CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-825

Clinical Pharmacology and Biopharmaceutics Review

PHARMACOLOGY/TOXICOLOGY MEMORANDUM TO NDA 20-825

Date: 12/20/00
Drug: (ziprasidone) capsules
Sponsor: Pfizer Central Research
Indication: schizophrenia
Reviewer: Lois M. Freed, Ph.D.
Re: response to labeling issues, submitted as desk copy (letter date: 12/12/00).

Taking into consideration the information provided for the sponsor, the following labeling is recommended:

Mutagenicity

Ziprasidone was tested in the Ames bacterial mutation assay, the *in vitro* mammalian cell gene mutation mouse lymphoma assay, the *in vitro* chromosomal aberration assay in human lymphocytes and the *in vivo* chromosomal aberration assay in mouse bone marrow. There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes.

Pregnancy

In animal studies ziprasidone demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses. When ziprasidone was administered to pregnant rabbits during the period of organogenesis, an increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) was observed at a dose of 30 mg/kg/day (3 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m2 basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 8 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg (2 and 8 times the MRHD) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD on a mg/m2 basis).

There was an increase in the number of pups born dead and a decrease in postnatal survival through the first 4 days of lactation among the offspring of female rats treated during gestation and lactation with doses of 10 mg/kg/day (0.5 times the MRHD on a mg/m^2 basis) or greater. Offspring developmental delays and neurobehavioral functional impairment were observed at doses of 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis) or greater. A no-effect level was not established for these effects.

There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-825	Submission Date: October 20, 2000
Compound:	(ziprasidone)
Formulation (s):	Capsules (20, 40, 60, 80 mg)
Sponsor:	Pfizer
Type of Submission:	Response to Approvable Letter (September 8, 2000)
Indications:	Schizophrenia
Reviewer:	Sayed Al-Habet, Ph.D.
Date Review:	November 17, 2000

Background:

Pfizer Pharmaceuticals has submitted a response to the Agency's approvable letter dated September 8, 2000. The sponsor has accepted the dissolution method and specification recommended by the Agency (OCPB review dated March 3, 1998). Based on our review of the labelling in this submission the following minor comment should be conveyed to the sponsor:

On page 5 of the labelling-Clinical Pharmacology (Hepatic Insufficiency) the ' should be deleted.

Recommendation:

The revised labelling is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. Please convey the above comment to the sponsor.

Reviewer

/S/

Sayed Al-Habet, Ph.D. 11/21/00
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by R. Baweja, Ph.D. ---------- /S/ 11/21/00

cc: NDA # 20-825, HFD-120, HFD-860 (Al-Habet, Baweja, and Mehta), Drug file (Biopharm File, Central Document Room).

RECEIVED MAR 0 4 1998
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:			
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:

(ziprasidone, CP-88,059-1) is a 5HT2A and D2 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 marke 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 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.

APPEARS THIS WAY
ON ORIGINAL

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 Cmax, 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 Cmax 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.

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 Cmax 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_2PO_4 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_2PO_4 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.

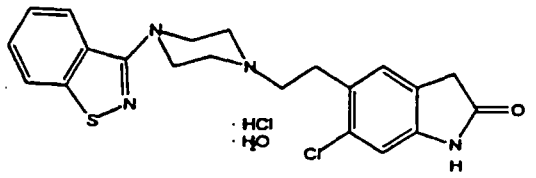
BACKGROUND

Ziprasidone hydrochloride [redacted], 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-2*H*-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:

[redacted] 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 1 ng/ml (see appendix).

Pharmacokinetics (Dose Proportionality and Multiple Dose)

1. The AUC and Cmax 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 α1-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 volunteeers 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 dodecylsufate-SDS, 0.05 M NaH_2PO_4 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_2PO_4 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 Cmax 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, Tmax 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 Cmax 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.

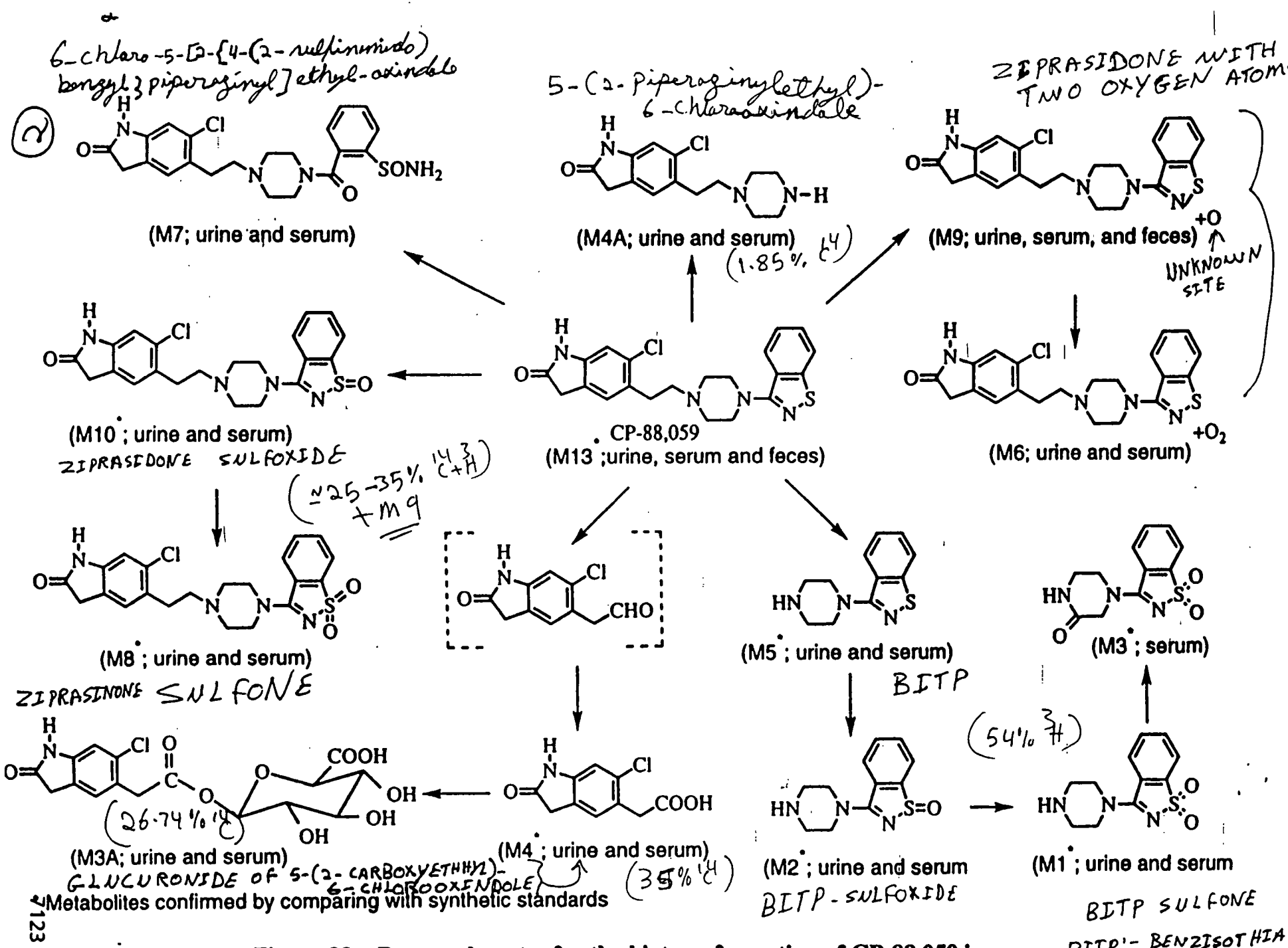

Figure 33. Proposed routes for the biotransformation of CP-88,059 in man

In urine:-

M2 = 54% 3H M4 = 35% 14C M5+M1·M7 = 8% (14C+3H)

