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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**20-919**

**Clinical Pharmacology and Biopharmaceutics  
Review**

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-919

Submission Dates: December 18, 1997  
January 17, 1998

Generic Name: Ziprasidone Mesylate Trihydrate (CP-88,059-27)

Brand Name: ZELDOX IM™

Strength(s): 20 mg/mL Upon Reconstitution With 1.2 mL of Sterile Water  
For Injection

Formulation: Solution For Intramuscular Administration Upon  
Reconstitution

Sponsor: Pfizer Inc.  
Groton, CT

Type of Submission: NDA

Reviewer: Sayed Al-Habet, Ph.D.

Date of Review: May 22, 1998

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### SYNOPSIS:

This is a continuation of the recently reviewed NDA for ziprasidone hydrochloride capsules for oral administration in psychotic (schizophrenic) patients (NDA 20-825). The sponsor later submitted this NDA for ziprasidone mesylate trihydrate (ZELDOX IM™, CP-88,059-27) for IM administration to be used for the acute control and short-term management of the agitated psychotic (schizophrenic) patients. Ziprasidone mesylate is the methanesulfonic acid salt of a benzisothiazolylpiperazine. It has antagonistic activity at both dopamine D2 and serotonin 5-HT2A receptors. Since the studies conducted on capsules (NDA 20-825) were extensively cross referenced because they fully describe the clinical pharmacology and the metabolism of ziprasidone, a copy of the OCPB review summary can be found in Appendix III. It should be noted that the focus of this NDA is on the parent drug because it is believed that all the metabolites of ziprasidone are pharmacologically inactive.

The sponsor is proposing to market ZELDOX IM™ as a single dose vial of 20 mg ziprasidone mesylate trihydrate powder with 1.2 mL sterile water for injection. Upon reconstitution, each mL of ziprasidone mesylate for injection will contain 20 mg of ziprasidone, 4.7 mg of

methanesulfonic acid and 294 mg of cyclodextrin. The proposed initial dose is 10 to 20 mg with subsequent doses of 10 mg every 2 hours or 20 mg every 4 hours. The maximum daily dose is 80 mg. It should also be noted that administration of ziprasidone IM for more than 3 consecutive days has not been studied. All the pharmacokinetics studies in this NDA were conducted using the final to-be-marketed formulation. These studies support the sponsor's labeling relevant to the Clinical Pharmacology and Dosage and Administration Sections.

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## **RECOMMENDATION:**

The NDA # 20-919 submitted for ZELDOX IM™ has been found to be acceptable by the Office of Clinical Pharmacology and Biopharmaceutics including the sponsor proposed labeling related to Clinical Pharmacology Section.

## **COMMENTS TO THE CLINICAL DIVISION:**

1. Cyclodextrin is excreted by filtration and no studies were conducted in renal failure after IM administration. However, in the sponsor proposed labeling, it is indicated that caution should be taken when administering Zeldox IM in patients with renal impairment.
2. The fate of cyclodextrin has not been investigated in this NDA. It is not known what happens to cyclodextrin at the muscular site after multiple injections.
3. In terms of safety, the effect on QTc prolongation is dose, concentration, and time dependent. This is similar to that found after oral administration (Appendix III).
4. The drug causes marked and sudden drop in both the systolic and the diastolic blood pressure by about 70 to 100 mmHg after the IM administration of doses >10 mg. This sudden drop in blood pressure was: (i) associated with orthostatic hypotension in some subjects, (ii) dose dependent, and (iii) coincided well with ziprasidone Tmax. This sharp drop in blood pressure may require immediate attention in some patients.
5. Ziprasidone causes clinically significant sedation in all subjects at doses >10 mg. The maximum degree of sedation occurred within 2 hours of drug administration; the time coincides with the Tmax.

## **COMMENTS TO THE SPONSOR:**

6. The sponsor is encouraged to provide information on comments 1 and 2.
7. The sponsor is encouraged to provide explicit information on the relationship between ziprasidone serum concentration at Cmax of the highest recommended IM dose and QTc prolongation.

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<b>APPENDIX III</b>	(Review Summary and OCPB Labeling of NDA 20-825, Zeldox capsules)

### **SECTION A: IM FORMULATION NDA (20-919)**

#### **PHARMACOKINETICS**

Single dose, 5, 10 and 20 mg IM (Study # 128-038)

Escalating single doses, 5, 10, 20, and 40 mg (Study # 128-033)

Escalating multiple doses, 20, 40, and 80 mg (Study # 128-046)

#### **BIOAVAILABILITY**

Absolute bioavailability, single dose 5 mg IV, 5 mg IM and 20 mg PO (Study # 128-037)

### **SECTION B: ORAL FORMULATION NDA (20-825)**

#### **METABOLISM AND ELIMINATION**

##### ***IN VIVO***

See NDA 20-825 (Appendix III)

##### ***IN VITRO***

See NDA 20-825 (Appendix III)

**SPECIAL POPULATIONS**

See NDA 20-825 (Appendix III)

**DRUG-DRUG INTERACTIONS**

*IN VIVO*

See NDA 20-825 (Appendix III)

*IN VITRO*

See NDA 20-825 (Appendix III)

**PROTEIN BINDING**

See NDA 20-825 (Appendix III)

**PHARMACODYNAMICS**

See NDA 20-825 (Appendix III)

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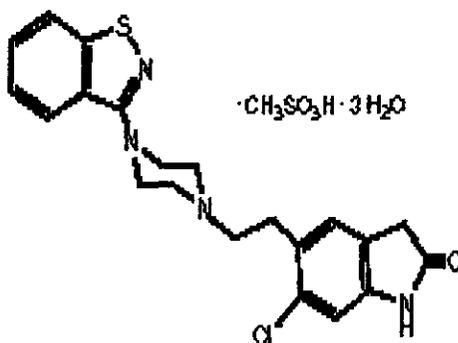
## BACKGROUND

Ziprasidone mesylate trihydrate (ZELDOX IM™, CP-88,059-27) is the methanesulfonic acid salt of benzisothiazolypiperazine which was developed for the acute control and short-term management of agitated psychotic (schizophrenic) patients. It has antagonist activity at both dopamine D2 and serotonin 5-HT2A receptors. Its relative affinity for serotonin 5-HT2 receptors is approximately eleven-fold greater than its affinity for dopamine D2 receptors.

### Physico-Chemical Properties:

Ziprasidone mesylate trihydrate exhibits slightly higher aqueous solubility (1.1 mg/ml) than ziprasidone hydrochloride monohydrate (0.075 mg/mL) used for oral administration, making the mesylate salt the preferred salt for use in the injectable formulation. The molecular weight of the ziprasidone mesylate is 563.09 and its pKa is 6.62.

### Structural Formula of Ziprasidone Mesylate:



### Chemical Formula:

5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, methanesulfonate, trihydrate

**Molecular Formula of Ziprasidone Mesylate:** C<sub>21</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>5</sub>·CH<sub>3</sub>SO<sub>3</sub>H·3H<sub>2</sub>O

**Indications and Usage:**

ZELDOX IM is being proposed for the acute control and short-term management of agitated psychotic (schizophrenic) patients.

**How Supplied:**

Ziprasidone mesylate (ZELDOX IM™) for injection will be supplied in a sterile, preservative free, single dose vial for intramuscular use only. Each vial is reconstituted to 20 mg ziprasidone/mL with 1.2 mL of Sterile Water for Injection. Each mL (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether beta-cyclodextrin sodium as a molecular inclusion complex.

**Proposed Dosage and Administration:**

The recommended starting dose of ziprasidone mesylate is 10 to 20 mg. Subsequent doses of 10 mg may be administered as often as every 2 hours, or 20 mg every 4 hours as needed. The maximum recommended dosage is 80 mg/day. Administration of ziprasidone intramuscular for more than 3 consecutive days has not been studied. If continuation of therapy is indicated, follow-on oral ziprasidone therapy may be started at a dose of 40 to 80 mg twice daily. In clinical trials, treatment with oral ziprasidone has been initiated at doses up to 80 mg BID following treatment with ziprasidone intramuscular at doses up to 20 mg QID.

**Manufacturer and Manufacturing Site:**

Ziprasidone mesylate IM will be manufactured, labeled and packaged by Pfizer Inc. at the following manufacturing site:

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## **SUMMARY REVIEW OF PHARMACOKINETICS AND BIOAVAILABILITY**

### **Introduction:**

This is a continuation of the recently reviewed full NDA for ziprasidone hydrochloride in which forty-six clinical pharmacology studies were conducted following the oral administration of capsules to fully characterize the pharmacokinetics and the metabolism of ziprasidone hydrochloride (NDA 20-825). A copy of the OCPB review summary and labeling for NDA 20-825 appears in Appendix III.

In the current NDA, four clinical pharmacology studies have been conducted to evaluate the pharmacokinetics and the bioavailability of ziprasidone mesylate after IM administration in humans. The analytical assay used in this NDA for the determination of ziprasidone serum level is the same as that used in NDA 20-825 (i.e., HPLC method with LLOQ of  $\sim$  ag/mL). The four studies conducted using IM formulation were limited to investigate the bioavailability and the pharmacokinetics after single and multiple IM doses. Detailed individual study reports are presented in Appendix I. Summary statements are as follows:

### **Pharmacokinetics:**

1. AUC and C<sub>max</sub> increased in a dose-related manner over the range of 5 to 40 mg IM doses.
2. Dose proportionality was not apparent at 80 mg IM dose.
3. In some situations, the occurrence of side effects limited the administration of the 40 mg IM doses.
4. Overall the half life after IM administration appears to be slightly shorter (approximately 4-5 hours) than that after oral administration (approximately 7 hours). Similar to that observed after oral administration, the half life after IM administration was slightly longer after multiple doses than after a single dose.

### **Absorption and Bioavailability:**

1. The absorption of the drug after IM administration was rapid and T<sub>max</sub> was attained within 1 hour of drug administration. It should be noted that the maximum degree of sedation occurred within 2 hours.
2. The absolute bioavailability of a single 5 mg IM dose of ziprasidone mesylate was 100%.

### **Metabolism:**

This has been extensively studied in the NDA 20-825 for the ziprasidone hydrochloride (Appendix III). No metabolic studies have been conducted to investigate the metabolism of ziprasidone mesylate after IM administration. In addition, no studies have been conducted to investigate the fate of cyclodextrin, the solubilizing agent used in the IM formulation.

### **Drug Interactions:**

See Appendix III.

### **Special Population Studies:**

#### **Renal Impairment:**

Only oral ziprasidone hydrochloride was studied in renal impairment patients. No studies have been conducted in renal impairment patients using IM formulation (ziprasidone mesylate). It should be noted that cyclodextrin in the IM formulation is excreted mainly by filtration. In the sponsor's proposed labeling, it is stated that ziprasidone IM should be given with caution in renal impairment patients.

#### **Hepatic Impairment:**

See Appendix III.

#### **Age and Gender Effects:**

See Appendix III.

#### **Race:**

See Appendix III.

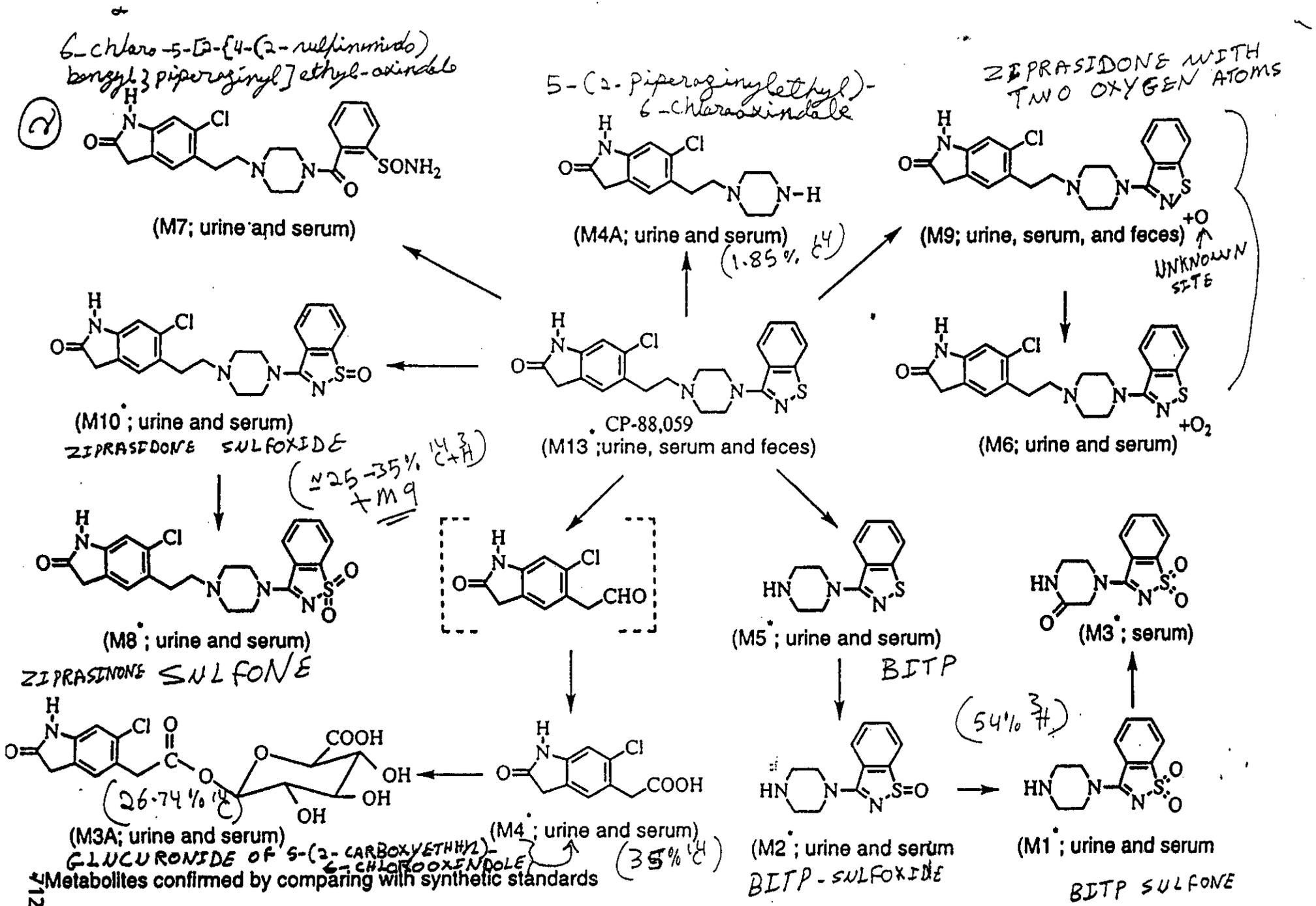


Figure 33. Proposed routes for the biotransformation of CP-88,059 in man

BITP: - BENZISOTHIAZOLYL PIPERAZINE

7/123

**Smoking Status:**

See Appendix III.

**Pharmacodynamics:**

See also Appendix III.

**Safety:**

Similar to that found after oral administration (Appendix III) QTc interval appears to be dose, concentration and time dependent. On day 2 the mean changes in QTc (i.e., delta QTc) was 3.5, 11.0, 12.5, and 5.3 msec and on day 4 was -3.5, 23.9, 18.5, and 0.8 msec after 20, 40, and 80 mg IM doses and placebo treatments, respectively. In addition, there was a linear relationship between delta QTc and the ziprasidone serum concentration after the IM doses of 20, 40 and 80 mg doses.

ClinPharm/Biopharm Briefing on: May 21, 1998

**Briefing Attendees:** Drs: Sayed Al-Habet, Raman Baweja, Mei-Ling Chen, Ed Fisher, Lois Freed, Roberta Glass, Shiew-Mei Huang, Tom Laughren, Henry Malinowski, Mehul Mehta, Andy Mossholder, Arzu Selen, Eric Turner, and Mona Zarifa.

Reviewed by: AS

✓ AS May 26, 1998

Sayed Al-Habet, Ph.D.  
Office of Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph.D. AS

AS 5/26/1998

cc: NDA # 20-919 (Orig.), HFD-120, HFD-860 (Al-Habet, Baweja, Malinowski),  
HFD-19 (FOI), and Drug files (Barbara Murphy, CDR).

# **APPENDIX A**

**(Sponsor's Proposed Labeling)**

19 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

X § 552(b)(5) Draft Labeling

**APPENDIX I**  
**(Individual Study Reviews)**

**1. Study 038 (Single doses of 5, 10 and 20 mg, cyclodextrin-based IM formulation)**

**Study Design and Summary:**

(see attachments 1-3)

**Results:**

(See attachments 4-5)

**Reviewer's Comments:**

1. Cmax was attained within 1 hour after the three doses (attachments 2 and 4).
2. AUC and Cmax increased proportionally with increases in the dose (attachments 5 and 6).
3. Sedation was dose related and it reached its peak in about 1-2 hours (attachment 7).
4. There was a clinically significant drop in the standing systolic and diastolic blood pressures at the 10 and 20 mg doses (attachment 8 and 9).

**Conclusions:**

1. There was dose proportionality over 5 to 20 mg doses.
2. There was a marked drop in the standing systolic and diastolic blood pressures causing orthostatic hypotension in some subjects.

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**PROTOCOL 128-038: PHASE I INVESTIGATOR-BLIND, PLACEBO-CONTROLLED EVALUATION OF THE SAFETY, TOLERATION AND PHARMACOKINETICS OF ZIPRASIDONE MESYLATE FOLLOWING SINGLE CYCLODEXTRIN-BASED (SBCD) INTRAMUSCULAR DOSES IN HEALTHY SUBJECTS**

**Principal Investigators:** [ 1

**Study Publication:** None

**Study Dates:** 12 February 1996 - 19 April 1996

**Study Objective:** To determine the safety, toleration, and pharmacokinetics of ziprasidone in healthy subjects given single intramuscular doses ranging from 5 to 20 mg.

**Study Design:** This was a randomized, investigator-blind, placebo-controlled study of escalating single intramuscular doses of ziprasidone. Sterile normal saline injected intramuscularly served as placebo. Three dose levels of ziprasidone (5 to 20 mg) were examined and subjects were assigned in groups of eight. Each subject received only one dose of study drug. The dose escalation sequence was 10, 20, and 5 mg, corresponding to subject groups 1, 2 and 3, respectively.

**Evaluation Groups:**

	Ziprasidone			Placebo
	5 mg IM	10 mg IM	20 mg IM	
Entered Study	6	6	6	6
Completed Study	6	6	6	6
Evaluated for Pharmacokinetics	6	6	6	6
Assessed for Safety				
Adverse Events	6	6	6	6
Laboratory Tests	6	6	6	6

**Subjects:** Healthy volunteers ranging in age from 21 to 45 years.

**Drug Administration:**

**Dosage Form**

Drug	Lot Number	FID Number	Potency	Formulation
Ziprasidone	ED-O-448-Z95	G00875AA	20 mg/ml	I.M. lyophile

**Dosing:** Study medication was administered as a single intramuscular injection to the upper arm (non-dominant) of each subject after an overnight fast of at least 8 hours. A standard meal was served four hours following dosing.

**Pharmacokinetic and Safety Evaluations:** Blood samples for determination of serum ziprasidone concentrations were collected prior to and up to 24 hours following the injection. Serum concentrations were used to determine pharmacokinetic parameters ( $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ , half-life, and AUC). Laboratory tests including several measurements of renal function (urinary NAG [N-acetyl- $\beta$ -D-glucosaminidase], creatinine, total protein, microalbumin and  $\beta$ -2 microglobulin) were evaluated up to 48 hours after dosing. Subjects completed a self-evaluation for the presence of sedation prior to and up to 24 hours following dosing. Subjects were monitored for adverse effects and changes in vital signs.

**Analytical Methods:** Serum concentrations of ziprasidone were determined by a validated HPLC assay [ ]

**Statistical Methods:** Pharmacokinetic and safety results were summarized through appropriate data tabulations, descriptive statistics and graphical presentations.

#### Pharmacokinetic Results:

Mean  $\pm$  Coefficients of Variation (%CV) of Pharmacokinetic Parameters (n = 6)

Parameter	Ziprasidone					
	5 mg IM		10 mg IM		20 mg IM	
AUC <sub>0-t</sub> (ng•hr/ml) <sup>a, b</sup>	222	$\pm$ 23	460	$\pm$ 12	841	$\pm$ 29
AUC <sub>0-<math>\infty</math></sub> (ng•hr/ml) <sup>a</sup>	229	$\pm$ 23	463	$\pm$ 12	846	$\pm$ 29
$C_{max}$ (ng/ml) <sup>a</sup>	76	$\pm$ 7	156	$\pm$ 14	244	$\pm$ 37
$T_{max}$ (hr)	0.50	$\pm$ 38	0.65	$\pm$ 37	0.71	$\pm$ 52
$K_{el}$ (hr <sup>-1</sup> )	0.289	$\pm$ 22	0.309	$\pm$ 7	0.233	$\pm$ 20
$T_{1/2}$ (hr) <sup>c</sup>	2.40	--	2.24	--	2.97	--

<sup>a</sup>geometric mean

<sup>b</sup>t=time of the last pharmacokinetic blood sample with quantifiable concentrations of ziprasidone.

<sup>c</sup>mean  $T_{1/2} = \ln(2)/\text{mean } K_{el}$

#### Safety Results:

Number of Subjects With/Evaluated For:	Ziprasidone			Placebo
	5 mg IM	10 mg IM	20 mg IM	
Adverse Events (All Causality)	5/6(0)	6/6(0)	6/6(0)	0/6(0)
Adverse Events (Treatment-emergent, Treatment-related) <sup>a</sup>	5/6(0)	6/6(0)	6/6(0)	0/6(0)
Clinically Significant Laboratory Test Abnormalities	3/6 (0)	1/6 (0)	2/6 (0)	3/6 (0)

( )Subjects discontinued

<sup>a</sup>All adverse events were treatment-emergent except for one (cold symptoms) in the 10 mg group. All treatment-emergent adverse events were treatment related except one (epistaxis) in the 20 mg group.

#### Summary and Conclusions:

Rapid attainment of peak ziprasidone concentrations was observed following intramuscular doses of ziprasidone at each dose level.  $T_{max}$  was generally attained less than one hour post injection (range 0.33 to 1.5 hours, overall mean 0.62 hours).

In this parallel study, mean AUC increased in a dose-related manner as the dose was escalated. Mean  $C_{max}$  increased in a dose-related manner from 5 to 10 mg but less so from 10 to 20 mg, which had higher variability.  $T_{1/2}$  values ranged from 1.8 to 3.5 hours with a mean across all doses of approximately 2.5 hours.

All adverse events were treatment-emergent except for one (cold symptoms), in the 10 mg group. All treatment-emergent adverse events except one (epistaxis) were considered by the investigator to be possibly related to treatment. All of the adverse events were mild to moderate in severity. There were no discontinuations due to adverse events. Overall, ziprasidone injections were well tolerated at the 5 mg dose, with the major effect being sedation. The most frequently reported adverse events were somnolence, orthostatic hypotension, nausea and dry mouth. Other adverse events reported included asthenia, vasodilation, dizziness, euphoria, sweating, and abnormal vision.

There were no notable differences among the groups for the renal function parameters that were plotted by study day.

While there was no notable sedation among the placebo subjects, the ziprasidone group showed varying levels of peak sedation. The 5 mg, 10 mg, and 20 mg dose groups peak sedation occurred at between one and two hours, with sedation increasing with increasing doses.

Standing vital signs showed a marked difference from placebo in the 10 and 20 mg dose groups. There was a greater decrease in standing systolic and diastolic blood pressure recordings in the 20 mg group than the other groups. No subjects in the 5 mg group experienced any significant changes in standing blood pressure.

