfenadine 60mg BID	8 ± 3*	18 ± 5**	NA	NA
Ziprasidone 80mg BID	8 ± 2^	15 ± 2^^	NA	16 ± 3^^

* from Pratt *et al.*[90]; **placebo-corrected value, calculated from HMR data;
*** trough values, from Honig *et al.*[99]
^ Ziprasidone NDA, unspecified timing of QTc values; ^^ Study 054
# ketoconazole
NA: not available

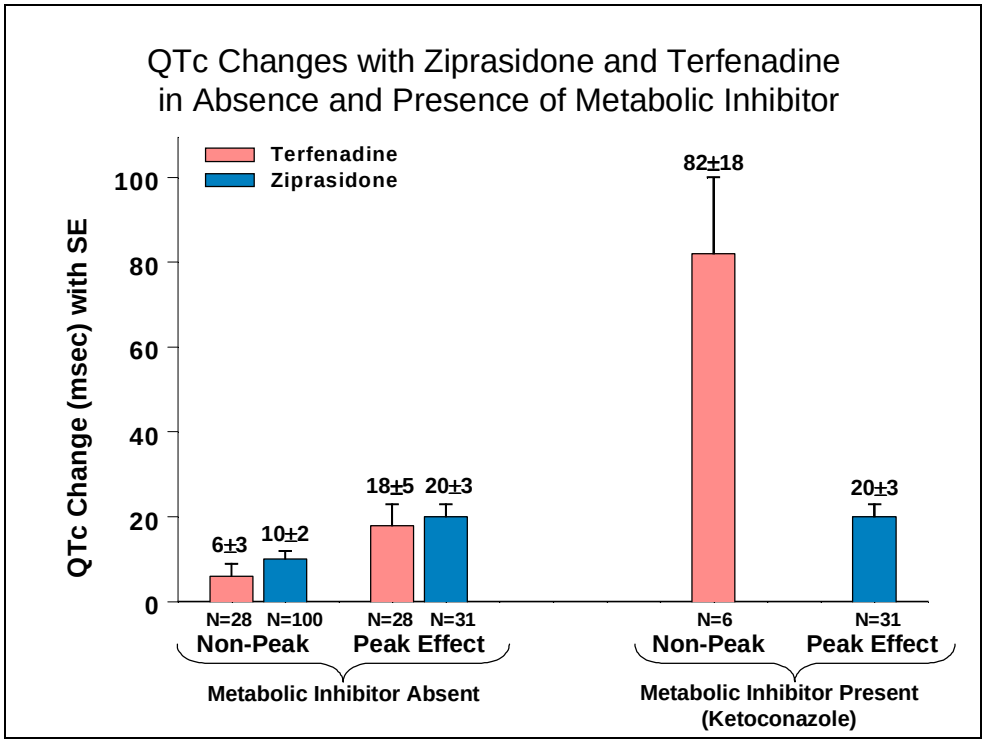


Figure 25. QTc (Bazett Correction) Changes Associated with Ziprasidone and Terfenadine in the Absence and Presence of Metabolic Inhibitor

E.6 Comparison with Sertindole QTc Effect

Recent clinical and regulatory experience with sertindole, an atypical antipsychotic agent, may be considered relevant to a discussion of ziprasidone. However, these compounds differ in several ways:

- As reported at the Psychopharmacology Advisory Committee in July 1996, sertindole caused a mean QTc increase of 21 to 30 msec at its recommended dose of 24 mg/day. In contrast, ziprasidone caused a mean QTc increase of <10 msec at the highest recommended dose of 160 mg/day.

- Noticeably, 7-8% of sertindole patients receiving the recommended dose were reported at the Psychopharmacology Advisory Committee in July 1996 to have had one or more QTc values ≥500 msec. In the ziprasidone Phase 2/3 clinical program, <0.1% of ziprasidone patients had one or more QTc values ≥500 msec (see Section E.4.1).

The high incidence of QTc > 500 msec with sertindole is confirmed in a study comparing sertindole with haloperidol (N = 141 in each treatment group) from which it is reported that: "One sertindole-treated patient and none of the haloperidol-treated patients had a QT interval that exceeded 500 msec. Eight percent of sertindole-treated patients had QTc intervals of at least 500 msec compared with none in the haloperidol group ($p \leq 0.05$)."[100]

- Sertindole is a substrate for CYP3A4 and CYP2D6, properties that led to considerable variability in exposure across a population. The metabolism of ziprasidone is not mediated by CYP2D6, and the pharmacokinetics of ziprasidone is affected only slightly by inhibition or induction of CYP3A4. Most importantly, the QTc effect of ziprasidone has been demonstrated to remain stable in the presence of potent CYP3A4 inhibition

In comparing the QTc values of sertindole and ziprasidone, it is important to note that the magnitude of change detected in QTc is a function of the conditions under which the ECG recordings are made. Pfizer is not able to describe the conditions in which the QTc effect of sertindole has been measured. However, the extremely low incidence of QTc >500 msec in the ziprasidone clinical trial database is supported by the absence of such QTc values in patients being administered the maximum recommended dose, with concomitant ketoconazole (Study 054).

E.7 Summary

The effect of ziprasidone on the QTc is modest. Bazett QTc values ≥500 msec have been recorded for only 2 of 3095 patients (0.06%) who have received oral ziprasidone and who have ECGs in the database at the time of the most recent Final Safety Update of 5 February 2000, a total of 7876 tracings. One patient who had a QTc of 503 msec had a history of prolonged QTc; the other patient, at the

time of a QTc of 593 msec, had stopped taking ziprasidone and was receiving thioridazine.

In short-term, fixed-dose, placebo-controlled trials in the NDA database (Studies 104, 106, 114, and 115), ziprasidone was associated with a prolongation of <10 msec relative to baseline over the therapeutic range (80 to 160 mg daily). There was no further prolongation in QTc in patients given a 200 mg daily dose in the short-term trials.

Consistent with preclinical evidence that many antipsychotic agents, including haloperidol and the more recently introduced atypical compounds, block I_{Kr} channels,[101,102] the sponsor notes that each of the agents in Study 054 was found to be associated with a mean increase in the QTc. No patient in any group had a QTc ≥500 msec.

The mean QTc effect of ziprasidone measured in Study 054 did not increase following metabolic inhibition, although serum concentrations of ziprasidone and M9 increased by 39% and 55%, respectively. This observation is consistent with the flattening of the dose-response seen in STFDPC trials, at the highest dose of 200 mg/day. Although variability in the QTc response may explain the failure to detect a slight increase associated with these changes in dose (STFDPC trials) or concentration (Study 054), the overdose experience with ziprasidone (10 patients; see Section F.4) provides further reassurance when considering limits to the effect of ziprasidone upon the QTc.

The effect of ziprasidone 80 mg BID on the QTc is similar to that of terfenadine 60 mg BID, in the *absence* of metabolic inhibition. Clinical experience and epidemiological data have shown that terfenadine in the *absence* of metabolic inhibition was not associated with increased risk of fatal arrhythmia. In the presence of metabolic inhibition, the QTc effect of ziprasidone remains unchanged, while the QTc effect of terfenadine markedly increases. The absence of this drug interaction liability predicts a favorable clinical profile for ziprasidone.

F. CLINICAL SAFETY

Review of the ziprasidone clinical database reveals no excess in mortality or reported syncope. There have been no reported cases of TdP, and there have been no reports of significant cardiac events in association with overdose.

The following sections present data on mortality, torsade de points, syncope, and overdose for the oral ziprasidone program. Death rates for other antipsychotics are presented for comparison.

In summary:

- The oral ziprasidone safety database has shown no excess of rapid and unexpected deaths compared with placebo or with marketed antipsychotic agents.
- No episodes of torsade de pointes have been reported among 4571 patients taking oral ziprasidone for a total exposure of 1733 patient-years.
- The rate of syncope among ziprasidone-treated patients is comparable to that reported for marketed antipsychotics.
- There have been no reports of significant cardiac events in association with ziprasidone overdose or documented high ziprasidone exposure in clinical trials.

F.1 Mortality

As of 5 February 2000 (data cut-off for the most recent Safety Update submitted to the FDA), 4571 patients have taken oral ziprasidone in Phase 2/3 trials, for a cumulative total of 1733 patient-years exposure; 991 of these patients have received ziprasidone for more than 6 months, and 605 for more than one year, and 151 for longer than 2 years (see Section A.2.1). Mortality rates for deaths overall, deaths occurring within 30 days and within 6 days of the last day of study treatment, and rapid and unexpected deaths are shown below for ziprasidone, placebo, and the two active comparators (Table 37). There is no evidence of an increased death rate in the ziprasidone group compared with placebo and active comparator groups. The mortality in the ziprasidone group has declined slightly since the NDA was filed, and is less than that measured in the placebo group, in each reporting category.

Table 37. Incidence of Death in the Ziprasidone Phase 2/3 Clinical Program

	Ziprasidone	Placebo	Haloperidol	Risperidone
NDA Database to 31 October 1996				
N	2163	366	407	206
patient-years exposure	626	51	86	84
deaths / 100 patients years (N)	4.2 (26)	13.7 (7)	3.5 (3)	1.2 (1)
deaths / 100 patients years ≤30 days (N)	2.2 (14)	5.9 (3)	3.5 (3)	1.2 (1)
deaths / 100 patients years ≤6 days (N)	1.8 (11)	3.9 (2)	2.3 (2)	1.2 (1)
deaths / 100 patients years - rapid, unexpected* (N)	0.8 (5)	0	0	1.2 (1)
Cumulative to 5 February 2000				
N	4571	605	1071	426
patient-years exposure	1733	92	299	196
deaths / 100 patients years (N)	2.9 (50)	10.9 (10)	1.0 (3)	1.0 (2)
deaths / 100 patients years ≤30 days (N)	1.6 (28)	5.4 (5)	1.0 (3)	0.5 (1)
deaths / 100 patients years ≤6 days (N)	1.4 (24)	3.3 (3)	0.7 (2)	0.5 (1)
deaths / 100 patients years - rapid, unexpected* (N)	0.6 (10)	1.1 (1)	0	0.5 (1)

* rapid, unexpected = within twenty-four hours of the onset of symptoms; includes those due to known conditions, if the patient had been stable prior to the event; excludes known suicide and homicide cases.

Table 38 is a summary of 37 deaths that occurred within 30 days of the last dose of ziprasidone (28 deaths) or one of its comparators (placebo: 5 deaths; haloperidol: 3 deaths; risperidone: 1 death). The table includes all available QTc values recorded for these patients. As in the original submissions, these QTc values are calculated using the Bazett formula. Of the 21 ziprasidone patients for whom QTc values were obtained during drug treatment, only patient 22 in Table 38 had a QTc >440 msec. It is noteworthy that this patient was receiving thioridazine at the time of QTc prolongation, having been discontinued from ziprasidone treatment. (The course of events for this patient is described in Section E.4.1.)

Table 38. Deaths Within 30 Days of Last Ziprasidone Dose, All Events to 5 February 2000

Patient No.	Death Within 6 Days	^Rapid & Unexpected Death	Age (yrs)	Sex	Days on Rx	Dose mg/day	Days since Last Dose	QTc (msecs)		Narrative
								Pre-Drug	On Drug	
Ziprasidone										
1			43	M	16	40	30	397 412	430	Asphyxiation due to aspiration of vomitus Treated with risperidone and off ziprasidone for 30 days
2			44	F	44	80-120	24	444 443	433 440 407 423	Found dead in bed 24 days after last dose of ziprasidone Autopsy revealed probable mitral valve myxoma
3			79	F	30	80	30	416*	413*	Died one month after ending study due to cardiac arrest
4			53	M	2	20	17	not done	not done	Suicide by hanging
5	X		21	F	54	160	1	382 400	417	Suicide by gunshot to the head
6	X		24	M	99	40-240	0	362 357	365	Suicide by hanging
7	X		51	M	205	120	1	404 418 430	408 411	Multiple trauma as a result of exiting a 10th story window
8	X		40	M	54	160	4	425 396	414 381	Accidental drowning: drove car off cliff after a sleep-deprived EEG and being advised not to drive; Post-mortem ziprasidone serum concentration: 2.4 ng/ml
9	X		46	M	7	80	5	405	not done	Left hospital on his own and drowned
10	X		22	M	179	80-120	0	371	not done	Suicide by falling under a train

^Rapid: Within 24 hours after the onset of symptoms.
Bazett QTc values were provided by a central reader, or calculated using HR and QT provided by the central reader (except values noted *).

Table 38. Deaths Within 30 Days of Last Ziprasidone Dose, All Events to 5February 2000 (continued)

Patient No.	Death Within 6 Days	^Rapid & Unexpected Death	Age (yrs)	Sex	Days on Rx	Dose mg/day	Day of Death Post-Rx	QTc (msecs) Pre-Drug	QTc (msecs) On Drug	Narrative
Ziprasidone										
11	X		63	M	74	80	0	400	407 416 401	Collapsed: autopsy found ruptured aortic aneurysm and gross diffuse atherosclerosis
12	X		41	F	46	80	1	427 404	394 405 433	Suicide due to self-inflicted knife wounds
13	X		47	M	14	80	4	402	not done	Suicide by hanging
14	X		34	M	10	120-160	0	400	388 379	Suicide by drowning
15	X		37	F	13	60	0	362	374	Cardio-respiratory arrest due to fire which started while patient was smoking in bed Neighbor knocked on patient's door after fire started and patient stated she was "all right"
16	X		23	M	53	160	0	408	418	Suicide by gunshot
17	X	X	70	F	5	2	0	452 441 429 426	not done	Cardiac arrest History of chronic obstructive pulmonary disease, smoking, hypertension, dementia, right bundle branch block, hypothyroidism, organic brain syndrome
18	X	X	39	F	8	80	0	433 434	not done	Found in apartment History of diabetes and alcohol abuse
19	X	X	46	M	61	80	1	366 393	395	Collapsed after exertion in extreme heat Autopsy found asthmatic bronchitis and granulomatous myocarditis; Post – mortem ziprasidone serum concentration: 6.1 ng/ml

^Rapid: Within 24 hours after the onset of symptoms.
Bazett QTc values were provided by a central reader, or calculated using HR and QT provided by the central reader (except values noted *).

Table 38. Deaths Within 30 Days of Last Ziprasidone Dose, All Events to 5 February 2000 (continued)

Patient No.	Death Within 6 Days	^Rapid & Unexpected Death	Age (yrs)	Sex	Days on Rx	Dose mg/day	Day of Death Post-Rx	QTc (msecs)		Narrative
								Pre-Drug	On Drug	
Ziprasidone										
20	X	X	49	M	466	160	1	432 395	396 417 393	Acute myocardial infarction History of hypertension, obesity, asthma, chronic nicotine addiction, elevated cholesterol and triglycerides, chronic obstructive pulmonary disease, and chronic alcohol and substance abuse Post-mortem ziprasidone serum conc.: 14 ng/ml
21	X	X	54	M	71	120	1	391 383	367 391	Found in hospital bed History of chronic obstructive pulmonary disease, hypertension, arteriosclerotic peripheral vascular disease Autopsy found generalized atherosclerosis and cardiac hypertrophy
22	X	X	28	F	57	120	2	416	391 443 481 518 593 491 487 468	Died in the hospital 2 days after discontinuing ziprasidone and while treated with thioridazine History of anorexia (42 Kg) Autopsy found atrophy/dystrophy of cardiac myocytes
23	X	X	48	M	162	120	1	428	418	Found in apartment 1 day after discontinuing ziprasidone and after 1 day of treatment with haloperidol 20 mg/day History of polydipsia, hyponatremia, and seizures
24	X	X	52	M	221	80	0	381	399 385	Found in bed History of cigarette smoking

^Rapid: Within 24 hours after the onset of symptoms.
Bazett QTc values were provided by a central reader or calculated using HR and QT provided by the central reader (except values noted *).