M1 = 27% 14C M4A = 2% 14C M8+M9 M10 = 27% (26-35%) 14C+3H

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 μM) was about 100 times higher than the expected Cmax (~250 ng/ml i.e. ~ 0.5 μM) 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 Cmax, respectively. Tmax 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 Cmax 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 Cmax 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 comprable 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, ethinyloestradiol (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 Cmax 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. Therfore, 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: /S/ 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. /S/ - 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)

21 pages redacted from this section of the approval package consisted of draft labeling

TABLE OF CONTENTS

Multiple Dose, 1 X 40 vs 2 X 20 mg, Commercial Capsules (Study # 128-040)
Multiple Dose, 1 X 40 vs 2 X 20 mg, Commercial Capsules, Repeat-Pivotal (Study # 128-047)
Single Dose, 1 X 60 mg vs 3 X 20 mg (Study # 128-018)
Single Dose, 1 X 80 mg vs 4 X 20 mg (Study # 128-019)

METABOLISM AND ELIMINATION

IN VIVO

Mass-Balance, 20 mg Single Dose, Pivotal (Study # 128-027)
Mass Balance, single 20 mg dose (Study # DM-95-128-20)
Mass Balance, single 20 mg dose (Study # DM-95-128-19)

IN VITRO

Determination of Enzymes (Study DM-95-128-29)
Characterization of CYP-Isozymes (Study # DM-95-128-33)

SPECIAL POPULATIONS

Renal Impairment (Study # 128-026)
Hepatic Impairment (Study # 128-030)
Age and Gender (Study # 128-028)

DRUG-DRUG INTERACTIONS

IN VIVO

Cimetidine and Antacid (Study # 128-039)
Carbamazepine (Study # 128-049)
Lithium (Study # 128-025)
Oral Contraceptives (Study # 128-203)
Ziprasidone Effect on CYP 2D6, Dextromethorphan study (Study # 128-048)
Ketoconazole in Healthy Subjects (Study# 128-050-Interim Report)

IN VITRO

Ketoconazole (see Metabolism and Elimination Section
for studies # DM-95-128-29 and DM-95-128-33)

PROTEIN BINDING

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

APPENDIX II:	(Dosage Form Formulations)
APPENDIX III:	(Dissolution Methodology and Specification)
APPENDIX IV:	(Analytical Methodology)

APPENDIX I

(Individual Study Reviews)

Study 043 (Dose Proportionality, 20, 40, and 80 mg BID):

Study Design and Summary:

(see attachments 1-3)

Results:

(See attachments 4-9)

Reviewer's Comments:

1. From the data shown in attachment 4, the ratios of dose normalized mean AUCs are shown below:

Dose (mg)	AUC (ng.h/ml)	AUC/Dose	Expected AUC (Based on 20 mg)	% Difference (based on 20 mg)
20	462	23.1		
40	768	19.2	462 X 2 = 924	-16.9
80	1551	19.3	462 X 4 = 1848	-16.0

2. From the above data, it appears that the PK of ziprasidone is dose proportional (see also attachment 5-9). It should be noted that within some subjects, dose proportionality was not clearly defined (attachment 4).

3. The sponsor should have included a lower dose of 5 or 10 mg to accurately assess the linearity of the drug. However, it appears that there is a dose proportionality considering that the mean AUC values at 5 mg dose level in the previous study (#013) which was 109 ng.h/ml.

4. The sponsor did not calculate the half life in this study, possibly due to the limitation of the data. As shown in attachment 9, the mean plasma concentration-time profiles appear to be flat, especially at 20 and 40 mg doses.

Conclusions:

1. Overall, it appears that there is a trend for proportional increase in the AUC and Cmax with dose.

2. The half-life was not calculated in this study, possibly, due to the limitation in the data.

PROTOCOL 128-043: PHASE I OPEN, MULTIPLE DOSE, ORAL STUDY TO ASSESS THE DOSE PROPORTIONALITY OF ZIPRASIDONE IN NORMAL, HEALTHY SUBJECTS

Principal Investigator: T. Hunt, M.D.

Study Publication: None

Study Dates: 06 March 1996 to 19 April 1996

Study Objective: To assess the dose proportionality of ziprasidone over the 20 to 80 mg BID dose range, titrated from 20 mg BID up to 80 mg BID.

Study Design: This was an open, non-randomized, three-way crossover study to evaluate the multiple dose pharmacokinetics of ziprasidone in the same subjects. The study consisted of three (3) three-day periods with no wash-out between periods.

Evaluation Groups:

	Ziprasidone		
	20 mg BID	40 mg BID	80 mg BID
Entered Study	12	12	11
Completed Study	12	11	9
Evaluated for Pharmacokinetics	9	9	9
Assessed for Safety			
Adverse Events	12	12	11
Laboratory Tests[a]	0	0	0

[a] Laboratory tests were performed only at screening and prior to the first dose, unless follow-up was required.

Subjects: Young subjects ranging in age from 22 and 44, of either sex.

Drug Administration:

Dosage Form: CP-88,059-1, Lot #N5056, 20 mg capsule (FID #QC2327)
CP-88,059-1, Lot #N5155, 40 mg capsule (FID #QC2214)

Dosing: A 20 mg ziprasidone commercial capsule was administered twice daily for the first period (days 1-3), a 40 mg ziprasidone commercial capsule was administered twice daily for the second period (days 4-6), and two 40 mg ziprasidone commercial capsules were administered twice daily for the third period (days 7-9), each given for three days, with only a morning dose given on day 9. The doses of ziprasidone were administered 12 hours apart (approximately 7 a.m. and 7 p.m.) For the morning and evening dose, breakfast and dinner, respectively, were to be consumed over a 20 minute period and study medication was then administered immediately with 50 ml of water.

Pharmacokinetic and Safety Evaluations: Blood samples for the determination of ziprasidone concentrations were collected prior to and up to 12 hours after drug administration on days 3, 6 and 9. Subjects were monitored for adverse effects.

Analytical Methods:

Statistical Methods: Pharmacokinetic and safety results were summarized using descriptive statistics and graphical presentations. Geometric means and standard deviations were calculated for AUC_{0-12}, and C_{max}. Serum concentrations were plotted as a function of time. No specific statistical hypotheses was tested.

To assess dose proportionality, the 40 and 80 mg groups AUC and C_{max} were normalized to the 20 mg group. Natural log transformed AUC and C_{max} and untransformed (or raw) T_{max} were analyzed using PROC GLM in SAS. A model containing subject and normalized dose was used. Comparisons to the 20 mg group were used to assess the dose proportionality of each of the doses.