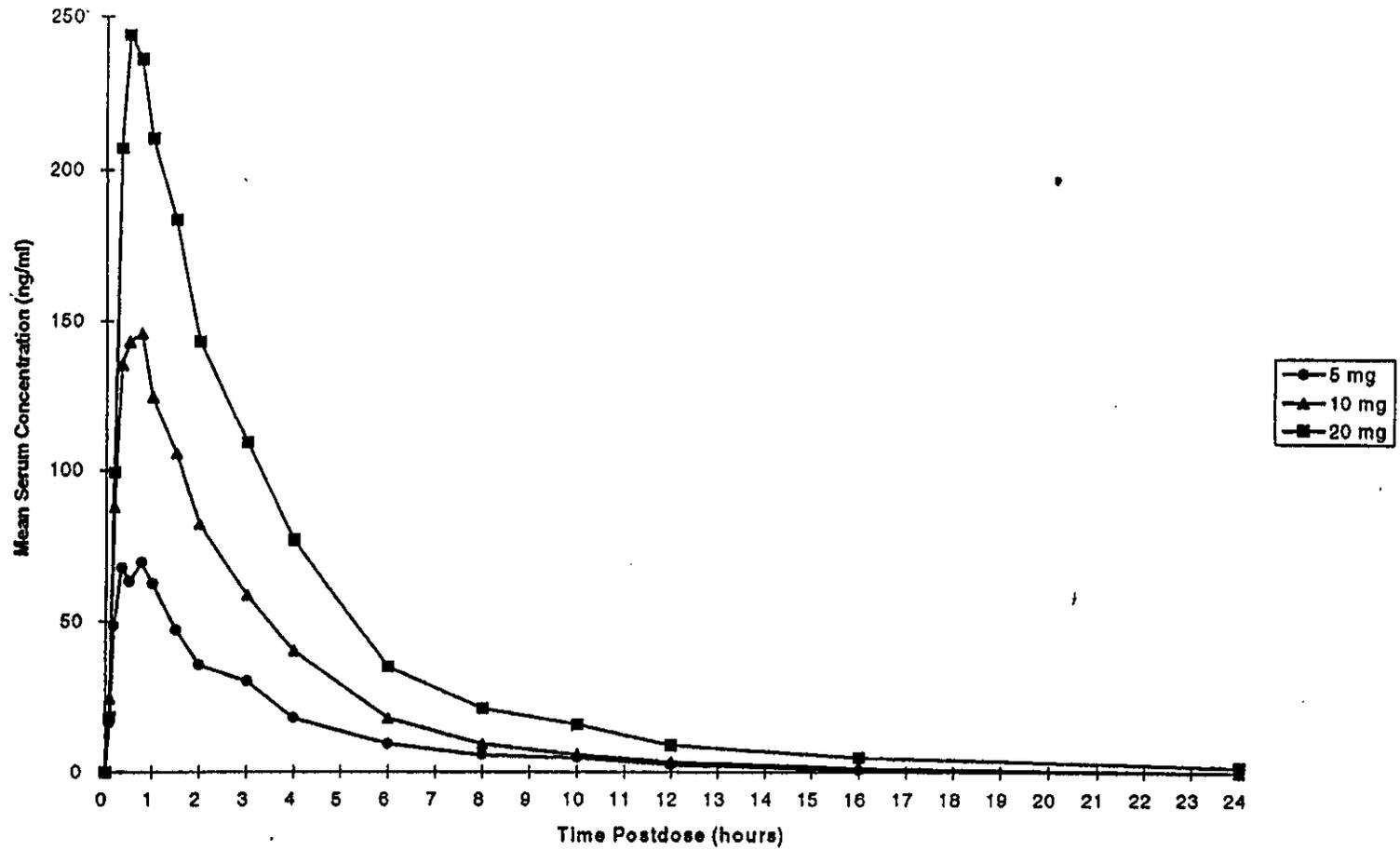
In summary, after the administration of single intramuscular doses of ziprasidone under fasting conditions rapid attainment of peak ziprasidone concentrations was observed at each dose level.  $T_{max}$  was generally attained within one hour of dosing. Exposure to ziprasidone appeared to be proportional to the dose received. Overall, ziprasidone injections were well tolerated in the 5 mg dose, but there were significant adverse events at the 10 and 20 mg doses. However, there were no serious adverse events reported in this trial. Subject self-rating of sedation increased with increasing doses.

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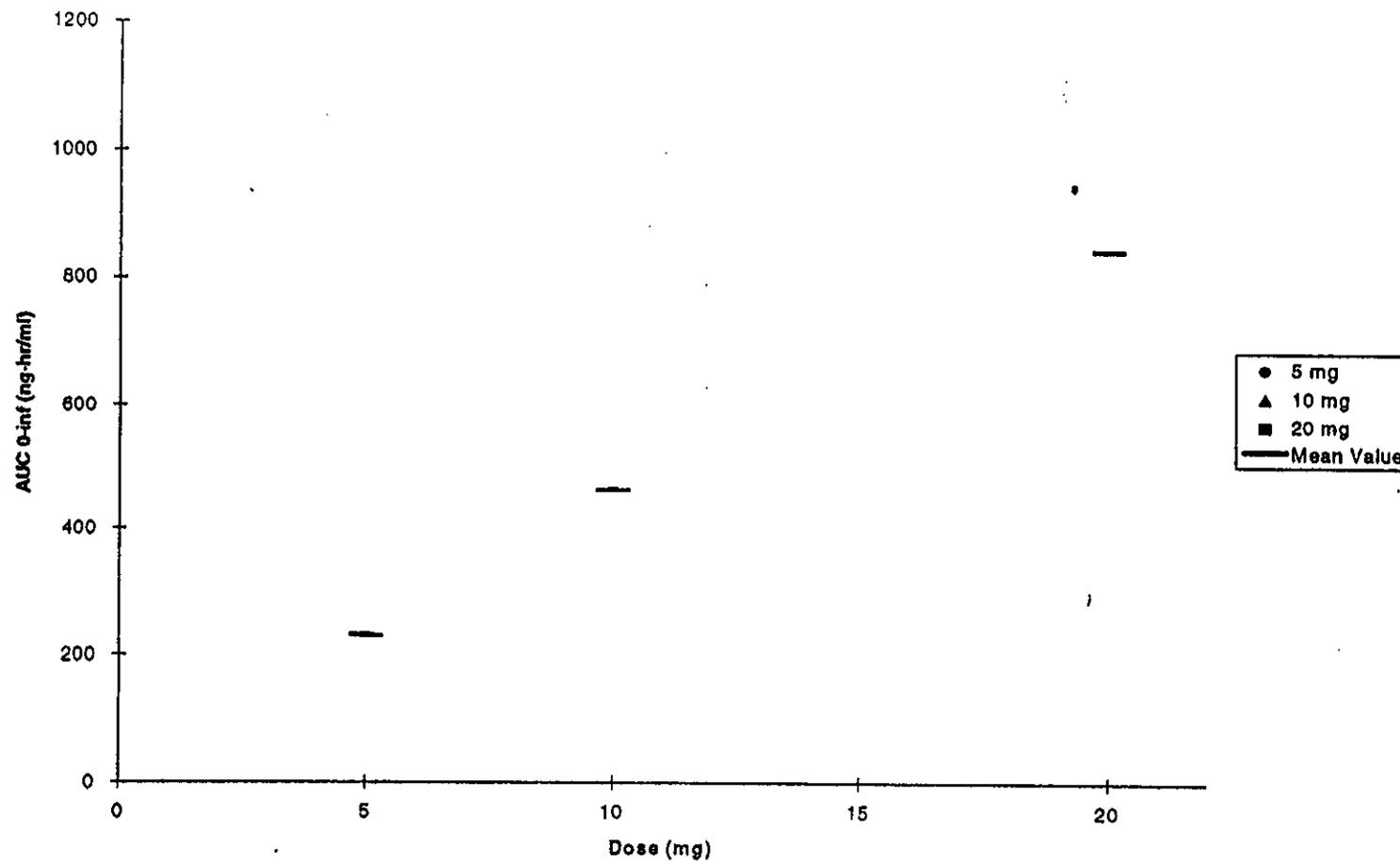
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Figure 1.1 Mean Serum Ziprasidone Concentrations vs Time Following Intramuscular Doses of Ziprasidone  
Ziprasidone Protocol 038



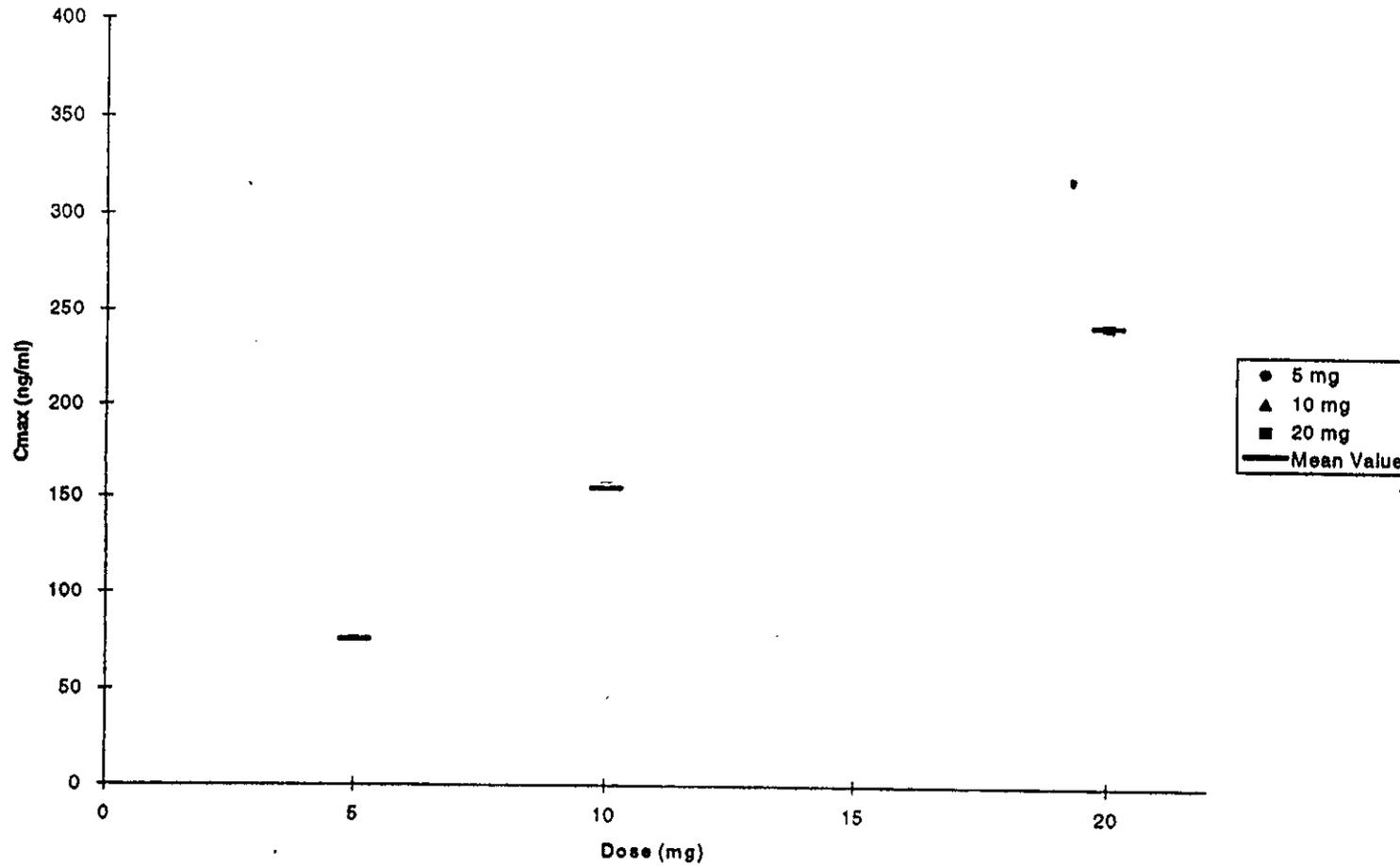
Source Data: Appendix IV, Table 1

Figure 1.5 Individual and Mean AUC<sub>0-∞</sub> vs Dose Following Intramuscular Administration of Ziprasidone  
Ziprasidone Protocol 038



Source Data: Appendix IV, Table 1

Figure 1.6 Individual and Mean Cmax vs Dose Following Intramuscular Administration of Ziprasidone  
Ziprasidone Protocol 038

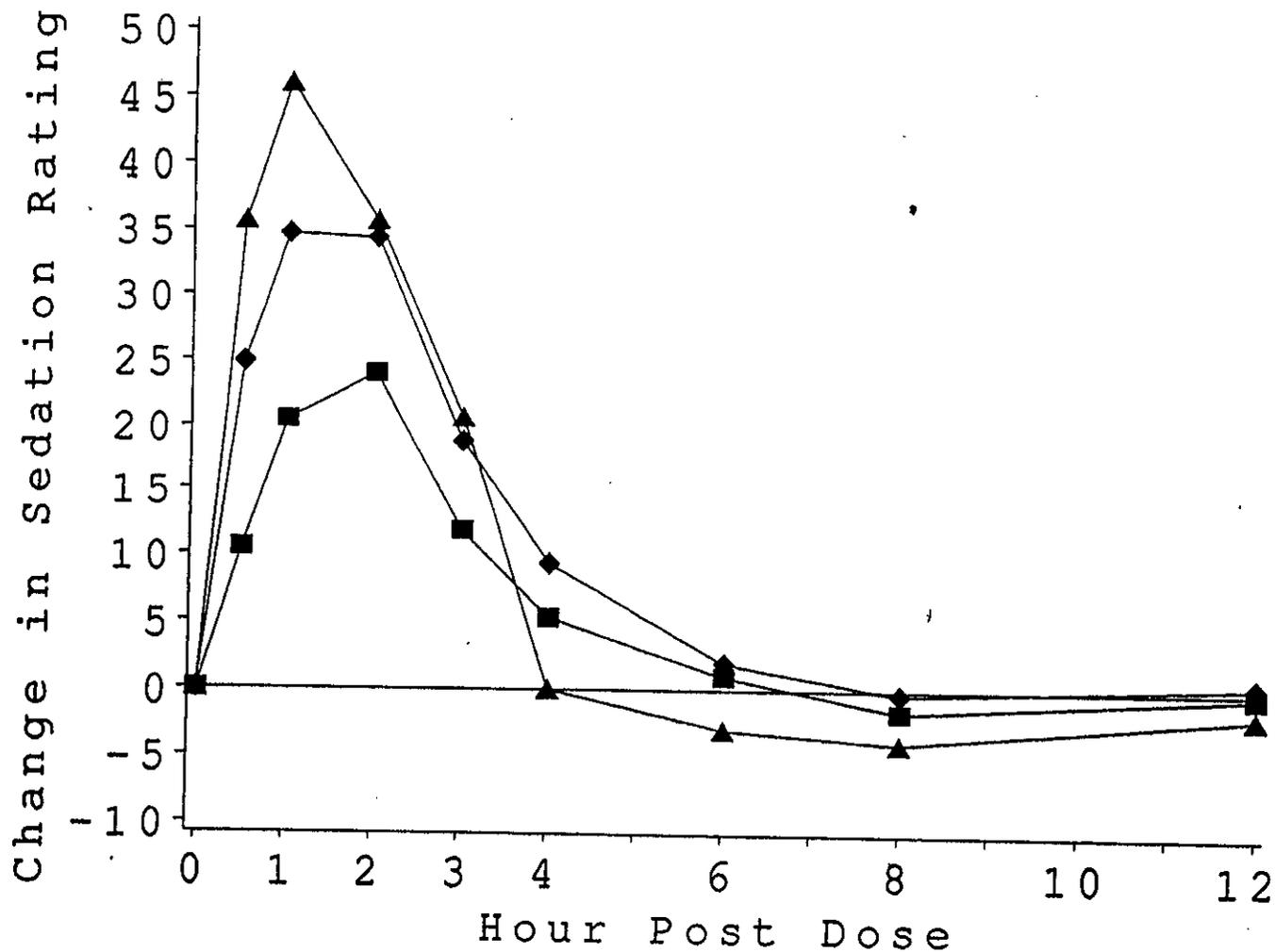


Source Data: Appendix IV, Table 1

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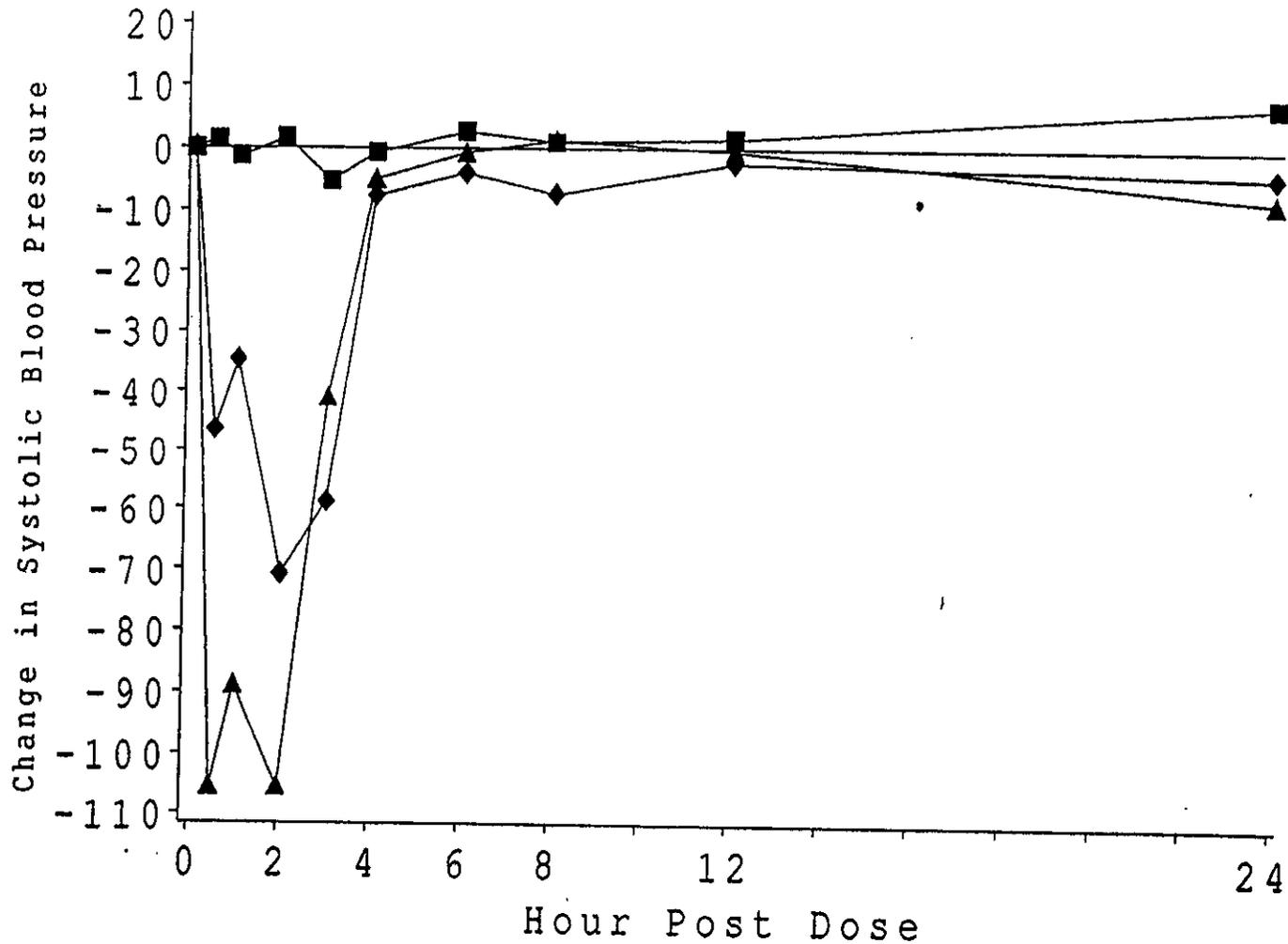
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FIGURE 2  
Mean Placebo Adjusted Change in Subject Self-Rating of Sedation by Hour Post Dose  
Ziprasidone Protocol 038



■ Ziprasidone 5 mg I.M.    ◆ Ziprasidone 10 mg I.M.    ▲ Ziprasidone 20 mg I.M.  
Sedation Rating refers to the sum of the twelve parameters that comprise the Sedation Self-Rating Scale.  
Source Data : Appendix III Table 1    Date of Data Extraction : 21AUG96    Date of Figure Generation: 21AUG96

FIGURE 3.1  
 Mean Placebo Adjusted Change from Baseline Standing Systolic Blood Pressure (mmHg) by Hour Post Dose  
 Ziprasidone Protocol 038

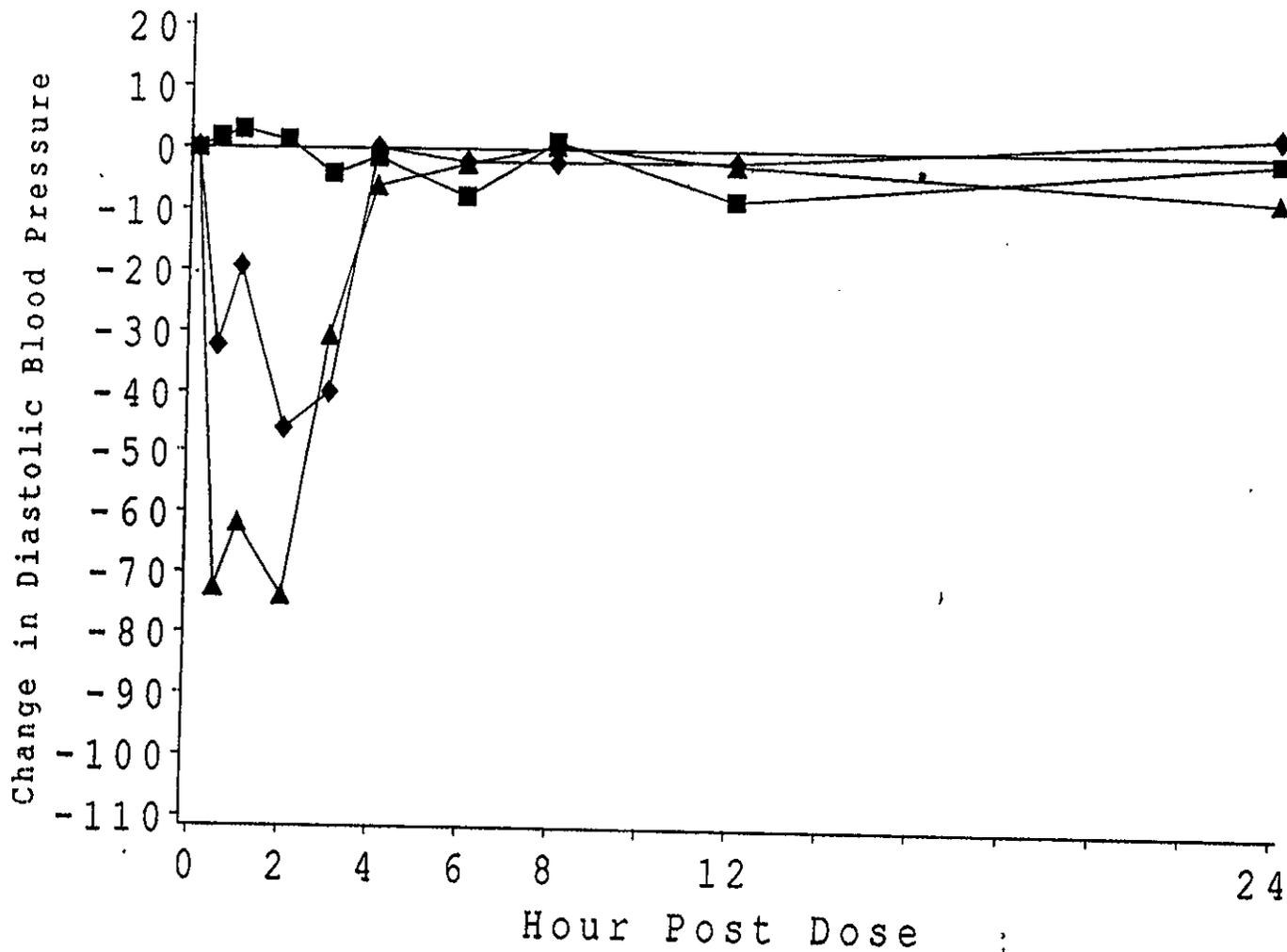


■ Ziprasidone 5 mg I.M.    ◆ Ziprasidone 10 mg I.M.    ▲ Ziprasidone 20 mg I.M.