Table 38. Deaths Within 30 Days of Last Ziprasidone Dose, All Events to 5 February 2000 (continued)

Patient No.	Death Within 6 Days	^Rapid & Unexpected Death	Age (yrs)	Sex	Days on Rx	Dose mg/day	Day of Death Post-Rx	QTc (msecs)		Narrative
								Pre-Drug	On Drug	
Ziprasidone										
25	X	X	50	M	6	40	0	359	398 349	Suspected acute respiratory or cardiac event. Complained of palpitations, nausea, feeling unwell, and feverish; suspected upper respiratory infection treated with OTC antibiotic, flomoxef. Patient smoked.
26	X		20	M	8	160	0	400*	Not done	Subject drowned while swimming in the sea, death is not considered a suicide attempt. Past history of palpitations and acute dystonia.
27	X		51	M	152	80	0	428	425 393 416	Two days prior to death, subject reported "not feeling well" with complaints of sore throat and was described as lethargic. Autopsy report showed a left meningioma without evidence of brain injury. Cardiac risks include hypertension, hypercholesterolemia and obesity. Post-mortem ziprasidone serum conc: 7.5 ng/ml
28	X	X	34	M	320	90-100	0	377	413 390 409 397 378 425 366 407 391 390 405 397 429	Death described as sudden with unknown etiology. Subject reported aches and pains after shoveling snow including chest pain. Subject took naproxen and went to work; during the day stated that he "felt like he was having a heart attack". Coroner reported official cause of death was "occlusive coronary arteries." Father and paternal grandfather both had myocardial infarctions at age 50 yrs. Post mortem ziprasidone level: not detectable

^Rapid: Within 24 hours after the onset of symptoms.
Bazett QTc values were provided by a central reader or calculated using HR and QT provided by the central reader (except values noted *).

Table 38. Deaths Within 30 Days of Last Ziprasidone Dose, All Events to 5February 2000 (continued)

Patient No.	Death Within 6 Days	^Rapid & Unexpected Death	Age (yrs)	Sex	Days on Rx	Dose mg/day	Day of Death Post-Rx	QTc (msecs)		Narrative
								Pre-Drug	On Drug	
Ziprasidone										
Haloperidol										
29			72	M	427	10	22	432 446	437 456 450	Cardiac ischemia and sepsis following right upper lobectomy for carcinoma
30	X		23	M	96	5-20	6	427 377	371	Suicide by gunshot
31	X		30	M	50	5-15	0	375 395	385	Suicide by intentional drug overdose
Risperidone										
32	X	X	65	M	201	4	0	443 424	440	Asphyxiation due to food aspiration
Placebo										
33			37	F	32	Placebo	7	not done	421 418 406	Suicide by ingestion of diphenhydramine and other drugs
34			43	M	13	Placebo	12	454	not done	Skull trauma (extradural hematoma) of unknown source
35	X		87	F	13	Placebo	4	494	383	Acute respiratory failure with arrest following aspiration pneumonia
36	X		76	M	15	Placebo	4	392*	not done	Bronchopneumonia
37	X	X	73	M	73	Placebo	1	398	510	Pneumonia and cardiac decompensation

^Rapid: Within 24 hours after the onset of symptoms.
Bazett QTc values were provided by a central reader or calculated using HR and QT provided by the central reader (except values noted *).

Mortality data from the development programs for risperidone, quetiapine, and olanzapine have been obtained from publicly available regulatory review documents . These are summarized in Table 39 for comparison with ziprasidone. The death rate for haloperidol is that reported by each sponsor based on data from the comparator trials in their respective clinical development programs. Though each program primarily included patients suffering from psychosis, differences between the populations may include site/country of origin, age, treatment settings, and concomitant medications. Nonetheless, the overall mortality rates for the five antipsychotics appear to be comparable, to each other and to the mortality rate reported in a recent meta-analysis (Figure 26).

Table 39. Mortality; Ziprasidone vs. Reported Data for Other Antipsychotic Agents

	Ziprasidone	Risperidone*	Quetiapine*	Olanzapine*
N	4571	2322	2523	2500
patient-years	1733	508	1103	1122
Deaths^	28	10	12	20
per 100 patient-years	1.6	2.0	1.1	1.8
Placebo death rate per 100 patient-years	5.4	0.0	0.0	7.4
Haloperidol death rate per 100 patient-years	1.0	1.6‡	2.4	1.6

^ Deaths ≤30 days.
* Source: Respective FDA review documents.
‡Risperidone NDA. A 1.7 value is reported for all active controls, representing 1 death in 61 patient-years exposure; however, since only 51 of the 61 patient-years of exposure were to haloperidol the correct rate based on this incidence should be 1.6.

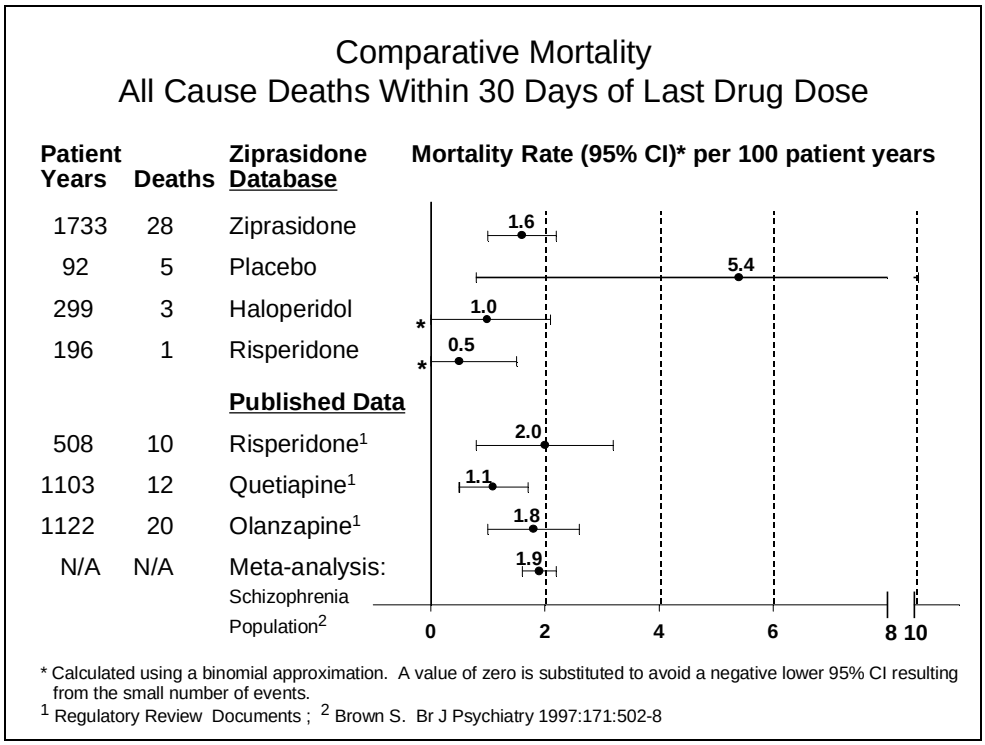


Figure 26. Summary of All-Cause Mortality Rates for Patients with Schizophrenia

F.2 Torsade de Pointes

Torsade de pointes (TdP) is a polymorphic ventricular tachycardia that, except in rare cases of congenital long QT syndrome, acquired heart block, or severe electrolyte disturbance (hypokalemia),[103] is characteristic of drug-induced prolongation of ventricular repolarization. Although TdP is a potentially lethal arrhythmia, it is rare and usually self-limiting.[104]

As of the 5 February 2000, 4571 patients have received oral ziprasidone in Phase 2/3 clinical trials for a total exposure of 1733 patient-years. No episodes of torsade de pointes have been reported.

F.3 Syncope

The incidences of syncope in all Phase 2/3 trials reported in the ziprasidone NDA and in completed and ongoing single-blind and open-label Central Research trials up to 5 February 2000 are shown in Table 40. The incidence of syncope in ziprasidone-treated patients has remained consistent with the incidence reported in the NDA and is comparable to that of comparator groups.

Table 40. Incidence of Treatment-Emergent Syncope Adverse Events in the Ziprasidone Phase 2/3 Clinical Program

	Ziprasidone	Haloperidol	Risperidone	Placebo
NDA Database, to 31 October 1996				
Duration of Exposure Patient -Years	626	86	84	51
No. of Patients	2163	407	206	366
No. of Patients with Syncope (%)	15 (0.7%)	3 (0.7%)	2 (1.0%)	0 (0.0%)
Rate of Syncope/100 Patient-years Exposure	2.4	3.5	2.4	
Cumulative to 5 February 2000				
Duration of Exposure Patient -Years	1658.0	270.0	164.8	86.0
No. of Patients	3834	686	322	506
No. of Patients with Syncope (%)	22 (0.6%)	6 (0.9%)	2 (0.6%)	1 (0.2%)
Rate of Syncope/100 Patient-years Exposure	1.3	2.2	1.2	1.2

The incidence of syncope in ziprasidone patients (22/3834, 0.6%) is similar to that reported in the respective US Package Inserts for risperidone (6/2607, 0.2%), olanzapine (15/2500, 0.6%), and quetiapine (22/2162, 1.0%).

F.4 Overdose

Patients who have taken high doses of ziprasidone provide additional information on the effects of ziprasidone on QTc. Review of the serious adverse event safety database up to 5 February 2000 identified 8 patients who had been randomized to ziprasidone and accidentally or intentionally took an overdose of ziprasidone, and one patient on blinded therapy who took an overdose of study drug -- either ziprasidone or risperidone. In addition, two patients who had taken >300 mg ziprasidone in a single dose and had an ECG within two days were identified in the project safety database. Although classified as excessive dosing rather than overdose, these patients provide relevant information and are included. Table 41 summarizes these overdose events together with QTc values and ziprasidone serum concentration values obtained within three days of the event. One patient randomized to ziprasidone who took an overdose of risperidone is also included in the table.

It can be seen from Table 41 that the effect of these high ziprasidone doses on the QTc has been negligible. There were no ziprasidone overdose cases that were accompanied by significant cardiovascular symptoms. The most common symptoms included sedation and nausea, consistent with data from ziprasidone clinical trials. Among the 8 patients in whom ECGs were taken subsequent to their ingestion of >300 mg ziprasidone, only one had QTc values >440 msec. This patient (ZIP-NY-97-002-0018) had intentionally taken 3240 mg of ziprasidone (40 times the recommended maximum single dose). ECGs recorded 4.5 and 6 hours after overdose showed QTc values of 476 msec and 472 msec, respectively. For comparison, pre-drug QTc values ranged from 454 to 458 msec (all Bazett values, as originally submitted). In summary, the current data available

on ziprasidone in overdose are reassuring and consistent with the overall safety profile of the compound.

F.5 Summary

Analysis of the ziprasidone safety database through 5 February 2000 showed no excess in rapid and unexpected deaths compared with placebo or other commonly prescribed antipsychotics and no reported cases of torsade de pointes among the 4571 patients treated with oral ziprasidone (cumulative total of 1733 patient-years). The incidence of syncope in ziprasidone-treated patients was comparable to that reported for other recently approved antipsychotics. No cases of ziprasidone overdose have been accompanied by significant cardiovascular adverse events.

Table 41. Ziprasidone Overdose and Effect on QTc, All Events to 5 February 2000

Patient No.	Age	Sex	QT_C (msecs) Pre-Drug	Date of Overdose	Dose (mg)	QT_C On Drug (msecs) (date/time)	Serum Concentration (ng/ml) (date)	Comments
ZIPRASIDONE								
1	50	M	371 362	21Feb97 18:30	240	393 22Feb97 11:34	87 22Feb97 06:30	Intentionally ingested 6 (40 mg) ziprasidone capsules and 8 valproic acid tablets
2	22	M	365 366	12Aug95	640	404 7Aug95 13:01 397 15Aug95 17:47	<1 15Aug95 12:00	Intentionally, impulsively ingested 16 (40 mg) ziprasidone capsules. Admitted to hospital with nausea, vomiting, shakiness, sweats and headache that resolved after 4 days.
3	29	M	331 385	21Mar96 16:30	1880	372 21Mar96 19:02	31 22Mar96 13:45	Patient reported intentionally taking 47 (40 mg) ziprasidone capsules with ethanol and paroxetine. Hospital evaluation showed no symptoms consistent with overdose; no pill fragments were recovered.
4	29	M	414	26Sep95	480	345 28Sep95 09:00	15 27Sep95 18:00	Accidentally took ziprasidone; was noted to have slow speech and unsteady gait.
5	53	M	380	7-10Sep95	840/4 days	no ECG within 3 days after the event	no assay within 3 days after the event	Accidentally took 840 mg ziprasidone over the course of 4 days. Was admitted to hospital with complaints of insomnia, restlessness and parkinsonism that were transient.
6	20	F	383	2Jul96	4600	378 3Jul96	no assay within 3 days after the event	Intentional overdose of at least 58 capsules; exact amount unknown. Patient vomited; gastric lavage performed.

Bazett QTc values were provided by a central reader, or calculated using HR and QT provided by the central reader.

Table 41. Ziprasidone Overdose and Effect on QTc, All Events to 5 February 2000 (continued)

Patient No.	Age	Sex	QT_C (msecs) Pre-Drug	Date of Overdose	Dose (mg)	QT_C On Drug (msecs) (date/time)	Serum Concentration (ng/ml) (date)	Comments
ZIPRASIDONE								
7	50	M	457 458 454	12Feb99 13:00	3240	476 12Feb99 17:33 472 12Feb99 19:05 478 12Feb99 22:40 475 13Feb99 02:42 450 13Feb99 06:27	no assay within 3 days after the event	Intentionally took 54 (60 mg) ziprasidone capsules; patient was alert and reported not ingesting any other medications or ethanol; had not vomited. Experienced mild sedation with speech slurring.
8	43	F	417 410	29Apr97	640	402 29Apr97 23:54	no assay within 3 days after the event	Intentionally took 16 (40 mg) ziprasidone capsules. Experienced moderate sedation, not requiring hospitalization.
9*	64	F	429 435	16Aug95	360	418 17Aug95 10:28	35 17Aug95 10:20	Accidentally took ziprasidone
10*	28	M	389	5Sep95 6Sep95	400 480	393 7Sep95 11:07	170 7Sep95 09:33	Accidentally took ziprasidone
ZIPRASIDONE or RISPERIDONE								
11	20	F	380 372	27Mar99	Unknown Ziprasidone or risperidone	366 30Mar99 15:13	no assay within 3 days after the event	Intentionally took seven capsules blinded therapy (ziprasidone or risperidone) combined with 2-3 flunitrazepam tablets; hospitalized 27Mar99; event resolved 28Mar99.
RISPERIDONE								
12	36	F	396	20Feb99	≤118	458 21Feb99	no assay within 3 days after the event	Receiving open-label ziprasidone (160 mg/day); Intentionally took up to 118mg of risperidone combined with alcohol; experienced postural hypotension.

