In short, while I agree that the clinical significance of a relatively small effect like 10 msec is not established, I don't agree that the finding is dismissible given any historical experience. I also think an even more important finding from study 054 than the experience with ziprasidone is that we can now conclude with much more certainty than in the past that risperidone, quetiapine, and olanzapine probably do not prolong the QT in their marketed dose range. This relative difference in effect between ziprasidone compared to some of the more recently approved antipsychotics raises significant need to inform investigators and patients under the ziprasidone IND about the findings from study 054.

My recommendations are (1) to include the findings from study 054 in the investigator brochure and to inform patients of these findings, in effect, conducting informed consent again for all patients exposed under the IND; (2) to ask the sponsor to try and get ECGs in patients that remain under the IND at c max and to consider discontinuing any patient with a prolonged QT; (3) to restrict any additional studies conducted under the IND to defining the level of risk from the QT effect or establishing a comparative efficacy benefit between ziprasidone and other antipsychotics, and (4) to consider withdrawing thioridazine from the market. At a minimum, I would recommend a boxed warning and reserving thioridazine for second line use.

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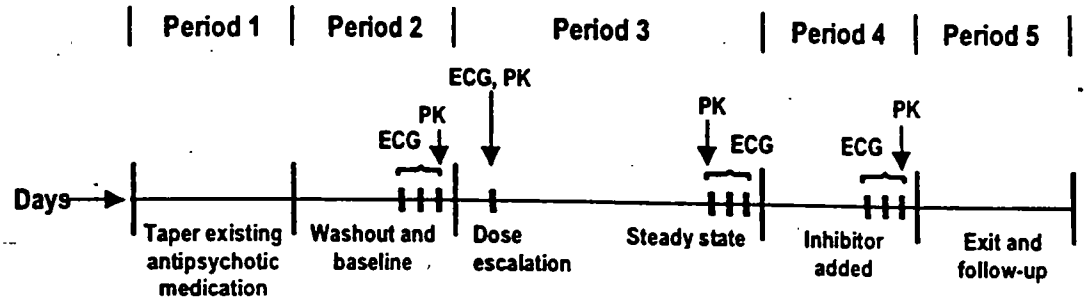
A diagram showing the general study design and the timing of critical measurements is given below.



During Period 1, each subject's antipsychotic medication was tapered to the lowest possible dose over about 7 days. The investigator was to contact subjects on alternating days during this one-week period.

One day prior to the start of Period 2 (day -5), subjects entered the clinical research facility and had liver function tests performed. Results of these tests had to be reviewed before subjects were randomized to treatment assignment via tele-randomization. During Period 2, subjects received placebo once daily at approximately 0800 hours for 5 days (days –4 to 0). To standardize circadian and meal effects on QTc, the exact time of morning dosing established on day -4 was to remain fixed for the remainder of the study.

On the last 3 days of Period 2 (days -2, -1, 0), baseline ECG measurements were obtained three times daily at times specified according to treatment assignment. The times were selected so that QTc would be assessed at timepoints surrounding the mean Tmax of each agent, controlling for post-prandial time. The schedule of ECG measurements, relative to the morning dose of placebo (Period 2), antipsychotic (Period 3), and antipsychotic plus metabolic inhibitor (Period 4) is listed in Section 5.4.

During Period 3, subjects received the assigned antipsychotic drug while under continuous medical supervision in the clinical research facility. Study drug was administered in open-label fashion. 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. The time to achieve steady-state conditions was estimated from the average t½ of each study drug or major metabolite. For the dosing regimen used, it was anticipated that the ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol groups would reach steady-state conditions by days 8, 16, 11, 10, 8, and 10, respectively. For risperidone, olanzapine, and quetiapine, the dose escalation schedule and the Tmax were based on information provided in product labeling; for thioridazine[1,2] and haloperidol[3], the estimate of Tmax was based on literature reports. The time to achieve steady-state conditions and the Tmax for ziprasidone were based on data from previous pharmacokinetic studies that used doses from 40 to 80 mg BID.

The duration of treatment and the maximal daily dose differed across study drugs as shown below:

Table 5.1 Summary of Mean (CV%) Concentrations (ng/ml) for Parent Drug Obtained at the Time of Expected Peak Systemic Exposure
Protocol 128-054

Drug Group	Period 3 Day 2	Period 3 Low Dose*	Period 3 Steady-State	Period 4 With Inhibitor	Ratio Period 4/3
Ziprasidone	49 (41)	N/A	171 (34)	224 (35)	1.39 (40)
Risperidone	14.8 (61)	24.8 (67)	58.7 (79)	124.0 (48)	2.47 (35)
Olanzapine	9.2 (54)	N/A	55.1 (39)	84.5 (27)	1.77 (45)
Quetiapine	175 (48)	N/A	1280 (61)	3740 (43)	4.03 (70)
Thioridazine	215 (43)	N/A	765 (46)	799 (50)	1.04 (20)
Haloperidol	2.1 (91)	N/A	16.1 (95)	27.1 (75)	1.94 (50)

Source: Section 13 Tables 1.2.1 – 1.2.6

* = Applies only to the risperidone treatment group; sample obtained on day 5.

N/A = Not applicable.

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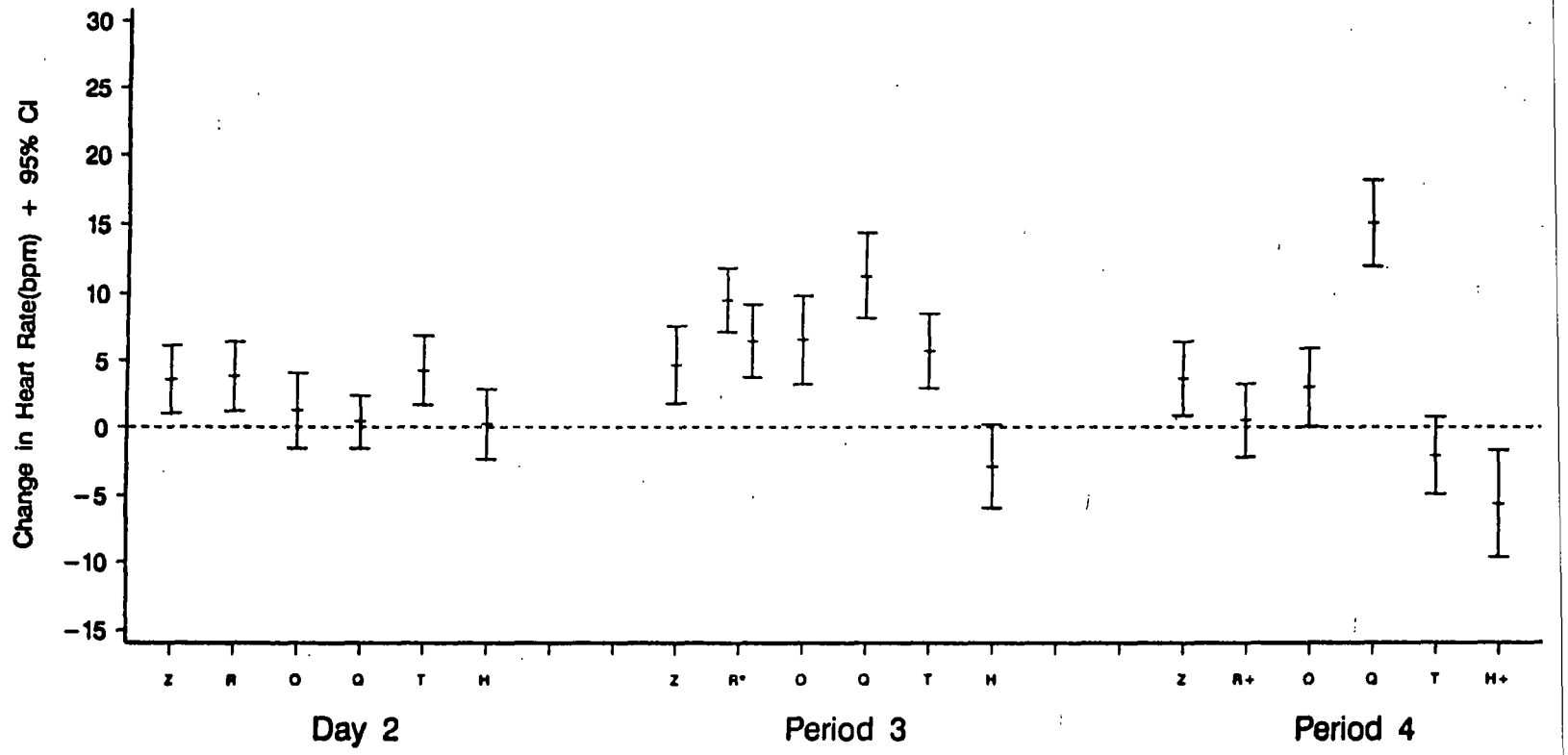
Figure 2.1

Mean Change from Baseline Heart Rate(bpm) and 95% Confidence Intervals at Each Period by Treatment Group – Completers

Ziprasidone Protocol 054



Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.

* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.

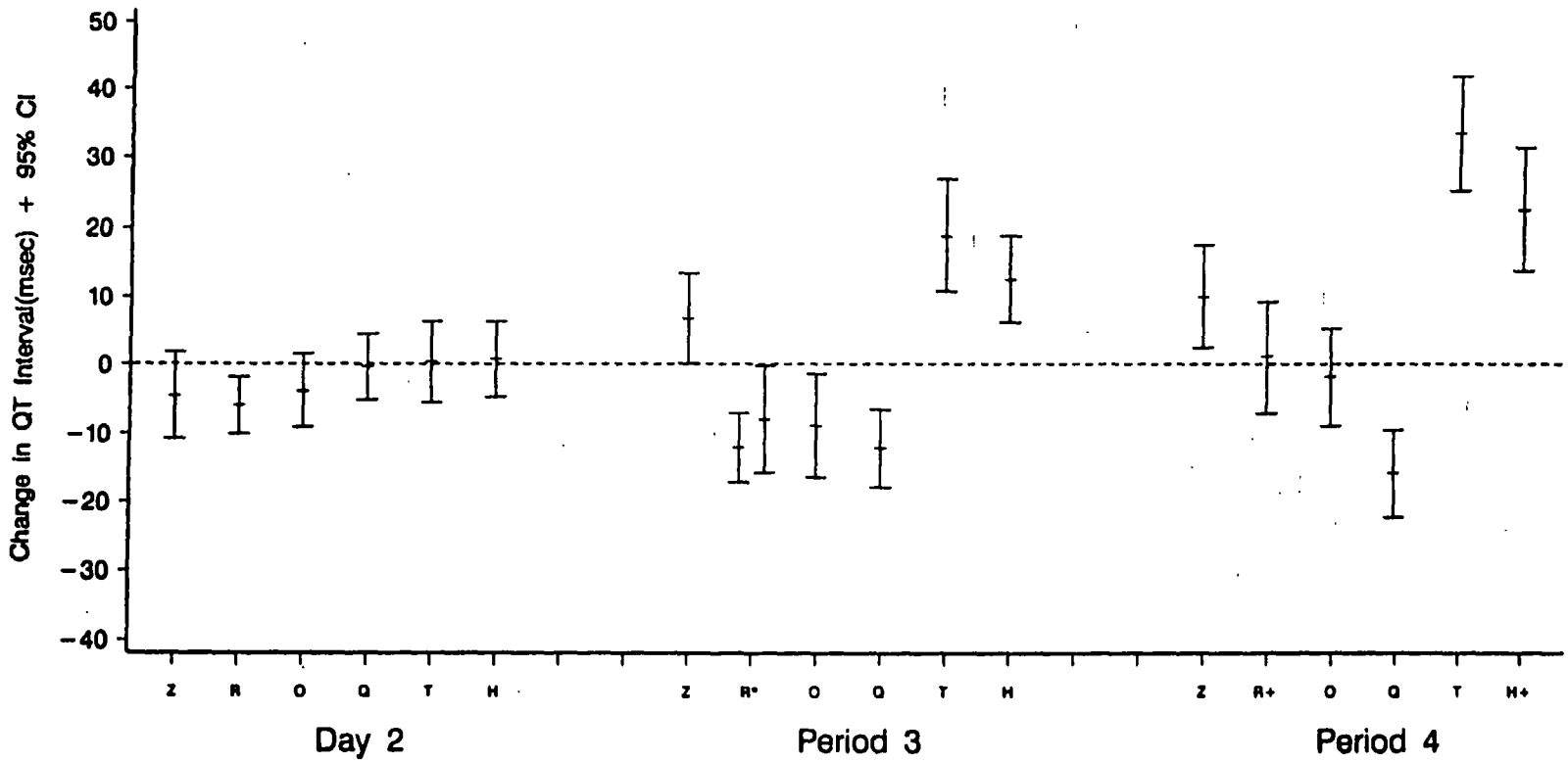
+ Contains only pre (3/16/99) amendment values, post – amendment values are provided in the listings.

Source Data: Table 5.2.2.1.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Figure 3.1

Mean Change from Baseline QT Interval(msec) and 95% Confidence Intervals at Each Period by Treatment Group – Completers

Ziprasidone Protocol 054



Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.

* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.

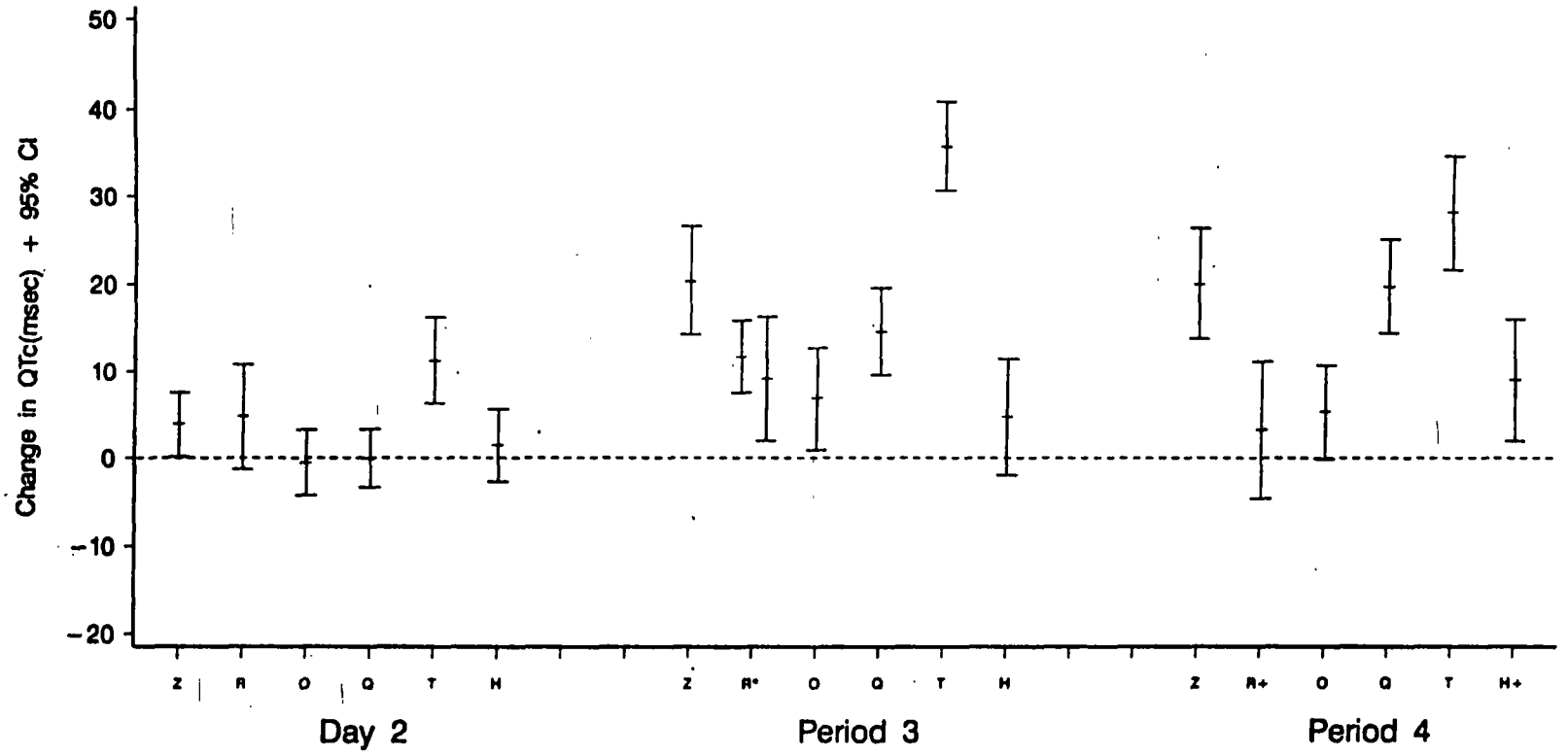
+ Contains only pre (3/16/99) amendment values, post-amendment values are provided in the listings.