Pharmacokinetic Results:

Mean + Coefficients of Variation (CV%) of Pharmacokinetic Parameters on the Third Day of Each Dosing Regimen

	Ziprasidone					
	20 mg BID		40 mg BID		80 mg BID	
	Mean	CV%	Mean	CV%	Mean	CV%
AUC_{0-12}* (ng•hr/ml)	462	36	768	35	1551	34
C_{max}* (ng/ml)	66	51	116	30	202	35
T_{max} (hr)	7.6	22	6.8	40	6.7	45

* = Geometric means

Safety Results:

	Number of Subjects [With/Evaluated (Discontinued)]		
	Ziprasidone		
Findings	20 mg BID	40 mg BID	80 mg BID
Adverse Events (All Causality)	8/12(0)	10/12(0)	10/11(2)
Adverse Events (Treatment-emergent, Treatment-related)	7/12(0)	9/12(0)	10/11(2)

( ) Subjects discontinued

Summary and Conclusions:

Visual inspection of the data indicated steady-state was generally obtained by the third day of dosing of each dosing regimen. Based on analysis of variance of the normalized data, mean AUC_{0-12} and C_{max} values increased in a dose proportional manner. T_{max} was similar across the doses. Due to the fact that the mean of the dose normalized data for both AUC and C_{max} were not different from each other, ziprasidone was shown to be dose proportional.

Adverse events increased with each increase in dose. The most common body system affected during this study was the nervous system, but the most common adverse event was different for each dosing group. The 20 mg BID group had five out of 12 subjects with somnolence, the 40 mg BID group had five out of 12 subjects with asthenia and insomnia, and the 80 mg BID group had six out of 11 subjects with agitation and anxiety. Two subjects in the 80 mg BID were discontinued; one had a severe extrapyramidal reaction and one had moderate orthostatic hypotension. All other adverse events were of mild to moderate severity. There were no serious adverse events in this study.

In conclusion, AUC and C_{max} values of ziprasidone were shown to be dose proportional over the range of 20 mg to 80 mg.

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Attachment # 4

Table 5.1 Individual and Mean Pharmacokinetic Parameters on the Third Day of Each Dosing Regimen
Ziprasidone Protocol 043

Subject #	AUC0-12 (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	AUC0-12 (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)	AUC0-12 (ng•hr/ml)	Cmax (ng/ml)	Tmax (hr)
	20 mg bid			40 mg bid			80 mg bid		
599-0001									
599-0002									
599-0004									
599-0005									
599-0006									
599-0007									
599-0009									
599-0011									
599-0012									
Mean[a]	462	66	7.6	768	116	6.8	1551	202	6.7
S.D.	166	33	1.7	271	35	2.7	532	72	3.0
CV%	36	51	22	35	30	40	34	35	45
599-0003[b]									
599-0008[b]									
588-0010[b]									

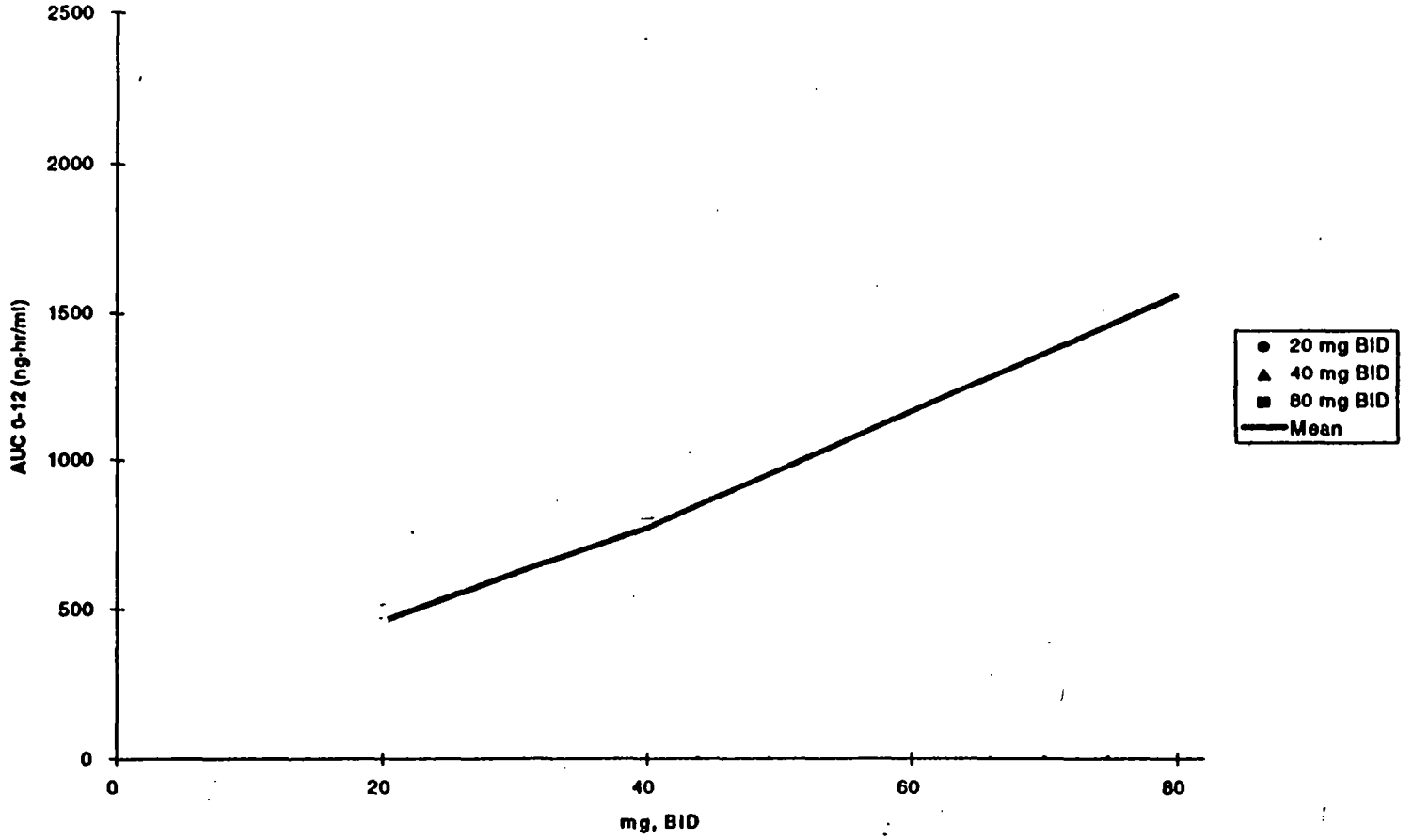
[a]Geometric means and standard deviations are reported for AUC0-12 and Cmax
[b]Subjects who did not complete the study and whose data were excluded from summary statistics