* not included in serious adverse event safety database
Bazett QTc values were provided by a central reader, or calculated using HR and QT provided by the central reader.

G. FAVORABLE EFFECT ON BODY WEIGHT AND SERUM LIPIDS COMPARED WITH ALTERNATIVE ANTIPSYCHOTICS

Ziprasidone has been shown, in both short-term and long-term clinical trials, to be "weight-neutral" and to have a favorable effect on lipids. Body weight gain adversely affects compliance and quality of life. Data derived from patient surveys demonstrate that BMI >30 is associated with a higher incidence of self-reported noncompliance among patients receiving treatment for mental illness. Both body weight and serum lipids are important and well-established cardiovascular risk factors.

The following section examines the effects of ziprasidone and other antipsychotic agents on body weight and serum lipid concentrations. Briefly, results showed that:

- In both short-term and long-term clinical trials (NDA database), ziprasidone-treated patients demonstrated a lower incidence of clinically significant weight gain than patients receiving marketed antipsychotics.

- In both short-term (Study 054) and long-term clinical trials, ziprasidone has been shown to have a uniquely favorable pattern of effects on serum lipids.

- In a 6-week trial, patients switched to ziprasidone from olanzapine and risperidone demonstrated statistically significant decreases in body weight and total cholesterol.

G.1 Body Weight

There is extensive evidence that excess body weight, independent of co-existing risk factors, is associated with increased risk of numerous medical conditions, including diabetes mellitus, hyperglycemia, dyslipidemia, hypertension, cardiovascular disease, ischemic stroke, and cancer.[105] A number of surveys indicate that the prevalence of obesity among adults is increasing in the United States[106,107] and globally.[108] Compared with the general population, the population with schizophrenia has been shown to have an even higher proportion of overweight and obese individuals,[3] (see Figure 29) and the high prevalence of smoking in this population[21] is likely to exacerbate the adverse health effects of increased body weight. The relationship between obesity and cardiovascular risk, with particular reference to the population with schizophrenia is more specifically discussed in Section H.2.

The following section summarizes weight changes observed with ziprasidone from the following sources:

- Short-term, placebo-controlled trials included in the ziprasidone NDA, presented in the context of weight gain in short-term, placebo-controlled

trials of other antipsychotic drugs as described in their US Package Inserts (USPIs).

- Patients in the ziprasidone clinical development program who have participated in completed or ongoing open-label trials of at least 6 months duration.

- Study 054, an open-label assessment of the effects of ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol.

- Six-week data from three switch studies in which patients who had received other antipsychotic drug treatment for at least 3 months changed their medication to ziprasidone.

Body weight changes were analyzed in terms of mean changes from baseline as well as the incidence of body weight increases ≥7% of baseline weight. A 7% weight gain is equivalent to a gain of approximately 5 Kg in a 70 Kg individual, and is a commonly quoted standard for clinically meaningful weight gain. Patients who participated in long-term trials were also characterized according to their baseline Body Mass Index (BMI), which is calculated as weight /height^2 and expressed as Kg/m^2. In the past the National Health and Nutrition Examination Survey (NHANES) used the sex-specific 85th percentile values from the 1976-1980 survey, corresponding to a BMI of ≥27.8 Kg/m^2 for men and ≥27.3 Kg/m^2 for women, to define overweight. Baseline BMI categories of <23, 23-27, and >27 Kg/m^2 were used to characterize the weight status of patients entering the ziprasidone clinical program.[121]

G.1.1 Short-Term Trials

Table 42 summarizes the weight changes in short-term placebo-controlled trials included in the ziprasidone NDA. For comparison, the table includes data reported in US Package Inserts for short-term trials with olanzapine, risperidone, and quetiapine. In combined results from the four short-term (4-6 week), fixed-dose, placebo-controlled (STFDPC) ziprasidone trials, the mean increase in body weight relative to baseline was 0.9 Kg for all ziprasidone-treated patients; in the same trials, the mean weight loss in placebo-treated patients was 0.4 Kg. In contrast, the mean weight increase reported in short-term trials with olanzapine and quetiapine was 2.8 Kg[52] and 2.3 Kg,[109] respectively. The incidence of clinically significant weight gain (≥7% of baseline weight) in the ziprasidone STFDPC trials was greater in the ziprasidone groups (9.8%) than in the placebo groups (4.0%). Figure 27 illustrates the incidence of clinically significant weight gain in the ziprasidone STFDPC trials together with comparable data reported in the USPIs for risperidone, quetiapine, and olanzapine.

Table 42. Weight Change from Baseline in Short-Term Placebo-Controlled Trials; Ziprasidone vs. Reported Data for Other Antipsychotic Agents

	Ziprasidone*		*Risperidone^*		*Quetiapine^*		*Olanzapine^*	
Duration of placebo (Pbo)-controlled trials	4 and 6 weeks		*6 and 8 weeks*		*3 and 6 weeks*		*Up to 8 weeks*	
	Zip	Pbo	*Risp*	*Pbo*	*Quet*	*Pbo*	*Olan*	*Pbo*
Mean weight change (Kg)	0.9	-0.4	*-*	*-*	*2.3*	*0.1*	*2.8*	*-0.4*
% patients gaining ≥7% of baseline weight	9.8%	4.0%	*18%*	*9%*	*23%*	*6%*	*29.3%*	*2.7%*

* Ziprasidone clinical database.
^ Risperidone[110] quetiapine[111,112] olanzapine[52] data from their respective USPIs and FDA review documents.

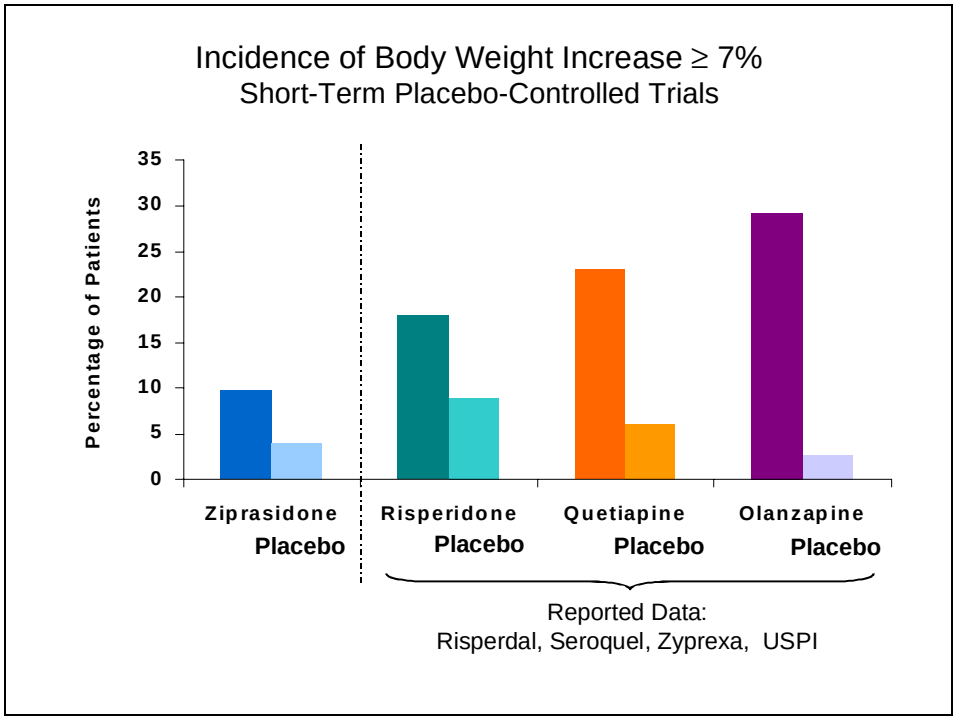


Figure 27. Incidence of Weight Gain ≥7% of Baseline Weight in Short-Term Placebo-Controlled Trials: Ziprasidone vs. Reported Data for Other Antipsychotic Agents

G.1.2 Long-Term Trials

Table 43 summarizes the weight changes for patients enrolled in long-term trials (planned duration of 6 months or longer) with active comparators. This includes data from patients in completed trials or ongoing open label or single-blind trials up to 5 February 2000. Weight changes are presented for All Patients enrolled

using a LOCF analysis as well as for the subset of patients who had received treatment for 28 weeks or longer. The mean treatment duration for these long-term patients was 83 weeks for the ziprasidone group compared with 67 and 55 weeks for the haloperidol and risperidone groups, respectively.

Table 43. Weight Change from Baseline; Long-Term Active-Comparator Trials

	Ziprasidone		Haloperidol		Risperidone	
	≥28 weeks*	All Patients**	≥28 weeks*	All Patients**	≥28 weeks*	All Patients**
Mean Treatment Duration (weeks)	83.4	46.2	66.8	39.9	54.9	42.4
Number of patients	556	1124	150	285	113	162
Mean weight change (Kg)	0.23	-0.21	1.02	0.11	3.04	2.14
± SE	± 0.40	± 0.21	± 0.57	± 0.35	± 0.73	± 0.54
Incidence of weight gain ≥7% vs. Baseline	21.8%	14.0%	22.0%	14.4%	36.3%	29.0%

Weight change from baseline to last visit, patients with baseline and on treatment weight measurement.
* Patients with at least 28 weeks on treatment.
** All patients randomized to completed or ongoing open-label, active-comparator trials with duration ≥6 months up to 5 February 2000.

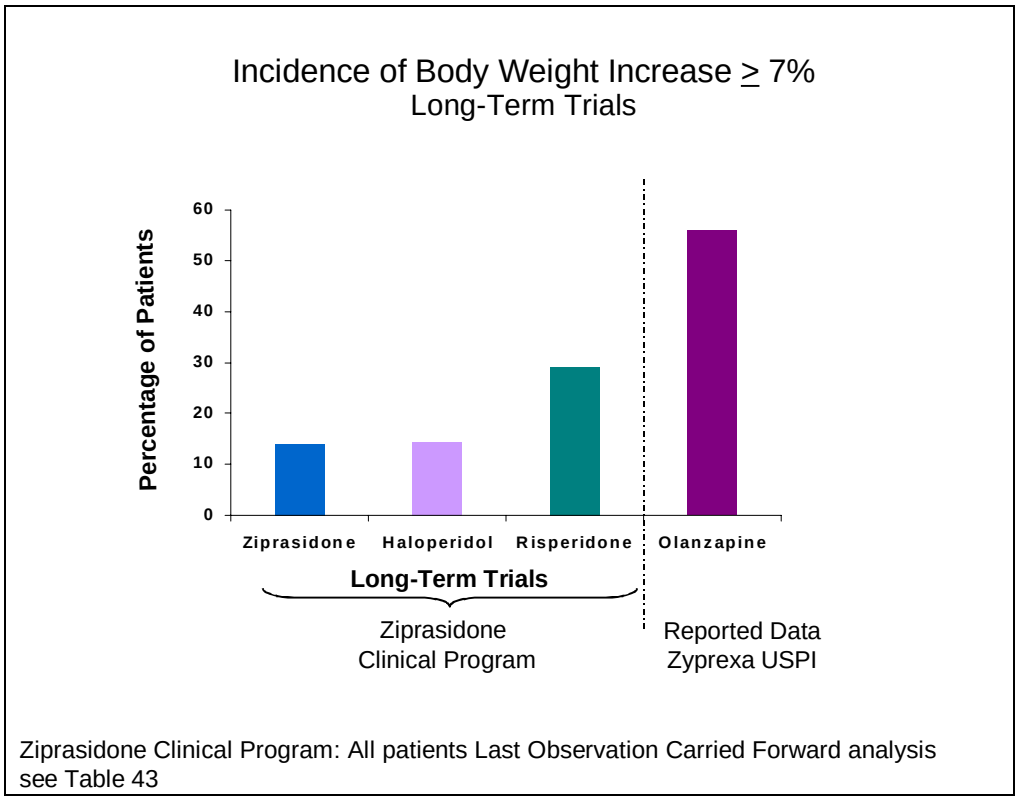
Negligible change in mean weight was observed for the ziprasidone group, whereas mean increases were observed in both the haloperidol and risperidone groups. There was little difference between the mean weight changes for the 556 ziprasidone patients who had received at least 28 weeks of treatment and the 1124 ziprasidone patients in the LOCF analysis. In contrast, patients who had longer treatment durations with haloperidol or risperidone had greater mean weight gains than those in the LOCF analyses. The incidence of clinically significant weight gain was highest in the risperidone group.

Additional information on long-term weight changes may be found in Package Inserts and Sponsors' Product Monographs for some of the atypical antipsychotic drugs (Table 44). Reported weight gain for patients on olanzapine, quetiapine or risperidone is substantially greater than that observed for patients on ziprasidone. Reported weight gain (manufacturer's Product Monograph) for patients on risperidone was comparable to the weight gain observed for risperidone-treated patients in the ziprasidone clinical program.

Table 44. Weight Change from Baseline in Long-Term Trials; Ziprasidone vs. Reported Data for Other Antipsychotic Agents

Drug	Reported Weight Gain	Source
Ziprasidone	0.23 Kg; over 6 months	See Table 43
Zyprexa (olanzapine)	5.4 Kg; median duration of exposure: 238 days	US Package Insert[52]
Seroquel (quetiapine)	5.6 Kg; over one year	Product Monograph[113]
Risperdal (risperidone)	2.3 Kg; over 6 months	Product Monograph[114]

Figure 28 illustrates the incidence of clinically significant weight gain that has been observed for treatment groups in active-comparator long-term maintenance trials (LOCF analyses). For comparison with these Pfizer-sponsored trials, the figure also includes the percentage of patients (56%) who gained ≥7% of their baseline weight during long-term continuation therapy with olanzapine cited in the USPI[52] (median duration of treatment 238 days).



Ziprasidone Clinical Program: All patients Last Observation Carried Forward analysis see Table 43

Figure 28. Incidence of Weight Gain ≥7% of Baseline Weight; Long-Term Trials

Table 45 summarizes both the mean weight change and the incidence of clinically significant weight gain in patients with BMI <23 ("low"), 23-27 ("normal") or >27 ("high"). These categories permit comparison with the published body weight data for patients on olanzapine.[115] The distribution of baseline BMI among the patients participating in ziprasidone long-term trials is noteworthy in that 44.2% (695/1571) of these patients already had a BMI >27 at entry to the trials.