Source Data: Table 5.2.3.1.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Figure 1.1.1

Mean Change from Baseline QTc Interval(msec) and 95% Confidence Intervals at Each Period by Treatment Group – Completers

Ziprasidone Protocol 054



Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.

* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.

+ Contains only pre (3/16/99) amendment values, post – amendment values are provided in the listings.

Source Data: Table 5.2.1.1.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Table 6b. QTc Change (FDA Correction (0.37 Power)) from Baseline to Last Observation; Study 054 Completers

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Baseline						
Mean (msec)	391.1	388.9	389.0	388.3	389.2	384.8
(95% CI)	(384.4, 397.8)	(382.8, 394.9)	(381.5, 396.4)	(381.3, 395.3)	(383.1, 395.3)	(378.6, 391.0)
Period 3: Steady-State (except days 5-7 for Risperidone)						
Mean Δ (msec)	16.5	4.9	2.3	6.9	30.8	6.8
(95% CI)	(11.1, 21.8)	(1.2, 8.5)	(-3.1, 7.8)	(2.9, 10.9)	(25.6, 36.1)	(1.4, 12.2)
% Δ	4.3	1.3	0.7	1.8	8.0	1.8
(95% CI)	(2.9, 5.7)	(0.3, 2.2)	(-0.8, 2.1)	(0.7, 2.8)	(6.6, 9.3)	(0.4, 3.2)
Period 3: Steady-State for Risperidone						
Mean Δ (msec)		4.3				
(95% CI)		(-2.3,10.9)				
% Δ		1.2				
(95% CI)		(-0.6, 2.9)				
Period 4: Inhibitor Present						
Mean Δ (msec)	17.0	2.7	3.3	9.5	29.3	12.8
(95% CI)	(11.0, 23.0)	(-4.6, 10.0)	(-1.7, 8.3)	(4.7, 14.3)	(23.2, 35.5)	(7.0, 18.6)
% Δ	4.5	0.7	0.9	2.5	7.6	3.4
(95% CI)	(2.9, 6.0)	(-1.2, 2.7)	(-0.4, 2.2)	(1.2, 3.7)	(6, 9.3)	(1.8, 4.9)

Source: Data on File

Table 6c. QTc Change (Framingham Linear Correction) from Baseline to Last Observation; Study 054 Completers

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Baseline						
Mean (msec)	389.4	388.2	388.4	388.1	388.5	383.7
(95% CI)	(383.5, 395.3)	(382.6, 393.9)	(381.3, 395.6)	(381.4, 394.9)	(382.6, 394.4)	(378.0, 389.3)
Period 3: Steady-State (except days 5-7 for Risperidone)						
Mean Δ (msec)	14.9	3.6	1.6	4.4	28.5	6.1
(95% CI)	(9.9, 19.8)	(-0.1, 7.3)	(-3.7, 6.8)	(0.8, 8.1)	(23.0, 34.0)	(1.0, 11.2)
% Δ	3.9	0.9	0.5	1.2	7.4	1.6
(95% CI)	(2.6, 5.2)	(0.0, 1.9)	(-0.9, 1.8)	(0.2, 2.1)	(6.0, 8.8)	(0.3, 3.0)
Period 3: Steady-State for Risperidone						
Mean Δ (msec)		3.7				
(95% CI)		(-2.2, 9.7)				
% Δ		1.0				
(95% CI)		(-0.6,2.6)				
Period 4: Inhibitor Present						
Mean Δ (msec)	15.5	2.5	2.8	5.9	28.6	12.8
(95% CI)	(9.7, 21.4)	(-4.5, 9.5)	(-2.0, 7.6)	(1.6, 10.2)	(22.2, 35.0)	(7.3, 18.2)
% Δ	4.1	0.7	0.8	1.6	7.4	3.4
(95% CI)	(2.6, 5.6)	(-1.2, 2.5)	(-0.4, 2)	(0.4, 2.7)	(5.7, 9.1)	(1.9, 4.8)

Source: Data on File

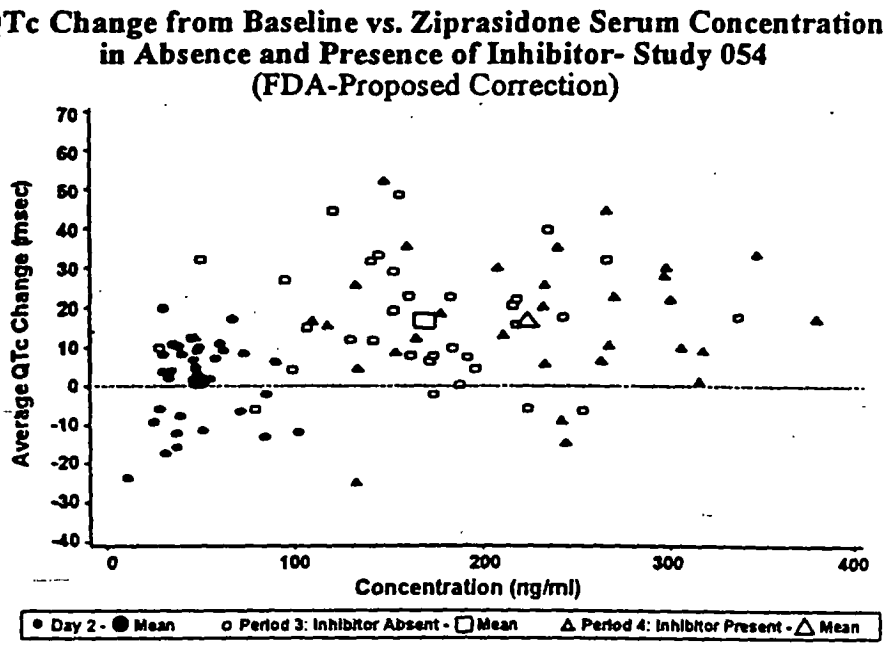


Figure 1b. Individual Mean QTc Changes (FDA-proposed Correction) from Baseline vs. Ziprasidone Serum Concentration; Study 054

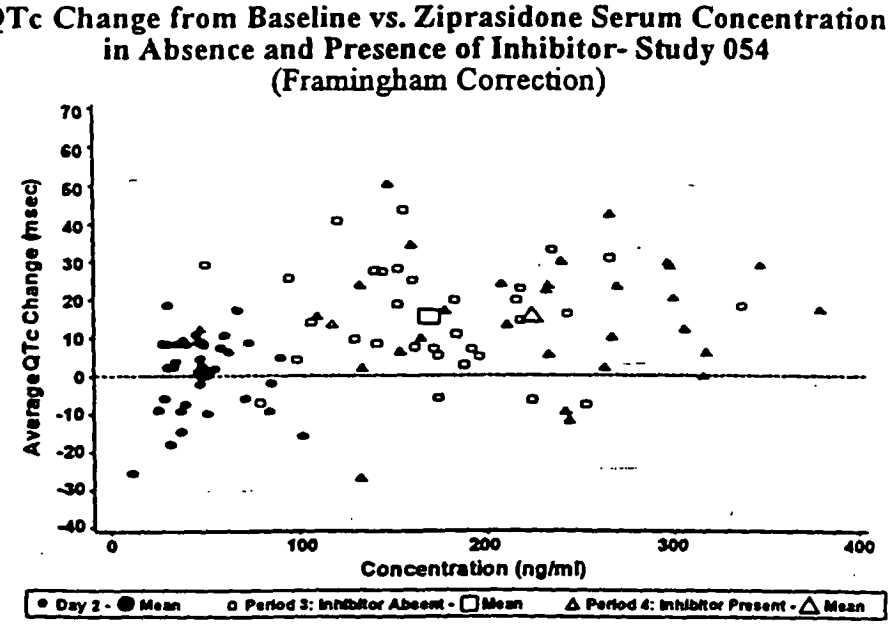


Figure 1c. Individual Mean QTc Changes (Framingham Correction) from Baseline vs. Ziprasidone Serum Concentration; Study 054

Table 5.2.3.1.1
Summary of QT Interval (msec) Baseline and Change from Baseline by Treatment Group - Completers
Ziprasidone Protocol 054

Period		Treatment Group					
		Ziprasidone	Risperidone+	Olanzapine	Quetiapine	Thioridazine	Haloperidol+
Baseline*	N	31	25	24	27	30	27
	Mean	362.2	368.9	365.0	362.4	371.3	358.7
	Std. Dev.	21.7	26.6	23.4	23.2	18.2	15.5
	Range						
	CI	(354.3, 370.2)	(358, 379.9)	(355.1, 374.9)	(353.2, 371.6)	(364.5, 378.1)	(352.6, 364.9)
Day 2	N	31	25	24	27	30	27
	Mean	-4.5	-5.9	-3.8	-0.3	0.4	0.8
	Std. Dev.	17.8	10.4	13.2	12.6	16.4	14.6
	Range						
	CI	(-11.1, 2)	(-10.2, -1.7)	(-9.3, 1.6)	(-5.3, 4.7)	(-5.7, 6.5)	(-4.9, 6.6)
Period 3#	N	31	25	24	27	30	27
	Mean	6.8	-12.1	-8.9	-12.2	18.7	12.5
	Std. Dev.	18.7	12.9	18.7	15.1	22.1	16.7
	Range						
	CI	(-0.1, 13.6)	(-17.4, -6.7)	(-16.8, -1)	(-18.2, -6.2)	(10.5, 27)	(5.9, 19.1)
Period 3^	N		25				
	Mean		-8.0				
	Std. Dev.		19.8				
	Range						
	CI		(-16.1, 0.2)				
Period 4	N	31	20	24	27	30	20
	Mean	10.0	1.1	-1.8	-15.8	33.3	22.5
	Std. Dev.	21.4	10.6	17.8	16.9	23.1	19.9
	Range						
	CI	(2.1, 17.8)	(-7.6, 9.8)	(-9.3, 5.7)	(-22.5, -9.1)	(24.7, 41.9)	(13.1, 31.8)

* Baseline is defined as the average of the planned ECGs collected on days -2, -1, and 0.
# Risperidone 6-8 mg
^ Risperidone 16 mg
+ Period 4 contains only pre (3/16/99) amendment values, post-amendment values are provided in the listings.
Source Data: Section 13 Table 18.1. Date of Data Extraction: 03JUN99. Date of Table Generation: 08JUL99.

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Table 5.2.2.1.1
Summary of Heart Rate (bpm) Baseline and Change from Baseline by Treatment Group - Completers
Ziprasidone Protocol 054

Period		Treatment Group					
		Ziprasidone	Risperidone+	Olanzapine	Quetiapine	Thioridazine	Haloperidol+
Baseline*	N	31	25	24	27	30	27
	Mean	75.1	70.5	72.2	73.0	68.9	73.5
	Std. Dev.	12.1	11.0	8.8	7.7	8.2	10.6
	Range						
	CI	(70.7, 79.6)	(65.9, 75)	(68.5, 75.9)	(70, 76)	(65.8, 71.9)	(69.4, 77.7)
Day 2	N	31	25	24	27	30	27
	Mean	3.6	3.8	1.2	0.4	4.3	0.3
	Std. Dev	7.2	6.6	7.0	5.2	7.1	6.0
	CI	(0.8, 6.2)	(1.1, 6.5)	(-1.7, 4.2)	(-1.6, 2.5)	(1.5, 7)	(-2.5, 3)
Period 3#	N	31	25	24	27	30	27
	Mean	4.6	9.5	6.5	11.2	5.7	-2.9
	Std. Dev.	8.2	6.0	8.2	8.2	7.7	8.2
	Range						
	CI	(1.6, 7.7)	(7, 11.9)	(3, 10)	(8, 14.5)	(2.8, 8.6)	(-6.1, 0.3)
Period 3^	N		25				
	Mean		6.4				
	Std. Dev.		6.0				
	Range						
	CI		(3.6, 9.3)				
Period 4	N	31	20	24	27	30	20
	Mean	3.6	0.5	3.0	15.1	5.1	5.7
	Std. Dev.	7.2	7.5	7.0	8.1	7.6	8.2
	CI	(0.7, 6.5)	(-2.4, 3.4)	(-0.1, 6)	(11.8, 18.3)	(-5.1, 0.9)	(-10, -1.4)

* Baseline is defined as the average of the planned ECGs collected on days -2, -1, and 0.
\# Risperidone 6-8 mg
^ Risperidone 16 mg
\+ Period 4 contains only pre (3/16/99) amendment values, post-amendment values are provided in the listings.
Source Data: Section 13 Table 18.1. Date of Data Extraction: 03JUN99. Date of Table Generation: 08JUL99.

Review of Clinical Data

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Review of Ziprasidone ECG Data

NDA:	**NDA 20-825**
Sponsor:	**Pfizer**
Drug:	**Ziprasidone**
Route of Administration:	**Oral**
Reviewer:	**Gerard Boehm, M.D., M.P.H.**
Review Completion Date:	**1/23/98**

In this document, I review the sponsor's ECG data presentation included in the NDA ISS. I follow by summarizing the reviews provided by Drs. Ganley and [redacted] I then provide the results of additional analyses that I conducted using the sponsor's data from the STFDPC trials, and from study 101. I conclude with a discussion of the evidence.

NDA ISS data

Description of the collection of ECG data

There were no studies specifically designed to evaluate the effect of ziprasidone on the QTc. For the analyses presented in the NDA, the sponsor examined data recorded by 12-lead ECG's and did not identify any studies that used Holter monitors. In selected studies, investigators recorded screening, baseline, on treatment, and end of study ECG's. Investigators obtained screening ECG's during recruitment and used them to identify volunteers with ECG abnormalities for the purpose of excluding them from the study. The sponsor defined the baseline ECG as the last tracing recorded before the first day of study treatment. Depending on the protocol, these tracings could have followed a washout period where investigators discontinued the medications that subjects were taking at the time of enrollment. In some cases, the baseline ECG's were the screening ECG's (ex studies 104,106). End of study or final ECG's were the last ECG's recorded while on study treatment or within six days after the last day of study treatment. Investigators may have recorded additional ECG's during the trials (depending on the individual study protocols). With few exceptions, protocols did not specify the timing of the ECG with respect to dosing. ECG machines measured the intervals for the tracings analyzed in the ISS. The one exception was study 303, where machines read the tracings on site but the investigators also forwarded ECG's to a central site for blinded reading using an accurate, digitized methodology. The sponsor entered the ECG data into a database and calculated mean values for various parameters. The sponsor compared the mean baseline QTc to the

mean final QTc to look for evidence of prolongation. Tables in the ISS presented the data from the oral dose Phase II/III studies, the short term placebo controlled fixed dose studies (104,106,114,115), and study 303. In addition to looking for mean changes in the study population, the sponsor examined individual tracings to identify outliers (criteria: QTc≥500 or an increase in QTc≥75).

NDA Presentation of ECG Data

The NDA included the initial review of the ECG data as well as the review by Dr[ ] the sponsor's cardiology consultant.

In all oral Phase II/III trials, the final mean QTc increased from baseline for ziprasidone treated subjects (3.8) and decreased for those treated with placebo (-2.5). Similarly, in the subset of short term fixed dose placebo controlled trials, the sponsor described an increase in the final mean QTc compared to baseline in ziprasidone treated individuals (6.6), and a decrease in placebo exposed subjects (-2.6). The apparent dose response relationship presented in the following table strengthened the argument for ziprasidone's effect for prolonging the QTc.

Change from Baseline to Last Observation in QTc
Short Term Fixed Dose Placebo Controlled Trials

Treatment Group	N	Mean Change QTc from baseline
Placebo	251	-2.6
Zip<40 BID	232	4.0
Zip 40 BID	137	4.5
Zip 60 BID	111	7.3
Zip 80 BID	100	10.5
Zip≥100BID	77	12.1
Haloperidol	76	0.2

From Sponsor's table H.5.23c p.1070 Vol. 1.1

The sponsor's analysis of mean QTc difference from baseline in Study 303, a 52 week inpatient study, did not demonstrate a dose response relationship (see appendix).

The sponsor identified few ziprasidone treated patients (n=13) who met outlier criteria. The percentage of ziprasidone exposed subjects who met outlier criteria was similar to the percentage of subjects given placebo or an active comparator who met the criteria. None of the outlier ziprasidone treated patients had adverse events associated with prolonged QTc (i.e. syncope, documented arrhythmia, sudden death) and none had a prolonged QTc on more than one occasion.

The sponsor's consultant, Dr[ ] found that the ECG interval measurements were incorrect in several instances. He re-measured the intervals from some of the tracings from the STFDPC trials. Following re-measurement, he did not find a dose response relationship for QTc prolongation, but he did describe a statistically significant increase

in mean final QTc compared to baseline. Dr.[ ]felt that ziprasidone's effect on the QTc was small and not clinically significant.