0/0 (systolic/diastolic) was substituted for subjects not able to stand for standing evaluations.

Source Data : Appendix III Table 2.1    Date of Data Extraction : 21AUG96    Date of Figure Generation: 21AUG96

FIGURE 3.2  
Mean Placebo Adjusted Change from Baseline Standing Diastolic Blood Pressure (mmHg) by Hour Post Dose  
Ziprasidone Protocol 038



■ Ziprasidone 5 mg I.M.    ◆ Ziprasidone 10 mg I.M.    ▲ Ziprasidone 20 mg I.M.  
0/0 (systolic/diastolic) was substituted for subjects not able to stand for standing evaluations.  
Source Data : Appendix III Table 2.2    Date of Data Extraction : 21AUG96    Date of Figure Generation: 21AUG96

**2. Study 033 (Escalating single IM doses of 5, 10, 20, and 40 mg)**

**Study Design and Summary:**

(see attachments 1-3)

**Results:**

(See attachments 4-9)

**Reviewer's Comments:**

1. Due to the adverse events that occurred at 20 mg dose, the 40 mg dose was not administered.
2. T<sub>max</sub> was attained by about 1 hour after all doses (attachments 4 and 5). Overall, the half life was about 3 hours and there was no evidence of dose dependency (attachment 4).
3. Clearly, the C<sub>max</sub> and AUC increased proportionally with increasing doses (attachments 5 and 6).
4. There was a good correlation between ziprasidone plasma concentration and the degree of sedation in which the maximum degree of sedation occurs at about the same time of the C<sub>max</sub> (Attachments 7 and 8).
5. Compared to 5 and 10 mg doses, at 20 mg dose, there was a sharp drop in the systolic and the diastolic blood pressure after approximately 1 hour of the drug administration (attachments 9 and 10). However, there was a rapid recovery within an hour, but the systolic blood pressure remained low compared to 5 and 10 mg doses. This drop in blood pressure is probably associated with the orthostatic dizziness observed by some subjects.

**Conclusions:**

1. The pharmacokinetics of ziprasidone is linear over the tested IM doses of 5 to 20 mg.
2. The drug causes significant sedation and dizziness at 20 mg dose.

**PROTOCOL 128-033: PHASE I INVESTIGATOR-BLIND, PLACEBO-CONTROLLED EVALUATION OF THE SAFETY, TOLERATION AND PHARMACOKINETICS OF ZIPRASIDONE FOLLOWING ESCALATING SINGLE CYCLODEXTRIN-BASED (CP-217,861-02) INTRAMUSCULAR DOSES IN HEALTHY, MALE VOLUNTEERS**

**Principal Investigator:** [ ]

**Study Publication:** None

**Study Dates:** 23 May 1995 - 16 July 1995

**Study Objective:** To determine the safety, toleration, and pharmacokinetics of ziprasidone in healthy male volunteers given single intramuscular doses ranging from 5 mg to 40 mg.

**Study Design:** This was a randomized, investigator-blind, placebo-controlled study of escalating single intramuscular doses of ziprasidone in 21 healthy, male subjects. Four doses of ziprasidone were scheduled (5, 10, 20 and 40 mg). Due to adverse events at the 20 mg dose, the 40 mg dose was not administered. Subjects were randomized to one of three dose groups. The dose groups were studied serially (beginning with the lowest dose group), and at no less than weekly intervals. Due to recruitment problems, enrollment was a total of 3 subjects short of the planned 8 subjects per dose group (6 ziprasidone, 2 placebo).

**Evaluation Groups:**

	Ziprasidone 5 mg	Ziprasidone 10 mg	Ziprasidone 20 mg	Placebo
Entered Study	5	5	6	5
Completed Study	5	5	6	5
Evaluated for Pharmacokinetics:	5	5	6	5
Assessed for Safety:			*	
Adverse Events	5	5	6	5
Laboratory Tests	5	5	6	5
Sedation	5	5	6	5

**Subjects:** Healthy, male volunteers ranging in age from 18 to 43 years.

**Drug Administration:**

**Dosage Form** 40 mg\* CP-88,059-18 (lyophile)(FID #G00700AA)  
(saline served as placebo)

\*Lyophile reconstituted with water, so that each ml of solution contained 20 mg of ziprasidone and 400 mg of CP-217,861-02

**Dosing** Subjects were administered single intramuscular doses of ziprasidone (5, 10 or 20 mg) or placebo to the upper non-dominant arm after fasting overnight, in an investigator blind fashion.

**Pharmacokinetic and Safety Evaluations:** Blood samples for determination of serum ziprasidone concentrations were collected prior to and up to 36 hours after dosing. Serum concentrations were used to determine pharmacokinetic parameters ( $AUC_{(0-\infty)}$ ,  $C_{max}$ ,  $T_{max}$ ,  $K_{el}$  and  $T_{1/2}$ ). Laboratory tests including several measures of renal function (urinary NAG [N-acetyl- $\beta$ -D-glucosaminidase], creatinine, total protein, microalbumin and  $\beta_2$  - microglobulin) were evaluated up to 48 hours after dosing. Sedation was evaluated using self-evaluations. Subjects were monitored for adverse events and changes in vital signs.

**Analytical Methods:** Serum concentrations of ziprasidone were determined by HPLC

**Statistical Methods:** Pharmacokinetic and safety results were summarized using data tabulations, descriptive statistics, and graphical presentations.

#### Pharmacokinetic Results:

Mean<sup>a</sup>  $\pm$  Coefficients of Variation (%CV) of Serum Pharmacokinetic Parameters

Parameter	Ziprasidone 5 mg	Ziprasidone 10 mg	Ziprasidone 20 mg
$AUC_{(0-\infty)}$ (ng•hr/ml)	206 $\pm$ 20	437 $\pm$ 21	1057 $\pm$ 13
$C_{max}$ (ng/ml)	72 $\pm$ 28	133 $\pm$ 36	313 $\pm$ 22
$T_{max}$ (hr)	0.7 $\pm$ 81	0.7 $\pm$ 74	0.8 $\pm$ 22
$K_{el}$ ( $hr^{-1}$ )	0.292 $\pm$ 18	0.216 $\pm$ 21	0.204 $\pm$ 25
$T_{1/2}$ (hr) <sup>b</sup>	2.4	3.2	3.4

<sup>a</sup> geometric means and standard deviations are reported for  $AUC_{(0-\infty)}$  and  $C_{max}$

<sup>b</sup> calculated as  $\ln(2)/\text{mean } K_{el}$

#### Safety Results:

##### Number of Subjects [With/Evaluated (Discontinued)]

Findings	Ziprasidone	Ziprasidone	Ziprasidone	Placebo
	5 mg	10 mg	20 mg	
Adverse Events (All Causality) <sup>a</sup>	4/5 (0)	5/5 (0)	6/6 (0)	1/5 (0)
Clinically Significant Laboratory Test Abnormalities	3/5 (0)	4/5 (0)	3/6 (0)	3/5 (0)

<sup>a</sup> All adverse events were treatment emergent except one case of upper respiratory infection in the 5 mg dose group, and one case each of sunburn and headache in the 20 mg dose group. All adverse events were considered to be treatment related except four (upper respiratory tract infection, musculoskeletal pain, sunburn and headache).

#### Summary and Conclusions:

Rapid attainment of peak ziprasidone concentrations were observed following intramuscular doses of ziprasidone at each dose level.  $T_{max}$  was generally attained prior to 1 hour post injection (overall mean 0.7 hours). Exposure to ziprasidone as measured by both  $AUC_{(0-\infty)}$  and  $C_{max}$  increased in a dose-related manner. Individual  $T_{1/2}$  values ranged from 2 to 6 hours with a mean across all doses of 2.9 hours.

The majority of adverse events were of mild to moderate severity and all but four were treatment-related. There were no discontinuations due to adverse events. The most frequently reported adverse event was somnolence, which was most commonly experienced by subjects in the 20 mg dose group and was severe in four subjects in that dose group. One subject in the 5 mg dose group experienced severe syncope and tremor within 2 minutes of receiving his injection which resolved within 1 minute. Other reported adverse events included dizziness, injection site reactions, pallor, hypoventilation, injection site pain/inflammation/complication, asthenia, musculoskeletal pain, nausea, rash, postural hypotension, depersonalization, hypertonia, and photophobia. Due to incidents of orthostatic dizziness, pallor, sedation and hypoventilation that occurred in the 20 mg dose group, the investigator elected not to dose any subjects at the 40 mg dose level. No serious adverse events were reported. Peak sedation occurred approximately 1 hour post dose for the 5 mg dose group, and approximately 2 hours post dose for the 10 and 20 mg dose groups. Subject rating of sedation increased in the 10 and 20 mg dose groups, and was very similar for both groups..

In summary, after the administration of single intramuscular doses of ziprasidone under fasting conditions rapid attainment of peak ziprasidone concentrations were observed at each dose level.  $T_{max}$  was generally attained within one hour of dosing. Exposure to ziprasidone appeared to increase in a dose related manner. Somnolence was reported as an adverse experience most frequently, predominantly in the 20 mg dose group. Subject self rating of sedation was greatest in the 10 and 20 mg dose groups. Overall, ziprasidone injections were well tolerated up to 10 mg. At the 20 mg dose, significant side effects were observed, which in the investigator's opinion prevented further escalation of the dose.

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**Table 5.1. Individual and Mean Pharmacokinetic Parameters Following Single Intramuscular Doses of Ziprasidone to Normal, Healthy Male Volunteers**

**Ziprasidone Protocol 033**

Subject #	AUC (0-∞) (ng•hr/ml)	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (hr)	K <sub>el</sub> (hr <sup>-1</sup> )	T <sub>1/2</sub> (hr)
708-0001					
708-0003					
708-0004					
708-0005					
708-0006					
Mean <sup>a</sup>	206	72	0.7	0.292	2.4 <sup>b</sup>
S.D.	41	20	0.5	0.051	
%CV	20	28	81	18	
10 mg dose					
708-0017					
708-0019					
708-0020					
708-0021					
708-0022					
Mean <sup>a</sup>	437	133	0.7	0.216	3.2 <sup>b</sup>
S.D.	91	48	0.5	0.044	
%CV	21	36	74	21	
20 mg dose					
708-0033					
708-0034					
708-0036					
708-0037					
708-0038					
708-0040					
Mean <sup>a</sup>	1057	313	0.8	0.204	3.4 <sup>b</sup>
S.D.	137	68	0.2	0.052	
%CV	13	22	22	25	
All Doses					
Mean			0.7	0.235	2.9 <sup>b</sup>
S.D.			0.4	0.061	
%CV			55	26	

Source Data: Appendix IV, Table 1

<sup>a</sup> Geometric Means and Standard Deviations are reported for AUC(0-∞) and C<sub>max</sub>.

<sup>b</sup> Calculated as  $\ln(2)/\text{Mean } K_{el}$ .

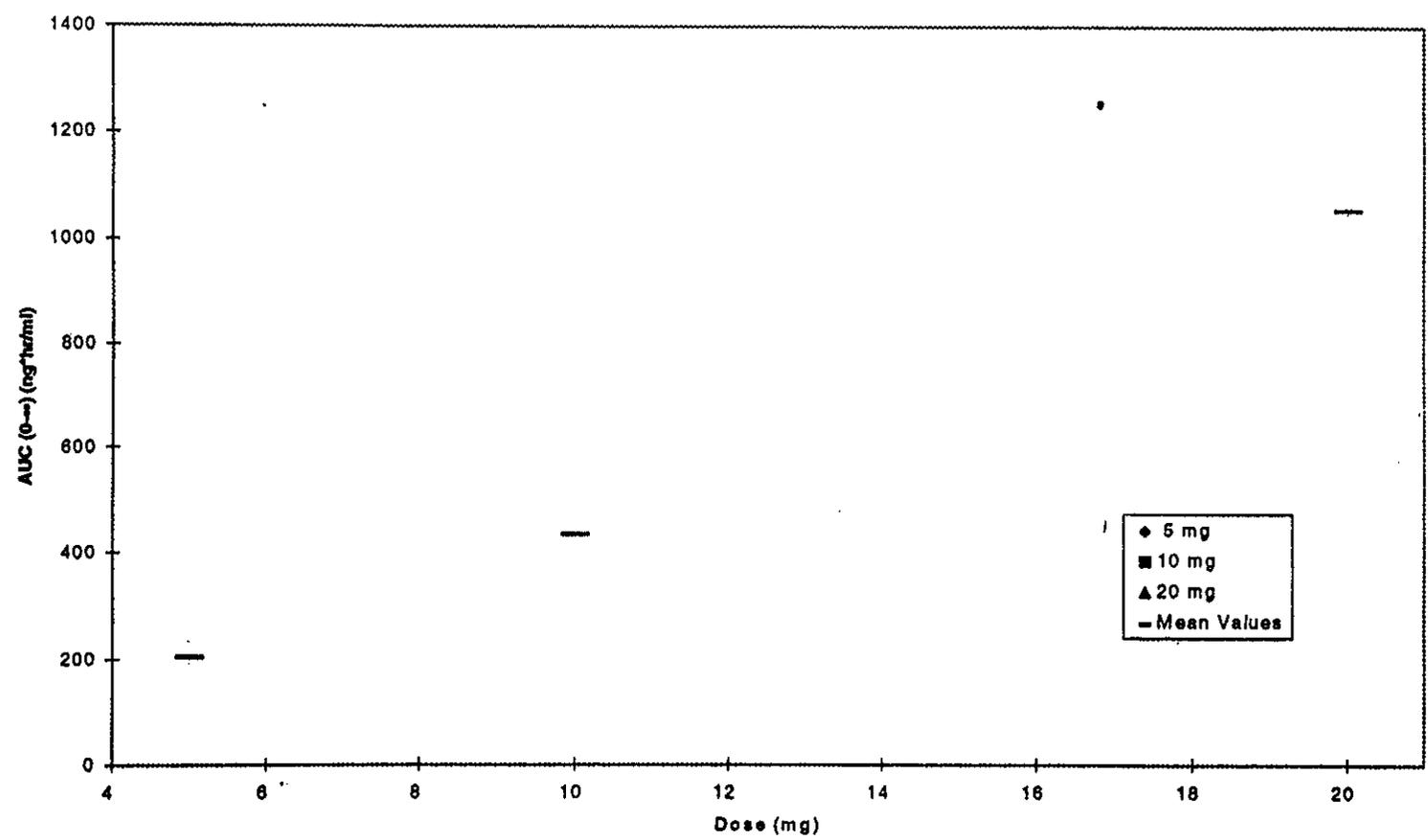
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Figure 1.6 Individual and Mean AUC(0-∞) vs Dose Following Intramuscular Administration of Ziprasidone to Normal, Healthy Male Volunteers

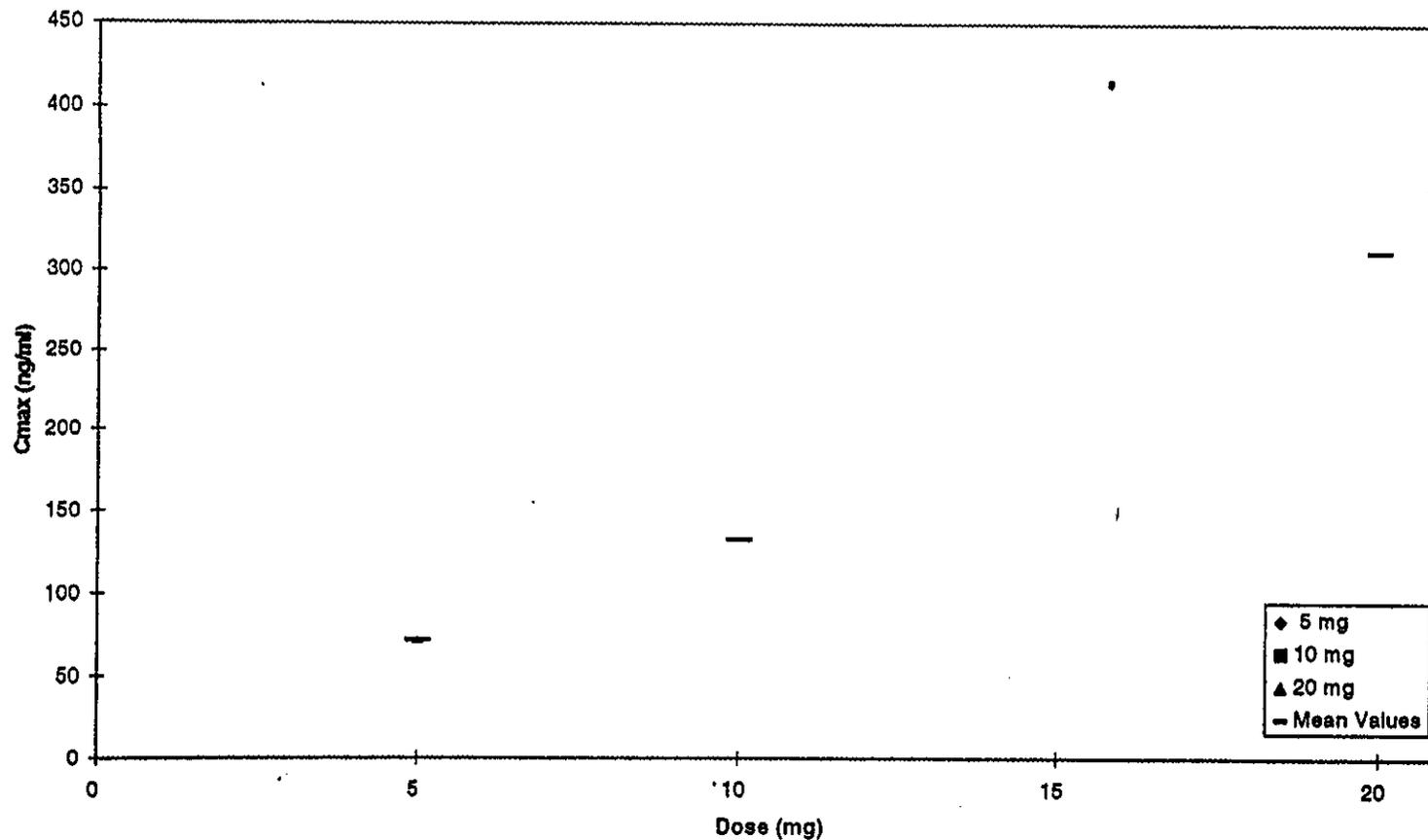
Ziprasidone Protocol 033



Source Data: Table 5.1

Figure 1.5 Individual and Mean Cmax vs Dose Following Intramuscular Administration of Ziprasidone to Normal, Healthy Male Volunteers

Ziprasidone Protocol 033



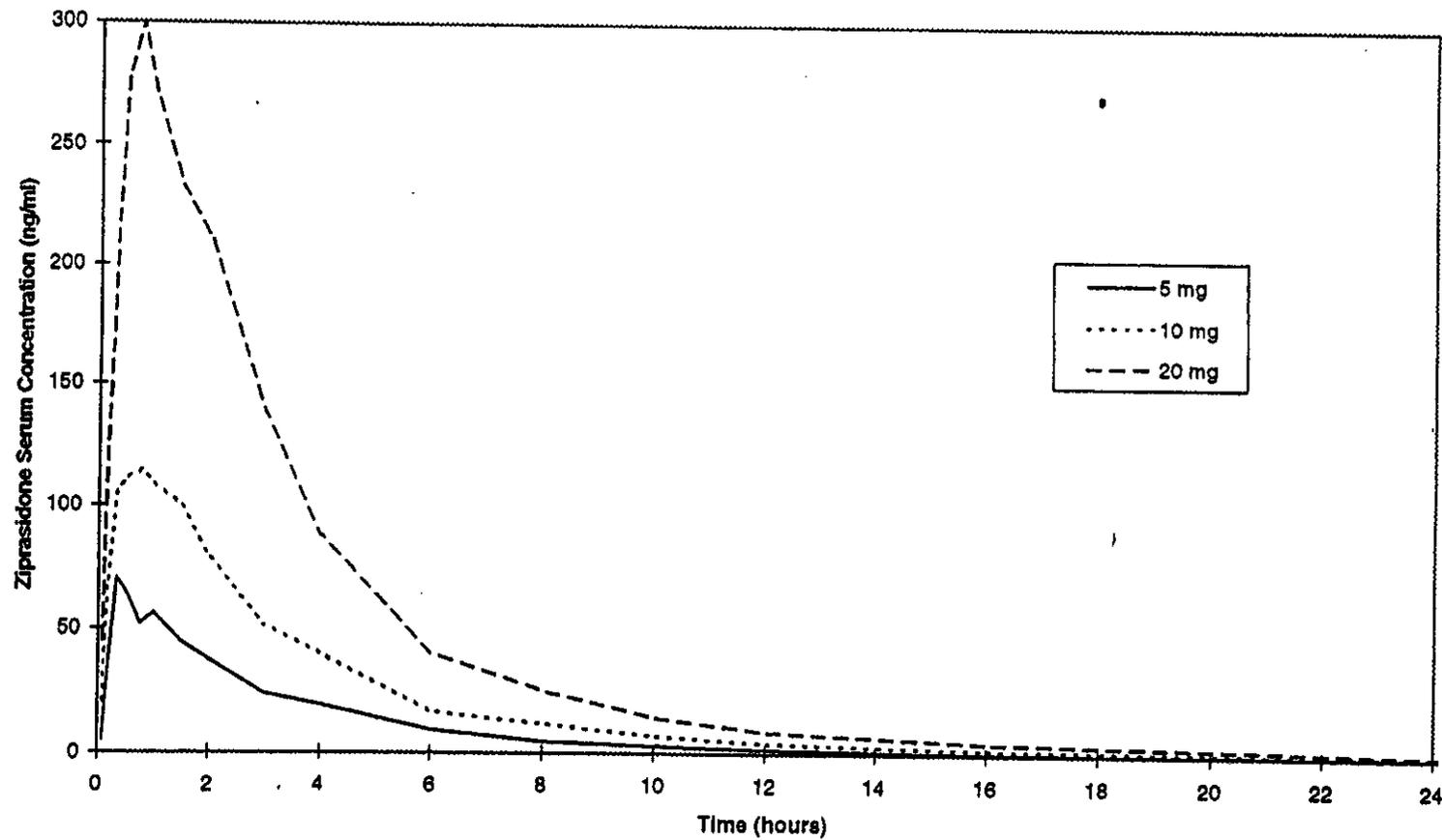
Source Data: Table 5.1

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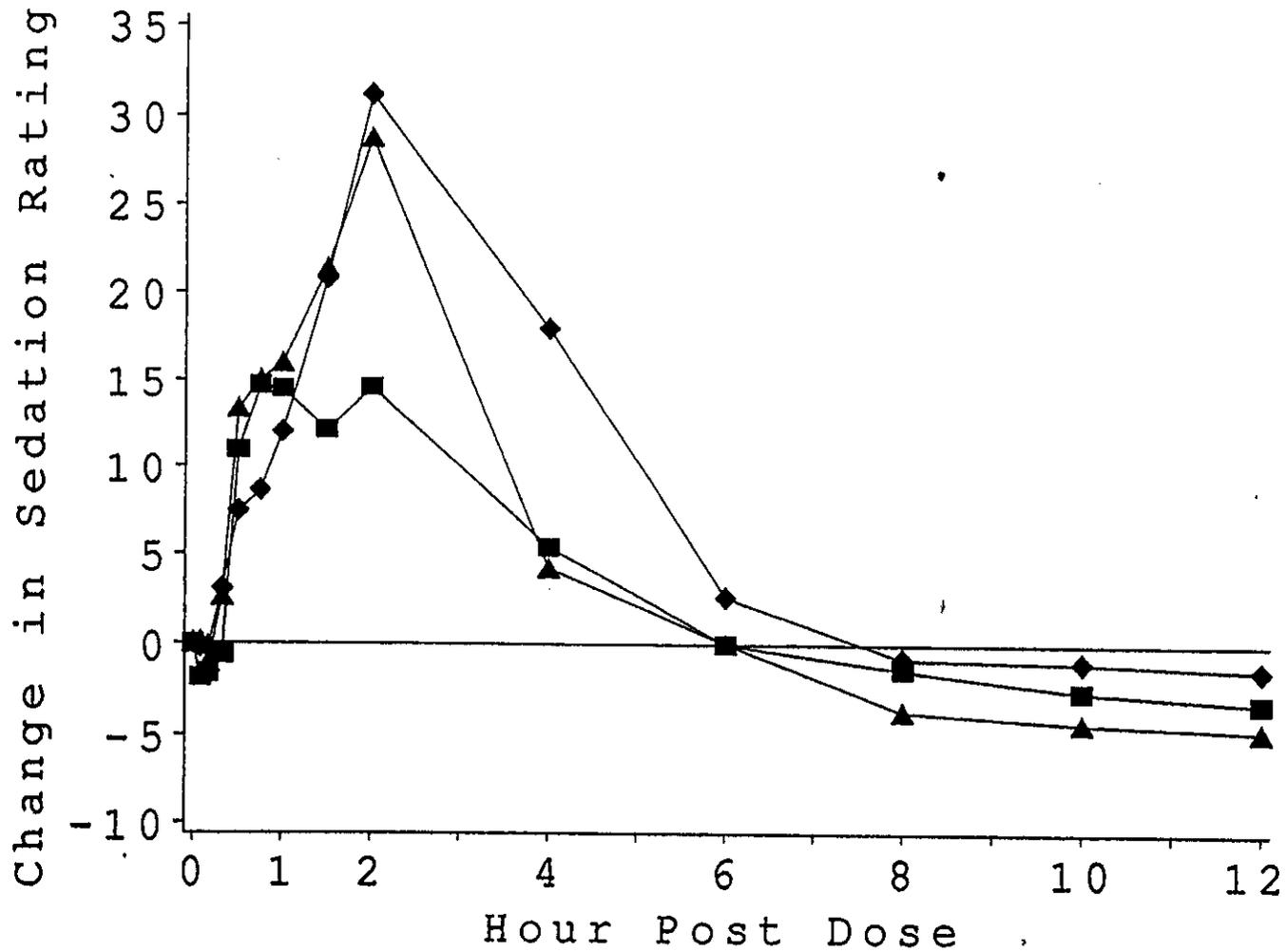
Figure 1.1 Mean Serum Ziprasidone Concentrations vs Time Following Intramuscular Doses of Ziprasidone to Normal, Healthy Male Volunteers