For all three drug treatment groups, the greatest mean weight gain as well as the highest incidence of clinically significant weight gain occurred among patients with "low" baseline BMI, although the risperidone treatment group showed substantially greater weight gain than the ziprasidone or haloperidol groups. Among patients receiving long-term treatment with ziprasidone, there was a mean weight gain of

1.4 Kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 Kg mean weight loss for patients who entered the program with a "high" BMI (Table 45). Considerable weight gain, evidenced by both the mean weight gain (2.6 Kg) and incidence of clinically significant weight gain (33.3%), was observed for risperidone-treated patients who had "normal" BMI at baseline.

Data from the *Zyprexa Product Monograph*[115] are also included in Table 45 for comparison. Olanzapine treatment was associated with a much higher incidence of clinically significant weight gain and a greater mean increase in body weight than any of the other drugs shown, irrespective of BMI category.

Table 45. Weight Change from Baseline by Baseline Body Mass Index; Long-Term Active-Comparator Trials

		Baseline Body Mass Index								
		<23 "low"			23-27 "normal"			>27 "high"		
	N^	n	Mean Change Kg	≥7% gain %	n	Mean Change Kg	≥7% gain %	n	Mean Change Kg	≥7% gain %
Ziprasidone*	1124	295	1.4	20.7	326	-0.0	12.6	503	-1.3	10.9
Haloperidol*	285	82	2.1	25.6	78	-0.5	11.5	125	-0.8	8.8
Risperidone*	162	44	4.4	40.9	51	2.6	33.3	67	0.3	17.9
BMI Distribution at Baseline										
All Patients N	1571	421			455			695		
%	100%	26.8%			29.0%			44.2%		
From Zyprexa Product Monograph:										
Olanzapine	*887*	*297*	*6.0*	*69*	*305*	*5.7*	*58*	*285*	*4.3*	*45*

^ N = patients who had a height measurement and baseline and on-treatment weight measurements.
*ziprasidone database (all patients in completed or ongoing open-label, active-comparator trials with duration ≥6 months up to 5 February 2000).

G.1.3 Study 054

Table 46 summarizes the changes in body weight from baseline to last visit in Study 054. This was a short study with treatment durations from 15 to 25 days (differences in drug labeling regarding dose titration schedules resulted in small differences in total treatment durations for the various treatment groups). Despite the short treatment period, a substantial number of patients in the risperidone and olanzapine groups (5 patients - 19% and 6 patients - 23%, respectively) gained ≥7% of their baseline body weight. In contrast, this occurred in only 2 patients (6%) and 1 patient (3%) in the ziprasidone and haloperidol groups, respectively. Correspondingly, mean weight changes were largest in the risperidone and olanzapine groups, and smallest in the ziprasidone and haloperidol groups.

Table 46. Weight Change from Baseline; Study 054

	Ziprasidone N=34	Risperidone N=27	Olanzapine N=26	Quetiapine N=29	Thioridazine N=31	Haloperidol N=29
Mean Treatment Duration (days)	14	24	20	16	16	17
Weight (Kg):						
Mean Baseline	84.4	85.1	85.4	85.0	90.0	77.2
Mean Change	0.7	2.6	3.1	1.8	1.8	-0.2
± SE	± 0.5	± 0.6	± 0.6	± 0.5	± 0.5	± 0.4
Incidence:						
Increase ≥7% n (%)	2 (5.9)	5 (18.5)	6 (23.1)	3 (10.3)	3 (9.7)	1 (3.4)

G.1.4 Switch Studies - Patients Changing to Ziprasidone from Other Antipsychotic Drugs

The effect of ziprasidone on body weight was studied in three open-label trials conducted to evaluate clinical outcomes in patients with schizophrenia or schizoaffective disorder who changed to ziprasidone treatment from a variety of 'typical' antipsychotics such as haloperidol, chlorpromazine, thioridazine and others (Study R-0553), olanzapine (Study R-0554), or risperidone (Study R-0555). Patients were required to have been on their previous drug treatment for at least 3 months and to have had only partial response or intolerable side effects with this treatment. Primary reasons for switching, ascertained from study coordinators in a retrospective questionnaire, are listed in Table 47. For patients switching from olanzapine and risperidone, weight gain was the side effect most frequently cited as the reason for switching therapy.

Table 47. Primary Reason for Changing Antipsychotic Therapy; Switch Studies

	Patients Switched to Ziprasidone From					
	Typical Antipsychotics (Study R-0553) N=127		Olanzapine (Study R-0554) N=88		Risperidone (Study R-0555) N=41	
Primary Reason for Change	n	%	n	%	n	%
Incomplete response to prior therapy	61	48.0	33	37.5	14	34.1
Weight gain	15	11.8	32	36.4	14	34.1
Sedation	9	7.1	8	9.1	2	4.9
Persistent negative symptoms	13	10.2	6	6.8	3	7.3
Persistent positive symptoms	6	4.7	2	2.3	5	12.2
EPS	11	8.7	3	3.4	0	0
Sexual dysfunction	4	3.1	0	0	0	0
Other	8	6.3	4	4.5	3	7.3

Ziprasidone treatment was administered at flexible doses between 40 mg and 160 mg daily. Results of analyses of patients treated for up to 6 weeks in these ongoing studies are shown in Table 48. Patients switched to ziprasidone from olanzapine showed a statistically significant mean decrease in body weight of

1.79 Kg during the approximately 6 weeks following the change in treatment. The mean reduction in body weight (0.83 Kg) for patients switching from risperidone was also statistically significant, although the magnitude of the change was smaller. A mean increase of 0.17 Kg was observed in patients switched from the 'typical' antipsychotics. These observations are consistent with the low occurrence of clinically significant weight gain in ziprasidone-treated patients observed in the short-term and long-term trials. The relative weight changes across the studies also reflect the known weight gain propensities of the prior antipsychotic treatments[5] (see Table 42).

Table 48. Weight Change from Baseline; Switch Studies

	Patients Switched to Ziprasidone From		
	Typical Antipsychotics (Study R-0553) N=100*	Olanzapine (Study R-0554) N=93*	Risperidone (Study R-0555) N=45*
Mean Treatment Duration on ziprasidone after switching (weeks)	5.2	5.6	5.4
Weight:			
Mean Baseline - Kg	90.1	93.5	87.8
Mean Change - Kg	0.17	-1.79	-0.83
p-value**	0.490	<0.001	0.050

* Patients who had baseline and on-treatment weight measurements.
** p-value computed from one-sample t-test for null hypothesis: mean change from baseline = 0.

G.1.5 Conclusion

Overall, data from a number of different sources, short-term and long-term trials as well as switch studies, show ziprasidone to be "weight neutral", a profile which contrasts sharply with that of other atypical antipsychotic agents. The differences in 7% weight gain caused by these agents are noteworthy in the context of the *FDA Guidance for Clinical Evaluation of Weight Control Drugs* (September 24, 1996), which considers a 5% reduction in body weight sufficient to qualify as a study endpoint.

G.2 Serum Lipids

The effects of ziprasidone and comparator antipsychotics on serum lipids including cholesterol and triglycerides are presented below as the median changes from baseline. Results expressed as mean changes from baseline were similar. With the exception of Study 054, serum lipids in clinical trials were measured from blood samples collected at random times during protocol-specified patient visits; consequently, these do not represent fasting values. Complete lipid profiles are presented for patients in Study 054 since these were measured from blood samples collected under fasting, controlled conditions.

G.2.1 Short-Term Trials

Changes in total cholesterol and triglycerides in the STFDPC trials are shown in Table 49. All three treatment groups showed median decreases in cholesterol

values and the ziprasidone and placebo groups had median decreases in triglycerides also.

In contrast to these results, the Seroquel (quetiapine) USPI[110] notes that in short-term, placebo-controlled trials, Seroquel-treated patients had increases from baseline in cholesterol and triglycerides of 11% and 17%, respectively, compared to slight decreases for placebo-treated patients.

Table 49. Median Change in Total Cholesterol and Triglycerides; Short-Term, Fixed-Dose, Placebo-Controlled Trials

	Ziprasidone			Haloperidol			Placebo		
	N	Median Baseline	Median Change*	N	Median Baseline	Median Change*	N	Median Baseline	Median Change*
Total Cholesterol mg/dl	682	185	-3	83	200	-4	261	186	-2
Triglycerides mg/dl	681	126	-6	83	127	8	260	130	-13

Serum lipids measured from samples collected at random times.
* From baseline to last observation.

G.2.2 Long-Term Trials

Cholesterol

Table 50 summarizes median changes in serum cholesterol observed with long-term treatment with ziprasidone, haloperidol and risperidone in the ziprasidone clinical trials. The data shown are for patients who were enrolled in trials of at least 6 months duration and who had a cholesterol measurement at baseline and at Weeks 28, 40, and 52, respectively.

A decrease in median cholesterol was observed in the ziprasidone LOCF analysis and was larger than that observed with either haloperidol or risperidone. Moreover, for ziprasidone-treated patients the median decreases were consistent across the LOCF and the analyses at each time point, i.e. weeks 28, 40, and 52.

The changes in total cholesterol values in ziprasidone-treated patients in these long-term maintenance trials are of greater magnitude than were observed in the hospitalized population treated in the STFDPC trials (see Table 49).

Table 50. Median Change in Total Cholesterol; Long-Term Active-Comparator Trials

	Total Cholesterol mg/dl								
	Ziprasidone			Haloperidol			Risperidone		
	N*	Baseline	Change	N*	Baseline	Change	N*	Baseline	Change
Week 28	334	198.5	-10.0	68	203.0	2.5	81	202.0	0.0
Week 40	168	204.0	-12.0	59	201.0	1.0	3	NA	NA
Week 52	104	187.0	-10.0	0	NA	NA	51	208.0	1.0
LOCF	1009	196.0	-10.0	141	195.0	-6.0	134	206.0	-2.0

Serum cholesterol measured from samples collected at random times.
* Number of patients with baseline and on treatment cholesterol measurement in completed or ongoing open-label, active-comparator trials with duration ≥6 months up to 5 February 2000.
Weeks 28, 40, 52: All patients with a cholesterol measurement from Days 183-210, 267-294, and 351-378, inclusive; LOCF: Last Observation Carried Forward.
NA: not applicable due to small sample size.

Triglycerides

Table 51 summarizes changes in median serum triglycerides observed with long-term treatment with ziprasidone, haloperidol and risperidone. Despite the fact that these triglyceride measurements were made on randomly drawn blood samples, there is a consistent decrease in the median changes for the ziprasidone group across all timepoints. The smaller magnitude of the median changes compared with the fasting measures obtained in Study 054 (see Table 53) is thought to be attributable to the increased post-prandial variability associated with nonfasting triglyceride measurements.

Table 51. Median Change in Triglycerides; Long-Term Active-Comparator Trials

	Triglycerides mg/dl								
	Ziprasidone			Haloperidol			Risperidone		
	N*	Baseline	Change	N*	Baseline	Change	N*	Baseline	Change
Week 28	334	132.0	-5.0	68	152.5	13.0	81	134.0	-4.0
Week 40	167	138.0	-3.0	59	149.0	16.0	3	NA	NA
Week 52	104	124.0	-2.5	0	NA	NA	51	150.0	-12.0
LOCF	1008	132.0	-7.0	141	132.0	-13.0	134	150.0	-7.5

Serum triglycerides measured from samples collected at random times.
* Number of patients with baseline and on treatment triglyceride measurement in completed or ongoing open-label, active-comparator trials with duration ≥6 months up to 5 February 2000.
Weeks 28, 40, 52: All patients with a triglyceride measurement from Days 183-210, 267-294, and 351-378, inclusive; LOCF: Last Observation Carried Forward.
NA: not applicable due to small sample size.

Effect of Weight Change on Lipid Changes

The influence of weight changes on the changes in total cholesterol and triglycerides for ziprasidone shown above in Table 50 and Table 51, respectively, was investigated by modeling the relationship between lipid change and change in weight (LOCF change from baseline; adjusted for study and center effects). While a positive linear association was found between weight change and lipid change

(i.e., +1.3 mg/dl and +3.4 mg/dl increase in total cholesterol and triglycerides, respectively, for every 1 Kg increase in weight), this had little influence on the long-term lipid changes. Relative to the mean change in total cholesterol (-12.1 mg/dl) and triglycerides (-14.9 mg/dl) the mean weight change in this population was negligible (-0.3 Kg). In addition, lipid mean changes calculated without adjusting for weight change were similar to lipid mean changes adjusted for weight change (evaluated at a zero weight change) (Table 52). The favorable effect of ziprasidone upon cholesterol and triglycerides is therefore not attributable to its weight-neutral profile.

Table 52. Effect of Weight Change on Changes in Total Cholesterol and Triglycerides; Long-Term Active-Comparator Trials

	Mean Change in Random Lipid Value – Baseline to Last Visit			
	N	Not adjusting for weight change	Adjusting for weight change	Slope (SE)
Total cholesterol (mg/dl)	876	-12.1	-11.7	+ 1.3 (0.1)
Triglycerides (mg/dl)	875	-14.9	-13.7	+ 3.4 (0.4)

Mean weight change in this population was -0.3 Kg.

G.2.3 Study 054

To evaluate lipid changes under less variable conditions, fasting lipid profiles were measured at baseline and end of Study 054. The median changes from baseline to last planned visit in serum cholesterol (total, LDL, and HDL) and triglycerides are summarized in Table 53.

Table 53. Change in Fasting Lipids; Study 054

Lipids (mg/dl)	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Total Cholesterol						
N	34	28	27	29	31	29
Median Baseline	197.5	204.0	201.0	196.0	186.0	193.0
Median Change	−14.5***	−3.0	4.0	5.0	21.0***	−22.0***
Median % Change	−7.5**	−1.6	2.1	2.4	13.7***	−11.5***
LDL Cholesterol						
N	33	25	26	28	29	29
Median Baseline	122.0	125.0	128.0	117.0	121.0	121.0
Median Change	−11.0	9.0	1.5	−0.5	20.0***	−14.0***
Median % Change	−8.5	6.5	1.1	−0.3	18.6***	−10.5***
HDL Cholesterol						
N	34	27	27	29	30	29
Median Baseline	43.5	41.0	44.0	45.0	41.0	43.0
Median Change	0.0	-2.0	-2.0	-3.0	1.5	−3.0**
Median % Change	0	−4.9	−4.6	−8.6	3.0	−6.0*
Triglycerides						
N	34	28	27	29	31	29
Median Baseline	141.0	158.0	148.0	124.0	120.0	118.0
Median Change	−37.0***	−17.0	43.0***	25.0***	9.0	−18.0**
Median % Change	−28.0***	−6.7	31.0***	18.3***	7.9	−18.0**
Total Cholesterol/HDL ratio						
N	34	27	27	29	30	29
Median Baseline	4.31	5.43	5.14	4.42	4.61	4.26
Median Change	−0.33**	0.31	0.28	0.48**	0.41**	−0.22*
Median % Change	−7.5**	5.9*	5.4*	10.8**	12.4***	−7.0*

* p<0.05, **p<0.01, ***p<0.001 Wilcoxon signed rank test on change from baseline values vs. 0 and percent change from baseline values versus 0.