An FDA cardiologist, Dr. Ganley, independently reviewed the sponsor's NDA ECG presentation as well as the ECG SAS data sets (see NDA consult dated November 18,1997). Without interval re-measurement, he found dose response relationships when analyzing all phase II/III studies and the subset of short term fixed dose studies. Dr. Ganley did not find a dose response relationship for QTc prolongation in study 303 (although he noted an increase in mean QT for the 80mg bid group accompanied by a decrease in mean heart rate which was not observed in the STFDPC trials). Dr. Ganley agreed with Dr.[ ]that the intervals were misread for many of the tracings. Despite the inconsistencies, he felt that the evidence suggested a dose response relationship for QTc prolongation and compared the change observed with ziprasidone to that seen with therapeutic doses of terfenadine. He could not estimate a risk of torsades from the data and recommended, in lieu of further clinical studies, in vitro studies of the effect of ziprasidone and its metabolites on action potential duration.

The sponsor hired Dr.[ ]to review ECG data from ziprasidone studies. He reassessed the previously identified outlier ECG tracings. Using his readings, none of these subjects had a QTc≥500 and only one met the criteria for a clinically significant change from baseline (QTc increased ≥75 over baseline). Re-measurement of intervals using the accurate, digitized methodology supported Dr.[ ]assessment.

Dr.[ ]analyzed data from study 301, and pooled data from studies 117, 108, 108E,(ongoing studies) and 303. These studies were selected because the ECG intervals had been measured using an accurate digitized methodology. He found no evidence of a dose response relationship for QTc prolongation in these data.

The sponsor then had the ECG's from the STFDPC trials re-measured using an accurate digitized methodology. After re-measurement, Dr.[ ]noted that the mean QTc difference from baseline increased with increasing ziprasidone dose for all dose groups except the ≥100mg bid group.

Change from baseline to Last Observation In QTc
Short Term Fixed Dose Placebo Controlled Trials

Treatment Group	N	Mean Change QTc from baseline
Placebo	250	-2.6
Zip<40 BID	230	0.6
Zip 40 BID	138	5.9
Zip 60 BID	111	7.7
Zip 80 BID	100	9.7
Zip≥100 BID	77	6.4
Haloperidol	76	-1.6

From Dr. . table H.5.23.2 Appendix IV

Dr[ ] provided an additional analysis of STFDPC trial data. He compared the ECG tracing with the largest QTc change at any time during the study with the baseline QTc. Aside from the greater magnitude of change, the results were similar to above (increasing mean QTc difference with increasing dose for all groups except the ≥100mg bid group).

When looking at the evidence in aggregate, Dr[ ] felt the data should be interpreted as showing no ziprasidone related dose changes. He felt that the lack of outliers argued against ziprasidone related prolongation. An additional analysis using the mean last QTc minus the mean screening QTc did not reveal a dose response relationship (contrary to what he found using the baseline QTc). He felt that if a true effect was present it should be seen regardless of the QTc used for comparison (baseline or screening). Therefore, he felt that natural variability, rather than drug effect, explained the observed changes. Additionally, the results of the analysis of study 301 did not support a dose response effect. Lastly, Dr[ ] presented the results of IM study 046. In this study, ziprasidone was dosed at 5 to 20mg intra-muscularly four times a day. Investigators obtained ECG's following the 4th dose on day 2. The mean QTc changes from baseline were: 5.3 for placebo; 3.5 for 20mg; 11 for 40mg; and 12.5 for 80mg. Prolongation did not appear to correlate with the estimated serum concentrations.

Re-analysis of ECG data from STFDPC Trials

Methods

Using the sponsor's data sets for the re-measured intervals from STFDPC trials, we were able to conduct our own analyses. I began by reviewing information about the individual trials to determine if it was reasonable to pool the results for analysis. Using the data sets provided, I attempted to replicate Dr[ ]'s findings. The sponsor included variables that identified the baseline QTc and last QTc for the patients from the STFDPC trials. I was able to reproduce the mean changes from baseline that were included with Dr.[ ]s results. Unfortunately, the sponsor did not include a variable that identified the QTc used in calculating the maximal QTc change from baseline. The results I obtained for this analysis are the same as Dr[ ]s for all the dose groups except for <40 and 40 which differ only slightly.

During the review of the QTc prolongation issue, we became concerned about the possibility of an effect due to the timing of the last ECG tracing (up to 6 days after the last day on study medication). We hypothesized that measurement of QTc after completing treatment could reflect the return to baseline and not the effect that would be observed if the tracing were recorded while the subject was taking the drug. If this were true, the measured effect would then underestimate the actual effect of the drug. I attempted to control for this potential effect by conducting two additional analyses. After excluding any QTc value from a patient whose last ECG was recorded greater than or equal to one day after discontinuing the medication, I compared the last QTc with the

baseline QTc values. In addition, since all of these trials included a day 14 ECG, I performed an analysis comparing the day 14 QTc and the baseline QTc values.

In reviewing Dr[redacted]'s analyses, the mean QTc change values using the re-measured intervals from the STFDPC trials appeared to depict a dose response trend. We were interested in evaluating the strength of the evidence for a dose response relationship. First, we wanted to determine if the mean QTc change values were significantly different. If they were, we would perform pair wise comparisons of the mean differences. If a dose response relationship was present, and there were adequate numbers of observations, we expected that the mean QTc differences would be significantly higher in the high dose categories compared to the lower dose categories, and placebo. The STFDPC trials data was provided with the following dose groups: placebo, <40mg bid, 40mg bid, 60mg bid, 80mg bid and ≥100mg bid. These categories were used for the independent variables and the mean QTc difference from baseline was the response variable. An analysis of variance was conducted to evaluate the difference between the mean QTc change for all dosage groups. The Tukey-Kramer means comparison test was used for pair wise comparisons of the mean QTc differences for each dosage group. Regression lines were fitted using first dose group, and then estimated dose (using 12.5mg as an estimate for the categorical group <40mg and the dose in mg for the rest of the groups) by mean QTc difference from baseline. A t-test was conducted to evaluate the slope of the resulting line.

Results

The STFDPC analyses use data pooled from 4 studies. One of the potential advantages of pooling data is to increase the precision of an estimate by increasing the number of observations. Unfortunately, pooling does not result in additional observations for the 80mg bid and 100mg bid doses because all the subjects for each of these dose groups came from one study.

The STFDPC trials include four separate studies. Studies 104 and 106 were 4 weeks long and had similar entrance criteria. As mentioned above, these protocols required only a screening ECG prior to beginning the study. They both allowed the use of low dose β-blockers and lorazepam during the washout and double blind phases of the studies. Study 104 looked at the use of ziprasidone at 5mg bid, 20mg bid, and 40mg bid doses. Study 106 used 20mg bid and 60mg bid doses.

Studies 114 and 115 were similar to each other but differed slightly from the studies mentioned above. These protocols required both screening and baseline ECG's. These studies were 6 weeks in duration and both allowed the use of lorazepam, but not β-blockers, in the washout period. Both studies allowed the use of lorazepam, benztropine, or β-blockers during the double-blind phases of the studies. Study 114 used 40mg bid and 80mg bid doses while study 115 used 20mg bid, 60mg bid, and 100mg bid doses.

The following table provides the mean QTc change from baseline for the individual studies, using the mean last QTc minus the mean baseline QTc (accurate measurement methodology).

Examination of individual studies, last QTc minus baseline QTc

Study	Placebo	<40mg bid	40mg bid	60mg bid	80mg bid	>=100mg bid
104	-3.4	2.1	2.2			
106	0.1	-3.4		5		
114	-3.7		7.3		9.7	
115	-2.3	1.2		9.2		6.4

Looking at the individual study results, in all but one dosage group, the drug exposed groups had a greater mean QTc difference than the group exposed to placebo. In 2 of the 4 studies the trend was for increased effect with increased dose. The study designs and results were similar and pooling of data was considered appropriate.

The following table lists the results of the analyses using QTc values obtained at different times to calculate the mean QTc difference from baseline. The Last-baseline analysis provide the findings from Dr[ ]s analysis. The last on treatment-baseline represents the analysis which excluded patients whose last ECG was not done on the day that treatment ended. The 14 day-baseline represents the results using the mean day 14 QTc compared to the mean baseline QTc. The QTcmax-baseline represents the results of my analysis which used the maximal mean QTc difference at any time during the study compared to the mean baseline QTc (see appendix for complete tables).

Ziprasidone Short term fixed dose placebo controlled trials (104,106,114,115)

Comparison	Placebo	<40mg bid	40mg bid	60mg bid	80mg bid	100mg bid
Last-baseline	-2.6	0.6	5.9	7.7	9.7	6.4
Last on tx-baseline	-4.2	0.8	4.6	7.9	8.8	8.0
14 day- baseline	-2.6	3.4	6.1	8.4	13.3	8.5
QTcmax-baseline	4.3	9.5	12.8	15.2	19.8	15.0

Comparison of the mean QTc differences

For all of the comparisons, the mean QTc difference from baseline increased with increasing dose for all ziprasidone dose groups except for the 100mg bid group. In each of the above analyses, the results of the one way ANOVA was consistent with different means ($p<.0001$). Appendix 1 provides the pair wise comparisons for the Tukey-Kramer test. Using the mean last QTc on treatment minus baseline analysis, all dosage groups except the <40mg bid group were significantly different from placebo, but differences between mean changes for the different ziprasidone dosage groups did not achieve statistical significance. For the remaining 3 analyses, the QTc difference from baseline was also significantly higher than placebo for all dose groups except the <40mg. Additionally, the 80mg bid group was significantly higher than the <40mg bid group. The

Mean QTc difference (final on treatment from baseline) Study 101

Haloperidol	Zip 2mg bid	Zip 5mg bid	Zip 20mg bid	Zip 80mg bid
0.1(n=17)	-5.4 (n=17)	0.3 (n=17)	4.9 (n=17)	3.4 (n=19)

I repeated this analysis using the sponsors' data set that was included with the NDA submission and my results were comparable to those above. To assess the potential effect of ECG's obtained after ziprasidone was stopped, I conducted additional analyses using the day 7 (prior to am dose) and day 21 (3-7 hours after the am dose) ECG tracings.

Mean QTc difference (day 7 from baseline, day 21 from baseline) Study 101

Comparison	Haloperidol	Zip 2mg bid	Zip 5mg bid	Zip 20mg bid	Zip 80mg bid
Day 7	-6.8 (n=13)	1.4 (n=14)	6.4 (n=14)	-1.3 (n=15)	3.0 (n=17)
Day 21	-11 (n=10)	-7.6 (n=10)	5.9 (n=7)	-5.8 (n=10)	-3.0 (n=13)

I did not find a dose response relationship for QTc prolongation when comparing the mean QTc on day 7, or day 21 to the mean baseline QTc. Separate analyses looking at QT intervals by dose group also show no evidence of prolongation.

Discussion

QTc prolongation has been associated with increased mortality in healthy individuals as well as in patients with ischemic heart disease.[1,2,3,4,5] Arrhythmias and death have been associated with drugs causing QTc prolongation either alone or in combination with other agents that compete for degradation pathways.[6,7,8,9] To evaluate the potential of ziprasidone to cause QTc prolongation, the sponsor examined ECG data collected during the development program and described conflicting results. Some evidence suggests that ziprasidone causes dose dependent increases in QTc while other evidence does not support such an effect. The ability of these data to accurately describe the effect of ziprasidone on QTc is limited for several reasons.

Previous research has demonstrated that the QTc is a dynamic parameter, with demonstrated variability within individuals.[10,11,12,13] The protocol instructions for collection of ECG data in the ziprasidone NDA trials did not take this variability into consideration. For example, the baseline ECG used in these studies was a single measurement at an unspecified time (defined as the last ECG recorded prior to taking the study medication).

Timing with respect to dosing was not specified in many of the study protocols. As a result, for the on treatment tracings, some of the measurements could reflect trough concentrations, some could reflect peak concentrations, and others could reflect an intermediate concentration. Additionally, there are problems with the timing of what the sponsor defines as the last ECG. The sponsor acknowledged that some of the last ECG's were done as many as 6 days after the last dose of study drug. This disregard for timing could limit the ability to detect a drug effect, if present.

differences between the remaining groups did not achieve statistical significance.[1]

These results demonstrate that in the STFDPC trials, the difference in mean QTc from baseline was greater in the groups exposed to ziprasidone than in the groups exposed to placebo. Within the ziprasidone dosage groups, the mean QTc difference generally increases with increasing dose, but the difference achieves statistical significance only for the 80mg bid group compared to the <40mg bid group. Use of different tracings from the database for comparison appeared to have little effect on the detected mean QTc difference. The mean QTc difference was smaller for the 100mg bid group than the 80mg bid group in each of these analyses.[1]

Simple regression lines were fitted using mean last QTc and mean day 14 QTc difference from baseline by categorical dose groups and estimated dose(see appendix). The slopes of the regression lines were positive and were significantly different than zero. These findings are consistent with a dose response effect, although the models did not explain the data well with an r^2 equal to .04.[1]

Analysis of ECG data from Study 101

Methods

To further explore the possible effect of ziprasidone on the QTc, I analyzed the ECG data collected from study 101. One of the previously identified potential sources of error in the development program was the lack of protocol instructions about the timing of ECG tracings with respect to dosing. I selected Study 101 because the protocol required that ECG's be done at specified times during the trial. The study design was reviewed with emphasis on ECG data collection. I compared the mean QTc from the day 7 and day 21 tracings to the mean baseline QTc to look for prolongation.

Results

This trial was a 4 week double blinded, haloperidol controlled study in acute exacerbation of schizophrenia and schizoaffective disorder. Patients were randomized to one of 5 treatment groups (ziprasidone 2mg bid, 5mg bid, 20mg bid, 80mg bid, or haloperidol 15mg daily). Twelve lead ECG's were recorded for each subject at screening and prior to the morning dose on days 1,3,7,10,and 14. ECG's were also done 3-7 hours after dosing on days 21 and 28. The intervals were reported from the study site and were not re-analyzed using the accurate, digitized methodology mentioned previously. The QTc was derived using the following formula(
The sponsor reported the ECG results in tabular format in the study report.
The results listed in table 9.1 are summarized in the following table.

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[1]Methods and results discussed with D. Hoberman, PhD.

The sponsor concludes that ziprasidone does not cause QTc prolongation. Although there is evidence to support this conclusion (analyses of studies 108,108E,107,and 301; 303;101) because of the known variability of the QTc and the identified limitations in the methods of data collection, the ability to detect an effect, if present, is expected to be low. The sponsor dismisses the results of the STFDPC trials despite finding an increasing QTc prolongation for each increasing dose group except the highest. Additional analyses demonstrate that for all groups except the <40mg group, mean QTc difference from baseline is significantly longer than placebo. The mean QTc difference from baseline is also significantly longer for the 80mg group compared to the <40mg group. If we are to accept that there is no relationship between ziprasidone and QTc prolongation, then the sponsor must adequately explain the circumstances that led to the apparent dose response relationship findings in the STFDPC trial data.

Like much of the safety data in drug development, the ECG information was collected without intent to evaluate a specific effect. The were no studies designed to determine if ziprasidone causes QTc prolongation. The results from these analyses are only useful for generating hypotheses. The finding of SUDs rates in ziprasidone trials that are higher than observed for other recently approved antipsychotic medications, further stresses the need for additional testing to clarify the effect of ziprasidone on the QTc.

Gerard Boehm, M.D., M.P.H.
Safety Reviewer, Neuropharmacological Drug Products, HFD-120

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1-23-98
In my opinion, there is significant evidence of a "dose-response" relationship between ↑ziprasidone dose + ↑ QTc interval. It would not be surprising to see "negative" studies given the difficulty in measuring the QT. Appropriately-powered clinical trials while carefully-designed, could address the issue further, it is hard to believe that the dose-response relationship in the short-term fixed dose studies reviewed from chance or bias.

/S/

Appendix

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Table H.5.23a
Change from Baseline to Last Observation in ECG Readings
All Oral Dosing Phase II/III Studies

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc Int (msec)	Ziprasidone	1460	409.0	408.7		412.8	412.6		3.8
	Haloperidol	281	410.3	410.5		408.7	406.7		-1.7
	Risperidone	165	409.9	407.6		407.3	407.1		-2.6
	Amisulpride	12	400.4	403.5		401.6	406.5		1.2
	Placebo	251	411.3	409.0		408.7	407.8		-2.5
QT Int (msec)	Ziprasidone	1460	364.9	364.0		366.6	364.0		1.7
	Haloperidol	281	365.0	360.0		364.6	362.0		-0.4
	Risperidone	165	367.3	365.0		363.9	362.0		-3.4
	Amisulpride	12	353.7	360.0		367.4	360.0		13.8
	Placebo	251	361.5	360.0		360.5	360.0		-1.0
Heart Rate (bpm)	Ziprasidone	1460	76.9	75.0		77.7	77.0		0.8
	Haloperidol	281	77.5	76.0		76.8	76.0		-0.7
	Risperidone	165	76.3	74.0		76.8	75.0		0.5
	Amisulpride	12	78.7	75.0		72.3	72.5		-6.3
	Placebo	251	79.3	77.0		78.9	78.0		-0.4
PR Int (msec)	Ziprasidone	1461	153.0	152.0		152.5	152.0		-0.5
	Haloperidol	283	155.4	159.0		155.4	160.0		0.0
	Risperidone	165	152.4	153.0		152.1	150.0		-0.2
	Amisulpride	12	163.4	160.0		155.5	160.0		-7.9
	Placebo	251	150.6	151.0		151.5	152.0		0.8
QRS Int (msec)	Ziprasidone	1464	85.1	84.0		84.9	84.0		-0.2
	Haloperidol	283	83.9	84.0		84.5	84.0		0.6
	Risperidone	165	84.6	83.0		85.8	85.0		1.2
	Amisulpride	12	66.7	66.5		65.9	70.0		-0.8
	Placebo	251	86.8	87.0		87.3	86.0		0.4

Protocols: 015,101,102,104,104E,106,106F,108,108E,109,109E,110,111,114,115,116B,117,118,122,301,302,304,305
*QTc Int =
Baseline = last ECG taken before the first day of study treatment.
Final = last ECG taken while on study treatment or within six days after the last day of study treatment.
Date of table generation: 10FEB97.