Source Data: Appendix IV, Tables 1 - 3

Attachment 5

5

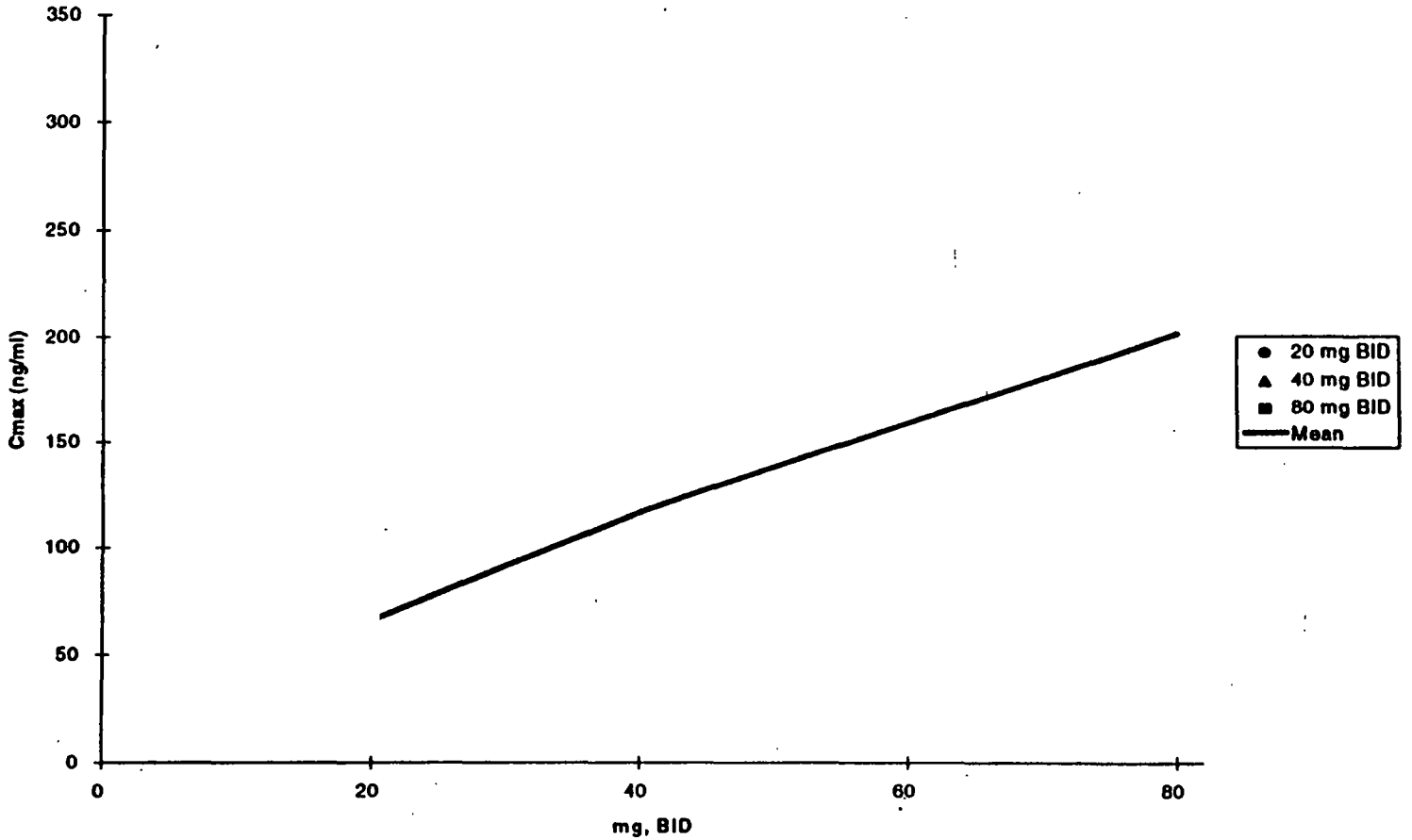
Figure 1.6 Individual and Mean AUC0-12 vs Dosing Regimen
Ziprasidone Protocol 043



Source Data: Appendix IV, Tables 1 - 3

Attachment 2 6

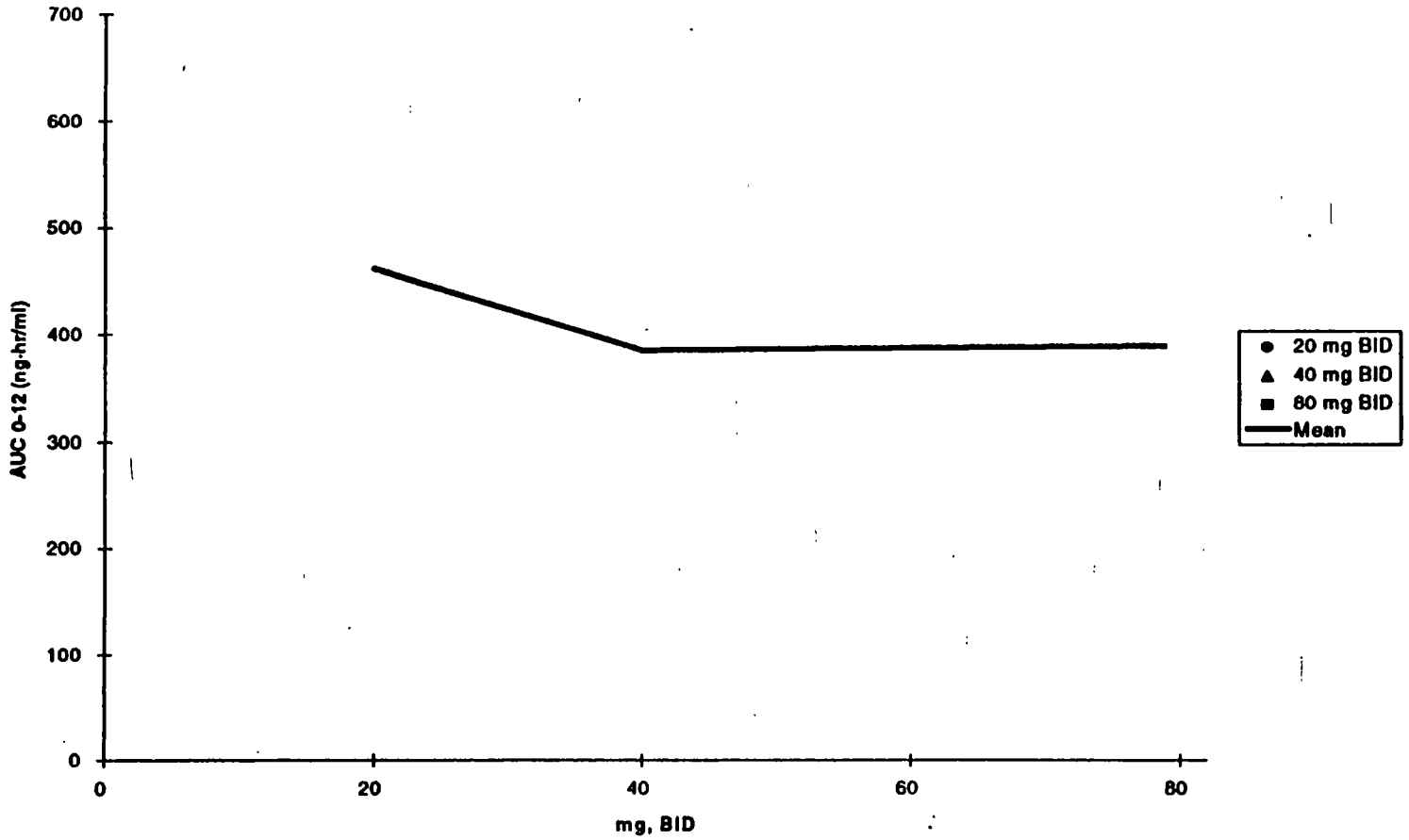
Figure 1.7 Individual and Mean Cmax vs Dosing Regimen
Ziprasidone Protocol 043