Ziprasidone Protocol 033



Source Data: Appendix IV, Table 1

FIGURE 2  
 Mean Placebo Adjusted Change in Subject Self-Rating of Sedation by Hour Post Dose  
 Ziprasidone Protocol 033



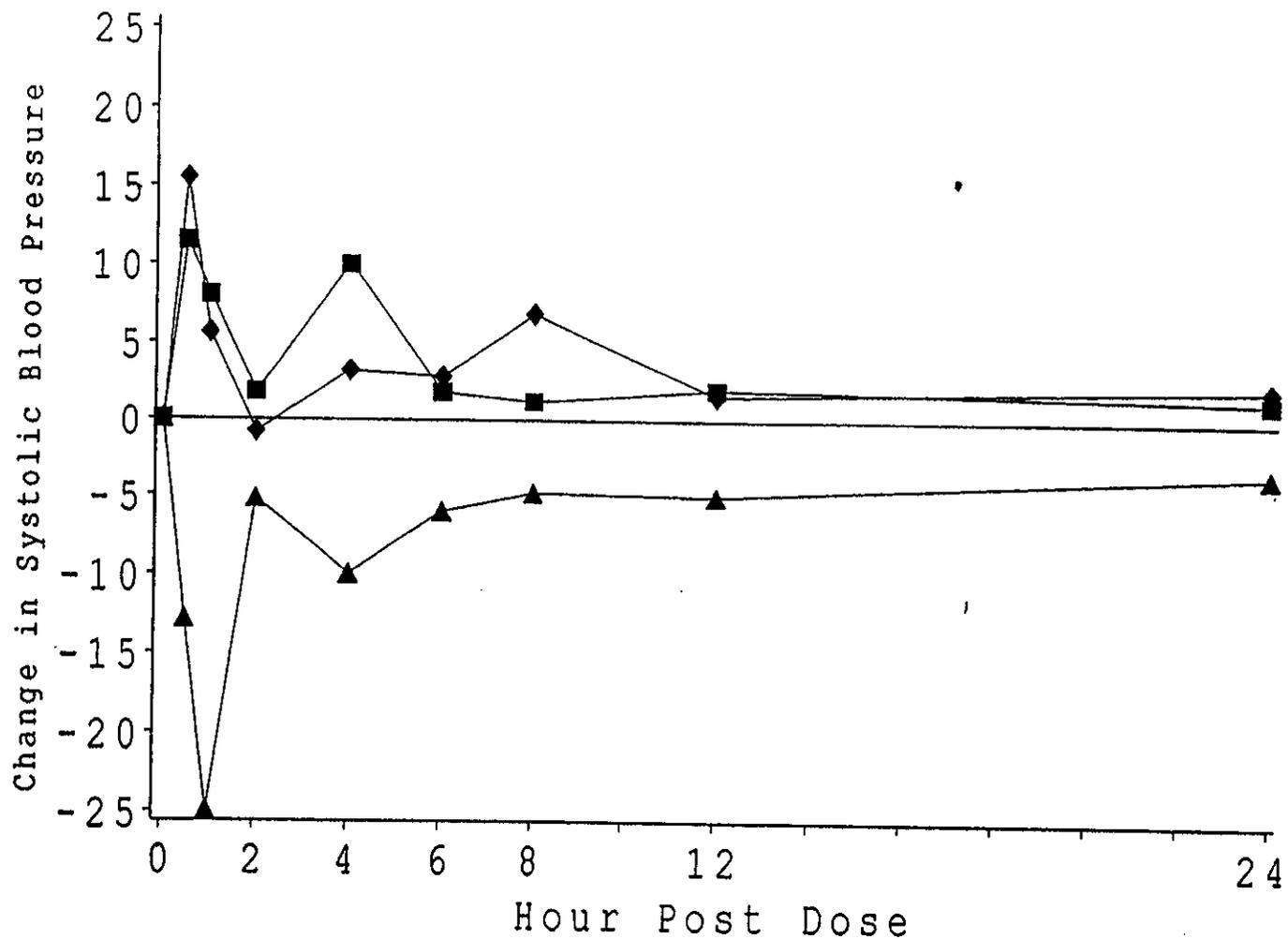
■ Ziprasidone 5 mg    ◆ Ziprasidone 10 mg    ▲ Ziprasidone 20 mg

Sedation Rating refers to the sum of the twelve parameters that comprise the Sedation Self-Rating Scale.  
 source Data : Appendix III Table 1    Date of Data Extraction : 13MAY96    Date of Figure Generation: 14MAY96

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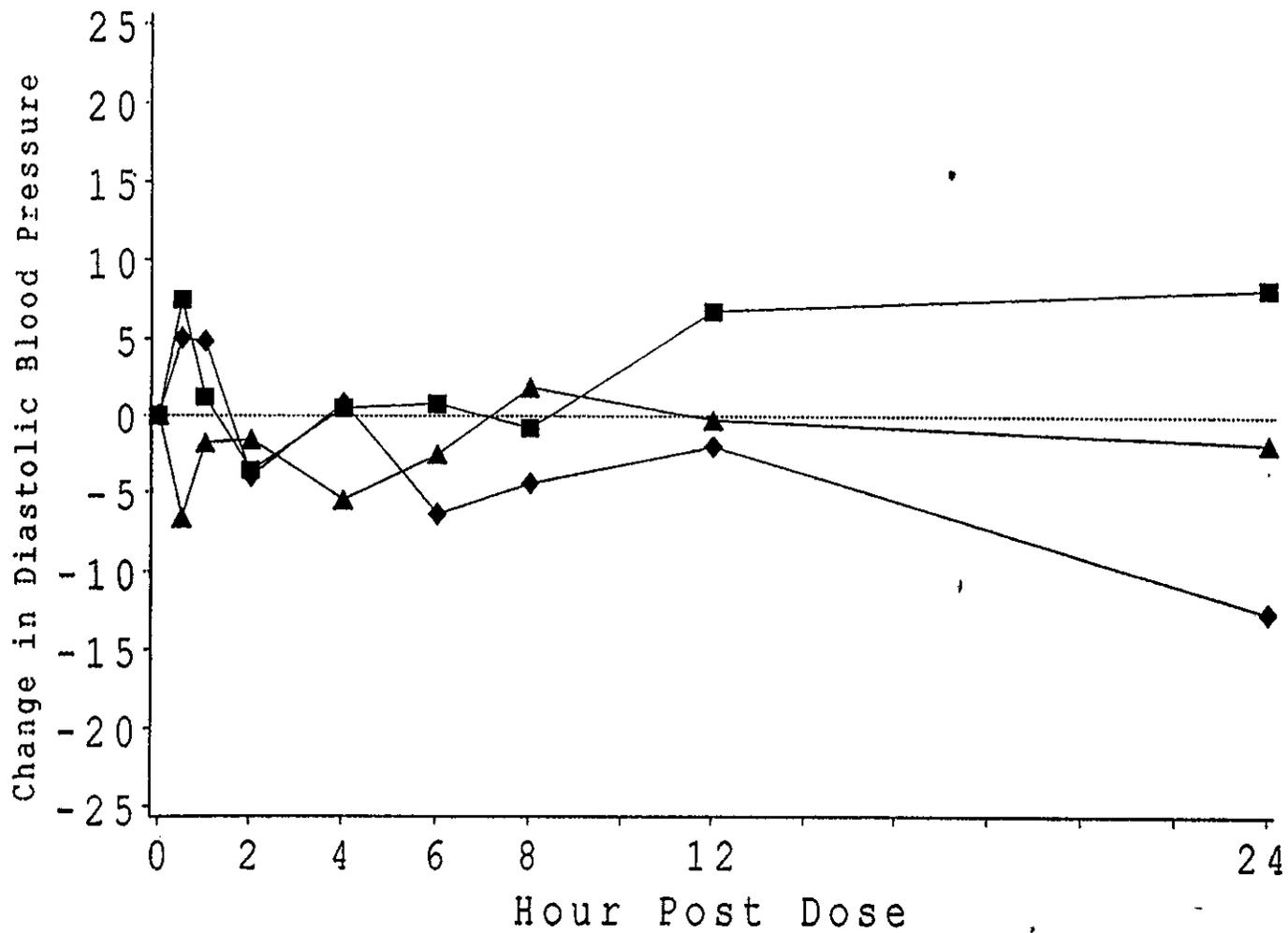
FIGURE 3.1  
Mean Placebo Adjusted Change from Baseline Standing Systolic Blood Pressure (mmHg) by Hour Post Dose  
Ziprasidone Protocol 033



■ Ziprasidone 5 mg    ◆ Ziprasidone 10 mg    ▲ Ziprasidone 20 mg

Source Data : Appendix III Table 2.1    Date of Data Extraction : 05APR96    Date of Figure Generation: 15MAY96

FIGURE 3.2  
Mean Placebo Adjusted Change from Baseline Standing Diastolic Blood Pressure (mmHg) by Hour Post Dose  
Ziprasidone Protocol 033



■ Ziprasidone 5 mg    ◆ Ziprasidone 10 mg    ▲ Ziprasidone 20 mg  
Source Data : Appendix III Table 2.2    Date of Data Extraction : 05APR96    Date of Figure Generation: 15MAY96

### 3. Study 046 (Escalating Multiple IM Doses of 20, 40 and 80 mg in Patients)

#### Study Design and Summary:

(see attachments 1-4)

#### Results:

(See attachments 5-15)

#### Reviewer's Comments:

1. The  $AUC_{0-24h}$  was doubled as the dose increased from 20 to 40 mg (attachment 2). However, there was no proportional increase in the AUC at the 80 mg dose. The mechanism (s) of the lack of dose proportionality is not clear. However, the absorption of the drug from the muscular site may be saturated and if this is the case, the drug may be accumulated at the muscular site.
2. There was no drug accumulation between day 1 and day 3 following all doses (attachments 2 and 5-7).
3. The mean changes in QTc interval on day 2 was 3.5, 11.0, 12.5, and 5.3 msec and on day 4 was -3.5, 23.9, 18.5, and 0.8 msec after 20, 40, and 80 mg and placebo treatments, respectively (attachments 8). Therefore, the effect of ziprasidone on QTc was greater on day 4 compared to day 2 as shown in attachment 8. The details of these data are in attachments 9 and 10.
4. Interestingly, it should be noted that there was no clear relationship between the QTc and the ziprasidone serum concentration (attachment 11). However, there was a linear relationship between delta QTc and the ziprasidone serum concentration (attachment 12). This suggests that the changes in delta QTc values are more relevant than the actual QTc values.
5. It is not clear as to why ECG measurements were not taken at the same time of PK blood sampling. In this study, PK samples were done on day 1 and day 3. ECG measurements were done on day 1 for baseline (i.e., at time zero), on day 2 where no blood samples were taken and at 24 h on day 3 where the ziprasidone serum concentrations were minimal. For day 2, the predicted ziprasidone serum concentrations were not obtained by the sponsor, but were read by the visual inspection of the Figures of each subject. The characteristic Figures for the 40 and 80 mg doses are shown in attachments 13 (i-ii). For day 1 and 3, serum PK samples are shown in attachment 14 (i-iii). Further, the attached Excel sheet shows the individual QTc and serum concentration data for each subject (attachment 15). From this data sheet, the Figures in attachments 16 and 17 were

prepared. Thus, from these Figures, it can be concluded that there is scatter plot for ziprasidone serum concentration and the actual QTc values on day 2 as shown in attachment 16. This is the modification of the sponsor's prepared Figure shown in attachment 11. However, when the differences in QTc values for day 2 and day 1 were plotted against the predicted serum ziprasidone concentration in day 2, a positive relationship was apparent as shown in attachment 17. This is the modification of the sponsor's prepared Figure shown in attachment 12.

**Conclusions:**

1. Dose proportionality occurs only over 20 and 40 mg doses.
2. It does not appear that there is drug accumulation over the three days treatments across all doses (20 to 80 mg /day).
3. The effect of ziprasidone on QTc intervals appears to be dose and concentration dependent.

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**PROTOCOL 128-046: PHASE I INVESTIGATOR-BLIND, PLACEBO-CONTROLLED EVALUATION OF THE SAFETY, TOLERATION AND PHARMACOKINETICS OF ZIPRASIDONE MESYLATE FOLLOWING MULTIPLE INTRAMUSCULAR DOSES IN SUBJECTS WITH CHRONIC OR SUBCHRONIC SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER**

**Principal Investigators:** [ ]

**Study Publication:** None

**Study Dates:** 11 November 1996 to 18 April 1997

**Study Objective:** To evaluate the safety, toleration and pharmacokinetics of ziprasidone in subjects with schizophrenia given multiple intramuscular doses ranging from 20 to 80 mg/day.

**Study Design:** This was a randomized, investigator-blind, placebo-controlled study of escalating multiple intramuscular doses of ziprasidone. Sterile normal saline injected intramuscularly served as placebo. Three dosing regimens of ziprasidone (20 to 80 mg/day) were examined and subjects were assigned in groups of eight. For each dosing regimen, six subjects received ziprasidone and two received placebo. This study was investigator-blind with respect to within-group assignment and single-blind with respect to between-group assignment. Groups 1 (20 mg/day) and 2 (40 mg/day) received 5 and 10 mg ziprasidone IM, respectively, every two hours (four times daily), on days 1, 2, and 3. On day 1, Group 3 (80 mg/day) received one dose of 10 mg ziprasidone IM followed by three doses of 20 mg IM, given every four hours, for a total daily dose of 70 mg. On days 2 and 3, Group 3 received 20 mg four times daily, every four hours.

**Evaluation Groups:**

	Ziprasidone			Placebo
	20 mg/day	40 mg/day	80 mg/day	
Entered Study	6	7	6	6
Completed Study	6	6	6	6
Evaluated for Pharmacokinetics	6	6	6	0
Assessed for Safety				
Adverse events	6	7	6	6
Laboratory tests <sup>a</sup>	6	7	6	6

<sup>a</sup>Laboratory tests were performed only at screening and prior to dosing on day 1, and 24 hours following the first IM dose on day 3, unless follow-up was required.

**Subjects:** Subjects of either sex ranging in age from 21-52 years, with a primary diagnosis of chronic or subchronic schizophrenia or schizoaffective disorder or schizotypal personality disorder.

**Drug Administration:**

<u>Drug</u>	<u>Lot Number</u>	<u>FID Number</u>	<u>Potency</u>	<u>Formulation</u>
Ziprasidone	ED-O-448-Z95	G00875AA	20 mg/ml	LYPH

**Dosing:** Study medication was administered as a single intramuscular injection to the upper arm (non-dominant) of each subject four times daily for three days. Ziprasidone or placebo were administered beginning in the early morning (approximately 8 am). Subject groups were studied serially, beginning with the lowest dose subject group (Group 1) and proceeding to the next highest dose subject group.

**Pharmacokinetic and Safety Evaluations:** Blood samples for the determination of serum ziprasidone were collected prior to and up to 24 hours following the injection on days 1 and 3. On day 3, additional samples were obtained up to 36 hours following the first injection. Serum concentrations were used to determine pharmacokinetic parameters. Subjects were assessed for extrapyramidal side effects, akathisia, and abnormal involuntary movements, and completed subjective evaluations of sedation. Laboratory tests including several measurements of renal function (urinary NAG [N-acetyl- $\beta$ -D-glucosaminidase], creatinine, total protein, microalbumin and  $\beta$ -2 microglobulin) were evaluated up to 48 hours after dosing. Subjects were also monitored for adverse effects and changes in vital signs, ECGs, and laboratory data.

**Analytical Methods:** Serum concentrations of ziprasidone were determined by a validated HPLC assay C

**Statistical Methods:** Pharmacokinetic and safety results were summarized through appropriate data tabulations, descriptive statistics and graphical presentations.

#### Pharmacokinetic Results:

Mean (Coefficients of Variation - %CV) of Pharmacokinetic Parameters (n=6)

Parameter	Ziprasidone					
	20 mg/day Group 1		40 mg/day Group 2		80 mg/day Group 3	
	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3
AUC <sub>0-24</sub> (ng•hr/ml) <sup>a</sup>	648(25)	590 (27)	1363 (26)	1116 (23)	1560 (22)	1504 (30)
Accumulation Ratio <sup>a</sup>	--	0.91 (17)	--	0.82 (9)	--	0.96 (17)
K <sub>el</sub> (hr <sup>-1</sup> )	0.152 (14)	0.085 (19)	0.176 (16)	0.067 (26)	0.180 (9)	--c
T <sub>1/2</sub> (hr) <sup>b</sup>	4.6	8.1	3.9	10.4	3.8	--c

<sup>a</sup>geometric mean

<sup>b</sup>T<sub>w</sub> = 0.693/mean K<sub>el</sub>

<sup>c</sup> Not determined due to an insufficient time interval over which to estimate K<sub>el</sub>.

#### Safety Results:

Number of Subjects With/Evaluated For:	Ziprasidone			Placebo
	20 mg/day	40 mg/day	80 mg/day	
Adverse Events (All Causality)	6/6(0)	6/7(0)	6/6(0)	5/6(0)
Adverse Events (Treatment-emergent, Treatment-related)	6/6(0)	5/7(0)	6/6(0)	2/6(0)
Clinically Significant Laboratory Test Abnormalities	1/6(0)	3/7(0)	2/6(0)	1/6(0)

(0)Subjects discontinued

#### Summary and Conclusions:

Across dose levels, systemic exposure increased with increasing dose on both days 1 and 3 based on AUC<sub>0-24</sub>. Exposure between Groups 1 and 2 appeared dose proportional. A dose proportionality assessment was not performed for Group 3 because of differences in serum sampling and drug administration schedule relative to Groups 1 and 2. However, a comparison of serum ziprasidone concentrations obtained 2 hours following the last IM injection on either day 1 or 3 suggested that exposure for Group 3 was dose-related. Due to the limited number of pharmacokinetic samples obtained on days 1 and 3, particularly near the time of peak exposure, C<sub>max</sub> and T<sub>max</sub> were not reported and AUC<sub>0-24</sub> values underestimate

overall ziprasidone exposure. Little drug accumulation was evident at any dose level following three days of drug administration. On the morning of day 4, serum concentrations were low and less than previously observed trough concentrations at steady-state following oral BID doses of 40 mg ziprasidone. No apparent difference in exposure was observed between males and females.

Mean terminal elimination half-lives were similar between groups, with values on day 1 ranging from 4 to 5 hours. On day 3, half-lives appeared longer compared to day 1, ranging from approximately 7 to 13 hours. The longer half-lives reported on day 3 were related to a longer sampling period following the last injection on day 3 which revealed the presence of an additional dispositional phase for all groups. Half-lives for Group 3 could not be estimated because of the shorter time interval over which to assess them during the terminal phase.

One subject was discontinued from the study for his dislike of the blood draws and injections.

All subjects in the 20 mg and 80 mg treatment groups, six out of seven subjects in the 40 mg group, and five out of six placebo subjects experienced at least one adverse event during the study. Of the 114 adverse events reported, 88 (77.2%) were treatment-emergent and the majority were treatment-related. No subject was discontinued due to adverse events.

There was one post-treatment serious adverse event reported in this study. Subject 557-0029, a 50 year old white male receiving ziprasidone 40 mg/day, experienced an exacerbation of schizophrenia on day 30, 27 days after completing the study (Appendix I, Table 5.1).

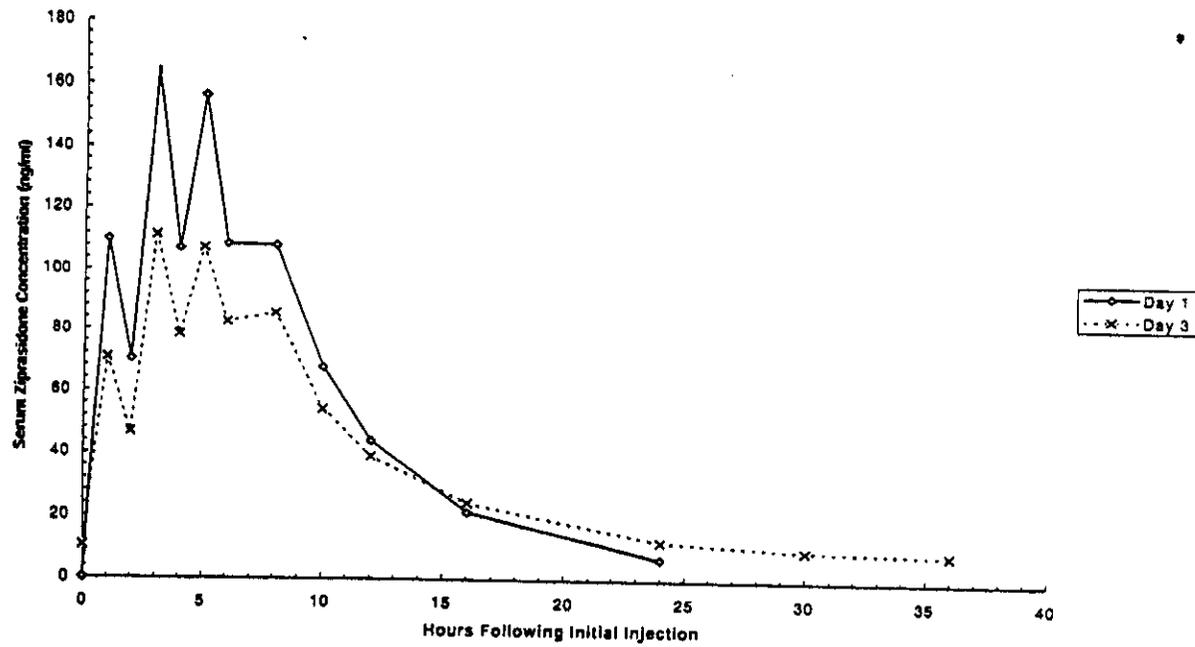
Subject 557-0039 in the 80 mg treatment group experienced severe hand tremors which were considered to be treatment-related. This was the only severe adverse event reported in the study.