Table 11.5.23b
Change from Baseline to Last Observation in ECG Readings
Short-Term Fixed-Dose Placebo-Controlled Oral Dosing Phase II/III Studies

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change	P-Value*
**QTc Int (msec)	Ziprasidone	657	410.2	408.0		416.8	415.0		6.6	0.001
	Haloperidol	76	409.7	411.6		409.9	409.0		0.2	
	Placebo	251	411.3	409.0		408.6	407.8		-2.6	
QT Int (msec)	Ziprasidone	657	364.6	364.0		367.2	364.0		2.7	0.253
	Haloperidol	76	366.1	363.5		365.7	364.0		-0.5	
	Placebo	251	361.5	360.0		360.2	360.0		-1.3	
Heart Rate (bpm)	Ziprasidone	657	77.5	75.0		78.9	78.0		1.4	0.322
	Haloperidol	76	76.8	75.0		77.0	75.5		0.2	
	Placebo	251	79.3	77.0		79.0	78.0		-0.3	
PR Int (msec)	Ziprasidone	655	150.8	150.0		149.8	150.0		-1.0	0.171
	Haloperidol	76	152.0	152.0		153.3	156.0		1.3	
	Placebo	251	150.6	151.0		151.7	152.0		1.1	
QRS Int (msec)	Ziprasidone	657	86.3	86.0		86.1	85.0		-0.1	0.619
	Haloperidol	76	85.1	85.5		85.7	84.0		0.6	
	Placebo	251	86.8	87.0		87.3	86.0		0.4	

Protocols: 104,106,114,115
*Two-tailed T-test

Baseline = last ECG taken before the first day of study treatment.
Final = last ECG taken while on study treatment or within six days after the last day of study treatment.
Date of table generation: 10FEB97.

Table H.5.2.3a
Change from Baseline to Last Observation in ECG Readings
Protocol 303

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc int (msec)	20mg BID	62	409.4	407.1		411.4	409.2		2.0
	40mg BID	61	399.9	401.4		403.5	406.7		3.5
	80mg BID	59	405.6	403.0		404.8	403.7		-0.8
	Placebo	48	406.1	408.3		401.4	404.8		-4.7
QT int (msec)	20mg BID	62	364.5	365.5		363.2	355.0		-1.3
	40mg BID	61	358.5	357.0		358.9	360.0		0.4
	80mg BID	59	358.1	358.0		367.3	365.0		9.2
	Placebo	48	365.4	365.0		358.1	351.0		-7.3
Heart Rate (bpm)	20mg BID	62	77.7	74.7		79.1	78.7		1.4
	40mg BID	61	76.1	74.3		77.5	75.7		1.4
	80mg BID	59	78.5	79.7		74.5	72.7		-4.0
	Placebo	48	76.6	73.4		77.0	75.8		0.5
PR int (msec)	20mg BID	62	149.1	145.0		148.8	149.0		-0.3
	40mg BID	60	157.3	157.5		153.5	155.0		-3.8
	80mg BID	59	151.7	153.0		151.5	146.0		-0.2
	Placebo	48	148.5	150.0		145.3	145.0		-3.2
QRS int (msec)	20mg BID	62	86.0	85.0		87.7	87.0		1.6
	40mg BID	61	87.4	86.0		87.2	87.0		-0.2
	80mg BID	59	86.5	86.0		84.9	84.0		-1.6
	Placebo	48	85.2	86.5		86.5	85.0		1.3

Protocol: [redacted]
*QTc int
Baseline = last ECG taken before the first day of study treatment.
Final = last ECG taken while on study treatment or within six days after the last day of study treatment.
Date of table generation: 12MAR97.

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EFFECT OF ZIPRASIDONE ON THE ECG

Objective: Purpose of the study was to determine the effect, if any, of varying doses of Ziprasidone on the ECG and to compare it with the effect of placebo and Haloperidol.

Material: The group included 658 individuals dosed with Ziprasidone, doses of 5, 20, 40, 60, 80 and 100 mg b.i.d. The N for Haloperidol and placebo was 79 and 245 respectively.

Method: The ECG variables included the heart rate, the P-R interval, QRS duration, intraventricular conduction defects, QT, QTc, ST-T, arrhythmias.

Results: There were no significant changes in heart rate, the P-R and intraventricular conduction after administration of Ziprasidone.

A statistically significant change at a p level of 0.05 or less was noted in the duration of the QT when compared with placebo at doses of 80 and 100 mg. The absolute prolongation was in the order of nsec respectively. No statistically significant change was noted at doses of 5, 20, 40 and 60 mg. The absolute difference between baseline and final mean for the 80 and 100 mg dose was 7.8 and 8.2 msec respectively.

A statistically significant prolongation of QTc, when compared with placebo, at a level of 0.05 or less, was noted at doses of 20, 40, 60, 80 and 100 mg. However, the respective absolute prolongation was No statistically significant change was noted at 5 mg dose. The absolute difference between the baseline and final mean for the 5 doses was 5.9, 3.6, 5.8, 10.6 and 8.4 msec respectively. In no instance did the QTc exceed 490 msec.

Conversion from normal to abnormal was observed in 37 (5.6%) of the 658 dosed individuals. Similarly, 39 (5.9%) converted from abnormal to normal during therapy. Of the 324 Haloperidol and placebo 15 (4.9%) converted from normal base to abnormal and 25 (7.7%) from abnormal to normal. The most frequent change was from normal ST-T to abnormal ST-T. Isolated prolongation of the P-R, QRS, appearance of LVH, LAFB, and rare PVCs were also noted.

Comment: As indicated there was no physiologically or statistically significant change in heart rate, P-R and QRS intervals. The ST-T changes most frequently noted are common, reflecting the very labile nature of repolarization (ST-T) and, thus, expected over the period of the trial. Furthermore, similar changes from abnormal ST-T to normal were observed. Similar incidence of conversion from normal to abnormal ST-T was recorded in the placebo group. Furthermore, the abnormalities did not appear dose related.

The isolated prolongation of the P-R, QRS, the LVH and the rare PVC are rarely if ever due to drugs.

Although there was some statistically significant prolongation of the QTc after dosing, and when compared with placebo and Haloperidol, the absolute prolongation was small and clinically insignificant.

Summary: There was no clinically significant effect of Ziprasidone on the ECG.

/S/

M.D.

Table H.5.23.2 (Pooled) - Centrally Read 108,108E,117, & 303
Change from Baseline to All Post Baseline Values in ECG Readings
By Actual Study Drug Dose Taken the Day of the Reading
Centrally Read Maintenance Oral Dosing Phase II/III Studies

	Zip <20mg BID			Zip 20-<40mg BID			Zip 40-<60mg BID			Zip 60-<80mg BID			Zip 80-<100mg BID		
	N	Base Mean	Mean**	N	Base Mean	Mean**	N	Base Mean	Mean**	N	Base Mean	Mean**	N	Base Mean	Mean**
*QTc int	234	405.1	0.3	172	406.8	2.8	309	407.0	3.0	71	410.0	-0.6	165	408.0	1.7
QT int	234	364.7	-2.5	173	368.3	0.6	309	366.3	3.5	70	371.1	2.1	165	366.3	9.6
Heart Rate	234	75.7	1.5	173	74.8	1.0	309	75.5	-0.2	70	74.9	-1.1	165	76.0	-3.2
PR int	233	153.9	-1.4	173	152.3	-1.2	306	155.8	-1.9	70	154.4	-0.7	165	151.7	-1.3
QRS int	234	86.1	-0.1	173	85.7	-0.7	309	85.5	-0.1	70	83.1	-0.8	165	84.6	0.1

(CONTINUED)
Protocols: 108,108E,117,303
*QTc int
** Mean change from baseline to subject baseline value using all post baseline readings.
Total Changed = number of postbaseline ECG values within six days after the last day of study treatment for which that dose level of study drug was taken the day of the ECG readings.
Date of table generation: 21OCT97.

Results of the reanalysis of ECG data from the STFDPC trials

Last minus baseline

	n	mean QTc baseline	mean QTc last	QTc difference	QT difference	pulse difference
Placebo	250	399	396.5	-2.6	0.3	-1.1
<40 mg	230	396.9	397.5	0.6	-4.4	2.4
40 mg	138	397.6	403.4	5.9	0.3	2.2
60 mg	111	398	405.7	7.7	7.1	-0.2
80 mg	100	394.6	404.3	9.7	7.2	0.4
>=100 mg	77	402.7	409.1	6.4	5.8	0.2

Last on treatment minus baseline

	n	mean QTc baseline	mean last QTc	QTc difference	QT difference	pulse difference
Placebo	152	399.8	395.6	-4.2	0.2	-1.4
<40 mg	147	397.1	397.8	0.8	-2.7	1.7
40 mg	78	398.6	403.1	4.6	1.8	1.1
60 mg	74	398.1	405.9	7.9	8.8	-0.9
80 mg	57	394.7	403.4	8.8	6	0.8
>=100 mg	52	403.1	411.1	8	7.9	-0.3

Day 14 minus baseline

	n	mean baseline QTc	mean d14 QTc	QTc difference	QT difference	pulse difference
Placebo	197	399.7	397.1	-2.6	0	-1.1
<40 mg	179	386.4	399.7	3.4	-5.9	4.1
40 mg	116	397.7	403.8	6.1	-1.2	3.3
60 mg	97	398.8	407.2	8.4	6.3	0.2
80 mg	92	395.7	409	13.3	4.1	3.2
>=100 mg	69	402	410.5	8.5	10.1	-0.8

QTc max minus baseline

	n	mean baseline QTc	mean max QTc	QTc difference	QT difference	pulse difference
Placebo	250	399	403.4	4.3	-1	2.2
<40 mg	230	396.9	406.4	9.5	-5.2	6.1
40 mg	138	397.6	410.4	12.8	0.6	4.6
60 mg	111	398	413.2	15.2	5.7	3
80 mg	100	394.6	414.4	19.8	6.2	4.6
>=100 mg	77	402.7	417.7	15	9.7	1.8

Tukey Kramer Pair wise comparison of the mean QTc differences

Using last on treatment minus baseline

	Placebo	<40	40	60	80	100
Placebo		-	+	+	+	+
<40	-		-	-	-	-
40	+	-		-	-	-
60	+	-	-		-	-
80	+	-	-	-		-
100	+	-	-	-	-	

+Significant difference

Using Last minus baseline

	Placebo	<40	40	60	80	100
Placebo		-	+	+	+	+
<40	-		-	-	+	-
40	+	-		-	-	-
60	+	-	-		-	-
80	+	+	-	-		-
100	+	-	-	-	-	

+Significant difference

Using Day 14 QTc-baseline

	Placebo	<40	40	60	80	100
Placebo		-	+	+	+	+
<40	-		-	-	+	-
40	+	-		-	-	-
60	+	-	-		-	-
80	+	+	-	-		-
100	+	-	-	-	-	

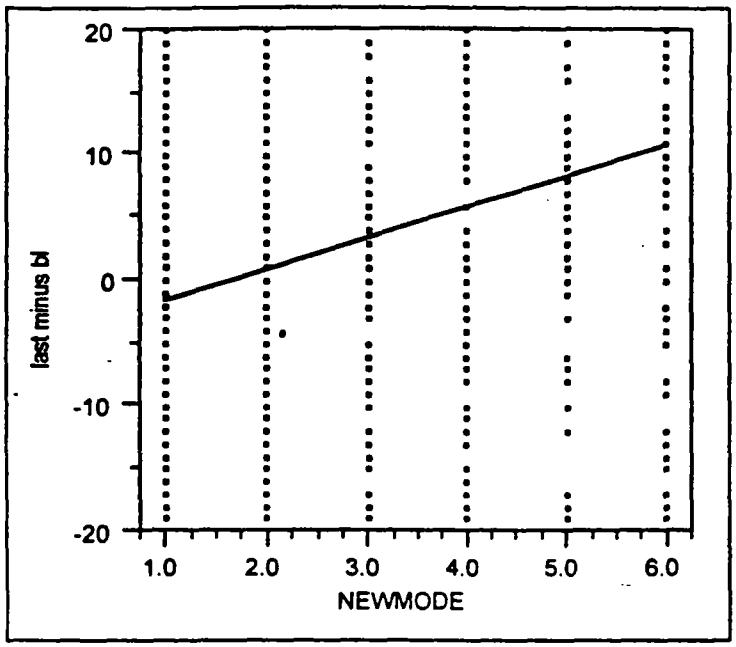
+Significant difference

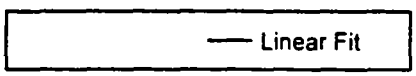
Using QTcmax minus baseline

	Placebo	<40	40	60	80	100
Placebo		-	+	+	+	+
<40	-		-	-	+	-
40	+	-		-	-	-
60	+	-	-		-	-
80	+	+	-	-		-
100	+	-	-	-	-	

+Significant difference

last minus bl By NEWMODE





Linear Fit

last minus bl = -4.0292 + 2.48476 NEWMODE

Summary of Fit

RSquare	0.038618
RSquare Adj	0.037555
Root Mean Square Error	20.17928
Mean of Response	2.909492
Observations (or Sum Wgts)	906

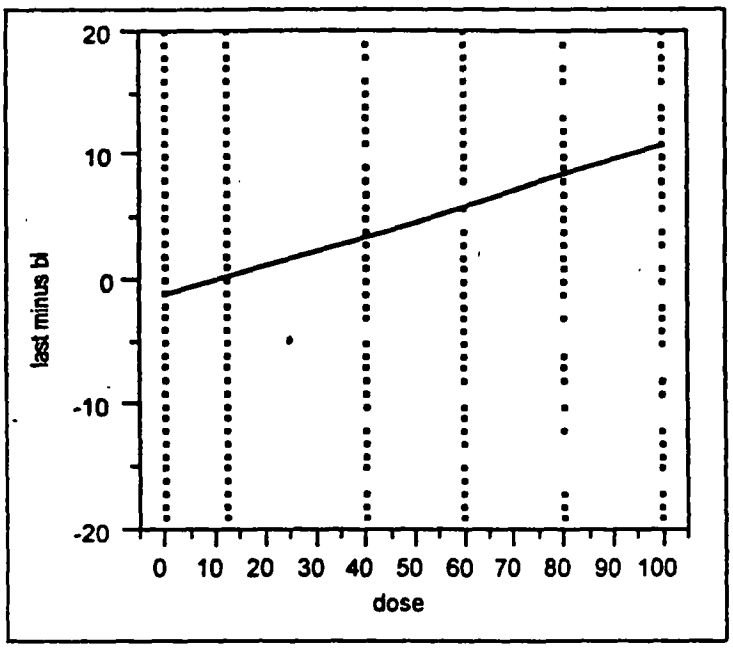
Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	14786.80	14786.8	36.3131
Error	904	368111.78	407.2	Prob>F
C Total	905	382898.58		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-4.0292	1.332402	-3.02	0.0026
NEWMODE	2.4847649	0.412338	6.03	<.0001

last minus bl By dose



Linear Fit

last minus bl = -1.1723 + 0.12024 dose

Summary of Fit

RSquare	0.038604
RSquare Adj	0.03754
Root Mean Square Error	20.17943
Mean of Response	2.909492
Observations (or Sum Wgts)	906