Source Data: Appendix IV, Tables 1 - 3

Attachment 37

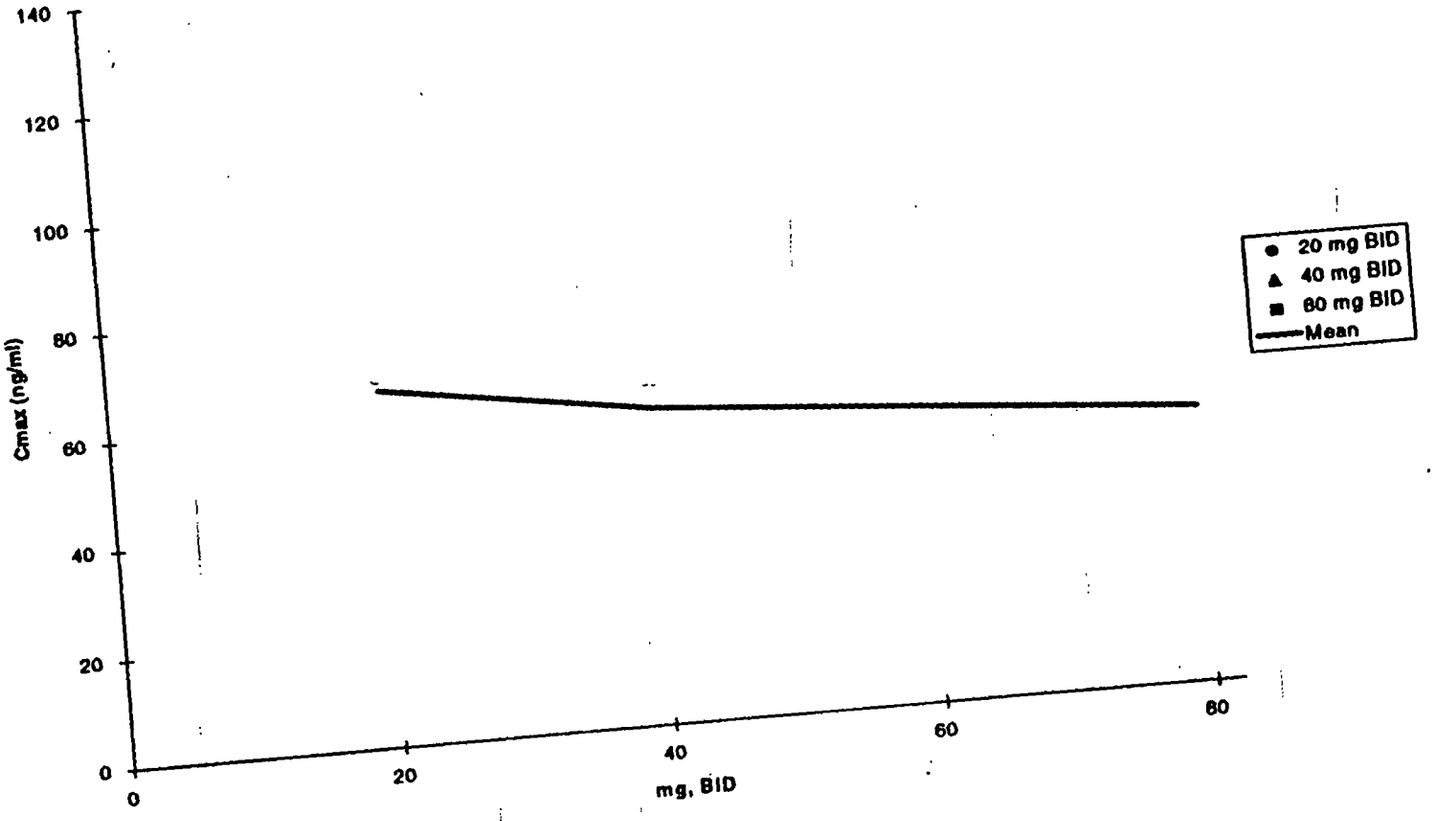
Figure 1.8 Individual and Mean AUC0-12 (Normalized to the 20 mg dose) vs Dosing Regimen
Ziprasidone Protocol 043



Source Data: Appendix IV, Tables 1 - 3

Attachment # 8

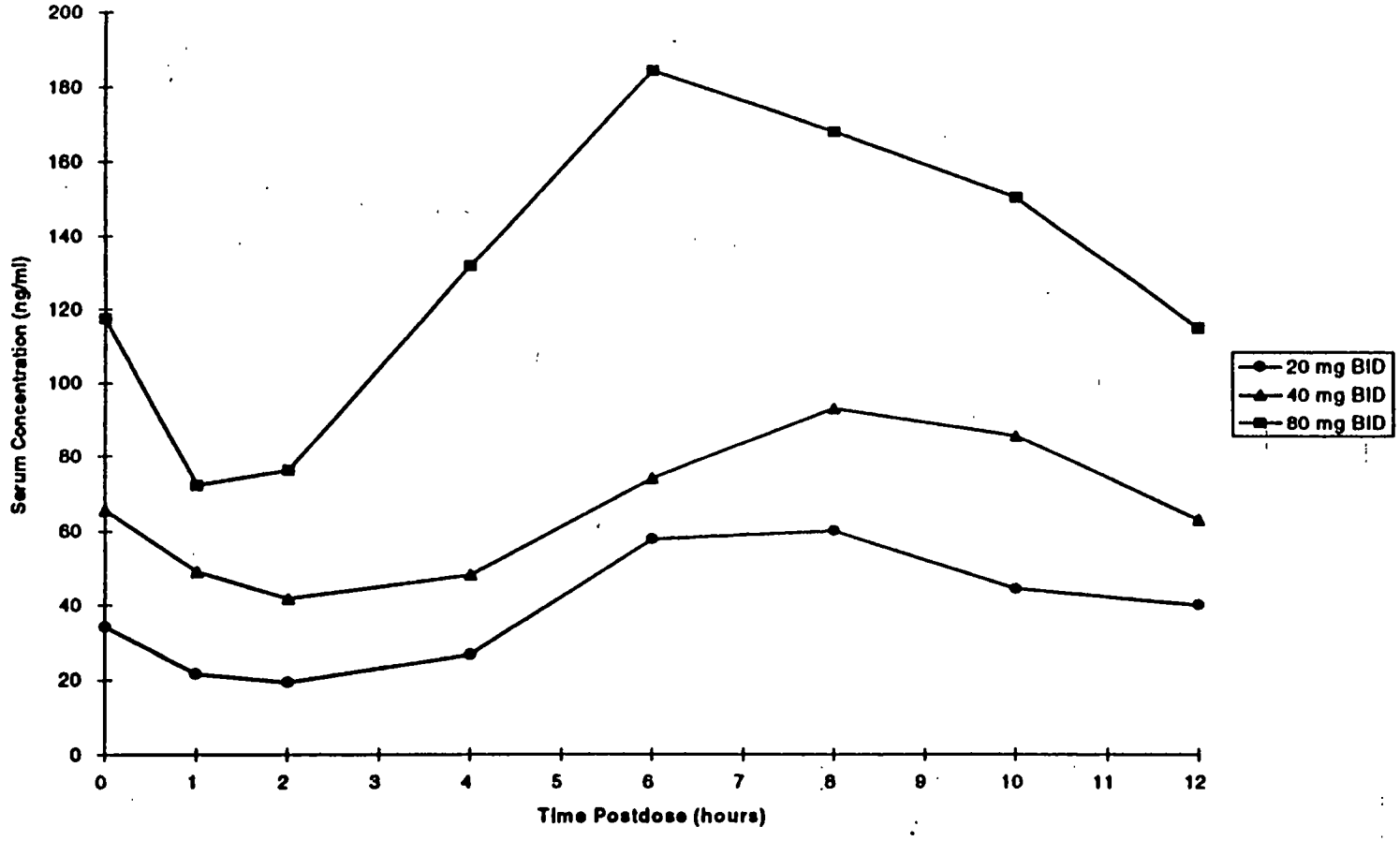
Figure 1.9 Individual and Mean Cmax (Normalized to the 20 mg dose) vs Dosing Regimen
Ziprasidone Protocol 043



Source Data: Appendix IV, Tables 1 - 3

Attachment # 9

Figure 1.1 Mean Serum Ziprasidone Concentrations vs Time Following Multiple Dose Administration
Ziprasidone Protocol 043



Source Data: Appendix IV, Tables 1-3

Study 005 (Safety and PK-Titration from 20 to 60 and 20 to 80 mg BID-multiple doses)

Study Design and Summary:

(see attachments 1 and 4)

Results:

(See attachments 5-14)

Reviewer's Comments:

1. The sponsor should have had only one treatment arm and one placebo arm instead of two treatment arms and one placebo arm. In other word, the study should have been conducted in the same group of subjects with escalating doses from 20, 40, 60, and 80 mg, instead of 20, 40, and 60 mg in one group and 20, 40, and 80 mg in the other group (see attachments 1 and 2 for the design). In this case, each subject will serve as own control.