All other adverse events reported were mild to moderate in severity. The more frequently reported adverse events were dizziness, insomnia, pain at the application site, postural hypotension, and nausea. Fourteen out of 19 patients on active drug and two out of six placebo subjects reported mild to moderate somnolence.

Clinically significant laboratory test abnormalities included elevations in non-fasting triglycerides found in one subject in the 20 mg treatment group, three subjects in the 40 mg treatment group, two subjects in the 80 mg treatment group, and one subject in the placebo group. One subject (557-0029) had an elevation in total bilirubin on day 4 of the study (2.0 mg/dl) which returned to normal by day 11. All other abnormalities were isolated and no trends were noted. There were no notable differences among the groups in urinary protein excretion rate, microalbumin excretion rate, NAG:creatinine ratio or  $\beta$ -2 microglobulin/creatinine ratio. There were no apparent changes in these parameters to indicate a treatment-related effect on renal function.

Ziprasidone 20 mg and 80 mg treatment groups showed a slight increase (13 and 8 mmHg, respectively) in median changes from baseline to last observation for standing systolic blood pressure. Clinically significant increases in standing heart rate (heart rate  $>120$  bpm but  $<156$  bpm, change  $\geq 15$ ) were noted in all four treatment groups: two subjects (33.3%) in the 20 mg/day group, four subjects (57.1%) in the 40 mg/day group, and one subject (16.7%) each in the 80 mg/day and placebo groups. The placebo group (16.7%) had clinically significant changes in both decreased standing systolic blood pressure (BP  $<90$  mmHg, change  $\leq -20$ ) and increased standing diastolic blood pressure (BP  $>105$  mmHg, change  $\geq 20$ ). The 40 mg treatment group (14.3%) had one subject with a clinically significant increase in supine heart rate (HR  $>120$  bpm but  $<152$  bpm, change  $\geq 15$ ).

Figure 1.2 Mean Serum Ziprasidone Concentrations for Group 2 on Days 1 and 3 in Subjects Receiving Intramuscular Injections of Ziprasidone 10 mg q2h X 4 for 3 Days  
Ziprasidone Protocol 046

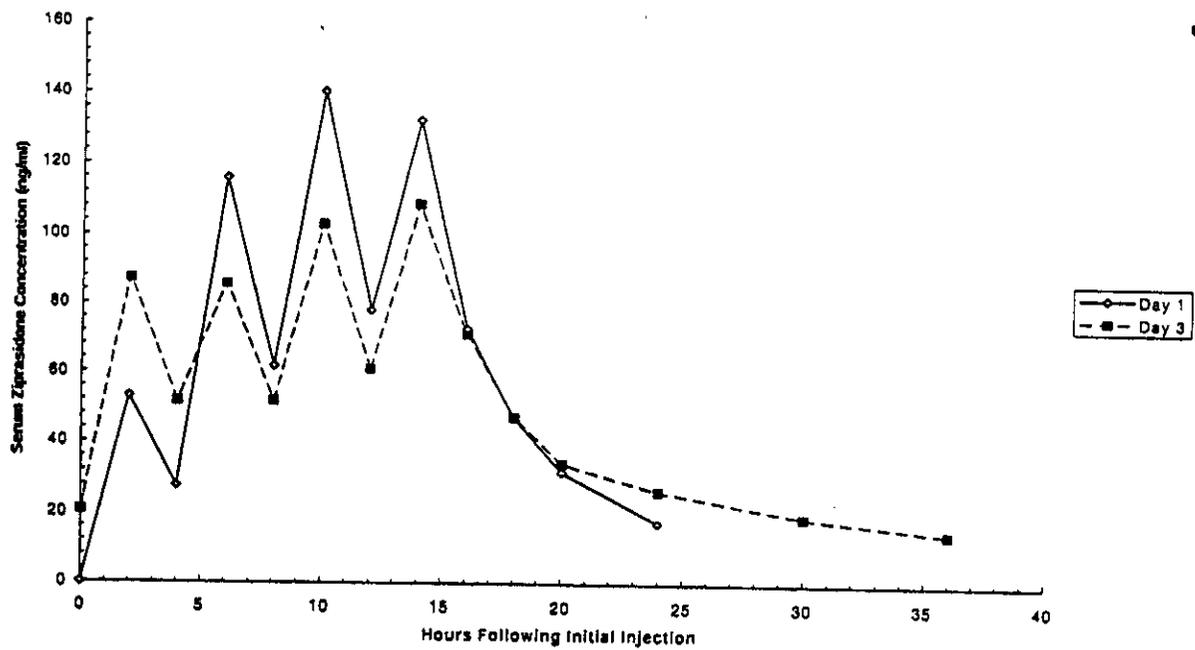


Source Data: Appendix IV, Table 2

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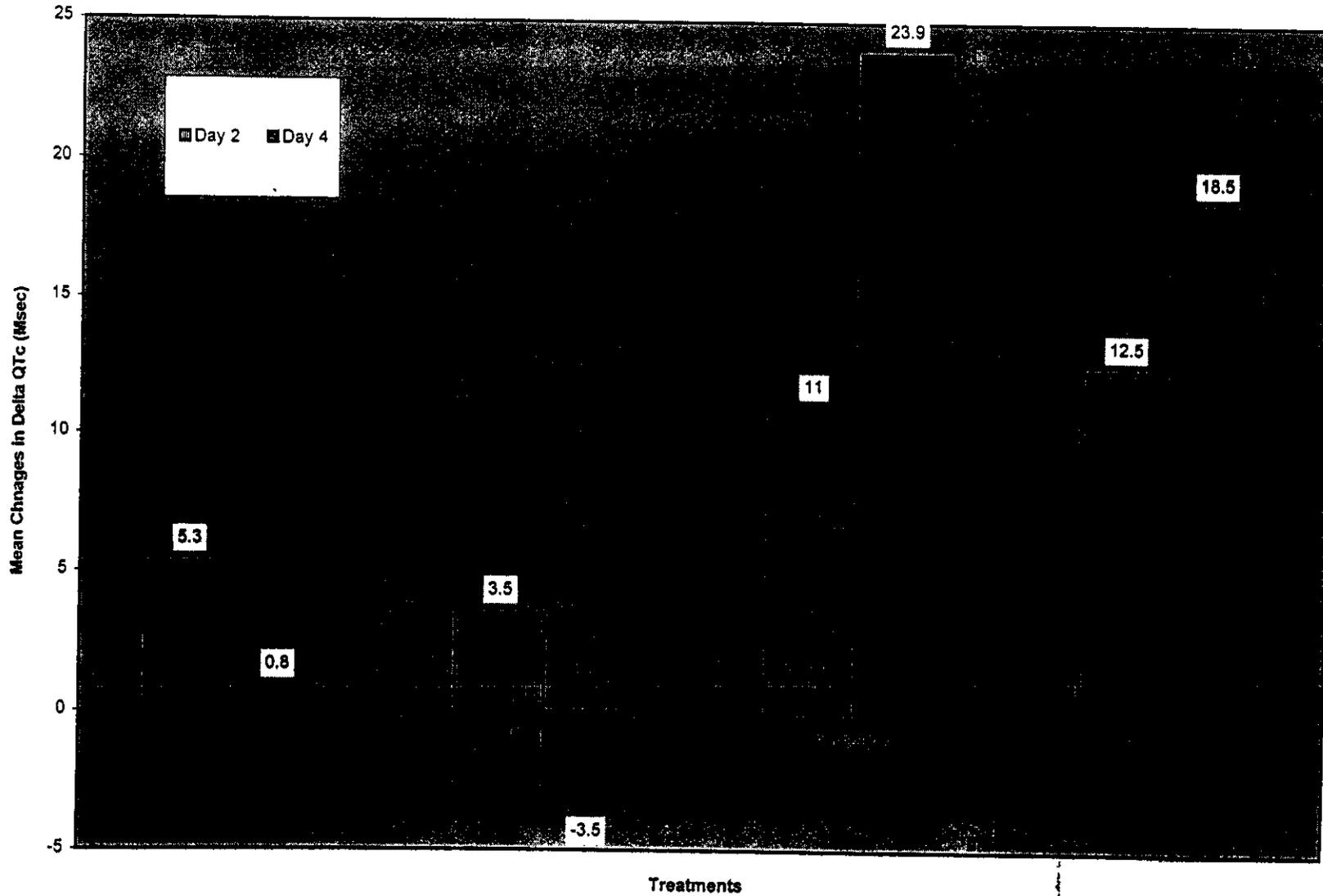
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Figure 1.3 Mean Serum Ziprasidone Concentrations for Group 3 on Days 1 and 3 in Subjects Receiving Intramuscular Injections of Ziprasidone - Day 1: 10 mg q4h X1 → 20 mg q4h X 3; Day 3: 20 mg q4h X 4 Ziprasidone Protocol 046



Source Data: Appendix IV, Table 3

Mean Changes in Delta QTc After Ziprasidone IM Administration



9

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Table 10  
 Change from Baseline to ECG Reading following Fourth IM Dose on Day 2  
 Protocol 046 - Central Reader Data

Page 1 of 1

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc int (msec)	20mg/day	6	404.3	404.5	389-418	407.8	411.0	369-437	3.5
	40mg/day	6	395.3	386.5	380-422	406.3	404.0	388-436	11.0
	80mg/day	6	399.5	401.0	375-422	412.0	410.5	380-440	12.5
	Placebo	6	398.7	396.0	385-413	404.0	402.5	382-424	5.3
QT int (msec)	20mg/day	6	352.8	352.0	311-395	344.8	346.0	291-388	-8.0
	40mg/day	6	339.3	336.5	295-390	333.5	336.5	286-373	-5.8
	80mg/day	6	337.0	336.5	328-347	345.3	345.5	322-379	8.3
	Placebo	6	341.3	339.0	321-370	343.0	339.5	324-381	1.7
Heart Rate (bpm)	20mg/day	6	79.8	77.5	66-94	84.7	82.5	76-97	4.8
	40mg/day	6	84.0	82.5	58-123	91.7	85.0	68-140	7.7
	80mg/day	6	84.5	84.0	77-94	86.0	82.5	78-106	1.5
	Placebo	6	82.0	81.5	74-89	84.0	87.5	67-92	2.0
PR int (msec)	20mg/day	6	139.0	136.5	123-165	137.3	136.0	124-157	-1.7
	40mg/day	6	153.5	154.5	126-176	138.2	139.0	124-150	-15.3
	80mg/day	6	152.5	154.5	136-168	147.0	148.0	123-165	-5.5
	Placebo	6	165.0	165.5	142-190	160.7	160.5	136-180	-4.3
QRS int (msec)	20mg/day	6	89.0	87.0	80-100	88.0	86.0	80-102	-1.0
	40mg/day	6	86.2	85.0	79-98	86.7	86.0	81-94	0.5
	80mg/day	6	89.0	88.5	85-94	91.3	93.0	82-96	2.3
	Placebo	6	88.5	88.0	81-97	90.0	89.5	82-101	1.5

\*QTc int = QT int/SQRT(60/(Heart Rate))

Baseline = last ECG taken before the first day of study treatment.

Final = last ECG taken while on study treatment or within one day after the last day of study treatment.

Subj. 05570021 (40mg/day) withdrew following the 2nd injection on Day 1 and is not included in this summary.

Source Data: Appendix V, Table 10

Date of Data Extraction: 24OCT97

Date of table generation: 05NOV97

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DAY 4

Table 9  
Change from Baseline to Last Observation in ECG Readings  
Protocol 046 - Central Read Data

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc int (msec)	20mg/day	6	404.3	404.5	389-418	400.8	406.0	371-429	-3.5
	40mg/day	7	395.1	389.0	380-422	419.0	427.0	394-431	23.9
	80mg/day	6	399.5	401.0	375-422	418.0	418.5	405-430	18.5
	Placebo	6	398.7	396.0	385-413	399.5	401.5	389-406	0.8
QT int (msec)	20mg/day	6	352.8	352.0	311-395	347.2	354.5	305-370	-5.7
	40mg/day	7	336.6	327.0	295-390	335.1	337.0	292-380	-1.4
	80mg/day	6	337.0	336.5	328-347	341.5	335.0	321-380	4.5
	Placebo	6	341.3	339.0	321-370	354.0	359.5	322-369	12.7
Heart Rate (bpm)	20mg/day	6	79.8	77.5	66-94	80.3	79.5	74-89	0.5
	40mg/day	7	85.0	83.0	58-123	96.3	88.0	71-131	11.3
	80mg/day	6	84.5	84.0	77-94	90.5	93.0	77-98	6.0
	Placebo	6	82.0	81.5	74-89	76.8	75.5	72-88	-5.2
PR int (msec)	20mg/day	6	139.0	136.5	123-165	137.0	132.5	124-160	-2.0
	40mg/day	7	152.3	153.0	126-176	146.3	146.0	131-167	-6.0
	80mg/day	6	152.5	154.5	136-168	151.8	151.5	137-168	-0.7
	Placebo	6	165.0	165.5	142-190	159.3	161.0	134-187	-5.7
QRS int (msec)	20mg/day	6	89.0	87.0	80-100	90.7	88.5	79-103	1.7
	40mg/day	7	86.7	86.0	79-98	87.1	85.0	80-96	0.4
	80mg/day	6	89.0	88.5	85-94	88.0	90.5	79-96	-1.0
	Placebo	6	88.5	88.0	81-97	86.7	84.0	81-97	-1.8

3

\*QTc int = QT int/SQRT(60/(Heart Rate))

Baseline = last ECG taken before the first day of study treatment.

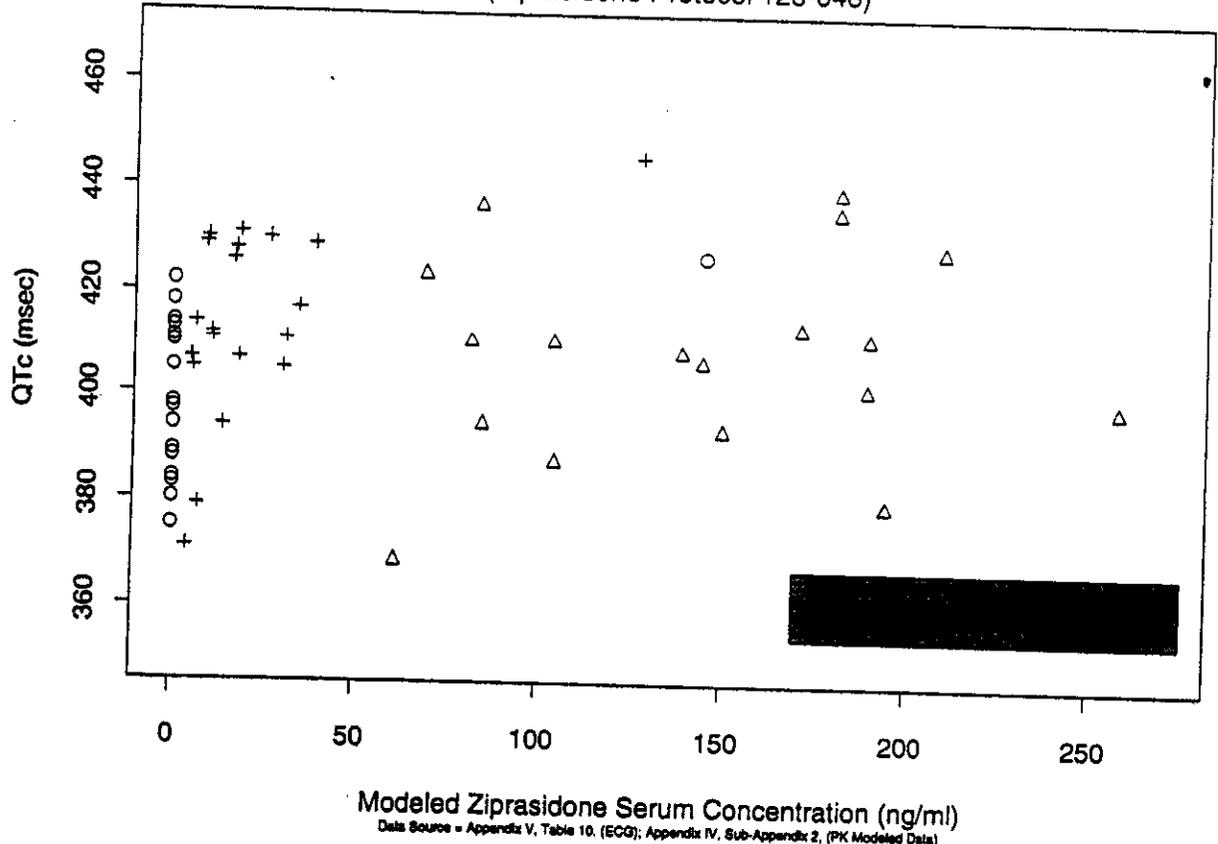
Final = last ECG taken while on study treatment or within one day after the last day of study treatment.

Source Data: Appendix V, Table 10 Date of Data Extraction: 24OCT97 Date of table generation: 24OCT97

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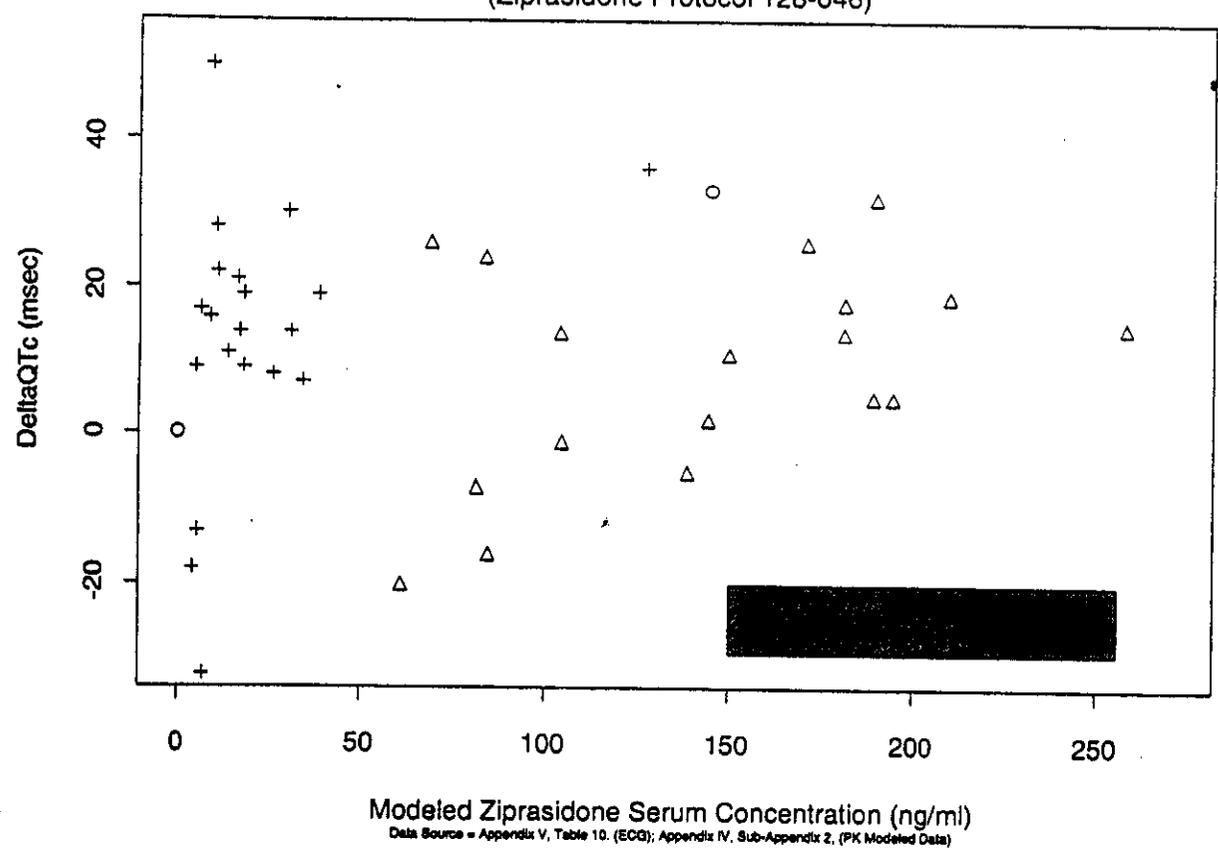
11

Figure 4.1. QTc Interval vs Modeled Ziprasidone Serum Concentration Following Intramuscular Doses of 5 to 20 mg Four Times Daily (Ziprasidone Protocol 128-046)



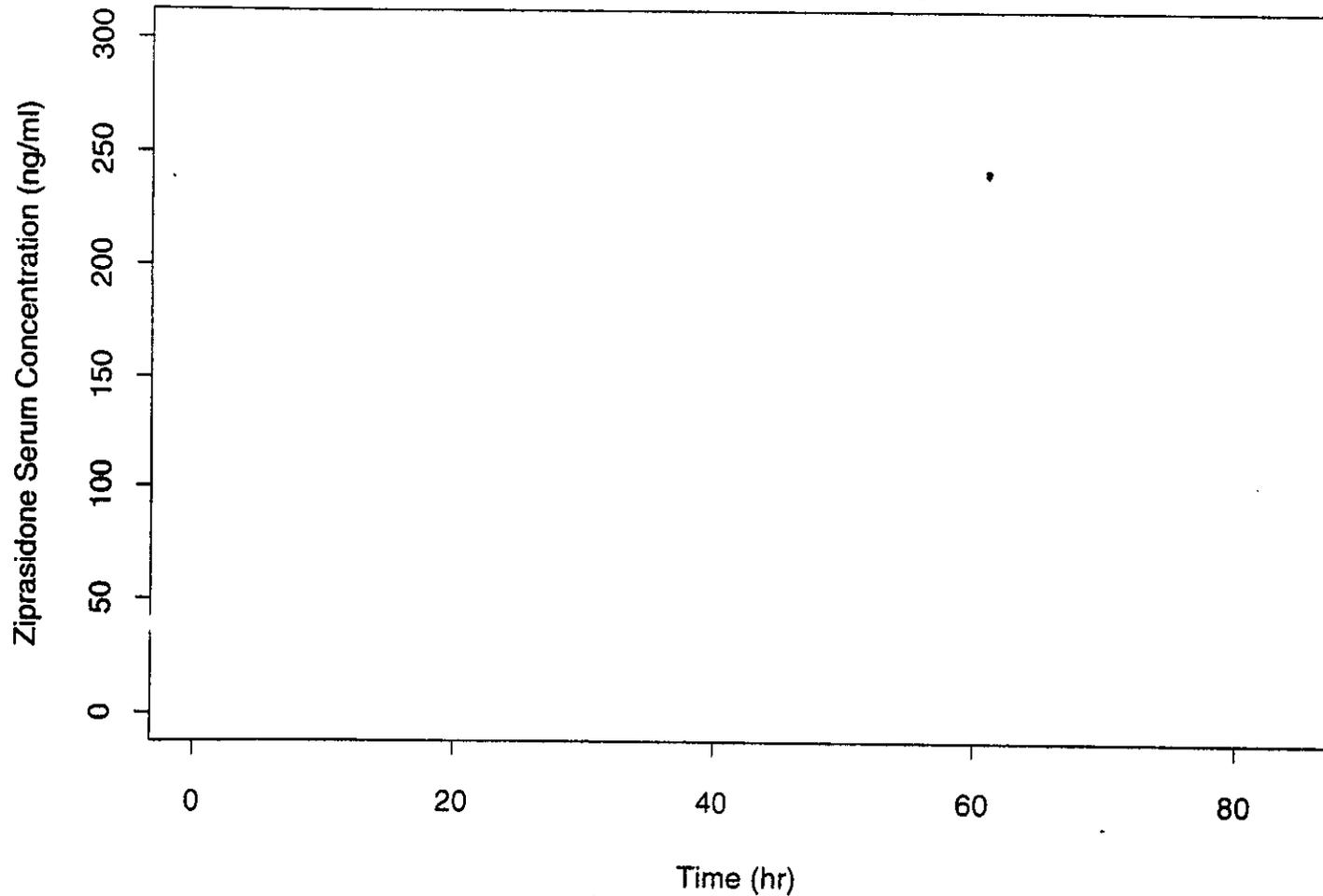
12  
12

Figure 4.2. DeltaQTc Interval vs Modeled Ziprasidone Serum Concentration Following Intramuscular Doses of 5 to 20 mg Four Times Daily (Ziprasidone Protocol 128-046)