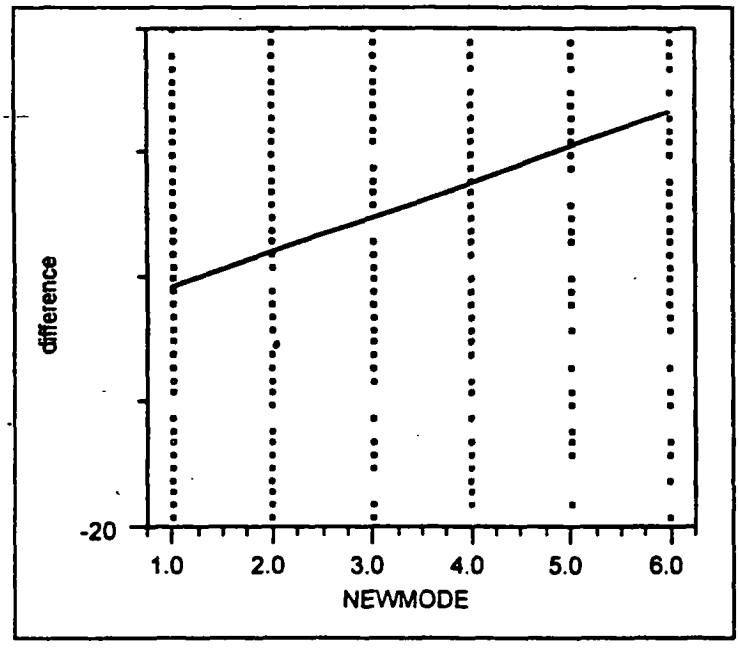
Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	14781.35	14781.4	36.2991
Error	904	368117.23	407.2	Prob>F
C Total	905	382898.58		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-1.172281	0.953125	-1.23	0.2190
dose	0.1202434	0.019958	6.02	<.0001

difference By NEWMODE



Linear Fit

difference = -3.6359 + 2.83924 NEWMODE

Summary of Fit

RSquare	0.049201
RSquare Adj	0.047929
Root Mean Square Error	20.62923
Mean of Response	4.56
Observations (or Sum Wgts)	750

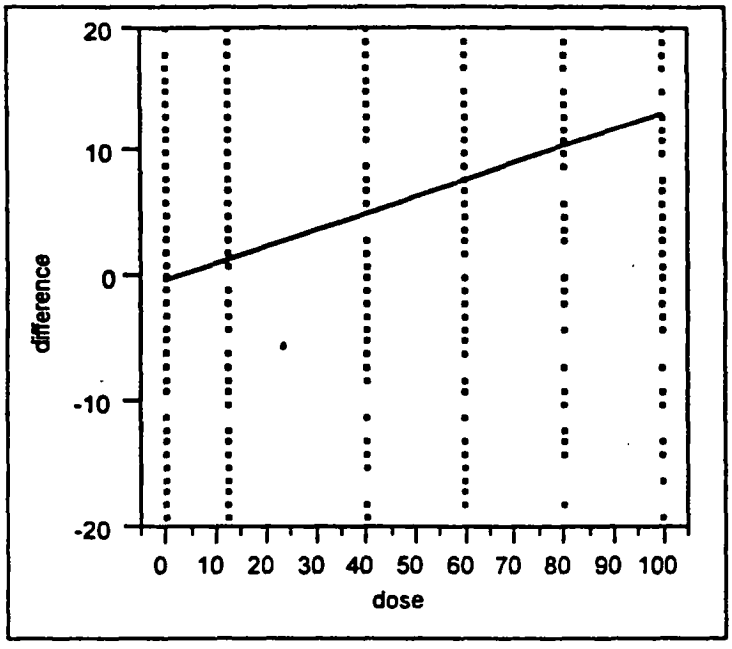
Analysis of Variance

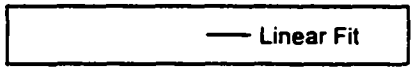
Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	16472.11	16472.1	38.7064
Error	748	318322.69	425.6	Prob>F
C Total	749	334794.80		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-3.635928	1.517522	-2.40	0.0168
NEWMODE	2.8392359	0.456362	6.22	<.0001

difference By dose





Linear Fit

difference = -0.2855 + 0.13481 dose

Summary of Fit

RSquare	0.047369
RSquare Adj	0.046095
Root Mean Square Error	20.64909
Mean of Response	4.56
Observations (or Sum Wgts)	750

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	15858.89	15858.9	37.1938
Error	748	318935.91	426.4	Prob>F
C Total	749	334794.80		<.0001

Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	-0.285523	1.095343	-0.26	0.7944
dose	0.13481	0.022105	6.10	<.0001

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13 Pratt C, Ruberg S, Morganroth J, McNutt B, Woodward J, Harriss S, Ruskin J, Moye L, Dose Response Relation Between Terfenedine (Seldane) and QTc Interval on the Scalar Electrocardiogram, Am Heart J 1996; 131: 472-480.

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NDA COMPLETED JUN 22 2000

MEMORANDUM

Food and Drug Administration
Center for Drug Evaluation and Research
Division of CardioRenal Drug Products
Consultation

Date: 6/14/00

To: Russell Katz, MD
Division Director, HFD-120

From: Maryann Gordon, MD /S/
Medical Reviewer, HFD-110

Through: Shaw Chen, MD. PhD /S/
Medical Team Leader, HFD-110

Dr. Raymond Lipicky /S/
Division Director, HFD-110

Subject: Ziprasidone, NDA# 20825
Study report of Clinical Pharmacology Protocol #128-054

Conclusion

Study 128-054 has demonstrated that the antipsychotic agents ziprasidone and thioridazine adversely affect cardiac repolarization in that these drugs prolong the QTc and QT intervals in a concentration-related manner. Patients who take drugs that prolong these ECG intervals are at risk of serious cardiac arrhythmias such as torsade de points (TdP) and sudden death. The effect on cardiac repolarization of the other antipsychotic agents used in study 128-054 for comparison appears to be minimal or absent.

Taking into account ECG data from this study as well as other trials, ziprasidone increases the QTc from baseline on average about 10-20 msec, thioridazine approximately 36 msec, and sertindole, an antipsychotic removed from the UK market for causing TdP and sudden death, about 21 msec. Although the magnitude of the increase of the QTc (and QT) is thought by experts to be important, it is not predictive of the degree of risk of TdP or other serious ventricular arrhythmias.

The co-administration of a metabolic inhibitor with ziprasidone and thioridazine increased blood levels and QTc only slightly compared to the use of these drugs alone. Therefore, drug-drug interactions similar to what occurred with terfenadine (when blood levels increased dramatically when ketoconazole was taken along with terfenadine) are much less of a concern with these agents.

In summary, a certain proportion of patients taking ziprasidone or thioridazine will have an increased risk of potentially fatal ventricular arrhythmias. The Cardio-Renal Division considers it essential that any agent with an added safety risk, unless efficacy data suggest superior benefit compared to other drugs for the same indication, should either not be made available or should be reserved for second line therapy.

Finally, adverse effects such as increases in total cholesterol and large weight gains reported with some of the other antipsychotic agents are unlike sudden death in that they can be identified early and the patient at risk can be switched to another agent. Therefore, the claim that ziprasidone has less cardiovascular risk factors because the drug causes less weight gain and/or improves lipid profile cannot offset its likely

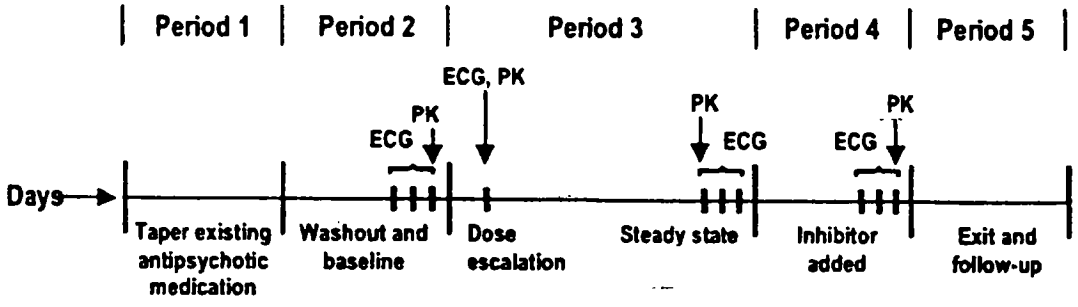
propensity to cause sudden death.

Introduction
(Please refer to previous consults written by Dr. C. Ganley and dated 12/17/98, 11/18/97, and 2/21/97)

The sponsor of ziprasidone was sent a letter by the Agency on 6-17-98 stating that the drug was not approvable because of its effect on cardiac repolarization. The concern was that the "modest" effect (QTc[1] prolongation of about 10 msec with the 160 mg dose) was an underestimation because the ECGs were not obtained at maximum drug concentration. The study reviewed here was specifically designed to address this issue and also to compare the effect of ziprasidone on cardiac repolarization to the effect of other approved antipsychotic drugs.

Study Design, protocol #128-054
This was a randomized, open-label, parallel, multi-center study in subjects with normal ECGs (QTc <450 msec) and psychotic disorders. Following a screening phase, the trial consisted of five different treatment periods:
Period 1: subjects who were eligible for enrolling in the study had their current medication tapered over several days as an out-patient;
Period 2: subjects entered a clinical research facility to be completely withdrawn from current therapy.
Period 3: subjects were randomized to one of six treatments (ziprasidone, risperidone, olanzapine, quetiapine, thioridazine or haloperidol) with the dose escalated over 10 to 19 days;
Period 4: after the maximum dose of randomized therapy was achieved, the metabolic inhibitor selected for each drug was administered;
Period 5: after steady state is reached with the combination of randomized therapy and a metabolic inhibitor, the subjects were withdrawn from therapy.

The study diagram is shown below.



ECGs were obtained at baseline, at start of study drug (day 2), at steady state (period 3), and with the inhibitor (period 4). ECGs were recorded at times estimated to correspond with the mean Tmax for each study drug.

Dosing and metabolic inhibitors

Subjects were to be titrated to the highest dose tolerated. The initial and maximum doses used for each

[1] Bazett's correction: QTc=QT/sqrt (60/hr rate)

treatment group and the doses of the metabolic inhibitors are shown below.

Study Drugs (Period 3)	Potency (mg)	Initial Dose (mg/day)	Maximum Dose (mg/day)
Ziprasidone	20, 40, and 80 (capsules)	40	160
Risperidone	1, 2, 3, and 4 (tablets)	2	16
Olanzapine	5 and 10 (tablets)	5	20
Quetiapine	25, 100, and 200 (tablets)	50	750
Thioridazine	25 and 100 (tablets)	50	300
Haloperidol	2, 5, and 10 (tablets)	2	15
Metabolic Inhibitors (Period 4)			
Paroxetine	20 (tablet)	20	
Ketoconazole	200 (tablet)	400	
Fluvoxamine	50 (tablet)	50	100

There were changes with the administration of the inhibitors during period 4:
Originally,
-ketoconazole (200 mg BID) was administered with ziprasidone and quetiapine,
-paroxetine (20 mg 00) was administered with thioridazine and risperidone,
-fluvoxamine (50 mg escalating to 100 mg QD) was administered with olanzapine.
-paroxetine (20 mg QD) and ketoconazole (200 mg BID) were administered with haloperidol.

Late in the study, ketoconazole (200 mg BID) was substituted for paroxetine as the metabolic inhibitor in the risperidone group, and the regimen for dosing ketoconazole to the haloperidol group was changed from 200 mg BID to 400 mg QD by protocol amendment.

Comments on the protocol raised by Dr. Ganley
1) the study was to enroll a sufficient number of subjects such that 150 subjects (25 per group) completed the entire study. There was no explanation in the protocol to justify the sample size.
2) The protocol was lacking in its description of how the QTc data should be interpreted. There was, however, an expectation that the change in QTc interval with ziprasidone therapy was to be different from haloperidol.

Study results

A total of 183 subjects were randomized and had evaluable ECG data. Patient demographics are shown below.

	Baseline Demographic Characteristics											
	Ziprasidone		Risperidone		Olanzapine		Quetiapine		Thioridazine		Haloperidol	
	M[a]	F[b]	M	F	M	F	M	F	M	F	M	F
Number of subjects	25	10	22	6	20	8	22	7	25	6	25	7
Mean age (yrs)	38.6	36.1	38.3	37.3	38.2	38.6	38.1	40.6	35.5	37.3	33.7	43.0
Age range (yrs)	22-58	20-47	20-55	29-47	22-58	25-53	26-47	27-57	21-48	30-44	20-47	35-49
Mean weight (kg)	85.9	79.8	84.1	88.0	86.0	86.2	83.9	87.7	90.5	87.1	77.9	75.6

[a]M=male; [b]F=female

Mean age and range, mean weight and number of subjects were reasonably similar for the different treatment groups.

There were 8 subjects (2 ziprasidone, 3 quetiapine, and 3 haloperidol who did not reach the protocol-specified maximum daily dose of study drug in Period 3. Seven of the eight were discontinued prematurely. The eighth received 600 mg of quetiapine at steady-state rather than 750 mg because of adverse events. This subject completed the study. One thioridazine subject required a dose higher than that specified in the protocol.

Heart rate and correction factors

QT interval is inversely related to heart rate (normally, the slower the heart rate the longer the QT interval). To compensate for normal variations in heart rate, the Bazett's correction, known as QTc, is used. The use of Bazett's correction factor is controversial with drugs that increase heart rate. Among the group of drugs studied here, quetiapine was the only one that consistently raised heart rate throughout the study. The mean change from baseline heart rate for the various agents are shown in the attachment.

QT/QTc

Baseline is defined as the average of the planned ECGs collected on days –2, -1, and 0.
All ECGs were obtained at Tmax and all were read centrally. QTc intervals were provided by the central reader.

Mean changes
The tables below show the mean change QTc and QT from baseline at the start of titration (day 2) and at steady state (period 3).

Start of titration

Mean change (SD) from baseline at Day 2: msec

	Zisprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QTc	3.0 (10.7)	4.7 (14.1)	0.3 (9.0)	-0.5 (8.6)	11.2 (13.2)	2.2 (12.4)
QT	-3.6 (17.3)	-5.3 (11.2)	-3.7 (12.8)	-0.1 (12.4)	1.1 (16.6)	-0.8 (15.6)

Tables 5.2.2.1 and 5.2.3.2.1

At the start of dosing, only thioridazine shows a substantial prolongation of the QTc (11.2 msec). Changes from baseline in QTc/QT are similar for ziprasidone and the rest of the agents.

Steady state

Mean change (SD) from baseline at Period 3: msec

	Zisprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QTc	20.6 (16.4)	10.0 (11.1)	6.4 (13.6)	14.5 (12.7)	35.8 (13.5)	4.7 (16.9)
QT	7.0 (18.40)	-11.8 (12.8)	-9.3 (18.0)	-12.2 (15.1)	19.7 (22.3)	12.5 (16.7)

Tables 5.2.2.1 and 5.2.3.2.1

Thioridazine at steady state caused a 35.8 msec increase in QTc (9% increase from baseline) and a 19.7 msec increase in QT (5% increase from baseline). The next largest increase was caused by ziprasidone with a 20.6 msec increase in QTc (5% increase from baseline) and a 7 msec increase in QT (2% increase from baseline). While risperidone, olanzapine, and quetiapine were associated with an increased QTc, the QT was decreased for these agents. Haloperidol increased QTc by 4.7 msec and it is generally accepted, perhaps erroneously, that its effect on QTc is not different from placebo.

With metabolic inhibitor

Mean change (SD) from baseline at Period 4: msec

	Zisprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Ratio^	1.39	2.47	1.77	4.03	1.04	1.94
QTc	20.4 (17.0)	3.2 (16.9)	5.3 (12.8)	19.7 (13.5)	28.0 (17.3)	8.9 (15.0)
QT	9.9 (21.0)	1.1 (18.6)	-1.8 (17.8)	-15.8 (16.9)	33.3 (23.1)	22.5 (19.9)

^drug concentrations period 4: period 3

Tables 5.2.2.1, 5.2.3.2.1, and page 38 of study report

Quetiapine showed the largest increase in plasma concentration when subjects were also given a metabolic inhibitor. Compared to steady state, the concentration of ziprasidone increased slightly while the mean QT/ QTc prolongation (20.4/9.9 msec) was basically unchanged.

Outliers

The tables below shows the number and percent of subjects with QTc increases from baseline of $\geq$30, $\geq$60, and $\geq$ 75 msec for the various drugs at steady state (period 3) and with the metabolic inhibitor (period 4).

Number and (percent) of subjects Period 3

Increase from baseline	Zisprasidone N=33	Risperidone 16 mg N=28	Olanzapine N=26	Quetiapine N=27	Thioridazine N=30	Haloperidol N=20
QTc: $\geq$ 30 msec	21 (64)	12 (46)	9 (35)	14 (52)	30 (97)	11 (41)
QTc: $\geq$ 60 msec	7 (21)	1 (4)	1 (4)	3 (11)	9 (29)	1 (4)
QTc: $\geq$ 75 msec	1 (3)	0	0	0	3 (10)	0

Table 5.3.3.2

Number and (percent of subjects) Period 4

Increase from baseline	Zisprasidone N=32	Risperidone N=20	Olanzapine N=24	Quetiapine N=27	Thioridazine N=30	Haloperidol N=20
QTc: $\geq$ 30 msec	25 (78)	8 (40)	8 (33)	8 (67)	27 (90)	9 (45)
QTc: $\geq$ 60 msec	4 (13)	0	0	4 (15)	6 (20)	0
QTc: $\geq$ 75 msec	1 (3)	0	0	0	4 (13)	0

Table 5.3.4.2

Only thioridazine and ziprasidone increased QTc by 75 msec or more in at least 1 study patient.