In contrast to the other atypical antipsychotics and thioridazine, the ziprasidone group demonstrated marked median decreases from baseline in total (-14.5 mg/dl) and LDL cholesterol (-11 mg/dl; p = 0.057), with no impact on HDL cholesterol. Haloperidol produced changes similar to those of ziprasidone in total and LDL cholesterol and triglycerides, but had an adverse effect on HDL cholesterol (median change: -3 mg/dl; p = 0.009).

There was a highly significant median decrease from baseline in triglyceride levels (-37.0 mg/dl) in ziprasidone-treated patients; in contrast, median changes in triglyceride levels in the quetiapine and olanzapine groups increased by 25.0 and 43.0 mg/dl, respectively.

Total, LDL cholesterol, HDL cholesterol, and triglyceride levels are important predictors of cardiovascular disease risk; the ratio of total to HDL cholesterol (or the log of the ratio) is a single measure which strongly correlates with cardiovascular risk. Using the total/HDL cholesterol ratio as a summary measure, ziprasidone and haloperidol treatments were associated with a significant decrease from baseline in this risk factor. Quetiapine and thioridazine, in contrast, were associated with a significant increase in this risk factor (Table 53).

G.2.4 Switch Studies - Patients Changed to Ziprasidone from Other Antipsychotic Drugs

In these 6-week studies, patients were switched from their previous antipsychotic treatment to ziprasidone therapy. Baseline values were measured at the time of switching to ziprasidone. Similar to the observations made for body weight (Table 48), a reduction in median random cholesterol was observed in each of these three patient groups after their switch to ziprasidone (Table 54). For patients switching to ziprasidone from olanzapine and risperidone the median decreases were statistically significant ($p < 0.001$ and $p = 0.005$, respectively). The median reduction in total cholesterol (nonfasting) for patients switching from a variety of "typical" antipsychotics was somewhat lower but still bordered on statistical significance ($p = 0.075$).

Table 54. Change in Total Cholesterol; Switch Studies

	Switch to Ziprasidone from		
	Typical Antipsychotics (Study R-0553) N*=82	Olanzapine (Study R-0554) N*=83	Risperidone (Study R-0555) N*=38
Random Cholesterol (mg/dl)			
Median Baseline	191.5	199.0	204.5
Median Change	-7.0	-17.0	-9.0
p-value**	0.075	<0.001	0.005

Serum cholesterol measured from samples collected at random times.
* Number of patients with baseline and on treatment cholesterol measurement.
** p-value computed from the sign test for the null hypothesis: median change from baseline = 0.

Three out of 4 patients who changed to ziprasidone from olanzapine or risperidone demonstrated a decrease in cholesterol at their final visit (Table 55).

Table 55. Total Cholesterol Change Summarized by Direction of Change; Switch Studies

	Switch to Ziprasidone from		
	Typical Antipsychotics (Study R-0553) N*=82	Olanzapine (Study R-0554) N*=83	Risperidone (Study R-0555) N*=38
	Number of Patients (%)* with Change in Cholesterol		
Change from Baseline to Last Visit			
Decrease	49 (60%)	62 (75%)	28 (74%)
No Change	1 (1%)	1 (1%)	0
Increase	32 (39%)	20 (24%)	10 (26%)

Serum cholesterol measured from samples collected at random times.
* Number of patients with baseline and on treatment cholesterol measurement.

Patients switching to ziprasidone from olanzapine and risperidone also demonstrated substantial median reductions in nonfasting triglycerides (Table 56), with the magnitude of change over the six weeks of the study being statistically significant ($p < 0.001$ and $p = 0.011$, for the olanzapine and risperidone groups, respectively).

Table 56. Change in Triglycerides; Switch Studies

	Switch to Ziprasidone from		
	Typical Antipsychotics (Study R-0553) N*=82	Olanzapine (Study R-0554) N*=83	Risperidone (Study R-0555) N*=38
Random Triglycerides (mg/dl)			
Median Baseline	154.5	206.0	171.5
Median Change	-4.0	-53.0	-24.0
p-value**	0.44	<0.001	0.011

Serum triglycerides measured from samples collected at random times.
* Number of patients with baseline and on treatment cholesterol measurement.
** p-value computed from the sign test for the null hypothesis: median change from baseline = 0.

G.2.5 Conclusion

Overall there is a substantial body of evidence that short-term and long-term ziprasidone treatment is associated with decreases in total cholesterol and triglycerides which are independent of changes in body weight. In addition, favorable effects on the total/HDL cholesterol ratio have been demonstrated in short-term treatment.

G.3 Treatment-Emergent Diabetes and Changes in Glucose Metabolism

An association between weight gain and an increased risk of diabetes has been well-documented.[116] A growing number of publications in the literature report an increased frequency of diabetes or glucose intolerance in patients treated with some atypical antipsychotics (see Section H.2.3). Additionally, the incidence of spontaneous reports to the FDA Adverse Event Reporting System of new onset diabetes mellitus, non-ketotic hyperosmolar coma, and diabetic ketoacidosis associated with atypical antipsychotics has prompted the Agency to ask sponsors for a comprehensive review of all clinical and preclinical data pertaining to hyperglycemia and diabetes.

The following sections summarize data in the ziprasidone clinical program regarding the occurrence of treatment emergent diabetes as well as changes in random serum glucose in short-term and long-term trials.

G.3.1 Diabetes

Cumulative data to 5 February 2000 (Table 57) revealed no cases of treatment-emergent diabetes mellitus in the ziprasidone group, one case in the haloperidol group (incidence 0.1%) and 2 cases in the risperidone group (incidence 0.6%).

Table 57. Incidence of Treatment-Emergent Adverse Event of Diabetes Mellitus in the Ziprasidone Phase 2/3 Clinical Program

	Ziprasidone	Haloperidol	Risperidone	Placebo
Cumulative to 5 February 2000				
Duration of Exposure, Patient -Years	1658	270	165	86
No. of Patients	3834	686	322	506
No. of Patients with Diabetes (%)	0	1 (0.1)	2 (0.6)	0

G.3.2 Glucose

G.3.2.1 Short-Term Trials

In the short-term, fixed-dose, placebo-controlled trials reported in the NDA, no median change in value for random glucose was observed in the ziprasidone group (Table 58). The incidence of clinically significant (>1.2xULN) abnormal elevations in random glucose was 8% in both the ziprasidone group and the placebo group, and 14% in the haloperidol group.

Table 58. Median Change in Random Serum Glucose; Short-Term, Fixed-Dose, Placebo-Controlled Trials

	Ziprasidone			Haloperidol			Placebo		
	N	Median Baseline	Median Change*	N	Median Baseline	Median Change*	N	Median Baseline	Median Change*
Glucose mg/dl	678	93	0	83	98	0	259	93	3

* From baseline to last observation.

G.3.2.2 Phase 2/3 Database

The overall incidence of clinically significant elevations (>1.2 x ULN) of random glucose in the ziprasidone Phase 2/3 clinical program to 5 February 2000 was 14.9% for patients receiving ziprasidone (N = 2362), compared with 12.2%, 16.3%, and 14.9% for patients receiving placebo (N = 393), haloperidol (N = 282), or risperidone (N = 134), respectively (see Table 20)

G.3.3 Conclusions

There is no evidence from short-term or long-term trials that ziprasidone treatment is associated with alterations in glycemic control.

G.4 Summary

Ziprasidone is differentiated from other atypical antipsychotics by a body weight-neutral profile in long-term treatment and by a beneficial effect on the serum lipid profile. Data from short-term and long-term trials in the NDA database indicated that ziprasidone-treated patients had a lower incidence of clinically significant weight gain than patients receiving other antipsychotics. The "weight neutral" profile of ziprasidone is further supported by the observations that patients with low BMI tend to increase body weight slightly, and those with high BMI tend to reduce weight slightly. Subsequently (in Study 054 and switch studies), ziprasidone was shown to decrease total cholesterol, triglycerides, and the total cholesterol/HDL ratio in contrast to other atypical agents which tended to increase these cardiovascular risk factors. In addition, there is no suggestion of any relationship between ziprasidone treatment and alterations in glycemic control, including the development of diabetes as has been reported for other antipsychotic agents (see Section H.2.3).

Because therapy of patients with psychotic disorders requires chronic treatment, the contrast between the lipid lowering effects and weight neutrality of ziprasidone and the adverse lipid effects and weight gain observed with the other atypical antipsychotic drugs has significant implications for the global, long term health of individuals with schizophrenia. Lipid elevations can be managed through diet, exercise and use of lipid-lowering agents. This approach, however, is problematic in this patient population due to their impaired access to nonpsychiatric healthcare and poor compliance. The public health consequences of increased lipids that are likely to be untreated or suboptimally managed are clear, and are only further amplified by putative associations between antipsychotic therapy and diabetes. Ziprasidone provides a treatment option that appears to be free of these liabilities.

H. CLINICAL SIGNIFICANCE OF THE FAVORABLE EFFECT OF ZIPRASIDONE ON BODY WEIGHT AND SERUM LIPIDS

H.1 Introduction

Serum lipid levels (total cholesterol, HDL cholesterol, and triglycerides) and body weight are cardiovascular risk factors with well-established effects on medical outcome. Ziprasidone can be distinguished from several currently approved antipsychotic drugs by its effects on these important risk factors.

In the following sections we describe first the distribution of risk factors in the target population, and the impact of approved therapies on those risk factors. The relevant literature on the risk associated with changes in total cholesterol, triglycerides (see Section H.5), and body weight (see Section H.6) is then summarized. Consensus risk estimates are available for unit changes in total cholesterol, triglycerides, and body weight as a result of the consistency of their causal relationship with a variety of clinical presentations of atherosclerosis. The predicted effect of ziprasidone on cardiovascular disease (CVD) risk follows.

It should be noted that the risks associated with changes in cholesterol and weight apply not only to cardiovascular disease mortality as described above, but also to other more common morbid presentations of atherosclerosis as well as metabolic syndromes such as insulin resistance, diabetes and hypertension. Hence, using only CVD mortality presents a conservative (under) estimate of the absolute impact of lipid and weight changes.

H.2 Cardiovascular Risk Factors in Patients with Schizophrenia Compared with the General Population

H.2.1 Smoking

Among patients with schizophrenia 70 - 90% smoke, compared to 25% of the general population.[21,117] This high prevalence of smoking has been observed in inpatients[118] and outpatients,[22] as well as patients reporting with their first schizophrenic episode.[119] Furthermore, smoking cessation programs have a low success rate in this population.[120]

H.2.2 Obesity and Dyslipidemia

Obesity in the general US population continues to increase, from already high levels.[121] Results from the National Health Interview Survey (1989)[122] support the prevailing clinical impression that obesity is more prevalent in the population with schizophrenia than in the general population with data that show that the proportion of patients with a high BMI (>27), is even greater among patients with schizophrenia (42%) than the general population (27%). Figure 29 displays the BMI distributions of the general population and the subset of individuals with

schizophrenia for the 1989 NHIS sample. Similar proportions of patients with BMI >27 were enrolled in the olanzapine and ziprasidone clinical development programs (see Table 45).

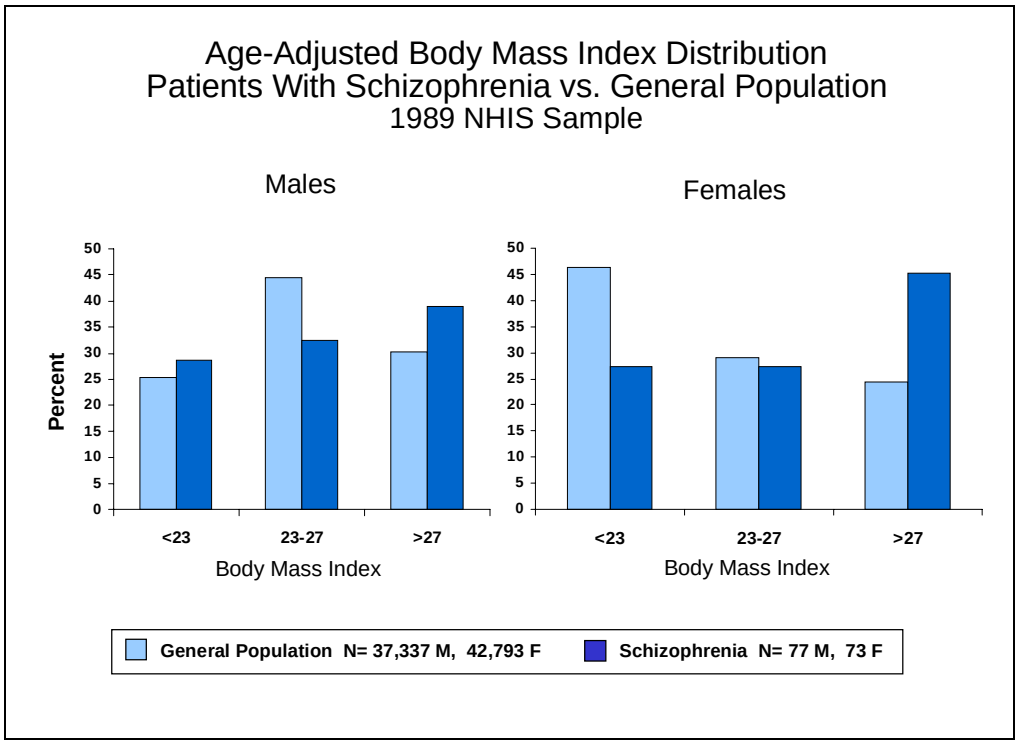


Figure 29. Age-Adjusted BMI Distributions for Males and Females with and without Schizophrenia

The prevalence of obesity in the population with schizophrenia is likely to be increased by treatment with antipsychotic medications. In a study of institutionalized psychiatric patients, 23% of males and 21% of females who were not receiving any antipsychotic medication were found to have body weight equivalent to the upper 15th percentile of a nonpsychiatric reference population. This increased to 32% of males and 38% of females who had been treated with neuroleptics (mainly haloperidol, thioridazine, fluphenazine) during the prior 2 years.[20] Importantly, the excess weight in patients treated with antipsychotic medications is more likely to be distributed as abdominal fat, which appears to be an independent risk factor for ischemic heart disease.[105,123,124,125,126] There is also increasing evidence that treatment with some of the newer generation of antipsychotic drugs, most notably clozapine and olanzapine results in substantial weight gain.[4,5,127,128] Mean weight gain of as much as 12 Kg at 1 year has been reported in patients treated with olanzapine at the higher recommended doses.[129]

Antipsychotic medications may also be associated with increased dyslipidemia. Recent evidence from a number of studies document clinically important increases in triglycerides with clozapine[130, 131, 132] and olanzapine[133] and increases in cholesterol have been reported with quetiapine.[110] One author reports severe hypertriglyceridemia (>600 mg/dl) in 2 patients on quetiapine and 11 patients on olanzapine, 3 of whom also developed new-onset diabetes.[134]

The molecular mechanisms responsible for the adverse profile of some antipsychotic drugs on lipids and weight have not yet been well investigated, but a recent report by Kikuoka[135] has implicated decreased lipoprotein lipase activity as a cause for hypertriglyceridemia with clozapine. Increased leptin levels have been found associated with weight gain on clozapine and olanzapine.[136]

H.2.3 Diabetes

The medical implications of weight gain and obesity include an increased risk of developing diabetes mellitus and its associated clinical complications. Even moderate obesity is associated with risk — among participants in the Nurses Health Study, a 16-fold increase in the relative risk of developing non-insulin-dependent diabetes mellitus (NIDDM) was found among individuals with a BMI between 27 and 28.9.[137]

The implications for this population are particularly significant, as increased prevalence of diabetes has long been noted in patients with schizophrenia.[16,138,139,140,141,142] The two databases described in Section A.1.1 showed a relative risk incidence of diabetes for patients with schizophrenia of 1.6 ($p<0.01$; Saskatchewan Health Database) and 2.7 ($p<0.001$ United HealthCare). Evidence that antipsychotic drug treatment may cause or contribute to glucose intolerance has been reported for chlorpromazine,[138,140,143,144,145,146] loxapine and amoxapine,[147] and supported by preclinical observations.[148] More recently, clozapine therapy has been linked to hyperglycemia, new onset diabetes and diabetic ketoacidosis[149,150,151,152,153,154,155,156,157] with average annual incidence rates of nearly 10% described:

Henderson *et al.*[157] described 82 patients, each followed over a 5-year clozapine treatment period. At least one elevated fasting blood sugar ($\geq$126 mg/dl) was observed in 67%, and a diagnosis of new onset diabetes was made in 37% of patients.