2. It is not clear as to why the Cmax and AUC were similar after 60 and 80 mg dose on day 18 (attachments 5 and 6). In fact, the values were slightly higher after 60 mg (118 ng/ml for Cmax and 755 ng.h/ml for AUC) than 80 mg (111 ng/ml for Cmax and 718 ng.h/ml for AUC) . The sponsor did not provide any explanations. This is in contrast to the sponsor claims of linear PK up to 80 mg. However, it should be noted that this study was conducted at fasting state, whereas the sponsor claim of the linear PK appears to be at fed state. The linearity of the drug should be clearly specified in the label to reflect the effect of food.

3. There was a high variability in the half life, which was longer on day 18 (~ 8 h ranged from 5.5 to 13 h) compared to day 1 (~6 h ranged from 3.5 9.5) in all subjects (attachments 5). The drug was detected in the serum for a longer period of time after the highest doses (60 and 80 mg) than a lower dose (20 mg), suggesting assay sensitivity limitations. This has also been observed in other studies.

4. There was no difference in prolactin serum level between day 1 and day 18 nor between the doses (20, 60 or 80 mg), despite of the increase in ziprazidone serum levels by about 4 folds (attachments 7-10). It is also interesting to note that there was a good correlation between the peak prolactin concentration (which occurred at about 2 to 3 hours after ziprasidone) and the ziprasidone peak concentration. However, it is not clear as to why prolactin level did not increase as the ziprasidone serum level increased after 60 or 80 mg

doses on day 18. These observations are consistent with other studies.

5. The data on the sedation scores are not clear as to why on day 1 the mean change from the baseline was higher for in one group and was lower in another group compared to a placebo (attachment 11), despite the fact that both groups received the same dose (20 mg). In addition, on day 18, there was no difference in the mean change from the baseline between the placebo and after 60 mg dose, but there was a considerable difference after 80 mg (attachment 12). No explanation was provided by the sponsor.

6. Similarly, it is not clear as to why only on day 18 the mean time to fall asleep was markedly increased and the mean number of hours of sleep markedly decreased in ziprasidone treated groups compared to a placebo as well as on day 1 to day 17 (attachments 13 and 14). No explanation by the sponsor was provided.

Conclusions:

1. This is extensive PK/PD study, but the study design and the data are very confusing and unexplainable.

2. It is not clear as to why the Cmax and AUC were similar after 60 or 80 mg doses. All previous studies were conducted at fed states.

3. The data on prolactin, sedation and sleeping pattern sedation are somehow confusing and unexplainable.

4. No PK conclusions can be drawn from this study.

PROTOCOL 128-005: PHASE I MULTIPLE DOSE, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF ORAL CP-88,059-1 TITRATED FROM 20 MG, BID TO EITHER 60 MG, BID OR 80 MG, BID IN NORMAL MALE VOLUNTEERS

Principal Investigator: N. Gerber, M.B.

Study Publication: None

Study Dates: 6 March 1991 - 13 August 1991

Study Objective: To assess the safety, toleration, and pharmacokinetics of multiple doses of CP-88,059-1 (ziprasidone HCl) when titrated from an initial dose of 20 mg BID to either 60 mg BID or 80 mg BID.

Study Design: This was a double-blind, multiple dose, placebo-controlled study of ziprasidone HCl administered orally, twice daily for 16 days (only the morning dose was administered on the first and last days). All doses are expressed as mg equivalents of ziprasidone free base. Two dose levels of ziprasidone were studied (20 mg BID titrated to 60 mg BID, and 20 mg BID titrated to 80 mg BID). Ziprasidone and placebo were administered as matching capsules under fasting conditions.

Evaluation Groups:

	Ziprasidone		
	20→60 mg BID	20→80 mg BID	Placebo
Entered Study	8	8	4
Completed Study	7	8	4
Evaluated for Pharmacokinetics	7	8	0
Evaluated for Pharmacodynamics	8	8	4
Assessed for Safety			
Adverse Events	8	8	4
Laboratory Tests	8	8	4
Simpson-Angus Rating Scale (EPS)	8	8	4
Akathisia	8	8	4
Abnormal Involuntary Movements (AIMS)	8	8	4
Sedation Self-Evaluations	8	8	4
Sleep Profile Self-Evaluations	8	8	4

Subjects: Healthy male volunteers ranging in age from 20 to 41 years.

Drug Administration:

Dosage Form

Drug	Lot Number	FID Number	Potency	Formulation
CP-88,059-1	ED-G-019-191	CS-90-031	20 mg	Capsules
Placebo	C0288-QC1693	QC1693	--	Capsules

Dosing: Subjects received a single dose of study drug on day 1, no drug on days 2-3, twice daily doses on days 4-17, and a single dose on day 18. Subjects randomized to 20→60 mg BID received a single 20 mg dose on day 1, 20 mg BID on days 4-6, 40 mg BID on days 7-9, 60 mg BID on days 10-17, and a single 60 mg dose on day 18. Subjects randomized to 20→80 mg BID received a single 20 mg dose on day 1, 20 mg BID on days 4-6, 40 mg BID on days 7-9, 80 mg BID on days 10-17, and a single 80 mg dose on day 18. Morning doses were administered after an overnight fast, and evening doses were administered 3 hours after the evening meal.

Pharmacokinetic, Pharmacodynamic, and Safety Evaluations: Blood samples for determination of serum ziprasidone concentrations were collected prior to and up to 72 hours after dosing on days 1 and 18, and just prior to the morning doses on days 10-17. Serum concentrations were used to determine pharmacokinetic parameters (AUC_{0-12}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, half-life). Serum prolactin concentrations were measured on days 1, 10-17, and 18. Subjects were assessed for extrapyramidal side effects (Simpson-Angus rating scale), akathisia, and abnormal involuntary movements (AIMS), and completed subjective evaluations of sedation and sleep profile.