Relationship to drug concentration.

The attached figures[2] show individual QTc and QT values plotted against drug concentration on a log scale for each of the antipsychotic agents. The steepness of the slope indicates the magnitude of increase in QTc and QT for every log increase in concentration.

Thioridazine and ziprasidone showed the steepest slope for both QTc and QT followed by haloperidol. While the effect of quetiapine on the QTc was impressive (slope of 15), the changes in QT was negative. Olanazepine had a small positive slope and the slope for risperidone was flat.

Lipid profiles

Median changes and median percent changes from baseline at last planned visit prior to discharge in fasting serum cholesterol and triglycerides are shown below by treatment group.

Serum Lipid Concentrations: Median Baseline (Median Change; mg/dl) and % Change from Baseline

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
Cholesterol						
Total	197.5(-14.5[c])	204.0(-3.0[a])	201.0(4.0')	196.0(5.0')	186.0(21.0[c,'])	193.0(-22.0[c])
% Change	-7.5[a]	-1.6[a]	2.1'	2.4'	13.7[c,']	-11.5[c]
HDL	43.5(0.0)	41.0(-2.0)	44.0(-2.0)	45.0(-3.0)	41.0(1.5)	43.0(-3.0[a])
% Change	0.0	-4.9	-4.6	-8.6	3.0	-6.0[a]
LDL	122.0(-11.0)	125.0(9.0[a])	128.0(1.5)	117.0(-0.5[a])	121.0(20.0[c,'])	121.0(-14.0[c])
% Change	-8.5	6.5[a]	1.1	-0.3[a]	18.6[c,']	-10.5[c]
Triglycerides	141.0(-37.0[c])	158.0(-17.0)	148.0(43.0[c,'])	124.0(25.0[c,'])	120.0(9.0[a])	118.0(-18.0[a])
% Change	-28.0[c]	-6.7[a]	31.0[c,']	18.3[c,']	7.9'	-18.0[a]
Total/HDL Ratio	4.31(-0.33[a])	5.43 (0.31[a])	5.14(0.28[a])	4.42(0.48[a,'])	4.61(0.41[a,'])	4.26(-0.22[a])
% Change	-7.5[a]	5.9[a,*]	5.4[a,*]	10.8[a,']	12.4[c,']	-7.0[a]

[a]p<0.05; [a]p<0.01; [c]p<0.001 versus baseline using Wilcoxon signed rank test on change from baseline values against 0; [a]p<0.05, [a]p<0.01, 'p<0.001 versus ziprasidone by two-sided Wilcoxon test.

The sponsor claims that ziprasidone has a beneficial effect on lipid profiles. In the Division's opinion, if patients need control of their lipids, treating them with a lipid lowering agent would be preferred.

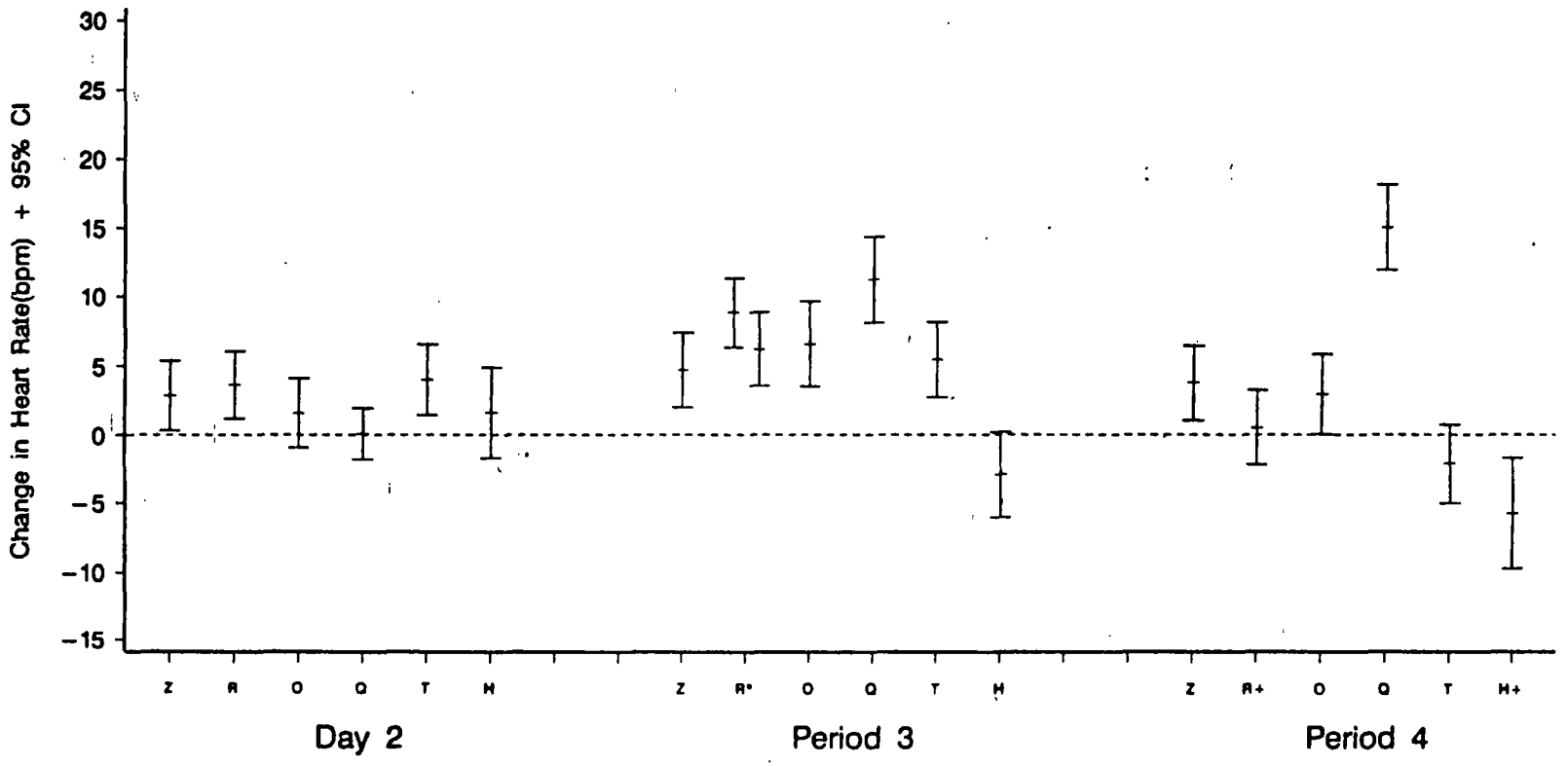
cc /S/
Orig.
HFD-110/SChen
HFD-120/RGlass/TLaughren

[2] courtesy of Dr. Gabriel Robbe, Biopharmacology Reviewer

Figure 2.2

Mean Change from Baseline Heart Rate(bpm) and 95% Confidence Intervals at Each Period by Treatment Group – All Subjects

Ziprasidone Protocol 054



Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.

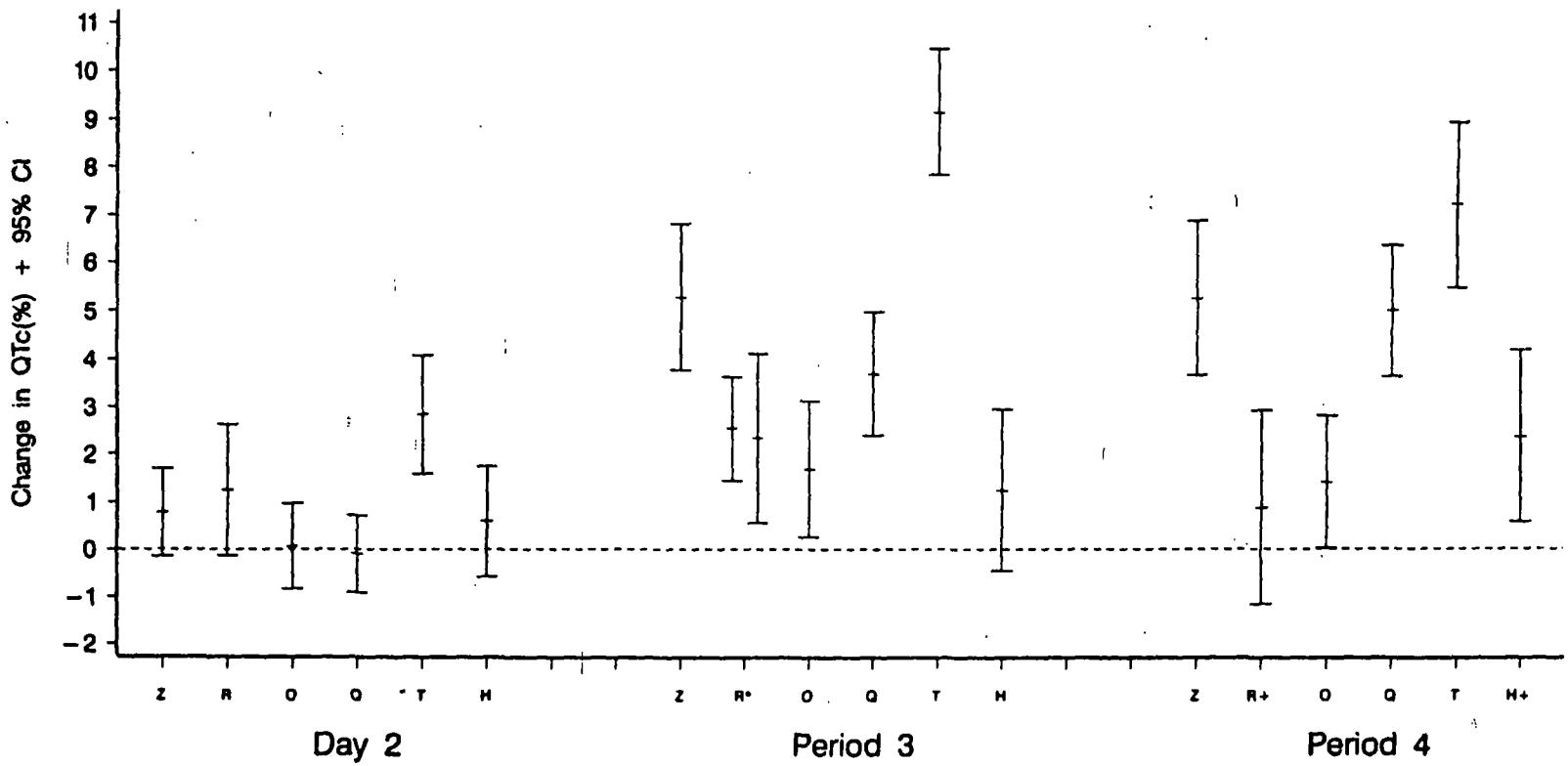
* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.

+ Contains only pre (3/16/99) amendment values, post – amendment values are provided in the listings.

Source Data: Table 5.2.2.2.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Figure 1.2.2

Percent Change from Baseline QTc Interval(msec) and 95% Confidence Intervals at Each Period by Treatment Group – All Subjects
Ziprasidone Protocol 054

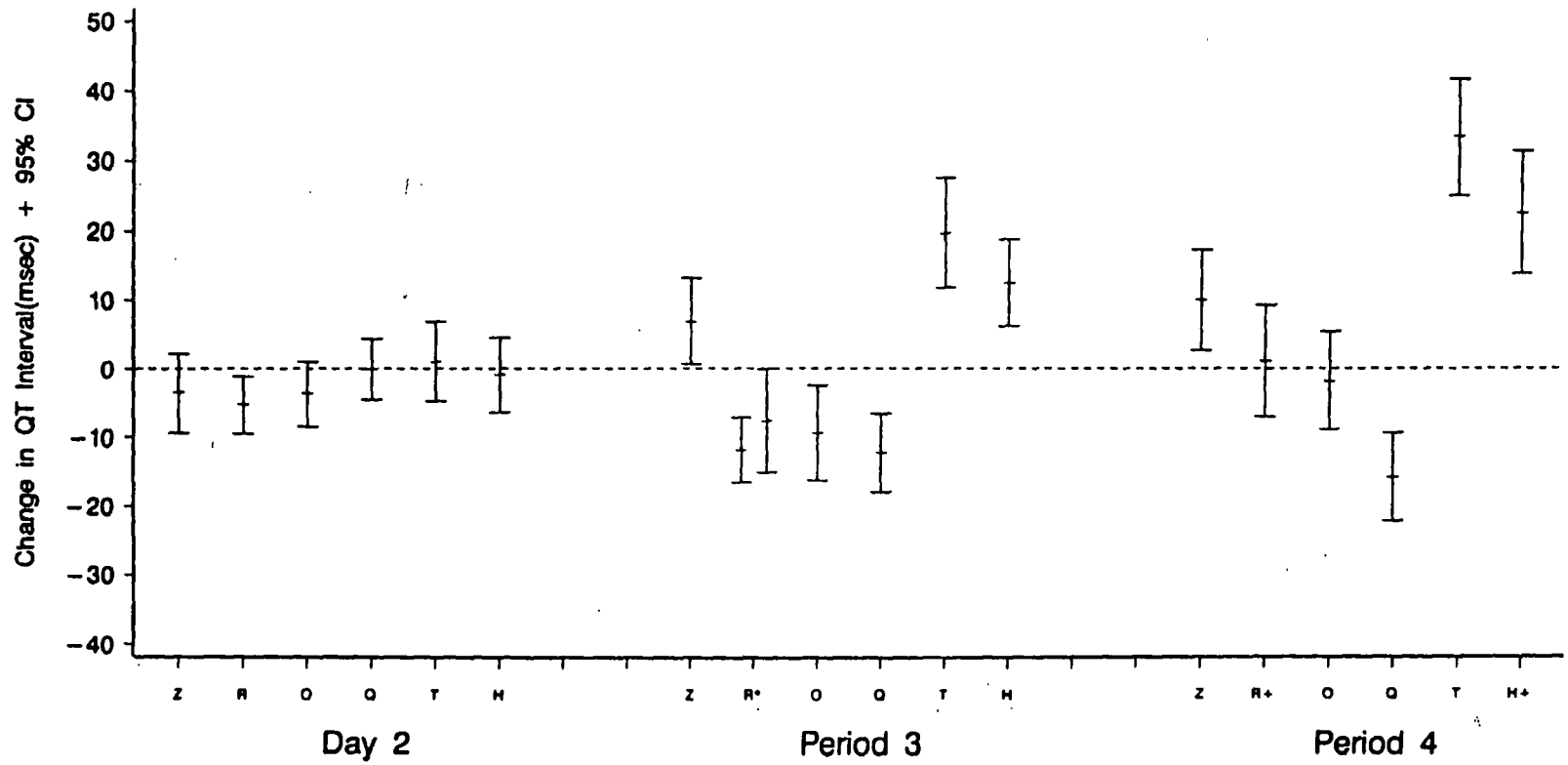


Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.
* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.
+ Contains only pre (3/16/99) amendment values, post – amendment values are provided in the listings.
Source Data: Table 5.2.1.2.2. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Figure 3.2

Mean Change from Baseline QT Interval(msec) and 95% Confidence Intervals at Each Period by Treatment Group – All Subjects

Ziprasidone Protocol 054



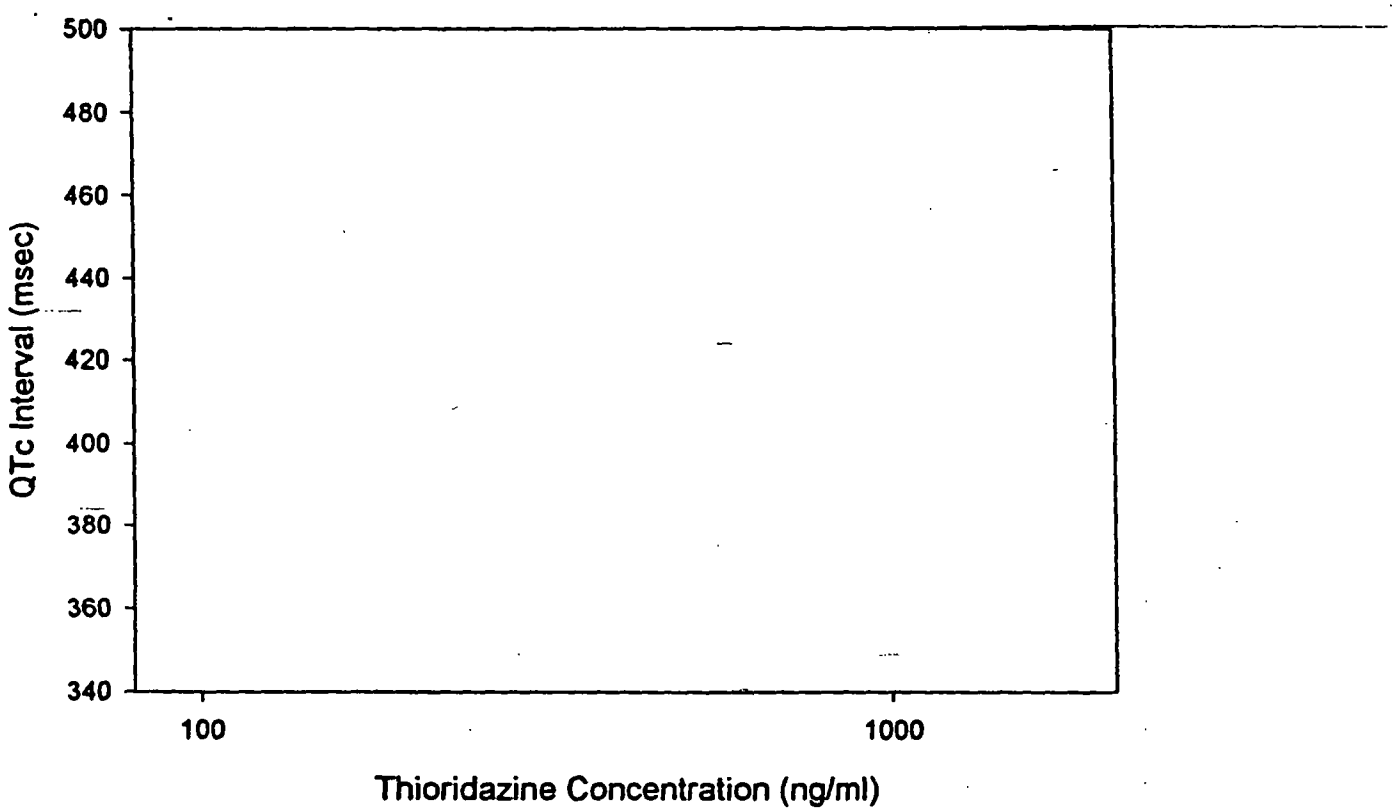
Z = Ziprasidone, R = Risperidone, O = Olanzapine, Q = Quetiapine, T = Thioridazine, H = Haloperidol.