Casey[156] reported on 29 patients treated with clozapine (mean duration 3.6 years), and 136 patients treated with olanzapine (mean duration 1.4 years). During treatment, conversion from normal ($\leq$110 mg/dl) to abnormal fasting glucose was noted in 38% of clozapine- and 18% of olanzapine-treated patients.

This cluster of literature reports has been summarized by a FDA Medical Reviewer at the 1999 Endocrinology meeting,[158] and reviewed.[159] Olanzapine, as well as

clozapine, has been linked to glucose intolerance[155,156,160,161,162,163,164,165,166,167] and reports of an association between quetiapine[163,168] and diabetes have also emerged. Even more recently, the FDA's Division of Neuropharmacologic Drug Products, in response to an apparent increase in spontaneous reports of glucose intolerance during treatment with antipsychotic agents, has asked sponsors of these drugs for a summary of relevant preclinical and clinical data.

It has been suggested that the increase in diabetes risk in clozapine-treated patients with schizophrenia is not adequately explained by weight gain alone, implicating suppression of insulin release, insulin resistance or impairment of glucose utilization as potential factors.[157,158,169] Regardless of mechanism, the implications for patients suffering from schizophrenia may be profound, particularly in view of the suboptimal health care and self-care which may be associated with this illness.

In contrast, the ziprasidone clinical database reveals no suggestion of an association with diabetes.

H.2.4 Conclusions

Risk factors for CVD in the general population are well defined and evidence exists for the increased prevalence of these risk factors in the population with schizophrenia. Though often understated, risk factor reduction or prevention are important interventions in a young population as well as in those older adults generally evaluated for such risks. A review of 204 autopsies on young adults (mean age 21 years) in the Bogalusa Heart Study found a significant correlation between the extent of atherosclerotic lesions and a history of cigarette smoking, body mass index, blood pressure, and concentrations of total cholesterol, LDL cholesterol and triglycerides.[170] Of particular relevance to the population with schizophrenia, the presence of multiple risk factors was associated with the most striking pathology, and an 8- to 12-fold increase in risk of coronary artery fatty streaks and fibrous plaques. Consequently, a quantitative analysis of lipids and weight change in patients with schizophrenia is an important component of complete medical care, from young adulthood, when therapy is often initiated.

H.3 Access to Health Care

The effect of ziprasidone upon serum lipids is quite different from the effects of other widely used antipsychotic agents, effects which should be kept in mind when considering the long term management of patients with psychosis. One option available to the prescriber of an antipsychotic drug which adversely affects lipids is to supplement this agent with lipid-lowering treatment, in an attempt to reduce cardiovascular risk in individuals who meet appropriate criteria. While this approach might seem logical for the general population (drug interaction issues aside), changes in cardiovascular risk are likely to be overlooked by physicians who may be primarily concerned with treating the psychotic condition. Redelmeier

et al.,[18] have demonstrated that patients with psychosis are in fact only one fourth as likely to receive treatment for hyperlipidemia as the general population, even when pharmacotherapy is free. Patients with schizophrenia also appear to receive suboptimal care following myocardial infarction, with a cardiac catheterization rate less than half that of non-schizophrenic patients.[19] Explanations for these findings may include poor compliance (see Section H.4), lack of insight and uncooperativeness associated with the psychiatric illness, unfamiliarity of psychiatric health care providers with management of medical illness, and reduced access to medical care due to socioeconomic factors.[171] The impact of compromised medical care is further amplified in this population by the prominence of other cardiovascular risk factors, including tobacco and alcohol use.

In addition, many antipsychotic agents are associated with weight gain, sometimes to a profound degree. This effect on body weight is particularly problematic in a population in which obesity is already overrepresented,[122] and for whom behavioral weight management interventions are frequently unsuccessful.[5] The association of some atypical antipsychotic agents with new onset glucose intolerance raises even more important questions concerning the burden imposed by antipsychotic pharmacotherapy.

In summary, there is evidence that

- currently available antipsychotic treatments adversely affect body weight, serum lipids and glucose tolerance,
- patients with schizophrenia experience a significant alteration of important cardiovascular risk factors as a result, and
- this population is particularly unlikely to receive successful risk factor intervention.

H.4 Compliance

Patients are less likely to comply with a treatment regimen that results in body weight gain. This has been reported in association with oral contraceptive use, where women who experienced weight gain were found to be 40% more likely to be noncompliant than those who did not experience this adverse effect,[172] as well as in patients treated with tricyclic antidepressants. In the latter group, although the degree of weight gain was less than what is often described in patients receiving antipsychotic therapy, Berken reported that "excessive weight gain was the most common cause of discontinuation of treatment, occurring in one-half of the patients".[173]

With regard to antipsychotic medication, a patient's subjective experience has been linked to compliance, clinical outcome, quality of life, suicidal behavior, and comorbid drug abuse.[174] Noncompliance is frequently cited to be a consequence of weight gain induced by antipsychotic treatment,[175,176] consistent with the

observation that "obesity often poses serious psychosocial problems, which is probably the main reason for noncompliance to treatment regimens that induce bodyweight gain".[177] Weiden[178] and Allison and Mackell,[179] have also reported an inverse correlation between weight gain and quality of life measures. In studies designed to assess the outcome of various switching strategies for stable outpatients who wished to switch from olanzapine or risperidone to ziprasidone, a retrospective assessment of reasons for switch was undertaken. Weight gain was cited as the primary rationale for switching in 34% (14/41) of patients switching from risperidone and 36% (32/88) of patients switching from olanzapine (see Table 47). Finally, hospital resource utilization has been linked to compliance attitudes in this population,[180] supporting the hypothesis that patients who are distressed by the adverse effects of their drug treatment are more likely to experience consequences of noncompliance, reflected in higher resource utilization.

H.4.1 Impact Of Weight Gain Associated With Antipsychotics: Results From A Patient Survey

With older, typical antipsychotic agents, side effects, such as EPS, have been shown to predict non-compliance.[181] However, the impact of weight gain, a frequently associated side effect of some atypical agents, has not been similarly evaluated.

Results of a survey of patients with schizophrenia, conducted among members of the National Alliance for the Mentally Ill (“NAMI”) and the National Mental Health Association (“NMHA”), help to elucidate the impact of antipsychotic-associated weight gain on the subjective experience of patients with schizophrenia, and shed light on the impact of weight gain on treatment compliance. Key findings of the survey regarding weight gain include the following:

- Body weight is important to a significant percentage of treated patients, with many patients reporting dissatisfaction with their weight.
- Weight gain associated with antipsychotic treatment is prevalent among those surveyed, and the reported incidence of weight gain is higher than that reported for several other side-effects typically associated with antipsychotic medication, including extrapyramidal symptoms (EPS) and sedation.
- A non-compliant attitude and general psychological distress occur more frequently in patients who have recently gained weight than in those who have not.
- As a reason for switching from atypical antipsychotics, weight gain is surpassed only by lack of efficacy.

- A higher incidence of self-reported non-compliance and citation of weight gain as a reason for discontinuing antipsychotic treatment are associated with obesity (body mass index > 30).

These findings suggest that weight gain is a significant problem for patients with schizophrenia, particularly for those taking newer antipsychotics. Beyond its impact on physical health, weight gain may negatively affect treatment compliance, contribute to depressive symptoms or demoralization, and influence general psychological well-being. Because of its potentially wide-ranging impact, weight gain warrants closer attention by treating physicians.

H.4.1.1 Survey Overview

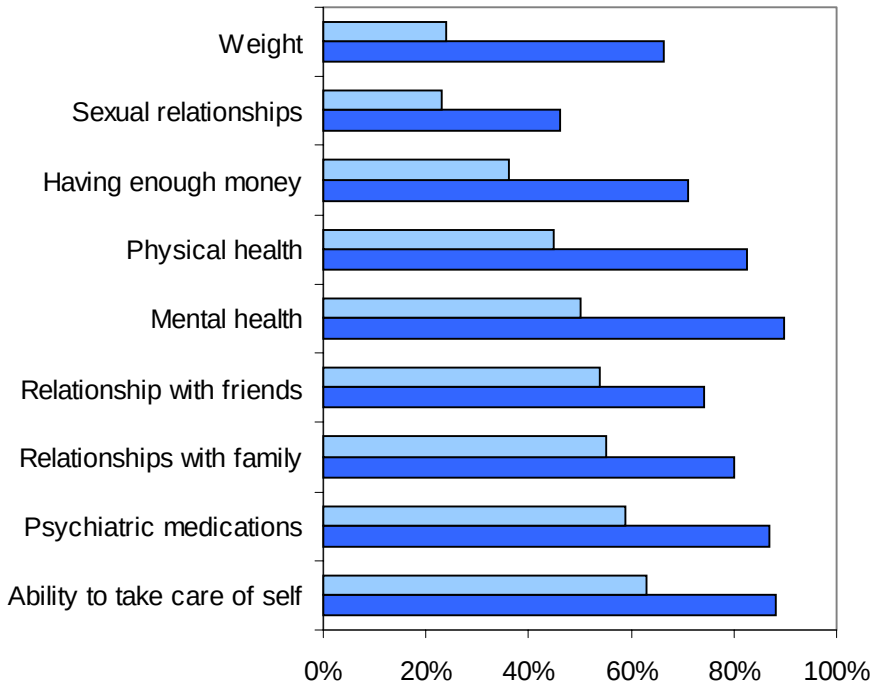
Consumer Health Sciences (CHS), an independent healthcare information organization, oversaw the development of a health questionnaire, designed in consultation with an expert advisory panel. The primary purpose of the CHS Schizophrenia Project, which is on-going, is to better understand the healthcare attitudes and behaviors of patients with schizophrenia. Individuals and caretakers are contacted through chapters of both the National Alliance for the Mentally Ill (NAMI) and the National Mental Health Association (NMHA). The self-administered questionnaire includes inquiries regarding general health, overall quality of life, current prescription medications, body weight changes, and general attitudes and opinions regarding health care. The survey also includes the following validated self-rating scales: a modified version of the Drug Attitude Inventory (DAI)[182,183] and the Psychological General Well-Being Index (PGWB).[184,185] The former addresses patient attitudes towards medication and several dimensions of subjective experience, and the latter addresses general psychological well-being. Following an initial trial mailing, the questionnaire was sent to a cohort of patients with schizophrenia ("Wave 2;" Number of respondents = 438).

As only patients currently taking antipsychotic medication were included in the data presented here, this sample is likely to represent a more compliant group than the general population of patients with schizophrenia, and may therefore reflect a conservative estimate of attitudes and behaviors that influence compliance. Not all of the total number of questionnaire respondents answered all questions, and thus subsets (n) are noted below corresponding figures.

H.4.1.2 Results

Patient Attitudes Toward Weight

Patients were asked to rate the importance of specific aspects of their life, as well as the degree of satisfaction with each. Patients rated their body weight as being almost as important as their financial status. Notably, while a majority of patients rated body weight as being important, only 24% reported being satisfied with their weight. Of all aspects of life surveyed, the greatest discrepancy between importance and satisfaction was with body weight (Figure 30).



Of the total number of respondents to the survey (N=438), the numbers of patients responding to "Satisfied" and "Important" in each category were: Weight, 423/382; Sexual relationships, 401/369; Having enough money 418/383; Physical health, 413/379; Mental health, 422/385; Relationship with friends, 418/388; Relationships with family, 415/375; Psychiatric medications, 419/383; Ability to take care of self, 422/384.

Figure 30. The Importance Of and Satisfaction With Different Aspects of Life: Percentage of Patients who Responded to "Satisfied / Important"

Frequency Of Weight Gain Compared With Other Side-Effects

In order to understand the relevance of weight gain experienced by patients with schizophrenia in the context of other medication-associated events, patients were asked about the frequency with which they experienced certain side-effects in the previous month and the degree to which these side effects were bothersome or upsetting to them.

Among the 105 patients who were taking typical antipsychotics as well as among the 238 patients who were taking atypical antipsychotics, the proportion of patients reported weight gain as occurring "frequently" during the previous month was greater than the proportion reporting frequent occurrence of any other side-effect (Figure 31). Patients taking atypical agents reported weight gain more frequently than those taking typical agents.