Analytical Methods:

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

Pharmacokinetic Results:

Mean[a] ± Coefficients of Variation (%CV) of Pharmacokinetic Parameters

	Ziprasidone							
	20→60 mg BID				20→80 mg BID			
Parameter	Day 1		Day 18		Day 1		Day 18	
$AUC_{0-\infty}$ (ng•hr/ml)[b]	223.8	±20			190.6	±37		
AUC_{0-12} (ng•hr/ml)[b]	165.9	±24	755.8	±26	144.3	±41	718.8	±23
C_{max} (ng/ml)[b]	24.9	±28	118.0	±34	23.7	±42	111.0	±22
T_{max} (hours)	3.4	±38	3.1	±29	3.1	±45	2.1	±19
K_{el} (hr^{-1})	0.124	±33	0.097	±24	0.124	±35	0.067	±24
Half-life (hours)[c]	5.6		7.1		5.6		10.3	

[a]Mean data do not include subject 501-0016, who was discontinued from the study.
[b]geometric means; [c]calculated as 0.693/mean K_{el}

Pharmacodynamic Results:

Serum Prolactin Concentrations

	Mean (ng/ml) ± Standard Deviation			
	Day 1		Day 18	
Treatment Group	Baseline	Maximum Change	Change from Day 1 Baseline: Predose	Maximum Change from Day 1 Baseline
Ziprasidone 20→60 mg BID	5.68 ±1.20	12.60 ±4.57	-0.86 ±3.00	13.16 ±14.02
Ziprasidone 20→80 mg BID	5.56 ±1.43	16.41 ±12.13	-0.80 ±2.58	10.65 ±9.93
Placebo	5.30 ±0.48	2.23 ±3.66	-1.90 ±1.56	-4.30 ±0.48

Safety Results:

Findings	Number of Subjects [With/Evaluated (Discontinued)] Ziprasidone 20→60 mg BID	Ziprasidone 20→80 mg BID	Placebo
Adverse Events[a]	8/8 (1)	8/8 (0)	3/4 (0)
Clinically Significant Laboratory Test Abnormalities	4/8 (0)	1/8 (0)	3/4 (0)
Simpson-Angus Determinations[b]	0/8 (0)	1/8 (0)	0/4 (0)
AIMS Determinations[b]	0/8 (0)	0/8 (0)	0/4 (0)
Akathisia Determinations[b]	4/8 (0)	5/8 (0)	0/4 (0)

[a] All adverse events were treatment-related except one case of mild paresthesia in the 20→80 mg BID group.
[b] greater than or equal to 1 on the rating scale

Summary and Conclusions: Ziprasidone exposure was similar in the 20→60 mg BID and 20→80 mg BID groups following a single 20 mg dose on day 1. On day 18, similar exposure to ziprasidone was observed for both dose groups, suggesting that an increase in dose from 60 mg to 80 mg, administered twice a day in the fasted state, did not lead to an increase in exposure to ziprasidone. A longer half-life was observed on day 18 compared to day 1 for both dose groups. This was related to the ability to measure serum drug concentrations at later time points following administration of higher doses.

Single and multiple doses of ziprasidone were associated with increases in serum prolactin concentrations. Maximum increases were seen 2 to 3 hours following dosing, and returned to baseline concentrations during the 12 hour dose interval. Peak serum prolactin concentrations occurred at approximately the same time as peak serum ziprasidone concentrations. After continued administration of ziprasidone for 14 days, serum prolactin concentrations showed similar increases as on day 1, despite the 3 to 4-fold higher doses and approximately six-fold increase in serum ziprasidone concentrations on day 18.

A majority of subjects treated with ziprasidone experienced mild to moderate somnolence throughout the study. One subject in the 20→60 mg BID group was discontinued due to adverse events (moderate agitation and mild dyspnea). Five subjects in the 20→60 mg BID group had severe adverse events (somnolence, asthenia, postural hypotension, dizziness, agitation). One subject in the 20→80 mg BID group had severe asthenia and headache, and one placebo subject had a severe headache. Following cessation of double-blind treatment, 5/15 ziprasidone-treated subjects experienced mild to moderate agitation, and two subjects in the 20→60 mg BID group and one subject in the 20→80 mg BID group had mild tremors. All other adverse events were isolated and of mild to moderate severity. No serious adverse events were reported in this study.

For 1 to 2 days following the last dose of ziprasidone, the mean time to fall asleep increased and the mean number of hours of sleep decreased in both ziprasidone treatment groups.

In conclusion, multiple doses of ziprasidone titrated to either 60 mg or 80 mg BID in the fasted state were not as well tolerated as placebo in this study popluation, with symptoms occurring which are consistent with the pharmacologic properties of this compound.

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Table 5.1
Individual and Mean Ziprasidone Pharmacokinetic Parameters on Days 1 and 18 Following Single and Multiple Dose Administration of Ziprasidone HCl to Healthy Volunteers
Ziprasidone Protocol 005

GROUP 1: 20 mg SD Day 1, 20 mg bid Days 4 to 6, 40 mg bid Days 7 to 9, 60 mg bid Days 10 to 17, 60 mg SD Day 18

Subject	AUC(0-12) (ng•h/ml) Day 1	AUC(0-∞) (ng•h/ml) Day 1	AUC(0-12) (ng•h/ml) Day 18	Cmax (ng/ml) Day 1	Cmax (ng/ml) Day 18	Tmax (h) Day 1	Tmax (h) Day 18	Kel (h^{-1}) Day 1	Kel (h^{-1}) Day 18	T1/2 (h) Day 1	T1/2 (h) Day 18
501-0002											
501-0003											
501-0004											
501-0010											
501-0012											
501-0016											
501-0017											
501-0020											
MEAN[c,d]	165.9	223.8	755.8	24.9	118.0	3.4	3.1	0.124	0.097	5.6[e]	7.1[e]
SD	39.8	44.8	196.5	7.0	40.1	1.3	0.9	0.041	0.023	--	
CV%	24	20	26	28	34	38	29	33	24		

GROUP 2: 20 mg SD Day 1, 20 mg bid Days 4 to 6, 40 mg bid Days 7 to 9, 80 mg bid Days 10 to 17, 80 mg SD Day 18

Subject	AUC(0-12) (ng•h/ml) Day 1	AUC(0-∞) (ng•h/ml) Day 1	AUC(0-12) (ng•h/ml) Day 18	Cmax (ng/ml) Day 1	Cmax (ng/ml) Day 18	Tmax (h) Day 1	Tmax (h) Day 18	Kel (h^{-1}) Day 1	Kel (h^{-1}) Day 18	T1/2 (h) Day 1	T1/2 (h) Day 18
501-0001											
501-0005											
501-0007											
501-0009											
501-0011											
501-0013											
501-0014											
501-0019											
MEAN[d]	144.3	190.6	718.8	23.7	111.0	3.1	2.1	0.124	0.067	5.6[e]	10.3[e]
SD	59.2	70.5	165.3	10.0	24.4	1.4	0.4	0.043	0.016	--	--
CV%	41	37	23	42	22	45	19	35	24	--	--

NC = Reliable estimate of Kel could not be made since the length of the sampling interval was too short relative to the projected half-life.
DC = Subject 501-0016 was discontinued from the study after day 15.
[c] = Mean data does not include subject 501-0016.
[d] = Geometric mean and standard deviation for AUC(0-12), AUC(0-∞) and Cmax. Arithmetic mean and standard deviation for all other parameters except T1/2.
[e] = Calculated as 0.693/mean Kel.
Source Data: Appendix IV, Tables 1a and 1b.