Attachment  
13(i)

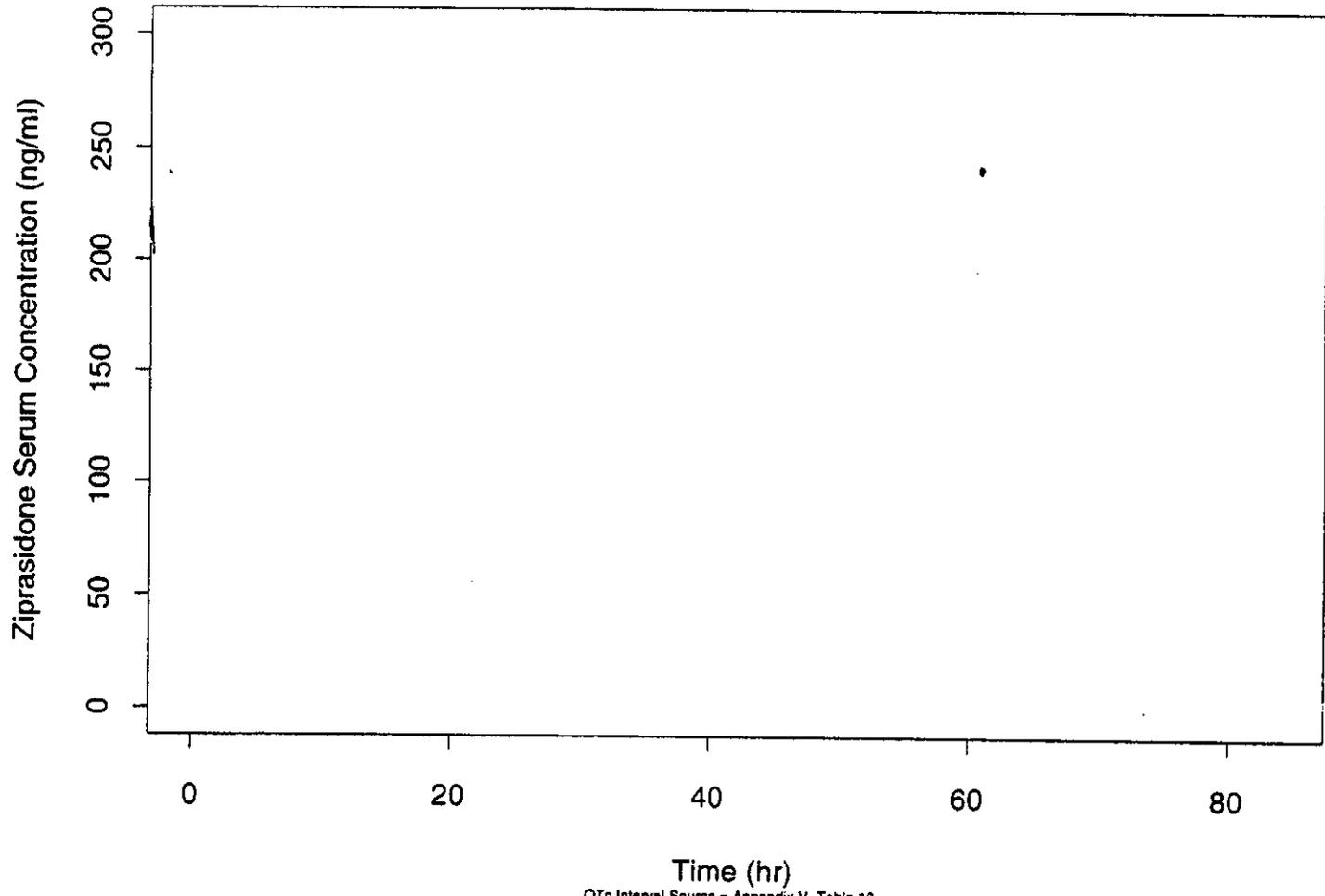
Subject 5570017  
Dose = 40 mg daily



QTc Interval Source = Appendix V, Table 10.

X = ECG (numerical value corresponds to QTc interval)  
• = Ziprasidone Serum Concentration

Subject 5570034  
Dose = 80 mg daily



QTc Interval Source = Appendix V, Table 10.

X = ECG (numerical value corresponds to QTc interval)  
• = Ziprasidone Serum Concentration

Appendix IV, Table 1  
 Serum Ziprasidone Concentrations for Group 1 on Days 1 and 3 in Subjects Receiving Four  
 Daily Intramuscular Injections of 5 mg Ziprasidone Every 2 Hours for Three Days  
 Ziprasidone Protocol 046

Day 1

Serum Ziprasidone Concentration (ng/ml) at Time (hours) Following First Injection of the Day												
Subject	0	1	2	3	4	5	6	8	10	12	16	24
557-0001												
557-0003												
557-0004												
557-0006												
557-0007												
557-0008												
Mean	0	43	28	66	45	72	50	54	34	23	12	4
SD	--	9	6	12	10	12	8	16	11	9	5	2
CV%	--	21	20	18	21	17	17	29	32	37	44	51

Day 3

Serum Ziprasidone Concentration (ng/ml) at Time (hours) Following First Injection of the Day														
Subject	0	1	2	3	4	5	6	8	10	12	16	24	30	36
557-0001														
557-0003														
557-0004														
557-0006														
557-0007														
557-0008														
Mean	5	43	28	53	37	60	42	46	30	22	13	6	4	3
SD	2	6	4	9	10	21	12	16	10	8	4	1	1	1
CV%	49	14	15	18	27	36	28	36	32	36	33	19	20	19

## Appendix IV, Table 2

Serum Ziprasidone Concentrations for Group 2 on Days 1 and 3 in Subjects Receiving Four Daily Intramuscular Injections of 10 mg Ziprasidone Every 2 Hours for Three Days Ziprasidone Protocol 046

## Day 1

Serum Ziprasidone Concentration (ng/ml) at Time (hours) Following First Injection of the Day

Subject	0	1	2	3	4	5	6	8	10	12	16	24
557-0017												
557-0018												
557-0019												
557-0023												
557-0024												
557-0029												
Mean	0	110	70	164	107	157	109	108	68	44	22	7
SD	--	31	19	39	25	50	31	43	21	13	4	1
CV%	--	28	28	24	23	32	29	40	31	29	18	13
557-0021 <sup>b</sup>	NR			NSR								

## Day 3

Serum Ziprasidone Concentration (ng/ml) at Time (hours) Following First Injection of the Day

Subject	0	1	2	3	4	5	6	8	10	12	16	24	30	36
557-0017														
557-0018														
557-0019														
557-0023														
557-0024														
557-0029														
Mean	10	71	47	112	78	108	83	86	54	39	25	13	10	9
SD	3	34	16	41	28	44	31	23	13	9	4	5	4	4
CV%	29	48	34	36	36	41	38	27	25	23	18	40	44	44

<sup>b</sup> = Subject did not complete the study; excluded from summary statistics.

NR = Not reportable due to endogenous interference in the sample.

NSR = No sample received.

Appendix IV, Table 3

Serum Ziprasidone Concentrations for Group 3 on Days 1<sup>a</sup> and 3 in Subjects Receiving Four Daily Intramuscular Injections of 20 mg Ziprasidone Every 4 Hours for Three Days Ziprasidone Protocol 046

Day 1

Serum Ziprasidone Concentration (ng/ml) at Time (hours) Following First Injection of the Day

Subject	0	2	4	6	8	10	12	14	16	18	20	24
557-0034												
557-0035												
557-0036												
557-0037												
557-0038												
557-0039												
Mean	0	53	28	116	62	141	78	133	73	47	32	17
SD	--	6	4	18	11	28	25	38	24	18	12	6
CV%	--	12	14	15	18	20	32	29	33	38	39	35

Day 3

Serum Ziprasidone Concentration (ng/ml) at Time (hours) Following First Injection of the Day

Subject	0	2	4	6	8	10	12	14	16	18	20	24	30	36
557-0034														
557-0035														
557-0036														
557-0037														
557-0038														
557-0039														
Mean	20	87	52	86	52	103	61	109	71	47	34	27	19	14
SD	7	30	17	17	10	35	21	40	32	17	12	9	5	3
CV%	34	34	33	20	20	34	35	37	45	37	35	34	26	23

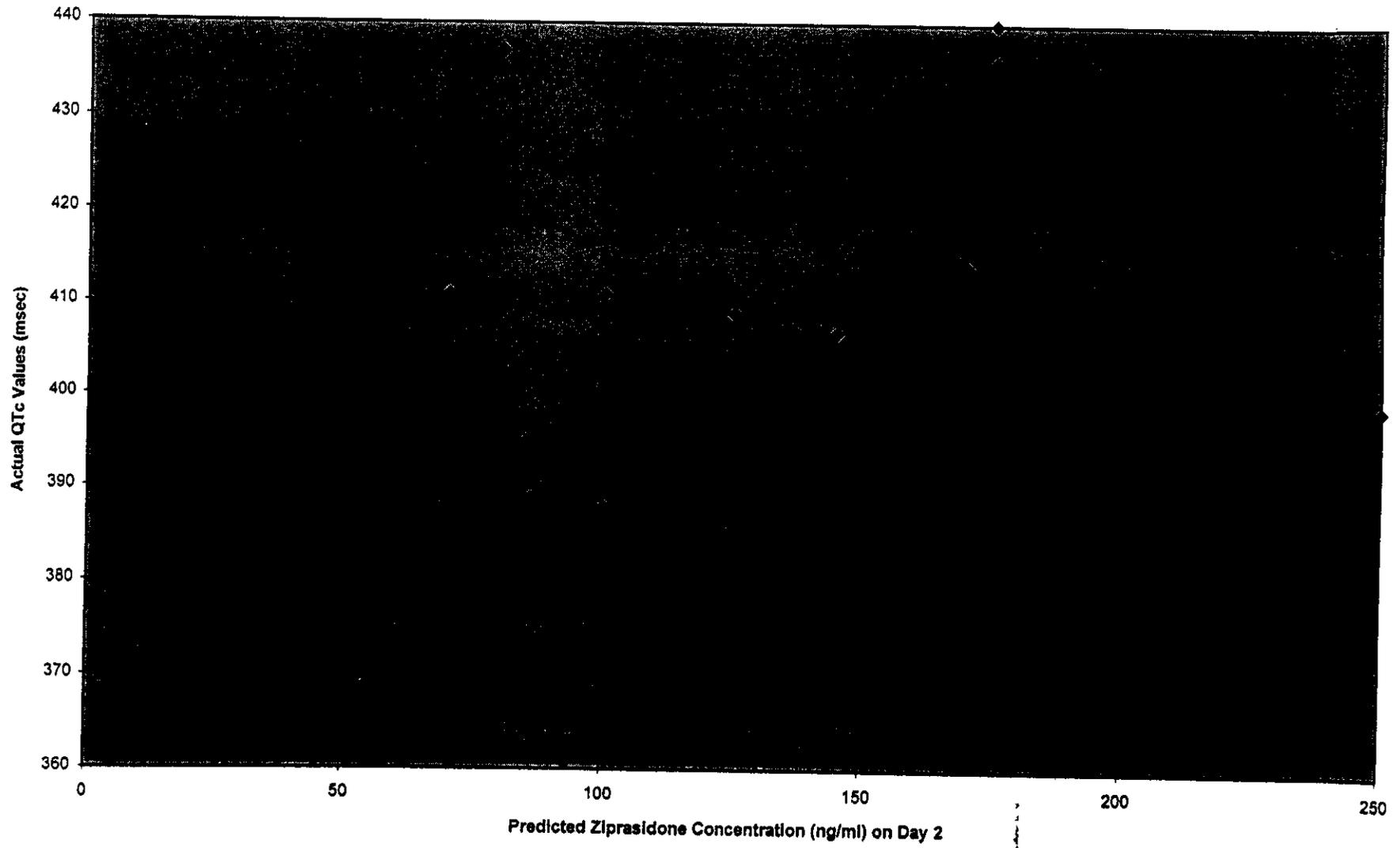
a = The first dose on day 1 was 10 mg; all others were 20 mg.

b = Concentrations less than 1 ng/ml are reported as 0 ng/ml.

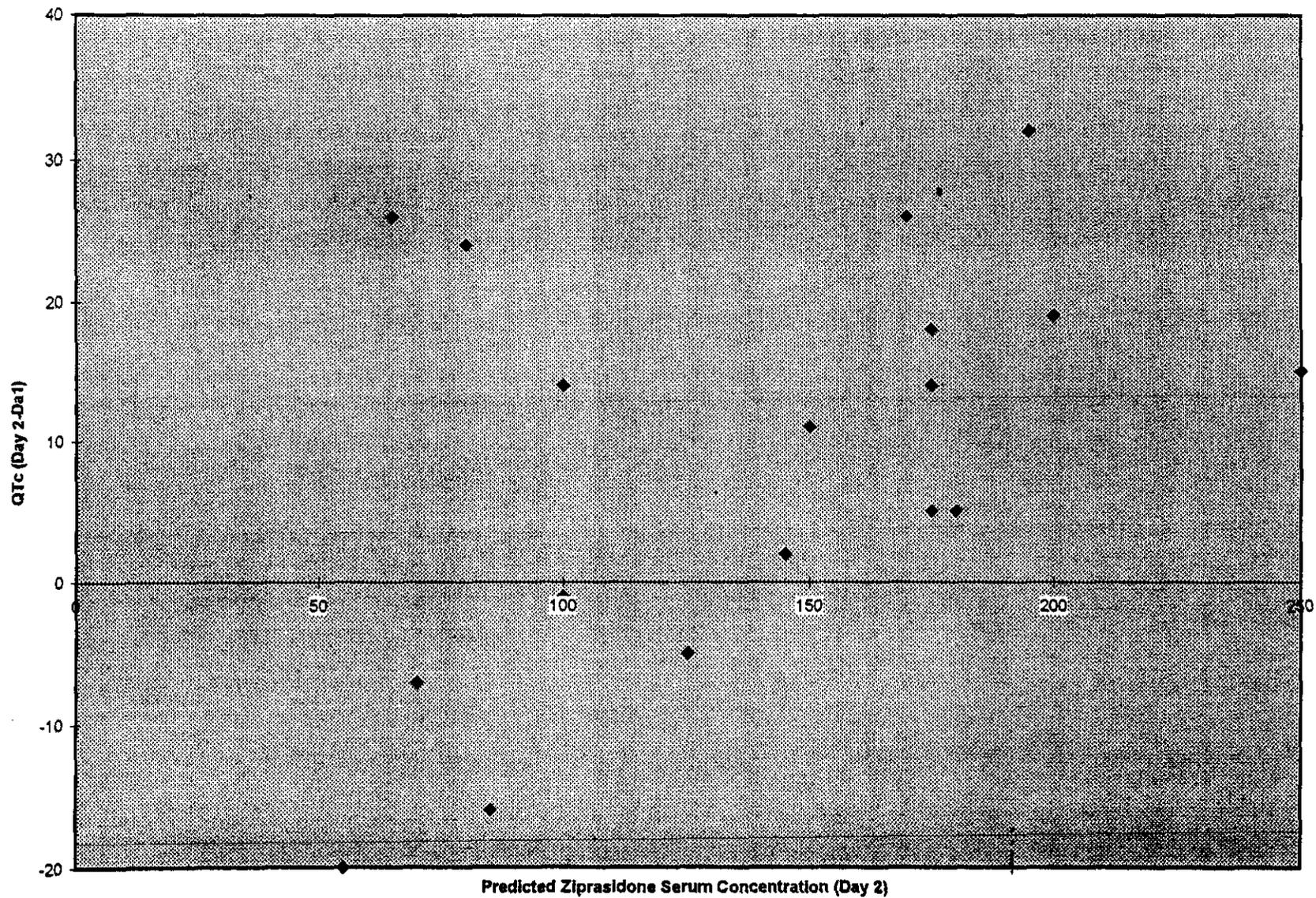
NR = Not reportable due to endogenous interference in the sample.

		QTc (msec)					Conc at QTc Measurement				
		Zero Time	7 h	24 h			(ng/m)				
		D1	D2	D3			Observ.	Pred. (~)	Observ.		
Dose	Sub	Baseline	D2 (Conc)	D2 (QTC)	Day 3	D2-D1	D3-D1	Day 1	D2 (Conc)	Day 3	
20 mg/day	1	411									
	3	389									
	4	418									
	6	398									
	7	397									
	8	413									
	40 mg/day	17	384								
		18	380								
19		389									
23		383									
24		422									
29		414									
80 mg/day		34	405								
	35	375									
	36	388									
	37	422									
	38	397									
	39	410									
	Mean		400		409	412	9	12			
SD		15		20	18	15	19				

Relationship Between The Actual QTc Values and The Predicted Ziprasidone Serum Concentration on Day 2



Relationship Between Individual Differences in QTc Data (Day 2-Day 1) and Predicted Ziprasidone Serum Concentration on Day 2



**4. Study 037 (Absolute Bioavailability 5 mg IV, 5 mg IM and 20 mg PO)**

**Study Design and Summary:**

(see attachments 1-3)

**Results:**

(See attachments 4-8)

**Reviewer's Comments:**

1. This was a single dose study and the selected 5 mg IM dose is lower than the recommended daily dose of 10 to 80 mg by this route of administration. The rate of absorption from the muscle may be different and/or dose dependent at higher doses.
2. The absolute bioavailability of ziprasidone was approximately 100% after IM administration and 60% after oral administration (attachment 2).
3. C<sub>max</sub> was attained within 1 hour of IM administration. Detailed data for IM, IV, and PO are in attachments 4-6. The T<sub>max</sub> after IM was more variable than after IV and oral administration. The CV for T<sub>max</sub> after IM was 60% whereas after IV and oral administration was 12% and 42%, respectively.
4. Typical plasma concentration time profiles were obtained after IM, IV, and oral administration (attachment 7).
5. There were similar sedation ratings for IM and IV which lasted for about 4 hours (attachment 8). However, there was about 6 hours delay in sedation after oral administration and this was about 2-3 times lower than that after IM and IV administration.

**Conclusion:**

Based on these data the absolute bioavailability of ziprasidone after IM administration is about 100%.

**PROTOCOL 128-037: PHASE I OPEN STUDY TO COMPARE THE PHARMACOKINETICS OF ZIPRASIDONE ADMINISTERED INTRAVENOUSLY, INTRAMUSCULARLY AND ORALLY TO HEALTHY SUBJECTS**

**Principal Investigators:** C J

**Study Publication:** None

**Study Dates:** 24 May 1996 to 18 July 1996

**Study Objective:** To compare the safety, toleration and pharmacokinetics of ziprasidone when administered intravenously, intramuscularly and orally to healthy subjects.

**Study Design:** This was an open, randomized, three-way crossover study to evaluate ziprasidone pharmacokinetics in the same subjects. This study consisted of three periods with at least seven days separating each period. Each subject received the following treatments in a randomized sequence:

- A. 5 mg ziprasidone intravenously over one hour
- B. 5 mg ziprasidone intramuscularly
- C. 20 mg ziprasidone orally (under fed conditions)

**Evaluation Groups:**

	Ziprasidone		
	5 mg IM	5 mg IV	20 mg PO
Entered Leg	13	12	13
Completed Leg	12 <sup>a</sup>	12	13
Evaluated for Pharmacokinetics	12	12	12
Assessed for Safety			
Adverse Events	13	12	13
Laboratory Tests	13	12	0 <sup>b</sup>

<sup>a</sup>Subject #0007 completed the IM phase but discontinued during the washout period.

<sup>b</sup>Laboratory tests were done only at screening and prior to dosing, unless follow-up was required.

**Subjects:** Normal, healthy volunteers, ranging in age from 19-37 years.

**Drug Administration:**

Drug	Lot Number	FID Number	Potency	Formulation
CP-88,059-1	N5056	QC2327	20 mg	Capsules
Ziprasidone	ED-O-448-Z95	G00875AA	20 mg/ml	LYPHA

<sup>a</sup>lyophilized powder, packaged in clear glass vials with fluted stoppers and aluminum shell

**Dosing:** For intravenous administration, 5 mg ziprasidone mesylate was infused at a constant rate over one hour (1 ml/min). For the intramuscular administration, 5 mg ziprasidone mesylate was administered as a single intramuscular injection to the upper arm (non-dominant) of each subject. For oral administration, ziprasidone 20 mg was administered as a 1 x 20 mg commercial capsule in the fed state in which a standard meal was completely ingested over a 20 minute period. The ziprasidone capsule was then immediately administered with 50 ml of water. There was at least a 7-day interval between dosing days.

**Pharmacokinetic and Safety Evaluations:** Blood samples for determination of serum ziprasidone concentrations were collected prior to and up to 24 hours following the administration of IM and IV ziprasidone and up to 36 hours following oral administration. Serum concentrations were used to determine pharmacokinetic parameters ( $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ , half-life, F (for IM and oral only), and AUC; Cl and  $Vd_{ss}$  for IV only). For the intravenous and intramuscular legs of the study, laboratory tests including several measurements of renal function (urinary NAG [N-acetyl- $\beta$ -D-glucosaminidase], creatinine, total protein, microalbumin and  $\beta$ -2 microglobulin) were evaluated up to 48 hours after dosing. Subjects completed a self-evaluation for the presence of sedation prior to and up to 24 hours following dosing. Subjects were monitored for adverse effects and changes in vital signs.

**Analytical Methods:** Serum concentrations of ziprasidone were determined by a validated HPLC assay C

**Statistical Methods:** Pharmacokinetic and safety results were summarized through appropriate data tabulations, descriptive statistics and graphical presentations.

#### Pharmacokinetic Results:

##### Mean and Coefficients of Variation (CV%) of Pharmacokinetic Parameters (n=12)

Parameter	Ziprasidone					
	5 mg IM		5 mg IV		20 mg PO	
$AUC_{0-\infty}$ (ng•hr/ml) <sup>a</sup>	223	(19)	217	(20)	514	(27)
$C_{max}$ (ng/ml) <sup>a</sup>	80	(32)	83	(21)	64	(28)
$T_{max}$ (hr)	0.47	(60)	1.01	(12)	8.2	(42)
$K_{el}$ (hr <sup>-1</sup> )	0.233	(13)	0.221	(15)	0.185	(17)
$T_{1/2}$ (hr) <sup>b</sup>	2.97	--	3.14	--	3.75	--
F (%)	103	(8)	--	--	60	(23)
Cl (ml/min/kg)	--	--	5.08	(14)	--	--
$Vd_{ss}$ (L/kg)	--	--	1.03	(16)	--	--

<sup>a</sup>geometric means and standard deviations

<sup>b</sup>mean  $T_{1/2} = \ln(2)/\text{mean } K_{el}$

**Safety Results:**

Number of Subjects With/Evaluated For:	Ziprasidone		
	5 mg IM	5 mg IV	20 mg PO
Adverse Events (All Causality)	9/13(0)	6/12(0)	7/13(0)
Adverse Events (Treatment-emergent, Treatment-related) <sup>a</sup>	9/13(0)	6/12(0)	5/13(0)
Clinically Significant Laboratory Test Abnormalities <sup>b</sup>	0/13(0)	1/12(0)	--

()Subjects discontinued

<sup>a</sup>All adverse events were treatment emergent. <sup>b</sup>20 mg PO group had no laboratory tests.