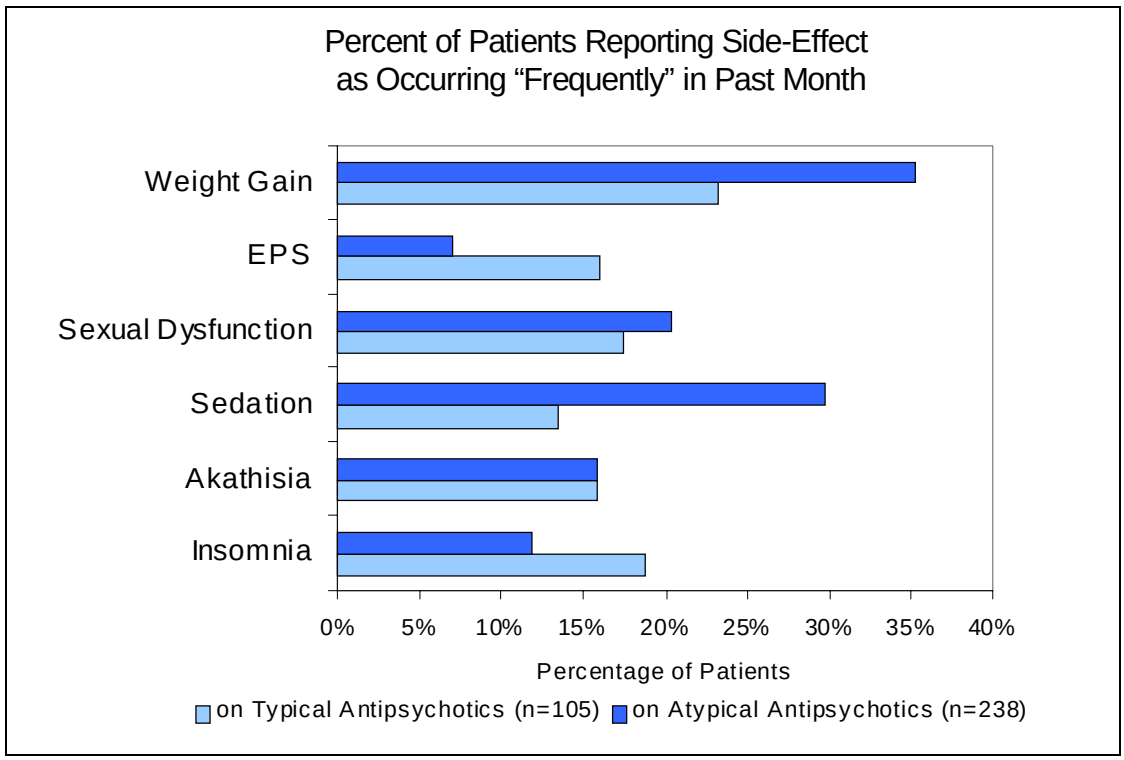


Figure 31. The Percentage of Patients on Typical, or Atypical Antipsychotics who Reported the Side-Effect as Occurring "Frequently" in the Previous Month

Association Between Weight Gain And Compliance Attitude And Psychological Well-Being

The frequency of weight gain also appeared related to patient attitudes toward treatment and overall psychological well-being as measured by the DAI. The DAI assesses a patient's compliance attitude over the previous month and provides a composite index of the subjective experience of the overall efficacy and tolerability of medication. Patients who reported weight gain in the previous year were more likely to be classified as having a non-compliant attitude, than those who did not report weight gain (scores range from -10 to 10; non-compliant represented a score of -10 to 0; somewhat compliant a score of 1 to 6; and very compliant a score of 7 to10). (Figure 32).

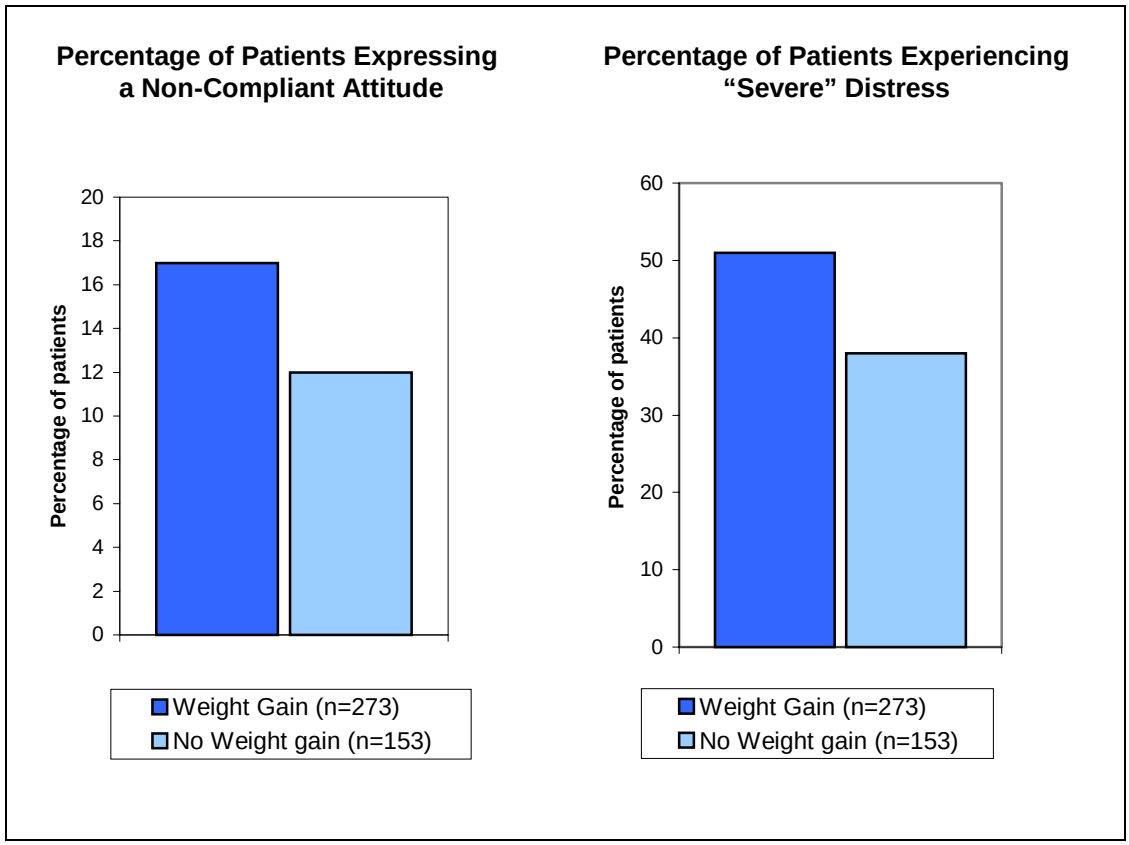


Figure 32. Patients' Compliance Attitudes (per DAI) and Psychological Well-Being (per PGWB) According to Weight Gain Experience in the Previous Year

In addition to the assessment of compliance attitudes and psychological well-being, patients were asked if they had switched their antipsychotic medication in the past 6 months, and to state the reason for the switch. Of the 438 respondents, 115 reported switching antipsychotic medication in the previous 6 months. Figure 33 shows the reasons for switching quoted by the subsets of these patients who were taking typical (n = 37) and atypical (n = 45) antipsychotic agents. While lack of treatment efficacy was overall the most common reason cited for switching, nearly 30% of patients on atypical agents cited weight gain as a reason for switching.

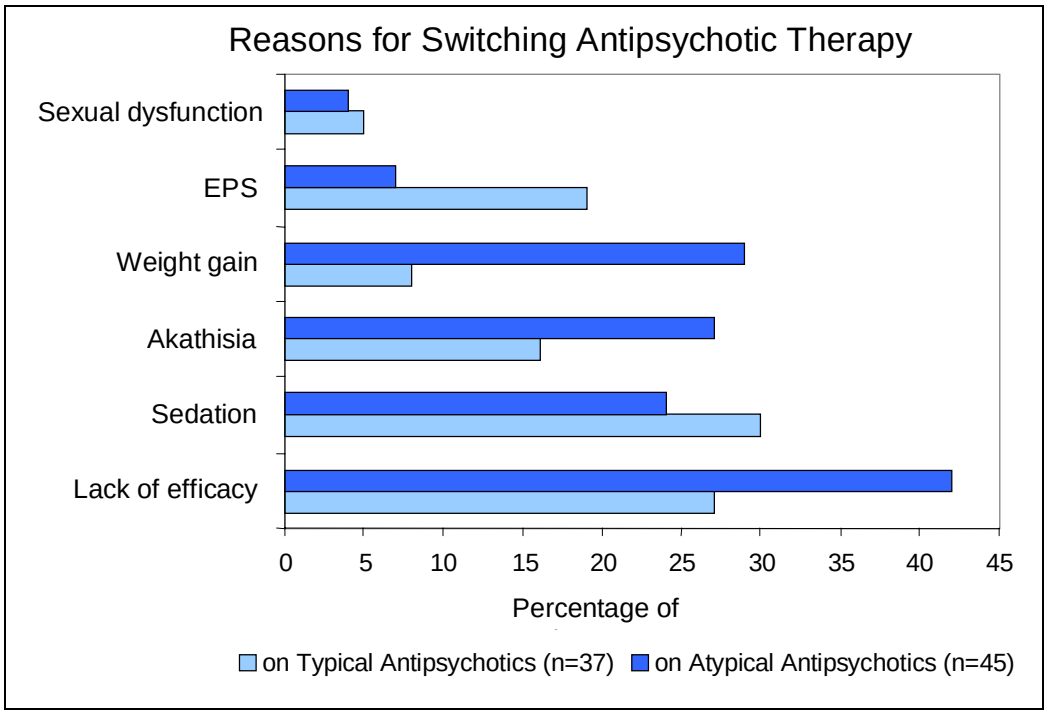


Figure 33. Reasons for Switching Medication in the Last 6 Months cited by patients on Typical and Atypical Antipsychotic Agents

Body Mass Index And Compliance With Antipsychotic Medication

As part of the ongoing CHS Schizophrenia Project, 277 patients with schizophrenia responded to a survey concerning body weight and compliance. In this survey, an association between a BMI > 30 (clinically equated to obesity) and a higher incidence of self-reported non-compliance was observed. Furthermore, weight gain was more frequently cited as a reason for discontinuing antipsychotic treatment in patients with higher BMI's (Table 59).

Table 59. Body Weight and Compliance with Antipsychotic Medication

	Missed Taking Antipsychotic Medication: How Often		
BMI	Ever	Never	*(n)*
NORMAL (<25)	26%	74%	62
OVERWEIGHT (25-30)	39%	61%	88
OBESE (>30)	47%	53%	89

	Stopped Medication Due to Problems with Weight Gain		
BMI	Yes	No	*(n)*
NORMAL (<25)	0%	100%	15
OVERWEIGHT (25-30)	20%	80%	25
OBESE (>30)	48%	52%	23

* No other significant differences were found between BMI and other reasons for stopping medications.

H.4.1.3 Survey Conclusions

This large patient survey provides cross sectional data on the association between weight gain and subjective response in a sample of patients with schizophrenia complying with drug therapy at the time of survey completion. In this sample, weight gain was prevalent and distressing to those who experienced it. Not surprisingly, weight gain was more widely reported by patients prescribed atypical agents than those prescribed typical antipsychotics. This finding is consistent with literature reports of weight gain liabilities associated with antipsychotic agents.[186]

The importance placed on weight, the accompanying poor compliance attitudes, and the need to switch medications as a result of antipsychotic-induced weight gain, all suggest weight gain's potential for adverse impact on treatment adherence and outcome. The association between a BMI > 30 (clinically equated to obesity) and a higher incidence of self-reported non-compliance, as well as the citation of weight gain as a reason for discontinuing antipsychotic treatment in patients with higher BMI's, reinforce these observations.

Recognizing the known obstacles to obtaining treatment for patients with schizophrenia, and the difficulties which challenge the physician who manages these patients, it is imperative that those factors which contribute to non-compliance with drug regimens be identified and understood. As previously noted, a patient's subjective experience with antipsychotic medication influences multiple aspects of treatment. Whether the impact of this negative experience manifests as treatment non-compliance, increased levels of negative or depressive symptoms, or some other impairment of function or rehabilitation is the subject for further study. However, it appears that the prominent side-effect of weight gain associated with several of the atypical antipsychotic agents raises the

risk of noncompliance in this population, with potential consequences for efficacy in addition to the direct impact on physical health.

H.4.2 Additional Implications of Non-Compliance in Patients with Schizophrenia

In the population of patients with schizophrenia, issues of compliance go beyond those associated with adherence to antipsychotic drug regimens. Although weight gain and hyperlipidemia may be viewed as modifiable risk factors, achieving sustained weight loss by diet alone is extremely difficult, even in the general population.[105,187] Consequently, adherence to diet to achieve lipid control and weight loss is unlikely to be successful in the population with schizophrenia, where compliance with treatment is a recognized problem.[157] This is supported by observations of weight gain in clinical trials that included weight management programs.[5]

Moreover, compliance with medical care in general may be compromised, a situation compounded by the fact that, in patients with schizophrenia, nonpsychiatric health risks are underappreciated and inadequately addressed, and socioeconomic downward drift creates in many a formidable obstacle to adequate medical care. Consequently, consideration should be given to risk factor prevention as well as reduction. Predictors of cardiovascular disease must be an important component of the global long-term health risk assessment of patients with schizophrenia, and the cardiovascular risk properties of individual antipsychotic drugs should be taken into account when assessing treatment options.

H.5 Lipid and Lipoprotein Effects

Reductions in total cholesterol have been documented in short- and long-term trials with ziprasidone, and in switch studies of patients switching to ziprasidone from other antipsychotic treatments. In addition, fasting lipid profiles were measured in Study 054. All of these studies showed a very consistent pattern of changes for ziprasidone and other antipsychotics, which are described in Section G.2.

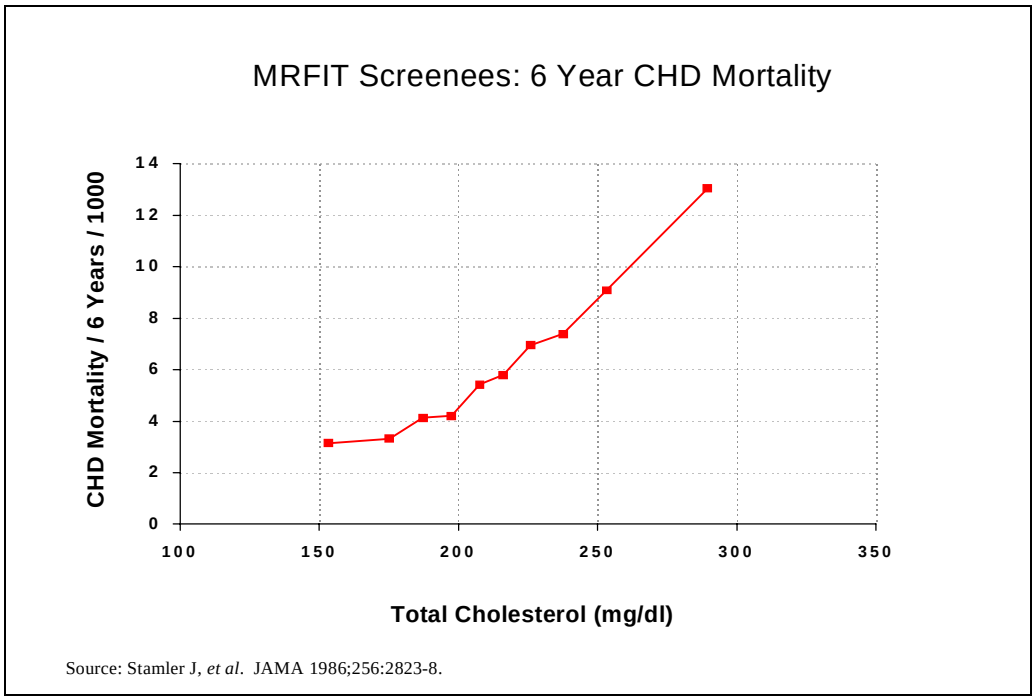
The following sections briefly summarize:

- evidence for the relationship between lipid levels and cardiovascular disease;
- based on data from the literature, the estimated changes in relative risk of cardiovascular disease that can be expected with the changes in total cholesterol and triglyceride levels observed with ziprasidone.

H.5.1 Total Cholesterol and CVD Risk

The relationship between cholesterol and clinical manifestations of atherosclerosis (including coronary heart disease, ischemic stroke, peripheral vascular disease) is well established.