* Bar on left is Risperidone 6 – 8 mg, bar on right is Risperidone 16 mg.

+ Contains only pre (3/16/99) amendment values, post – amendment values are provided in the listings.

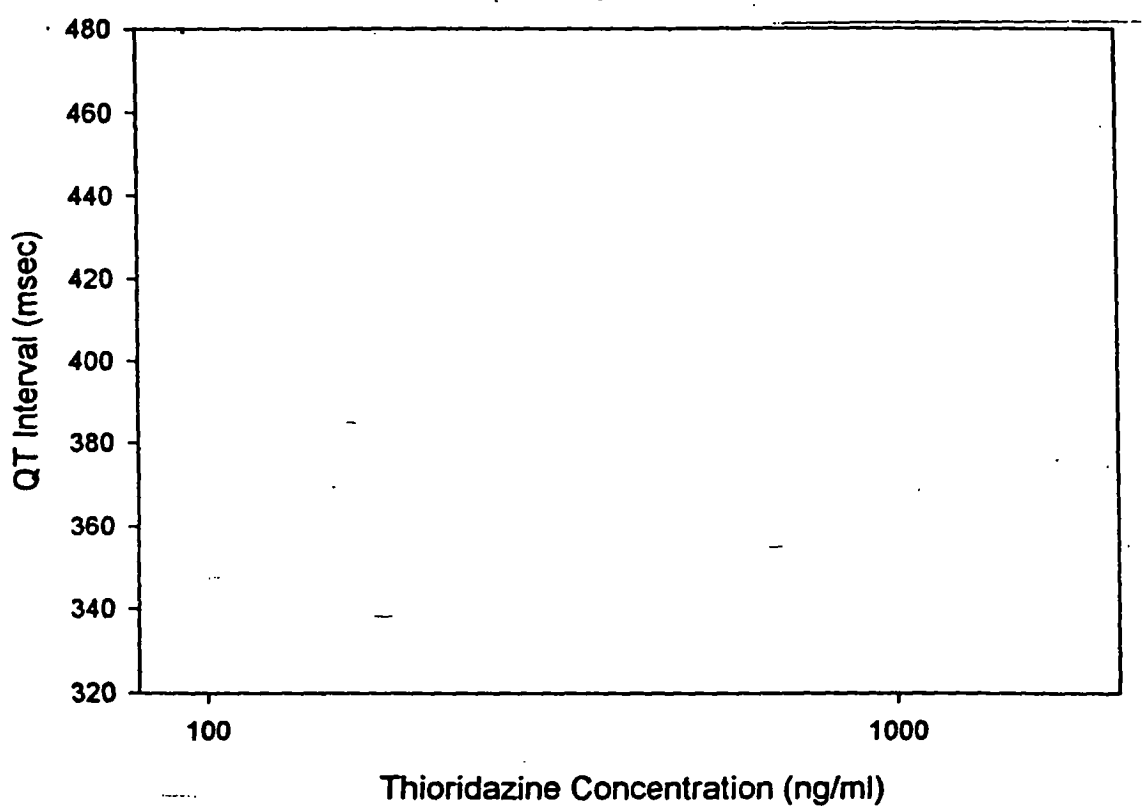
Source Data: Table 5.2.3.2.1. Date of Data Extraction: 03JUN99. Date of Figure Generation: 07JUL99.

Effect of Thioridazine on QTc Interval



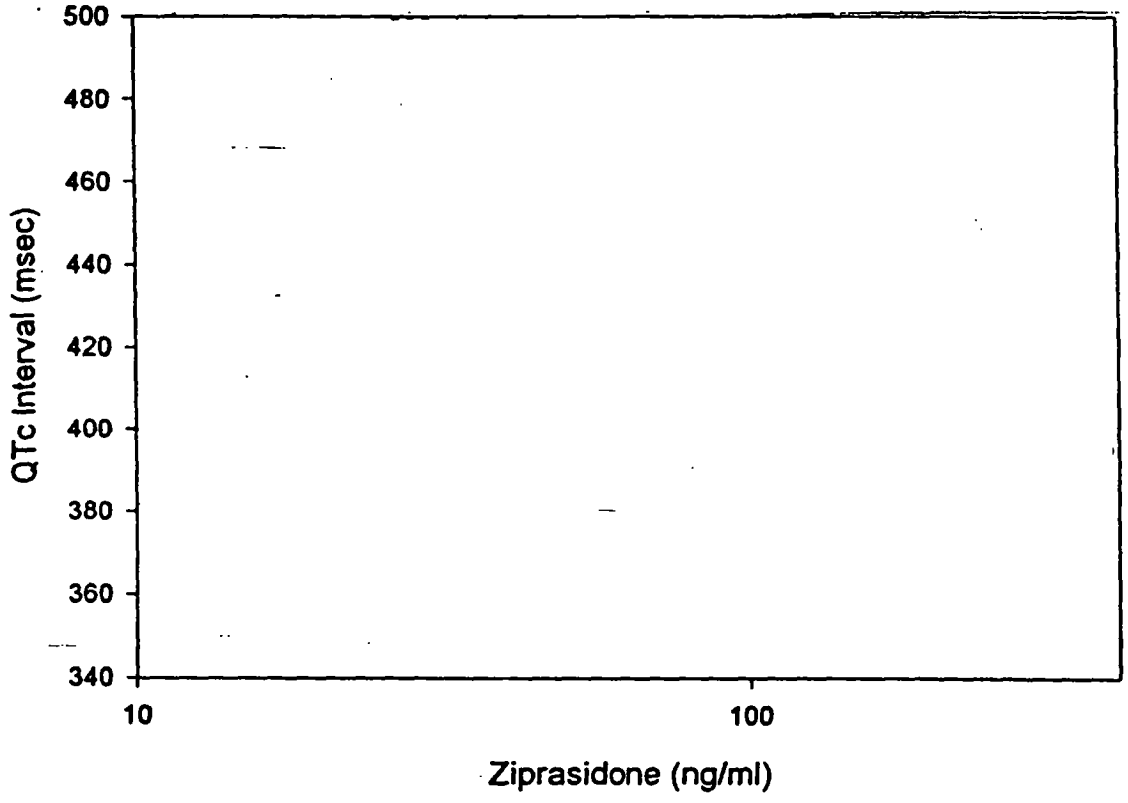
Intercept = 311.7693
Slope = 40.4152
r^2=0.248075

Effect of Thioridazine on QT Interval



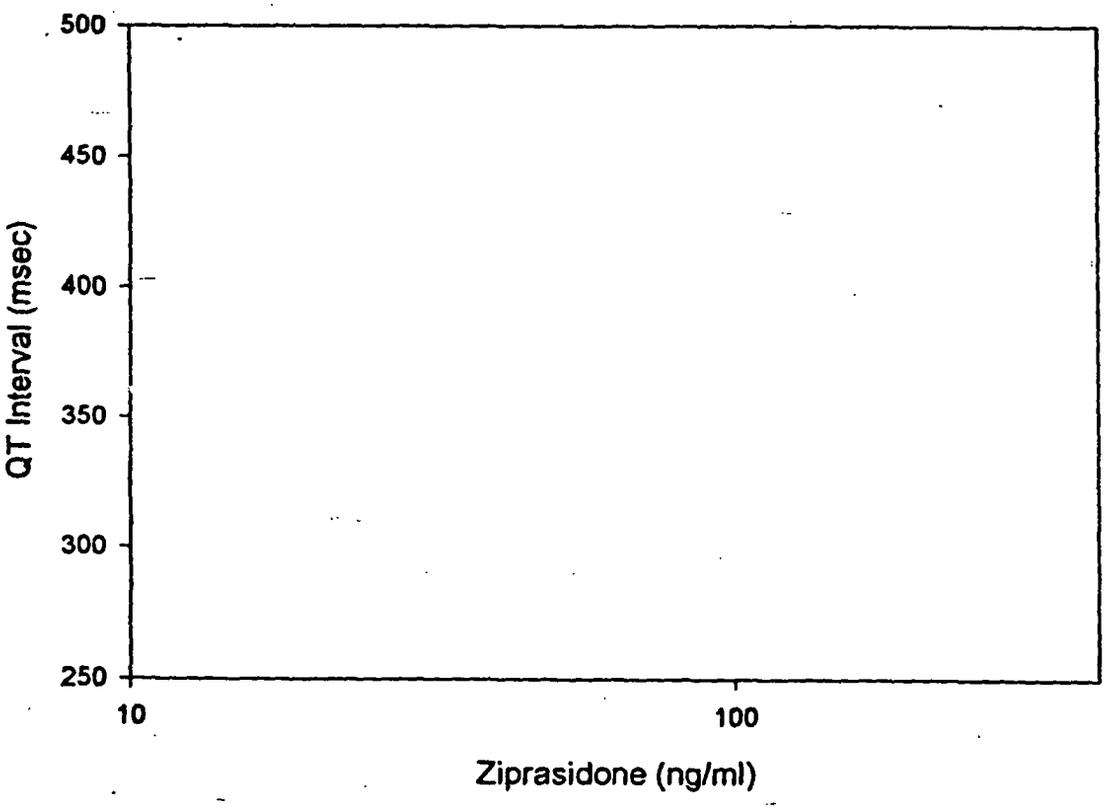
Intercept = 272.776
Slope = 44.17474
r^2=0.2164634033

Effect of Ziprasidone on QTc Interval



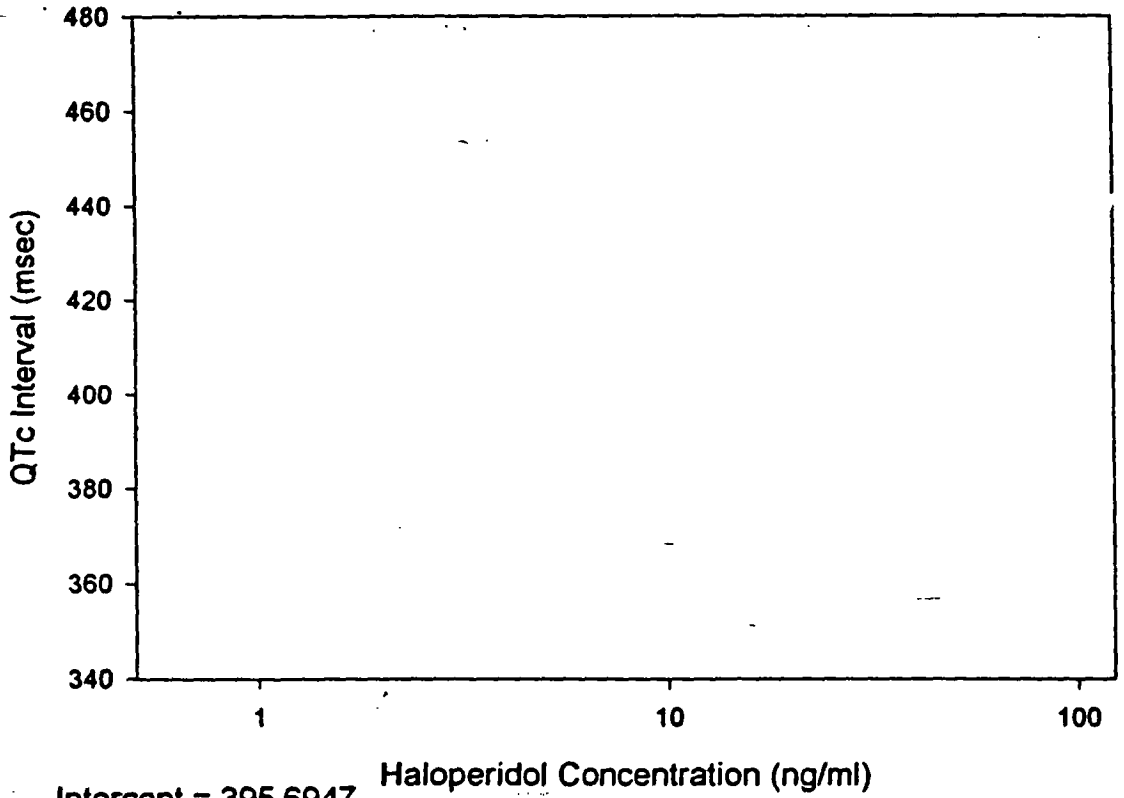
Intercept = 372.711
Slope = 21.57282
r2 = 0.09080

Effect of Ziprasidone on QT Interval



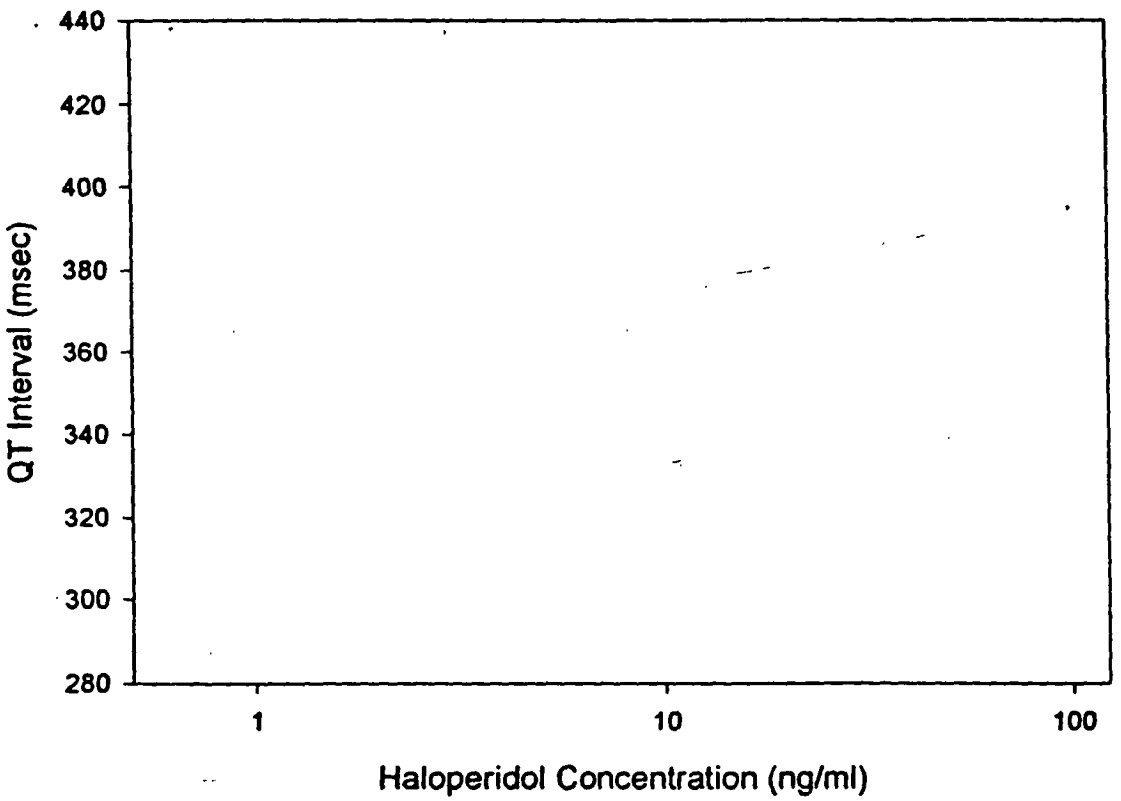
Intercept = 319.724
Slope = 23.342
r^2= 0.082985