**Summary and Conclusions:**

Following a 5 mg IV infusion of ziprasidone, the mean Cl and Vd<sub>ss</sub> were 5.08 ml/min/kg and 1.03 L/kg, respectively. Compared to the intravenous dose, the mean oral bioavailability of a 20 mg capsule in the fed state was 60% and mean IM bioavailability was approximately 100%. Although T<sub>max</sub> following IM dosing was somewhat variable, it was generally obtained within 0.5 hours of dosing. The mean T<sub>max</sub> following IM dosing was approximately 7.5 hours earlier than that observed with oral dosing. Terminal phase half-lives were consistently longer for the oral dosing compared with the IM or IV dosing. Ongoing drug absorption during the latter portion of the sampling period for the oral dosing may have been responsible for this difference.

All adverse events were treatment-emergent, and most were treatment-related. The most frequently reported adverse events were asthenia, postural hypotension, somnolence, headache, and hypotension, most of which were moderate in severity. The 20 mg oral group reported less somnolence than the other two groups. All other adverse events were isolated (one subject each) and of mild to moderate severity. There were no serious or severe adverse events or discontinuations due to adverse events in this study.

There were no notable differences among the groups with regard to the renal function parameters.

The IM and IV treatment groups showed similar trends in sedation with mean peak sedation occurring at two hours. The oral group mean peaked at six hours and was less than the IM and IV groups.

There was a slightly greater decrease in standing systolic and diastolic blood pressure recordings in the IV and IM groups than the oral group.

In summary, intramuscular ziprasidone had a higher bioavailability and shorter time to maximum concentration than oral ziprasidone. Ziprasidone was well tolerated and there were no serious or severe adverse events reported.

Table 5.1 Individual and Mean Ziprasidone Pharmacokinetic Parameters Following an Oral 20 Mg Dose of Ziprasidone Ziprasidone Protocol 037

Subject #	Body Weight (kg)	AUC <sub>0-t</sub> (ng·hr/ml)	AUC <sub>0-∞</sub> (ng·hr/ml)	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (hr)	K <sub>el</sub> (hr <sup>-1</sup> )	T <sub>1/2</sub> (hr)	F (%)
723-0001	87.1							
723-0002	79.4							
723-0003	73.0							
723-0004	62.6							
723-0005	65.1							
723-0006	74.4							
723-0008	71.7							
723-0009	84.0							
723-0010	70.8							
723-0011	75.8							
723-0012	96.6							
723-0018	82.6							
Mean		504 <sup>a</sup>	514 <sup>a</sup>	64 <sup>a</sup>	8.2	0.185	3.75 <sup>b</sup>	60
S.D.		138	141	18	3.5	0.032		14
CV%		27	27	28	42	17		23
723-0007 <sup>c</sup>	75.4	⌊						

<sup>a</sup>Geometric means and standard deviations

<sup>b</sup>Calculated as  $\ln 2 / \text{mean } K_{el}$

<sup>c</sup>Subject who did not complete the study and the data were excluded from summary statistics

Source Data: Appendix IV, Table 1

Table 5.2 Individual and Mean Ziprasidone Pharmacokinetic Parameters Following an Intramuscular 5 Mg Dose of Ziprasidone  
Ziprasidone Protocol 037

Subject #	AUC <sub>0-t</sub> (ng·hr/ml)	AUC <sub>0-∞</sub> (ng·hr/ml)	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (hr)	K <sub>el</sub> (hr <sup>-1</sup> )	T <sub>1/2</sub> (hr)	F (%)
723-0001							
723-0002							
723-0003							
723-0004							
723-0005							
723-0006							
723-0008							
723-0009							
723-0010							
723-0011							
723-0012							
723-0018							
Mean	217 <sup>a</sup>	223 <sup>a</sup>	80 <sup>a</sup>	0.47	0.233	2.97 <sup>b</sup>	103
S.D.	43	43	26	0.28	0.030		8
CV%	20	19	32	60	13		8
723-0007 <sup>c</sup>	⊥					⊥	

<sup>a</sup>Geometric means and standard deviations

<sup>b</sup>Calculated as  $\ln 2 / \text{mean } K_{el}$

<sup>c</sup>Subject who did not complete the study and the data were excluded from summary statistics

Source Data: Appendix IV, Table 2

Three ECGs were obtained during the study:

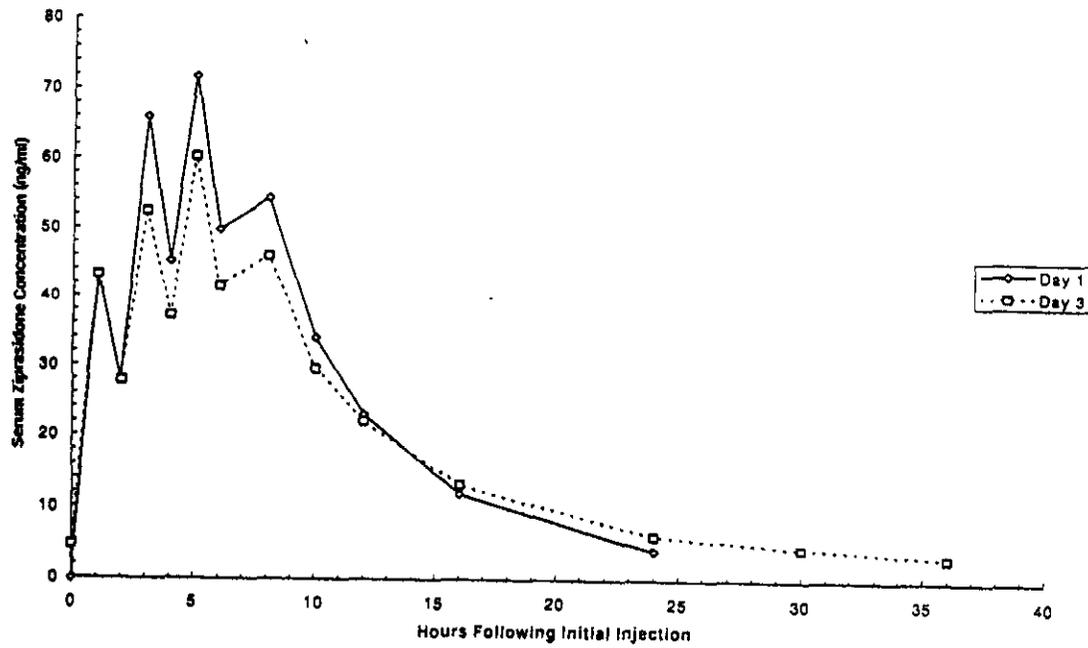
- 1) Baseline tracings were those obtained prior to the first IM dose on day 1.
- 2) A second tracing on each subject was obtained one hour following the fourth IM dose on day 2. This time (i.e. 7 hours after the first IM dose for Groups 1 and 2; 13 hours after the first IM dose for Group 3) was selected to approximate the time of predicted maximum ziprasidone concentration. The mean, median, range, and mean changes from baseline to this second tracing were calculated. QTc interval mean changes of 3.5, 11.0, 12.5 and 5.3 msec were observed in the 20, 40, and 80 mg and placebo treatment groups, respectively.
- 3) Final tracings were obtained on the morning of day 4. The mean, median, range, and mean changes from baseline to final were calculated. QTc interval mean changes of -3.5, 23.9, 18.5 and 0.8 msec were observed in the 20, 40, and 80 mg and placebo treatment groups, respectively.

No ziprasidone-treated subjects had a QTc interval  $\geq 450$  msec or a  $\geq 20\%$  increase in QTc interval in this study. Pharmacodynamic assessments relating QTc interval and serum ziprasidone concentrations obtained from observed and population pharmacokinetic modeled data did not suggest a trend towards QTc prolongation at higher systemic exposures to ziprasidone.

Conclusions: After administration of multiple intramuscular doses of ziprasidone, exposure appeared to increase with dose. Little drug accumulation was noted for any dosing regimen. Ziprasidone injections were well tolerated in all dosing groups. There was one serious adverse event of exacerbation of schizophrenia that occurred 28 days after completing the study. No ziprasidone-treated subjects had a QTc interval  $\geq 450$  msec or a  $\geq 20\%$  increase in QTc interval in this study. Pharmacodynamic assessment did not suggest a trend towards QTc prolongation at higher systemic exposures to ziprasidone.

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Figure 1.1 Mean Serum Ziprasidone Concentrations for Group 1 on Days 1 and 3 in Subjects Receiving Intramuscular Injections of Ziprasidone 5 mg q2h x 4 for 3 Days Ziprasidone Protocol 046



Source Data: Appendix IV, Table 1

6

6

Table 5.3 Individual and Mean Ziprasidone Pharmacokinetic Parameters Following an Intravenous 5 Mg Dose of Ziprasidone  
Ziprasidone Protocol 037

Subject #	AUC <sub>0-t</sub> (ng·hr/ml)	AUC <sub>0-∞</sub> (ng·hr/ml)	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (hr)	K <sub>el</sub> (hr <sup>-1</sup> )	T <sub>1/2</sub> (hr)	CL (ml/min/kg)	V <sub>dss</sub> (L/kg)
723-0001								
723-0002								
723-0003								
723-0004								
723-0005								
723-0006								
723-0008								
723-0009								
723-0010								
723-0011								
723-0012								
723-0018								
Mean	210 <sup>a</sup>	217 <sup>a</sup>	83 <sup>a</sup>	1.01	0.221	3.14 <sup>b</sup>	5.08	1.03
S.D.	45	44	17	0.12	0.033		0.71	0.16
CV%	21	20	21	12	15		14	16

<sup>a</sup>Geometric means and standard deviations

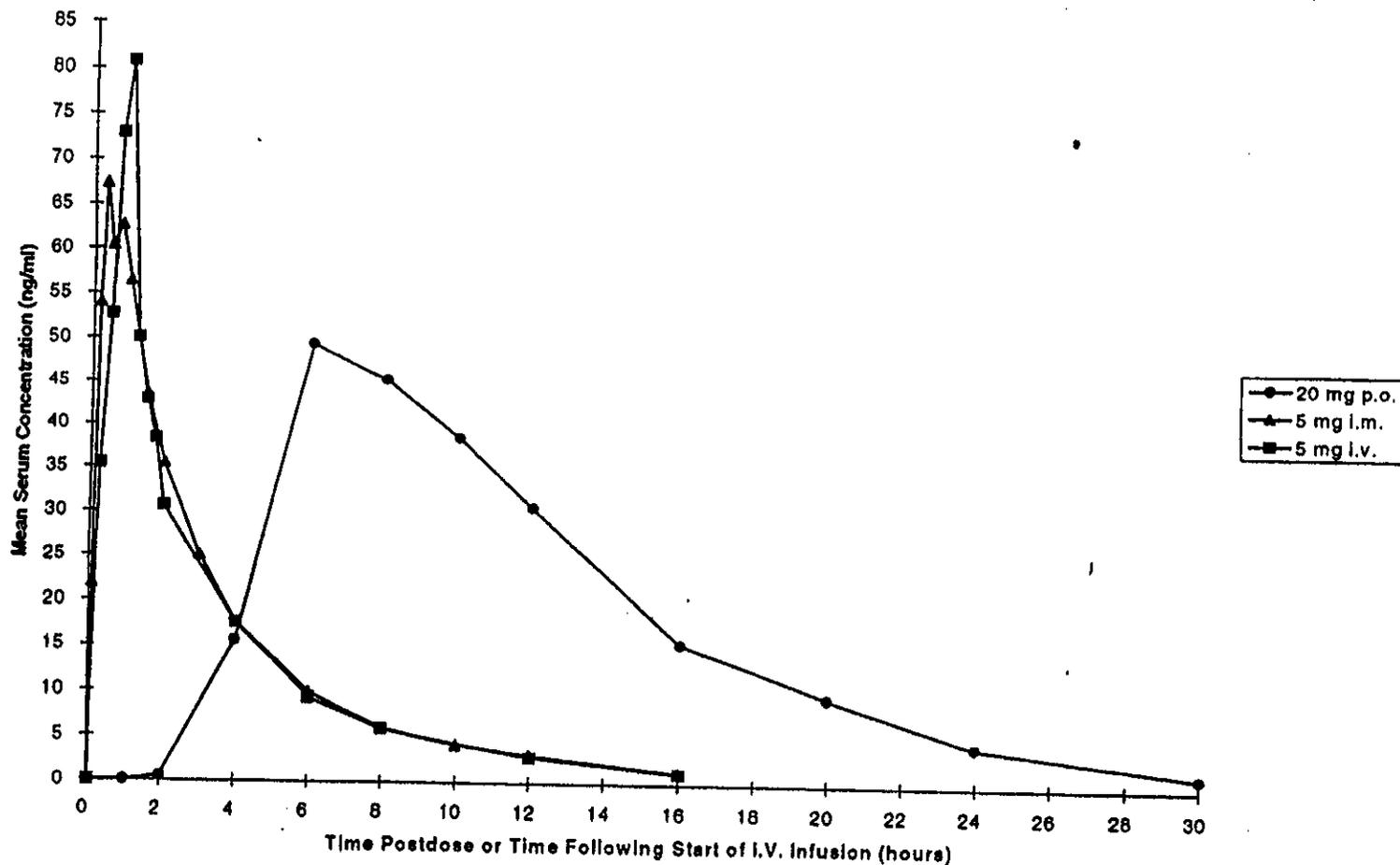
<sup>b</sup>Calculated as  $\ln 2/\text{mean } K_{el}$

Source Data: Appendix IV, Table 3

7

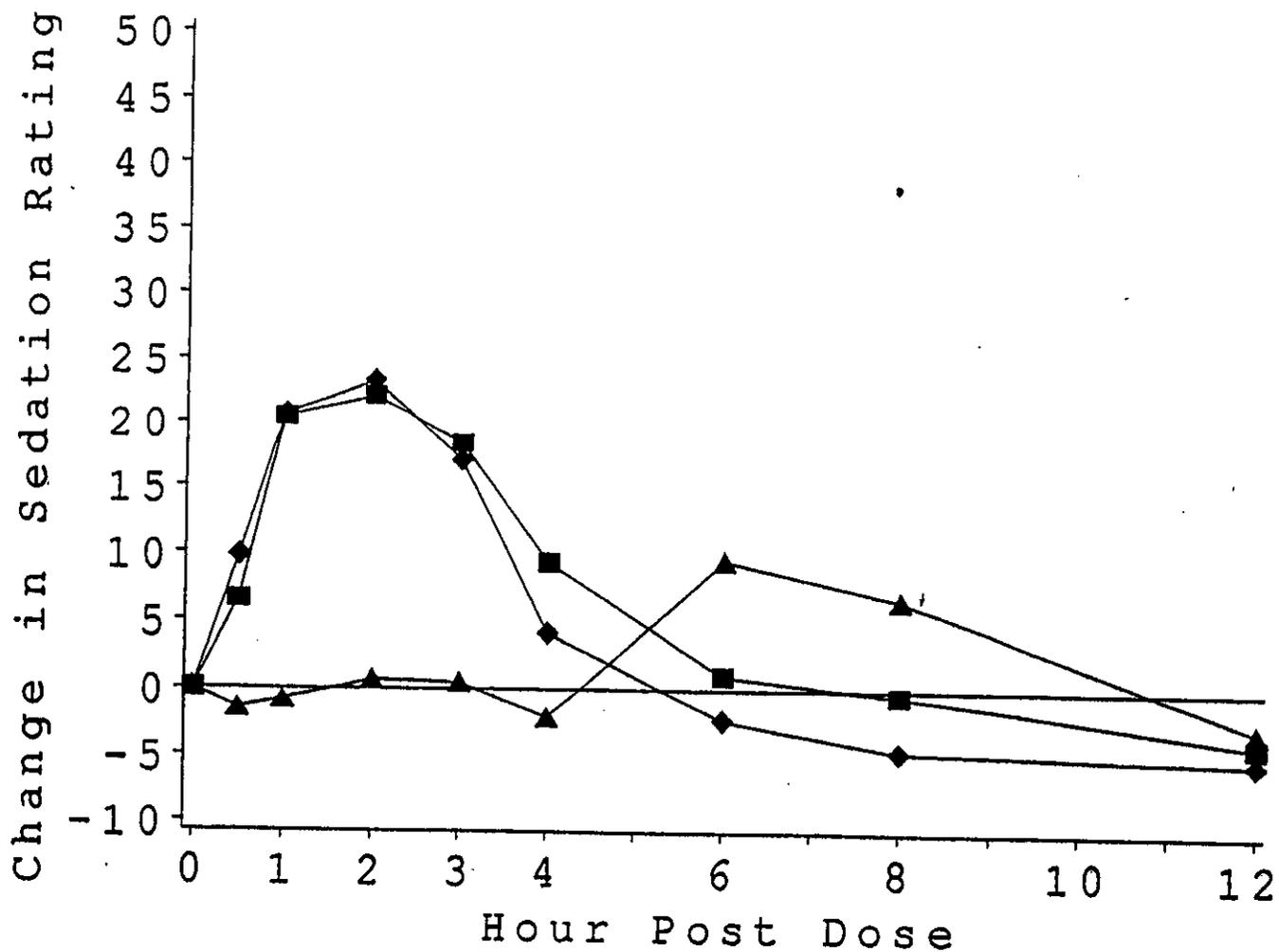
7

Figure 1.1 Mean Serum Ziprasidone Concentrations vs Time Following Oral, Intramuscular and Intravenous Administration of Ziprasidone  
Ziprasidone Protocol 037



Source Data: Appendix IV, Tables 1 - 3

FIGURE 3  
 Mean Change in Subject Self-Rating of Sedation by Hour Post Dose  
 Ziprasidone Protocol 037



■ Ziprasidone 5 mg I.M.    ◆ Ziprasidone 5 mg I.V.    ▲ Ziprasidone 20 mg Oral.  
 Sedation Rating refers to the sum of the twelve parameters that comprise the Sedation Self-Rating Scale.  
 Source Data : Appendix III Table 2    Date of Data Extraction : 26SEP96    Date of Figure Generation: 26SEP96

## **APPENDIX II**

**(IM Formulation)**

2 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

## **APPENDIX III**

**(Review Summary of Oral Ziprasidone-NDA 20-825)**

MAR 3 1998

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-825

Submission Dates: March 19, 1997  
October 30, 1997  
November 7, 1997  
November 13, 1997  
January 26, 1998  
January 30, 1998  
February 4, 1998  
February 11, 1998

Generic Name: Ziprasidone hydrochloride (CP-88,059-1)

Brand Name: ZELDOX™

Strength(s): 20, 40, 60, and 80 mg

Formulation: Capsules for Oral Administration.

Sponsor: Pfizer Inc.  
Groton, CT

Type of Submission: NDA (NME)

Reviewer: Sayed Al-Habet, Ph.D.

---

### SYNOPSIS:

ZELDOX™ (ziprasidone, CP-88,059-1) is a 5HT<sub>2A</sub> and D<sub>2</sub> antagonist. It is being proposed for the treatment of psychotic disorders (schizophrenia). It is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents.

The sponsor is proposing to market ZELDOX™ as 20, 40, 60, and 80 mg capsules for oral administration. The proposed daily dose is 40 mg BID up to 80 mg BID. Because it is believed that all the metabolites of ziprasidone are pharmacologically inactive, the focus of this NDA is on the parent drug.

---

### RECOMMENDATIONS:

The NDA # 20-825 submitted for ZELDOX™ capsules has been found to be acceptable provided

that the sponsor incorporates OCPB pharmacokinetics labeling and adopts dissolution methodology and specification as outlined in Comment 10. Please also convey Comments 6-9 to the sponsor.

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## COMMENTS TO THE CLINICAL DIVISION:

1. In the hepatic and renal impairment studies (#128-030 and #128-026), the administered dose was 20 mg BID, however, the recommended dose is 40 mg BID.
2. Although, it appears that there is a dose proportionality over the dose range (40 to 80 mg BID), the half life tends to increase with increasing doses (e.g., study # 128-013).
3. Carbamazepine therapy (200 mg BID for 21 days) caused an approximately 36% and 27% decrease in the ziprasidone AUC and C<sub>max</sub>, respectively. It should be noted that, the effect could be even greater at the commonly recommended carbamazepine maintenance doses of 800 to 1200 mg daily.
4. The concentration of ziprasidone used in *in vitro* enzyme inhibition study with ketoconazole was approximately 100 times higher than the expected C<sub>max</sub> after the highest recommended dose (study # DM-95-128-29).
5. In many studies, it has been shown that ziprasidone markedly increases the prolactin serum level for about 4 to 6 hours after administration. Hyperprolactinemia causes galactorrhea, amenorrhea and infertility in women and infertility, impotence and galactorrhea in men.

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## COMMENTS TO THE SPONSOR:

6. The pharmacokinetics of ziprasidone were well characterized in this NDA.
7. In future submissions, the *in vitro* metabolism and drug interaction studies should be conducted at drug concentration not greater than 10 or 20 times the C<sub>max</sub> observed after the highest recommended dose.
8. In future submissions, the sponsor should also submit *in vitro* drug interaction and metabolism information in Section VI-Human Pharmacokinetics Section.
9. In terms of safety in relation to QTc prolongation, the sponsor should provide the time of dosing and the time of ECG recording. In addition, serum drug concentrations should be determined at the time of ECG recording. This would be helpful in establishing meaningful PK/PD correlations.
10. The sponsor is requested to adopt the following dissolution methodology:

### Tier I Test:

Apparatus: USP (paddle)  
Speed: 75 rpm  
Medium: 900 mL  
(2% sodium dodecylsulfate-SDS, 0.05 M NaH<sub>2</sub>PO<sub>4</sub> buffer, pH 7.5)  
Temperature: 37 °C  
Specification (Q): Not less than % dissolved in 45 minutes.

### Tier II Test:

Apparatus: USP (paddle)  
Speed: 75 rpm  
Medium: 700 mL  
(1% pancreatin in 0.05 M NaH<sub>2</sub>PO<sub>4</sub> buffer, pH 7.5)  
Temperature: 37 °C

After 15 minutes incubation, 200 ml of phosphate buffer containing 9% of SDS is added to the above medium.

Specification (Q): Not less than % dissolved in 45 minutes.

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## **METABOLISM AND ELIMINATION**

### ***IN VIVO***

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### ***IN VITRO***

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*In vitro* plasma protein binding (Study # DM-95-128-31)  
Effect of warfarin and propranolol on the plasma protein binding of ziprasidone.  
(Study # DM-96-128-36)

## **PHARMACODYNAMICS (see also other individual studies)**

Akathisia, Multiple Dose, 40 mg QID and 80 mg QID (Study # 128-015)  
Sedation, Different Infusion Rates (Study # 128-032)  
ECG (QTc) Phase II-III Data

<b><u>APPENDIX II:</u></b>	(Dosage Form Formulations)
<b><u>APPENDIX III:</u></b>	(Dissolution Methodology and Specification)
<b><u>APPENDIX IV:</u></b>	(Analytical Methodology)

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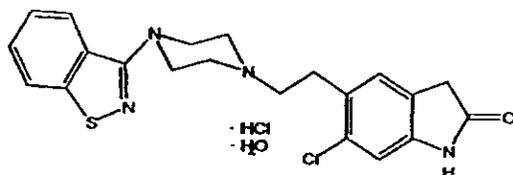
## BACKGROUND

Ziprasidone hydrochloride (ZELDOX™, CP-88,059) is the hydrochloride salt of a benzisothiazolylpiperazine which was developed for the treatment of psychotic disorders. It has antagonist activity at both dopamine D2 and serotonin 5-HT2A receptors. Its relative affinity for serotonin 5-HT2 receptors is approximately eleven-fold greater than its affinity for dopamine D2 receptors.

### Physico-Chemical Properties:

Ziprasidone hydrochloride is a white to slightly pink powder with a very low water solubility (0.075 mg/ml) and a pKa of 6.8.

### Structural Formula:



### Chemical Formula:

Ziprasidone is chemically known 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, monohydrochloride, monohydrate. It has an empirical formula of  $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$  and a molecular weight of 467.42 (free base).

### Indications and Usage:

Ziprasidone is being proposed for the treatment of psychotic disorders (schizophrenia).

### How Supplied:

Ziprasidone will be supplied as capsules of 20, 40, 60, and 80 mg for oral administration.

**Proposed Dosage and Administration:**

The recommended starting dose of ziprasidone is 40 mg BID with food. Doses above 80 mg BID did not show an increase in efficacy and the 80 mg dose is recommended only after clinical assessment.