Observational epidemiologic studies have demonstrated that increased total cholesterol levels are associated with an increased risk of coronary heart disease (CHD).[188] Coronary risk rises progressively with an increase in cholesterol level, even in populations with low levels[189] but especially when cholesterol levels rise above 200 mg/dl.[190] Figure 34 shows the relationship between total cholesterol levels and adjusted mortality rates due to coronary heart disease in 361,662 men screened for the Multiple Risk Factor Intervention Trial (MRFIT).[190]



Source: Stamler J, *et al*. JAMA 1986;256:2823-8.

Figure 34. Relationship between Total Cholesterol Levels and CHD Mortality in Men Screened for the Multiple Risk Factor Intervention Trial

Since the introduction of HMG-CoA reductase inhibitors (statins), the beneficial effects of cholesterol reduction have also been consistently demonstrated in randomized trials. Both secondary prevention trials (involving subjects with known coronary artery disease)[191,192,193] and primary prevention trials (involving subjects without evidence of coronary artery disease)[194,195] provide strong evidence of the benefits of cholesterol lowering in the reduction of major coronary events (fatal coronary events or nonfatal myocardial infarction), cerebrovascular events, and total mortality.

With respect to the magnitude of the reduction in coronary disease that can be achieved with cholesterol lowering, for each 10% decrease in elevated cholesterol level, there is a 20 to 30% decrease in risk of coronary disease.

It is important to point out that the effects of cholesterol increases begin to appear almost immediately; decreased vascular reactivity can be observed following a high fat meal, and functional changes in coronary flow can be demonstrated in months.[196] Analysis of 28 randomized controlled trials which investigated the effect of decreased serum cholesterol on the incidence of ischemic heart disease and which had a combined enrollment of nearly half a million men showed that the beneficial effect of reduced cholesterol is demonstrable within 1-2 years and appears to reach a plateau after 5 years (Table 60).[197] More recent findings with cholesterol lowering in women have demonstrated a similar relationship.[191]

Table 60. Reduction in Ischemic Heart Disease in Men for Each 10% Reduction (0.6 mmol/l) in Total Cholesterol According to Time in Trial

	% Reduction in Ischemic Heart Disease* Time since entry to trial		
	<2 yrs	2.1-5 yrs	5.1-12 yrs
All drug trials	10	21	22
All diet trials	9	14	37
No IHD at entry	11	25	24
IHD at entry	6	20	26
All trials (95%CI)	7 (0-14)	22 (15-28)	25 (15-35)

*Ischemic Heart Disease includes CHD death and nonfatal MI.

The 14.5 mg/dl cholesterol reduction observed with ziprasidone in Study 054 is consistent with that observed in the ziprasidone treatment groups in long term clinical trials (ranging from –12.0 to –10.0 mg/dl across weeks 28 to 52) as well as that observed after 6 weeks of ziprasidone treatment in patients switched from other antipsychotic drugs (–17.0 to –7.0 mg/dl) (see Table 50 and Table 54). Therefore, in clinical use, the effects of ziprasidone on total cholesterol are projected to potentially reduce the risk of CVD. By contrast, the cholesterol-raising effects of thioridazine, quetiapine, and possibly olanzapine, imply an increased risk.

H.5.2 Triglycerides and CVD Risk

The role of triglycerides as a risk factor in coronary artery disease is being increasingly recognized.[198] Evidence from the Physicians Health Study reveals elevated triglycerides to be an independent risk factor for myocardial infarction, with a significant multiplicative interaction between triglyceride levels and total cholesterol.[199] The metabolic interplay between triglyceride-rich and cholesterol-rich lipoproteins suggests both direct and indirect mechanisms by which elevated triglyceride levels could enhance atherothrombogenicity of these particles.[200] Direct effects include enhanced levels of atherogenic remnant lipoproteins (chylomicron and very low density lipoprotein [VLDL] remnants) that

may be taken up by peripheral tissues. In addition, hypertriglyceridemia is associated with abdominal obesity and an insulin-resistant state.[201] Indirect effects include remodeling of LDL particles to a preponderance of atherogenic small, dense LDL that are susceptible to oxidation.

While the balance of evidence strongly supports an independent role of triglyceride levels in atherogenesis, its quantitation has been problematic because of the strong inverse relationship between triglyceride levels and HDL cholesterol. The best estimate available for the magnitude of the association between triglyceride levels and cardiovascular disease is provided in a recent meta-analysis of 17 epidemiologic studies which included a total of 46,413 men and 10,864 women followed for 3-15 years.[202] Both fatal and nonfatal CVD endpoints were included but most studies focused on CHD death and nonfatal MI. The overall estimates associated a 1 mmol/l (88 mg/dl) increase in triglyceride with an increased risk of cardiovascular disease of 32% in men and 76% in women. A multivariate analysis limited to those studies that included HDL cholesterol as a covariate, showed that even when HDL and other risk factors (including total- and LDL cholesterol, smoking, BMI, and blood pressure) were taken into account, the overall increased risk for both men (14%) and women (37%) remained statistically significant.

Applying the average of the values for men and women in the multivariate analysis adjusting for HDL cholesterol and other risk factors, an increase in CVD risk of 25% for every 88 mg/dl (mmol/l) of triglyceride elevation, would be predicted. The median reduction in fasting serum triglycerides observed in Study 054 was 37 mg/dl (0.4 mmol/l) in the ziprasidone group, which compares favorably to each of the other five treatments in the trial.

H.5.3 Summary of CVD Risks Associated with Lipids and Lipoproteins

Because cardiovascular risk assessment is important in addressing the global long-term health status of patients with schizophrenia, all drug-induced changes in these variables are important. The rigorous evaluation of lipids conducted in Study 054 provides the best available information on antipsychotic effects on lipids. Decreases in total cholesterol and triglycerides observed with short-term ziprasidone treatment in Study 054, but supported as well by observations in long-term clinical trials, suggest that CVD risk will be improved in the long-term and will contrast with the potential adverse effects of quetiapine, olanzapine and thioridazine.

H.6 Obesity, Weight Gain and Health Risks of Ziprasidone Compared with Other Antipsychotic Drugs

H.6.1 Review

A dramatic rise in obesity is evident in Western societies.[203] In the period from 1980 to 1995, the proportion of the adult population considered obese (BMI >30)

has increased from 12 to 20% in men and 16 to 25% in women in the US and from 8 to 15% overall in Britain. In the US, 77,000 of 407,000 deaths from CHD and 60% of diabetic deaths can be attributed to obesity.[204]

The relationship between health risks and obesity has been reviewed by the National Heart Lung Blood Institute (NHLBI) Obesity Expert Panel.[105] Their summary supports a causal relationship between obesity and hypertension, dyslipidemia, type 2 diabetes, CHD, stroke, all-cause mortality, selected forms of cancer, gall bladder disease, osteoarthritis, sleep apnea and respiratory problems.

The potential improvement in health associated with weight loss has been difficult to substantiate in clinical trials because of the lack of efficacious intervention. One recent report from the Swedish Obese Subjects (SOS) trial provides dramatic evidence of the rapid improvement in CVD risk factors that can occur with sustained (via gastric banding) weight loss.[205] An interim report of the first 1690 patients at 2 years showed that the mean weight loss of 28 $\pm$ 15 Kg in the surgically treated patients (compared to 0.5 $\pm$ 8.9 Kg in the control group) was associated with significant estimated risk reductions in hypertension (60%), diabetes (97%), hypo-HDL (90%), and hypertriglyceridemia (90%).

Although this magnitude of weight change is not commonly seen with nonoperative treatment, the medical benefits of even modest weight loss (10% or less) include improvements in glycemic control, blood pressure and cholesterol.[206]

Quantitative estimates of the increased risk of CHD associated with weight gain are available from the Nurse's Health Study which suggests a 3.1% increase in risk for each Kg of weight gain.[207] Figure 35 illustrates the relative risk of CHD associated with categorical changes in weight in this study. This is supported by the results of the Gotenborg multi-factor intervention trial, which documented increased CHD mortality with even a modest (4-10%) amount of weight gain and a 2.4% increase in risk per Kg of weight gain for both genders.[208]

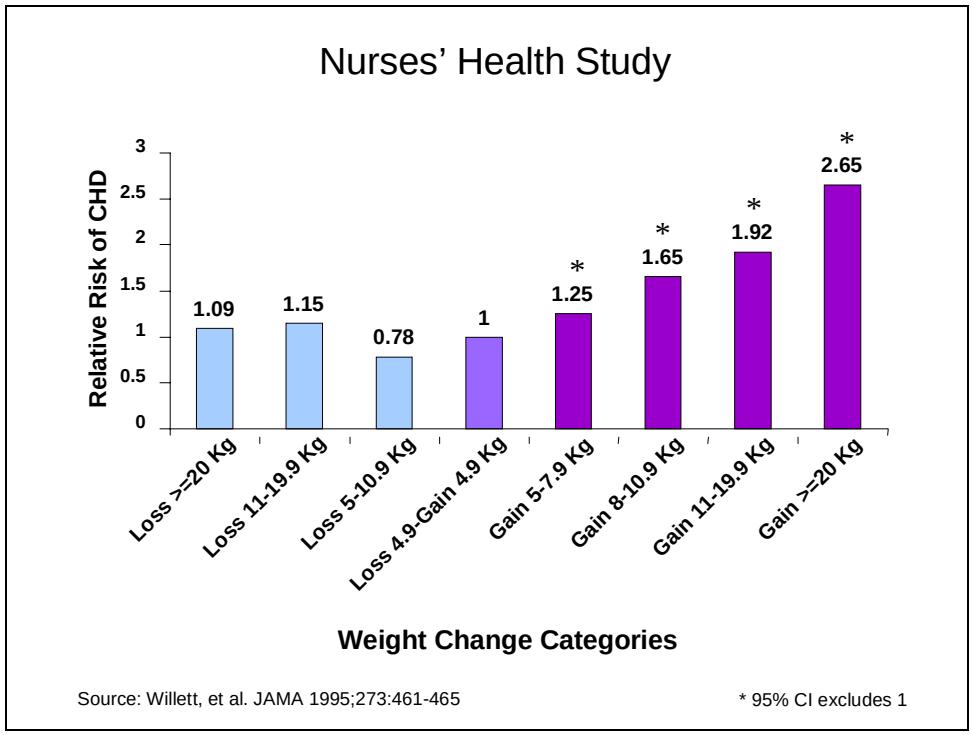


Figure 35. Relative Risk of CHD by Weight Change from 18 Years Old to 1976 – Nurses Health Study (CHD includes CHD death and nonfatal MI)

H.6.2 Effects of Ziprasidone and Other Antipsychotic Drugs

Weight changes observed in long-term trials with ziprasidone are described in Section G.1 and are summarized in Table 61, together with reported data from other clinical development programs. Considering the observations from the Nurse's Health Study and the Gotenborg Trial (2-3% increase in CHD risk for each Kg of weight gain), the negligible mean weight change observed in patients on ziprasidone over a six month period compares favorably with the effects of the other atypical antipsychotics upon predicted risk of coronary heart disease. Furthermore, since weight gain is also associated with increased incidences of hypertension, diabetes and osteoarthritis, the increased CHD risks are likely to be underestimates of the overall health burden.

Table 61. Weight Changes Observed in Long-Term Clinical Trials

	Mean Weight (Kg) Change*	
Quetiapine	+5.6	over 6 months
Olanzapine	+5.4	over approximately 8 months
Risperidone	+2.3	over 6 months
Haloperidol	+1.0	over 6 months
Ziprasidone	**+0.2**	**over 6 months**
Thioridazine**	--	

* Sources for weight change-- quetiapine: Seroquel Product Monograph.[113] olanzapine: Zyprexa US Package Insert,[52] risperidone: Risperdal Product Monograp.[114] ziprasidone and haloperidol: ziprasidone clinical development program see Table 43.

** No data available for weight change with long term thioridazine treatment.

H.7 Summary of CVD Risks Associated with Lipid Changes and Weight Gain

There is a consistent and well-documented relationship between changes in lipid levels and body weight and the risk of atherosclerotic disease. These risks apply throughout the distribution of change for a treated population. In addition, they impact upon more common clinical events that include myocardial infarction, ischemic stroke, other peripheral presentations of atherosclerosis, as well as metabolic syndromes such as diabetes.

Ziprasidone is the only antipsychotic studied that is associated with both improvements in lipid profile and no increase in weight. These well documented risk factors for cardiovascular disease strongly suggest a future reduction in risk relative to other agents.

I. CONCLUSIONS

Despite the fact that their use is associated with a number of adverse effects and untoward consequences, antipsychotic medications remain a sine qua non of the modern day management of schizophrenia. The routine use of neuroleptics by the medical profession reflects a judgment among health care professionals that the risks posed by neuroleptic treatment pale in comparison to those posed by untreated schizophrenia.

Several recently marketed, so-called 'atypical' antipsychotics, have been greeted with considerable enthusiasm by both practitioners and patients because they are relatively free of some of the more troubling untoward effects (e.g., EPS, tardive dyskinesia) associated with the use of the older antipsychotics. These newer antipsychotics are not without disadvantages and risk, however.

FDA's issuance of a not-approvable letter for ziprasidone in June 1998 was focused on the concern of QTc prolongation. This document addresses that concern.

The sponsor is mindful of the issues that underlie the agency's concern regarding the QTc issue, but the sponsor does not conclude, after extensive research and analysis, that the effect of ziprasidone upon the QTc is predictive of a significant risk of TdP.

This document describes the evidence in support of this conclusion, including:

- precise quantitation of a modest mean QTc effect
- extensive clinical database documenting only rare QTc measures >500 msec
- sudden death and syncope incidence rates comparable to control groups
- benign overdose experience
- demonstrated absence of CYP450 interaction liability
- extensive population pharmacokinetic database, providing correlations between serum concentrations of ziprasidone and its metabolites, with time-matched ECG data
- review of terfenadine 60 mg BID peak effect (comparable to ziprasidone), and drug interaction liability (contrasting sharply with ziprasidone)
- comparisons showing that the QTc effect of ziprasidone is noticeably less than the QTc effect of sertindole.

Evidence is also presented that demonstrates that ziprasidone is “weight neutral,” has a beneficial and sustained effect upon serum lipids, and does not impair glucose metabolism. These properties compare with the adverse effects of alternative atypical antipsychotic agents and predict a uniquely favorable benefit-risk profile for ziprasidone, with significant consequences for patient compliance.

The implications are significant for the long-term health of patients with schizophrenia, given the early onset of this disease, the extended treatment periods warranted for most patients, the high prevalence of other cardiovascular risk factors, and the exclusion of some patients from generally available treatments such as lipid-lowering therapy and revascularization procedures.

The unique advantages of ziprasidone described in this document are supported by the overall safety and efficacy profile of ziprasidone established in the course of its development, in well-controlled short-term and long-term clinical trials.

In particular, other risks associated with use of the newer agents, including hepatic transaminase elevation, cataract formation and hyperprolactinemia, are absent or nearly so with ziprasidone.

In summary, the choice of drug therapy for schizophrenia must reflect an informed judgement of the balance of benefits and risks attributable to various agents. Pfizer believes that the safety and efficacy of ziprasidone have been established by data acquired during the clinical development program, and that this conclusion is strongly supported by clinical experience with other psychotropic and nonpsychotropic agents and by available literature.

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