Effect of Haloperidol on QTc Interval



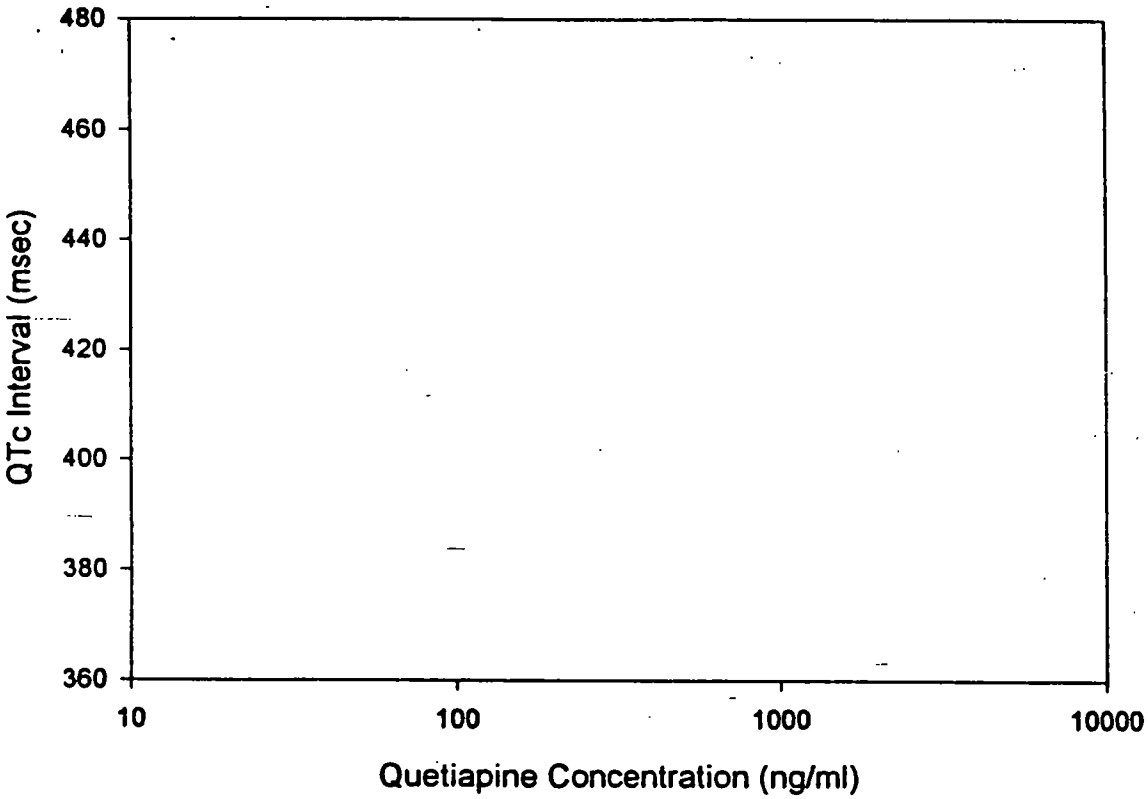
Intercept = 395.6947
Slope = 8.0848
r^2=0.02004478

Effect of Haloperidol on QT Interval



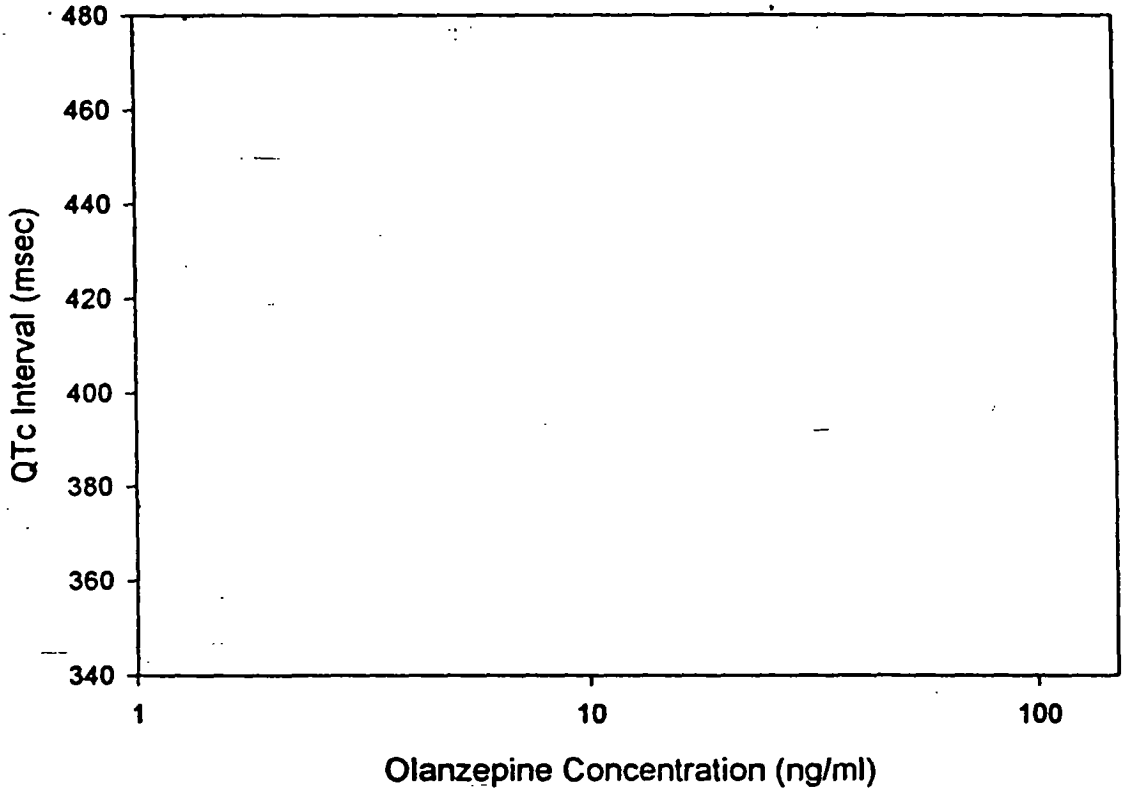
Intercept = 351.81535
Slope = 21.5923
r^2=0.1552740511

Effect of Quetiapine on QTc Interval



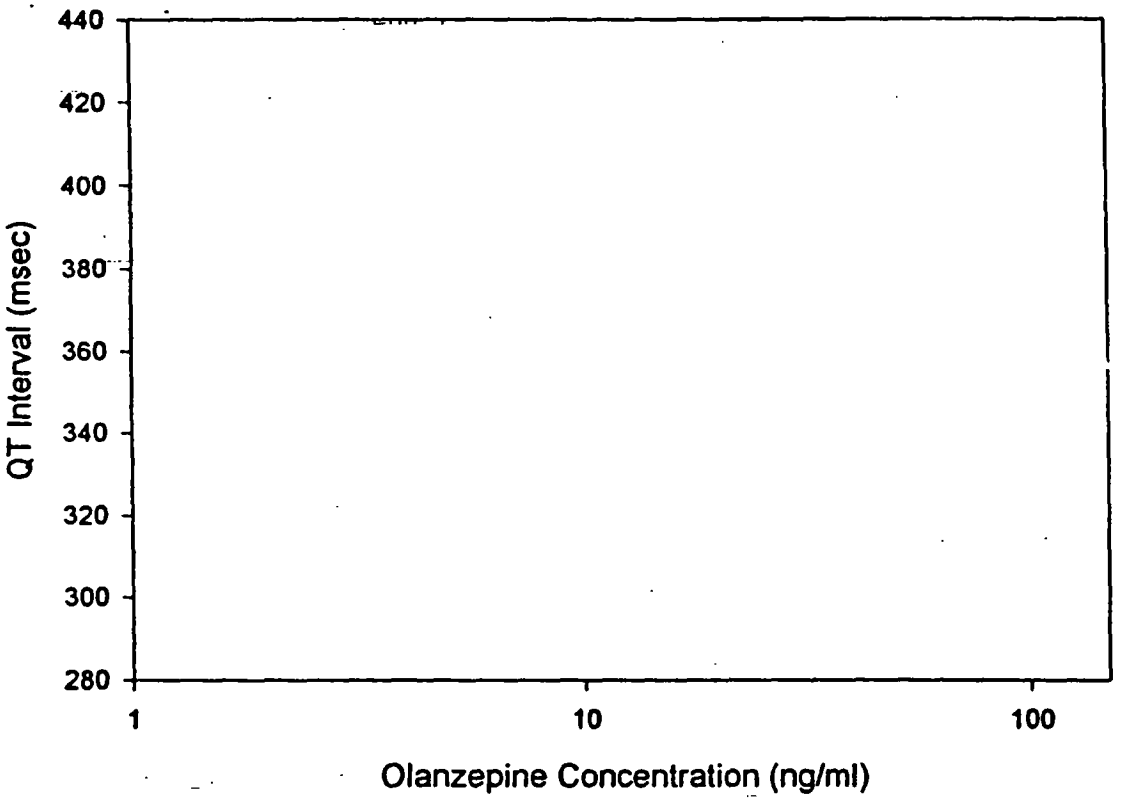
Intercept = 365.1656
Slope = 15.0783
r^2=0.1713726855

Effect of Olanzepine on QTc Interval



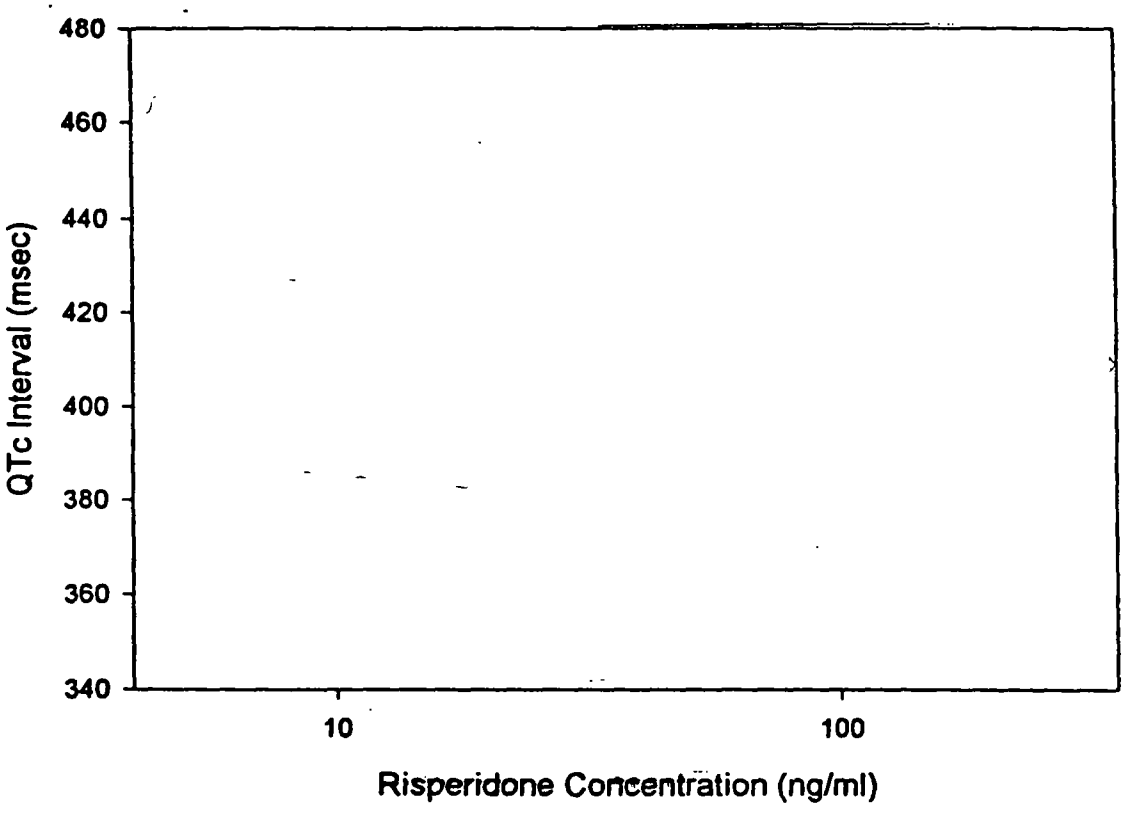
Intercept = 390.7492
Slope = 5.81969
r^2= 0.0177752817

Effect of Olanzepine on QT Interval



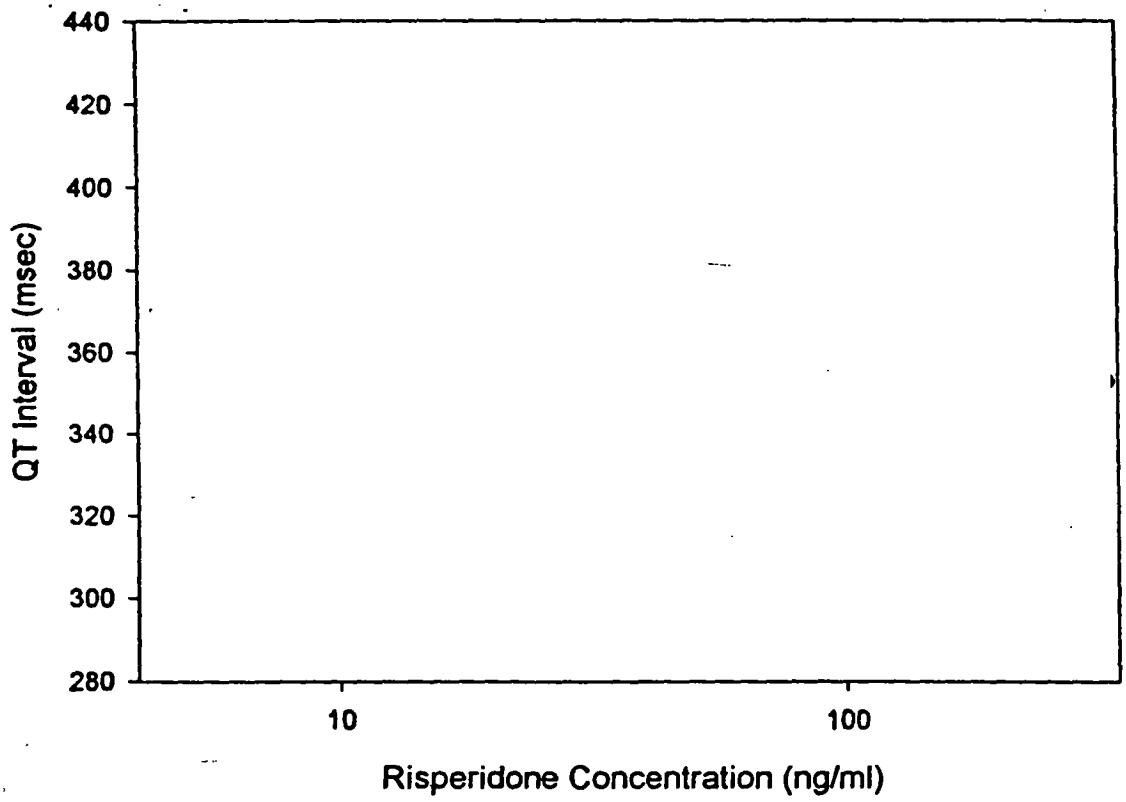
Intercept = 354.47023
Slope = 3.9619
r^2= 4.262398787e-3

Effect of Risperidone on QTc Interval



Intercept = 406.506151
Slope = -1.701107
r^2=1.2749627819e-3

Effect of Risperidone on QT Interval



Intercept = 367.81725
Slope = -3.157232
r^2=2.4245779374e-3

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 7, 1997
From: HFD-110
Subject: Comment on the Proposed ECG data displays for the ziprasidone NDA (#20-825)
Information Provided: volumes 2.1, 2.2
To: HFD-120

Background

HFD-110 has provided comments on the proposed submission of ECG QT and QTc interval data for NDA 20-825 (IND). The NDA has been submitted. HFD-120 requests comments on the submitted data displays.

Comments

- The sponsor has provided the data tables as proposed in the previous consult regarding the display of ECG data.
- Only post-randomization ECG recordings are provided in enclosure 3. The sponsor should provide baseline and any other post-randomization EKGs for the patients listed in enclosure 3.
- The data provided is sufficient to initiate a review of QT interval data. If a formal consult is requested to interpret QT interval data, additional pre-clinical and clinical information from the NDA will be needed from HFD-120.

/S/

Charles J. Ganley, M.D.

/S/

Raymond Lipicky, M.D.

cc: Division File
HFD-110/ganley
HFD-120/Hardemann/Laughren/