**Manufacturer and Manufacturing Site:**

Zeldox™ will be manufactured by Pfizer Inc, Brooklyn, New York

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## SUMMARY REVIEW OF PHARMACOKINETICS AND BIOAVAILABILITY

### Introduction:

Forty-six clinical pharmacology studies have been conducted to evaluate the pharmacokinetics, bioavailability and metabolism of ziprasidone in humans and of these twenty-seven studies were reviewed in addition to six relevant *in vitro* studies. These studies were divided into four subsections: pharmacokinetics in normal volunteers and special populations; bioavailability and bioequivalence; drug or food interactions; and radiolabel and disposition. All doses of ziprasidone HCl are expressed as the free base equivalent. In most of these studies, assays for ziprasidone in serum were performed using a LLOQ of  $\square$  ng/ml (see appendix).

### Pharmacokinetics (Dose Proportionality and Multiple Dose)

1. The AUC and C<sub>max</sub> increased in a dose-related manner over the range of 20 to 80 mg BID.
2. The steady-state serum concentration was attained by 1 to 3 days after BID administration and the accumulation ratio was approximately 1.5.
3. After multiple oral administration to fed subjects, maximal concentrations are generally attained 6 to 8 hours post-dose.
4. The overall mean half life is approximately 7 hours ranging from 3 to 18 hours in all studies. In some studies, the half life was slightly longer at steady-state than after a single dose. In addition, the half life does not appear to significantly vary between individuals on the basis of gender, age, renal or hepatic status.

### Distribution and Clearance:

1. The binding of ziprasidone to human plasma proteins is 99.9% at plasma concentration of 400 ng/ml. The drug primarily binds to albumin and  $\alpha$ 1-acid glycoprotein.
2. Following IV administration, ziprasidone total body clearance is approximately 5 ml/min/kg and the volume of distribution is approximately 1.0 L/kg.
3. There are no displacement interactions between ziprasidone and highly protein bound drugs such as warfarin and propranolol.

### Bioavailability:

1. The absolute bioavailability of 20 mg dose of ziprasidone under fed conditions is approximately 60%.
2. Intubation (sites) studies in normal volunteers demonstrated that the absorption of the drug is highest from the duodenum site compared to the distal region of the GI tract. The order of ziprasidone absorption is as follows: solution (duodenum), capsules (fed), solution (ileal/cecal), suspension (duodenum) and suspension (ileal/cecal).

### Bioequivalence:

1. The 20 mg commercial capsules (FID# QC2327) were bioequivalent to the 20 mg research capsules (FID# CS-90-031). Study # 128-035.
2. The 40 mg commercial capsules (FID# QC2214) were bioequivalent to 2X20 mg commercial capsules (FID# QC2327). Study # 128-047.
3. The commercial capsules of 60 mg (FID# QC2337), 80 mg (#FID# QC2338) and 100 mg (FID # QC2339) were prepared from the same common blend as the 40 mg commercial capsules (FID# QC2214). The drug was shown to be linear up to a dose of 80 mg BID. The *in vitro* dissolution profiles for the 40, 60 and 80 mg were similar. It should be noted that, the 100 mg capsules will not be marketed.

### Dissolution:

#### Tier I Test:

Apparatus: USP (paddle)  
Speed: 75 rpm  
Medium: 900 mL  
(2% sodium dodecylsulfate-SDS, 0.05 M NaH<sub>2</sub>PO<sub>4</sub> buffer, pH 7.5)  
Temperature: 37 °C  
Specification (Q): Not less than % dissolved in 45 minutes.

The mean % dissolved in 45 min are 100%, 91%, 93%, 90% and 92% for 20, 40, 60, 80, and 100 mg capsules. It should also be noted that the individual data also shows that the % dissolved in 45 minutes is %.

## Tier II Test:

Apparatus: USP (paddle)  
Speed: 75 rpm  
Medium: 700 mL  
(1% pancreatin in 0.05 M NaH<sub>2</sub>PO<sub>4</sub> buffer, pH 7.5)  
Temperature: 37 °C

After 15 minutes incubation, 200 ml of phosphate buffer containing 9% of SDS is added to the above medium.

Specification (Q): Not less than % dissolved in 45 minutes.

## Effect of Food:

1. The AUC and C<sub>max</sub> of single doses of ziprasidone at doses of 20 to 80 mg were significantly increased (up to two- fold) by the presence of food relative to the fasting state.
2. As expected, T<sub>max</sub> was delayed by approximately 2 to 4 hours.
3. In terms of timing and in comparison to the fasting state, food increases the AUC and C<sub>max</sub> by approximately 70% and 75% when the drug was administered concurrently with food compared to only 35% and 50% when the drug was administered 2 hours after food consumption, respectively.

## Radiolabel and Metabolism Studies:

### *In vivo* Metabolism:

1. Ziprasidone is extensively metabolized with 12 identified metabolites seen after oral administration and <1% of the dose was excreted unchanged in urine and <3% was present in feces.
2. The main pathways for the metabolism of ziprasidone are:
  - a. Cleavage of the molecule at the ethyl side chain attached to the piperazinyl nitrogen.
  - b. Oxidation at sulfur to form the sulfoxide and the sulfone.

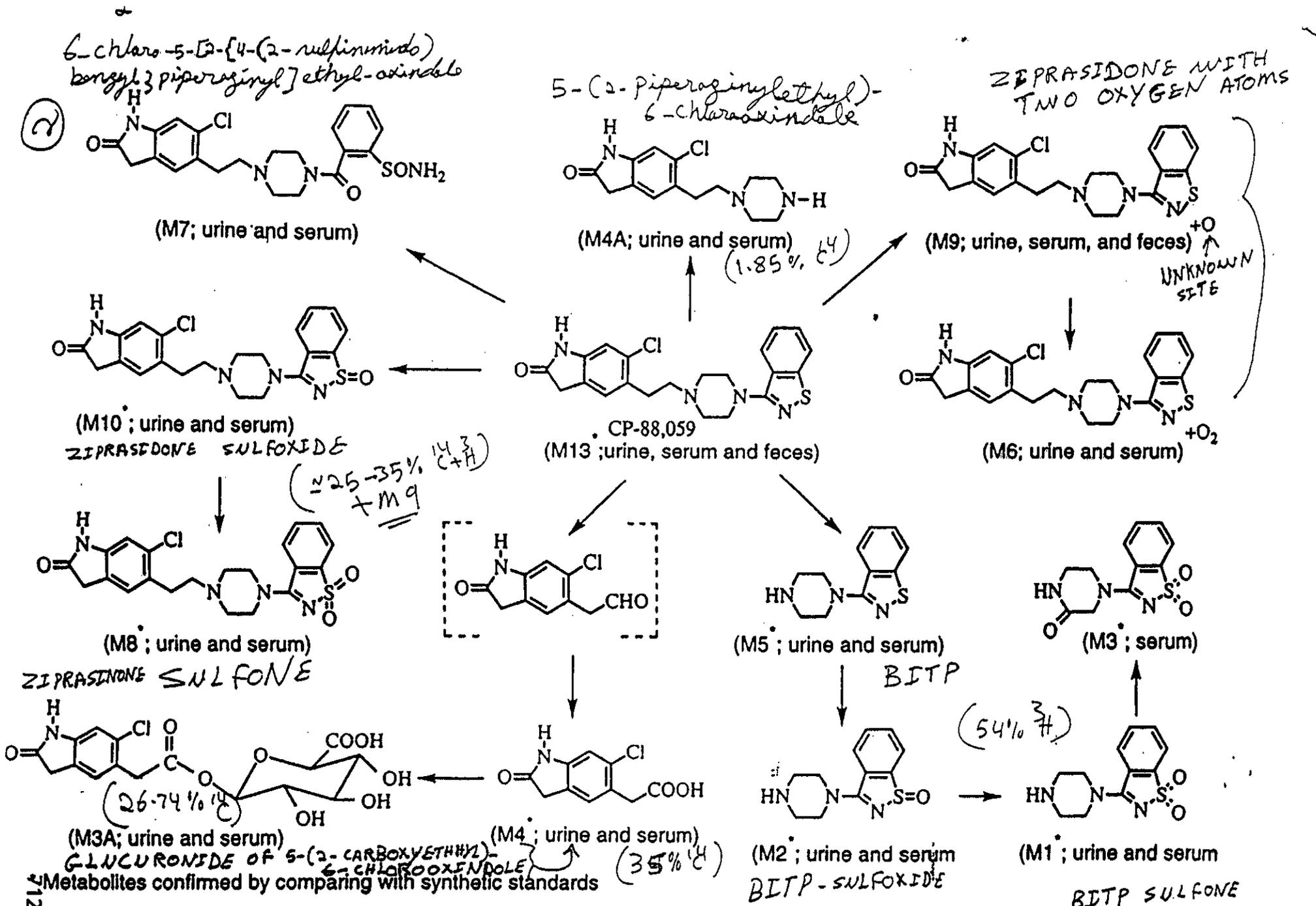


Figure 33. Proposed routes for the biotransformation of CP-88,059 in man

BITP: - BENZISOTHIAZOLYL PIPERAZINE

IN URINE:-

M1 = 54% <sup>3</sup>H  
 M4 = 35% <sup>14</sup>C  
 M5 + M1 = 8% (<sup>14</sup>C + <sup>3</sup>H)  
 M4A = 2% <sup>14</sup>C  
 M2 + M1 = 27% (26% <sup>14</sup>C + 1% <sup>3</sup>H)

7123

- c. Reductive cleavage of the benzisothiazole ring followed by methylation of the resulting thiophenol.
3. Approximately 20% of the dose was recovered in the urine, and 66% recovered in the feces.
4. The major circulating metabolites in humans are ziprasidone- sulfoxide and -sulfone. These metabolites have been found to possess <1% of the binding affinity of the parent compound for the D2 and serotonin 5HT2A receptors. Other metabolites are also inactive.
5. In serum, the parent drug ziprasidone which represents about 50% of total radioactivity was the major circulating specie.

#### ***In vitro Metabolism:***

The concentration of ziprasidone used in *in vitro* (50  $\mu$ M) was about 100 times higher than the expected C<sub>max</sub> (~250 ng/ml i.e. ~0.5  $\mu$ M) after the highest recommended dose of 80 mg. Thus, *in vitro* studies do not provide a meaningful interpretation to the isozymes involved in the metabolism of ziprasidone. Further, the numerous pathways of ziprasidone metabolism do not indicate any therapeutic concern.

#### **Drug Interactions:**

##### ***In Vivo Drug Interactions:***

###### **a. Effect of Other Drugs on Ziprasidone PK:**

1. Cimetidine did not affect the pharmacokinetics of ziprasidone. It should be noted that cimetidine was administered once daily for only two doses of 800 mg, prior to ziprasidone administration.
2. Carbamazepine therapy (200 mg BID for 21 days) caused an approximately 36% and 27% decrease in the ziprasidone AUC and C<sub>max</sub>, respectively. T<sub>max</sub> was not affected. It should be noted that, the effect could be greater at the commonly recommended carbamazepine maintenance doses of 800 to 1200 mg daily.
3. The bioavailability of ziprasidone was not significantly affected by the concomitant administration of Maalox (an antacid). However, there was a delay in the attainment of C<sub>max</sub> by approximately 3 hours.

4. Ketoconazole at the dose of 400 mg QD for 5 days in 13 healthy subjects increased both the AUC and C<sub>max</sub> of ziprasidone by about 30% relative to ziprasidone with placebo.

#### **b. Effect of Ziprasidone on Other Drugs:**

1. Based on dextromethorphan study, where it is used as a model for CYP 2D6 substrate in normal volunteers, the urinary dextromethorphan/dextrophan ratio were comparable between ziprasidone and placebo treatment groups. Thus, ziprasidone would not appear to inhibit drugs metabolized by CYP 2D6.
2. Ziprasidone at dose of 40 mg BID did not show any significant effect on lithium PK when it was given at a dose of 450 mg BID.
3. Ziprasidone at a dose of 20 mg BID does not appear to affect the PK of the oral contraceptives, ethinylloestradiol (0.03 mg) and levonorgestrel (0.15 mg).

#### ***In Vitro* Drug Interactions:**

1. Using human liver microsomes, ketoconazole caused approximately 80% reduction in the oxidation of ziprasidone to form sulfone and sulfoxide and 100% reduction in N-dealkylation process. However, as noted previously, the ziprasidone concentration used was about 100 times higher than the expected C<sub>max</sub> after the highest recommended dose of 80 mg BID.
2. Ziprasidone has little potential to inhibit CYP 1A2, 2C9, 2C19, 2D6 and 3A4 isozymes and hence unlikely to be of clinical concern.

#### **Special Population Studies:**

##### **Renal Impairment:**

The pharmacokinetic characteristics of ziprasidone following 8 days of treatment (20 mg BID) were similar among subjects with varying degrees of renal impairment, and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required. However, it is not clear as to why the AUC in the moderate renal impairment patient was about 40% higher than those with severe renal impairment as well as those with normal kidney functions. It should be noted that ziprasidone is highly metabolized drug with less

than 1% of the drug excreted unchanged in urine, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. Therefore, the conclusion was based only on the determination of the parent compound in serum and no data is available for the elimination of the metabolites in renal impairment, especially after chronic administration at the recommended maintenance dose (40 mg BID). Ziprasidone was not removed by hemodialysis.

#### **Hepatic Impairment:**

A multiple dose study at 20mg BID for 5 days in hepatic impaired patients (Child- Pugh Class A and B) showed 25% increase in AUC compared to normals.

#### **Age and Gender Effects:**

Based on multiple doses (8 days of treatment, 20 mg BID), there was no difference in the pharmacokinetics of ziprasidone between men and women or between elderly (> 65 years) and young (18 to 45 years) subjects.

#### **Race:**

No specific pharmacokinetics study was conducted to investigate the effects of race. However, pharmacokinetics screening has revealed no evidence of clinically significant race related differences. Therefore, from a PK standpoint dosage modification for race is not recommended.

#### **Smoking Status:**

*In vitro* studies utilizing human liver enzymes suggest that ziprasidone is not a substrate for CYP1A2 and thus, smoking should not have an effect on the pharmacokinetics of ziprasidone.

#### **Pharmacodynamics:**

1. There was a good correlation between the ziprasidone serum concentration and the increase in prolactin serum concentration. The relationship was not dose dependent.
2. Following multiple oral administration, there was some correlation between the ziprasidone serum concentration and the degree of sedation as well as sleeping times. In addition, following IV infusion, in some subjects, there was an anti-clockwise hysteresis relationship between serum ziprasidone concentration and sedation.
3. In a limited sample size (n= 3-4), it appears that there was some relationship between

serum drug level and the degree of akathisia.

**Safety:**

- 1 In terms of safety, the drug appears to cause ECG changes, particularly prolongation of QTc interval.
- 2 The QTc prolongation appears to be a dose related, since the mean increases in QTc were 0.6, 5.9, 7.7, 9.7, and 6.4 msec following <40 mg BID, 40 mg BID, 60 mg BID, 80 mg BID and 100 mg BID, respectively. However, the mean change in the placebo group was negative (-2.6 msec) and in the haloperidol group was -1.6 msec.

ClinPharm/Biopharm Briefing on: February 26, 1998.

**Briefing Attendees:** Drs: Sayed Al-Habet, John Balian, Raman Baweja, Jerry Collins, Glenna Fitzgerald, Lois Freed, Roberta Glass, Paul Hepp, John Hunt, John Koerner, Tom Laughren, John Lazor, Paul Leber, Larry Lesko, Henry Malinowski, Mehul Mehta, Wes Metz, Andy Mossholder, Ameeta Parekh, Arzu Selen, and Mona Zarifa.

Reviewed by: *ISI*

*March 3, 98*

Sayed Al-Habet, Ph.D.  
Office of Clinical Pharmacology and Biopharmaceutics  
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph.D. *ISI* *3/3/98*

cc: NDA # 20-825 (Orig.), HFD-120, HFD-860 (Al-Habet, Baweja, Malinowski),  
HFD-19 (FOI), and Drug files (Barbara Murphy, CDR).

# **APPENDIX A**

**(OCPB Labeling for NDA 20-825)**

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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling



*Harleman*

Food and Drug Administration  
Rockville MD 20857

NDA 20-919

Pfizer, Inc.  
Attention: Charles A. Ritrovato, Pharm.D.  
Senior Associate Director  
Eastern Point Road  
Groton, CT 06340

DEC 17 1998

Dear Dr. Ritrovato:

Please refer to your new drug application (NDA) dated December 17, 1997, received December 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zeldox IM (ziprasidone mesylate) Intramuscular for Injection.

We acknowledge receipt of your submissions dated:

May 12, 1998	September 10, 1998	October 1, 1998
October 9, 1998	October, 19, 1998	November 10, 1998
November 20, 1998(2)		

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

**REASONS FOR NOT-APPROVABLE ACTION:**

**Clinical**

You have not submitted sufficient clinical data to support the conclusion that Zeldox IM is approvable for the "acute control and short-term management of the agitated psychotic patient." The deficiencies are for safety, not efficacy. We do believe that you have demonstrated, with 2 adequate and well-controlled trials, that Zeldox IM is effective for this indication. However, the approval of the IM ziprasidone formulation is inextricably linked with the approval of the oral formulation. Indeed, your proposed labeling represents a blending of information for both formulations, and therefore, would not be approvable unless both formulations were approvable. The major issues continue to be (1) the finding that ziprasidone prolongs the QTc interval, and (2) the judgment that this represents a risk of potentially fatal ventricular arrhythmias that is not outweighed by a demonstrated and sufficient advantage of ziprasidone over already marketed drug products. While the finding of QTc prolongation is clearest for the oral ziprasidone formulation, there are data in the

Zeldox IM NDA, especially from study 046, that are suggestive of a similar effect for the intramuscular formulation. Until this issue can be resolved, as detailed in the 6-17-98 not-approvable letter for oral ziprasidone, we cannot reasonably take an approvable action for the IM product. This is especially true since the indication sought for ziprasidone IM is hardly one for which other treatments are not available. Several other antipsychotic drugs are available in intramuscular formulations, as are benzodiazepines and other sedative hypnotic drugs. While none of these drugs is specifically approved for agitation associated with psychosis, they are, nevertheless, widely used for this indication and represent a reasonable alternative.

### **Pharmacology/Toxicology**

One month toxicology studies in a rodent and a nonrodent species should be conducted prior to approval. For these studies ziprasidone mesylate in the beta-cyclodextrin sulfobutyl ether formulation should be administered by the intramuscular route, and plasma measurements should be included. We also recommend that an assessment of the effects on micronucleus formation be incorporated into the rodent toxicology study.

### **Chemistry, Manufacturing, and Controls**

#### **1. Drug Substance Manufacture**

It is not acceptable to notify the agency by means of an Annual Report when what is described as processing outside the Process Monograph Description is done. Please commit to revising this approach to include early notification of FDA, followed by submission of either a Changes Being Effected or Prior-Approval supplement, to cover the desired change(s).

#### **2. Sulfobutyl ether $\beta$ -cyclodextrin**

a. A deficiency letter in regard to your DMF  $\tau$  for sulfobutyl ether  $\beta$ -cyclodextrin sodium has been issued.

b. During the July 29, 1998, inspections of  $\tau$  facilities for sulfobutyl ether  $\beta$ -cyclodextrin, a number of CGMP violations were noted and conveyed to you or your suppliers by the inspector. A recommendation to withhold approval was then returned. Satisfactory inspections will be required before this application may be approved.

**ADDITIONAL DEFICIENCIES:**

Although not reasons for the Not Approvable action, we have the following comments and requests for information and ask that you respond at your earliest convenience.

**Pharmacology/Toxicology**

A reproductive and developmental toxicity study, also with ziprasidone mesylate in the beta-cyclodextrin sulphobutyl ether formulation administered by the intramuscular route, and which incorporates plasma level measurements, should be planned as a Phase 4 commitment.

**Clinical Pharmacology**

1. For the Zeldox IM NDA, only study 046 obtained ECGs near what would be expected to be peak concentrations for ziprasidone. Although this study was small, there was a strong suggestion of a dose-dependent increase in QTc, of similar magnitude to that seen with the oral formulation. You are encouraged to provide data from a more definitive study on the relationship between ziprasidone serum concentration at Cmax of the highest recommended IM dose and QTc prolongation.
2. Cyclodextrin is excreted by filtration and no studies were conducted in renal failure after IM administration. However, your proposed labeling indicates that caution should be taken when administering Zeldox IM in patients with renal impairment. Please comment on your plans to explore this concern.
3. The fate of cyclodextrin has not been investigated in this NDA. Please comment on your plans to explore the fate of cyclodextrin at the muscular site after multiple injections.

**Chemistry, Manufacturing, and Controls**

1. Please provide the following information in regard to [ ] of the drug substance:
  - a. [ ]
  - b. Anticipated values or permitted ranges for temperatures, volumes, and masses for the process
  - c. Further description of [ ] should be provided [ ]
2. Drug Substance Reference Standard
  - a. Residue on ignition should be determined and reported.

b. [ ] would be appropriate and should be added ]

3. Drug Substance Analytical Methods

You have provided no information in regard to sampling of the drug substance for release testing. Some information should be provided, at least concerning total sample taken and manner of sampling.

4. Drug Substance Stability

a. The stability data submitted for the drug substance justify an [ ] retest date, not [ ] as requested. If a [ ] retest date is desired, additional full shelf life stability data may be submitted.

b. A stability commitment should be provided.

5. According to the 1998 USP Dictionary of USAN and International Drug Names, ziprasidone mesylate does not have a U.S. Adopted Name. Please request from the USAN Council a U.S. Adopted Name for ziprasidone mesylate.

6. Drug Product Quality Control

a. You state that samples for in-process controls are withdrawn at appropriate intervals and that sampling for release testing is done in accordance with 21 CFR 431.1 (c) (8). The regulation you cite is for certification of antibiotic drugs. The correct citation should be 21 CFR 211.110. Please correct this.

b. The batch analyses submitted are satisfactory. However, the [ ] vial batch size for [ ] seems likely to be a typographic error, as all the other batches were of approximately [ ] vials. Please verify the correct size for this batch.

7. Drug Product Manufacture

You have indicated that the maximum commercial batch size will be [ ] vials. However, given the size of the [ ] batches presented here, the commercial batch size to be used as a baseline for any proposed post-approval changes is [ ] vials.

8. Drug Product Stability

a. The [ ] of 25°C/60% RH stability data you have presented, together with the [ ] of 40°C/70% RH data support a tentative expiration dating period of [ ] not [ ] as you have requested. You may submit additional data to

justify the longer expiration dating period.

- b. See below as well regarding the proposed storage statement.

9. Investigational Formulations

Please provide a tabular listing of all clinical studies performed with the batch of drug product used for each study.

10. Labeling

- a. You have submitted no data to support the labeling claim [

] Please submit such data or revise the label to remove the term.

- b. In the instructions for reconstituting the drug product, the statement, [

] closes this section. The statement [ ] is too general. *This solution and this container do [ ] which should be performed on each dose prepared. Moreover, no criterion is presented to permit a judgement as to whether the reconstituted material should be used, based on the [ ] The label should state that the solution should be colorless and essentially free of particles that can be observed on visual inspection.*

- c. The storage statement proposed for the drug product prior to reconstitution is, [

] The proposed storage statement for the drug product is too broad; the span of temperature is so large it is likely to cause confusion. While it is true that the you have provided stability data to support storage both at refrigerator and at controlled room temperature, it is not appropriate to have a storage statement that encompasses both. A more appropriate storage statement would be: "Store at 25°C (77°F); excursion permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in the dry form. PROTECT FROM LIGHT."

- d. The draft labeling states that the reconstituted solution [

] Your recommendations for storage of the reconstituted solution are appropriate in regard to duration and supported by the stability data submitted as noted above. However, controlled room temperature is not [ ] Per USP, controlled room temperature is "A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25° (68° to 77°F) that results in a mean kinetic temperature calculated to be not more than 25°; and that allows for

59 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

X § 552(b)(5) Draft Labeling