6

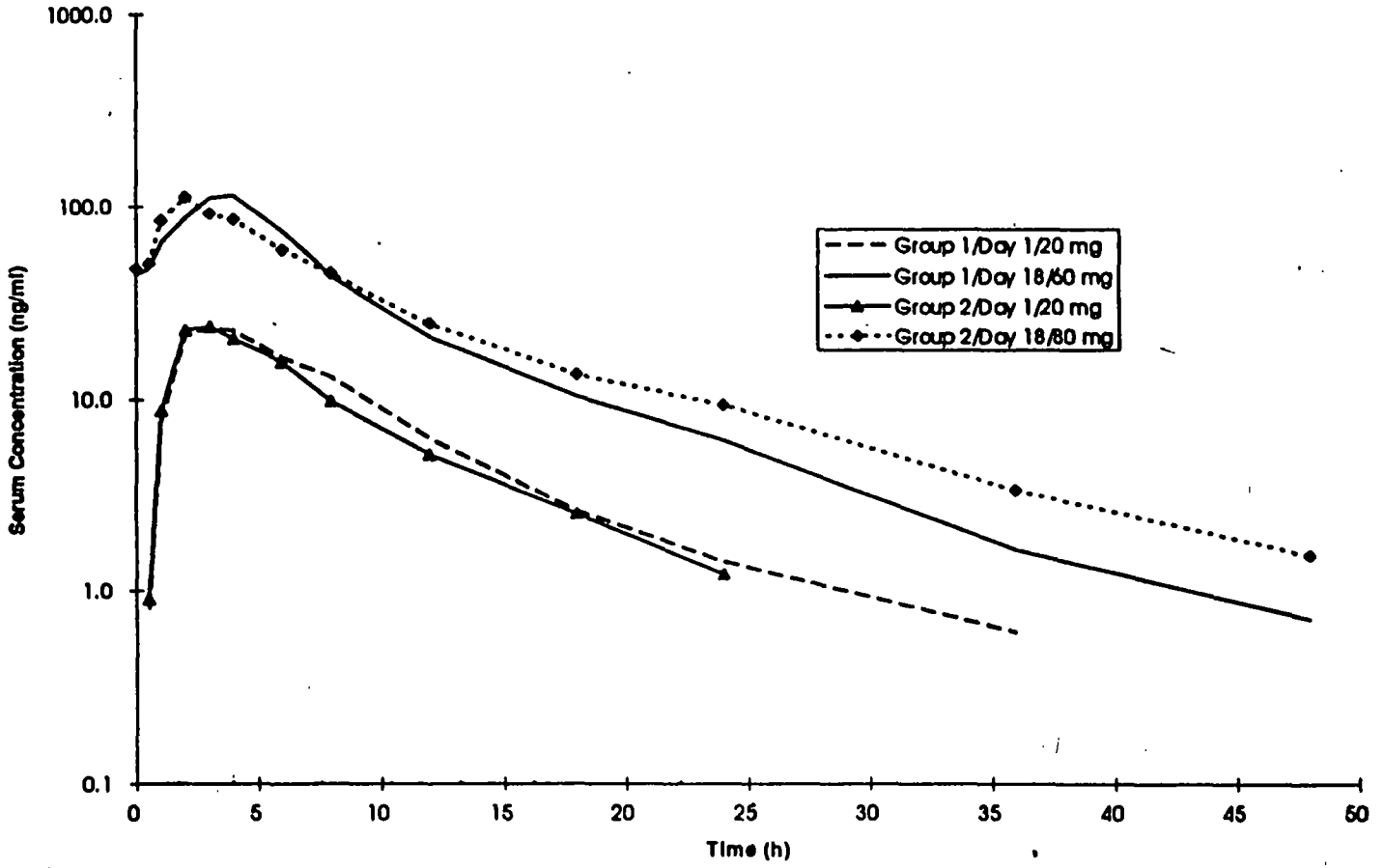


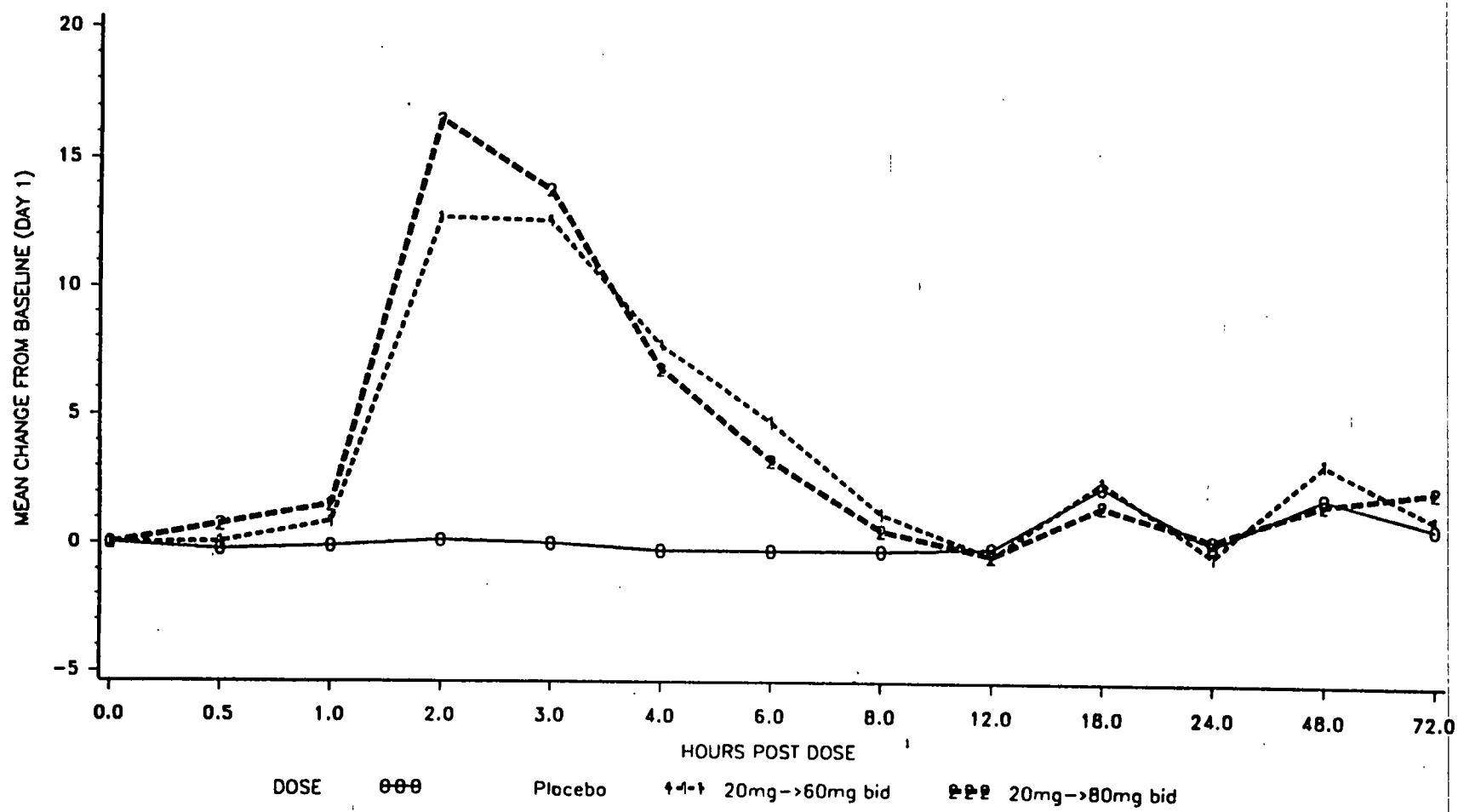
Figure 1.1 Mean Serum Ziprasidone Concentrations Versus Time Following Single and Multiple Dose Administration of Ziprasidone HCl to Healthy Volunteers - Days 1 and 18
Ziprasidone Protocol 005

Source Data: Appendix IV, Tables 1a and 1b

7

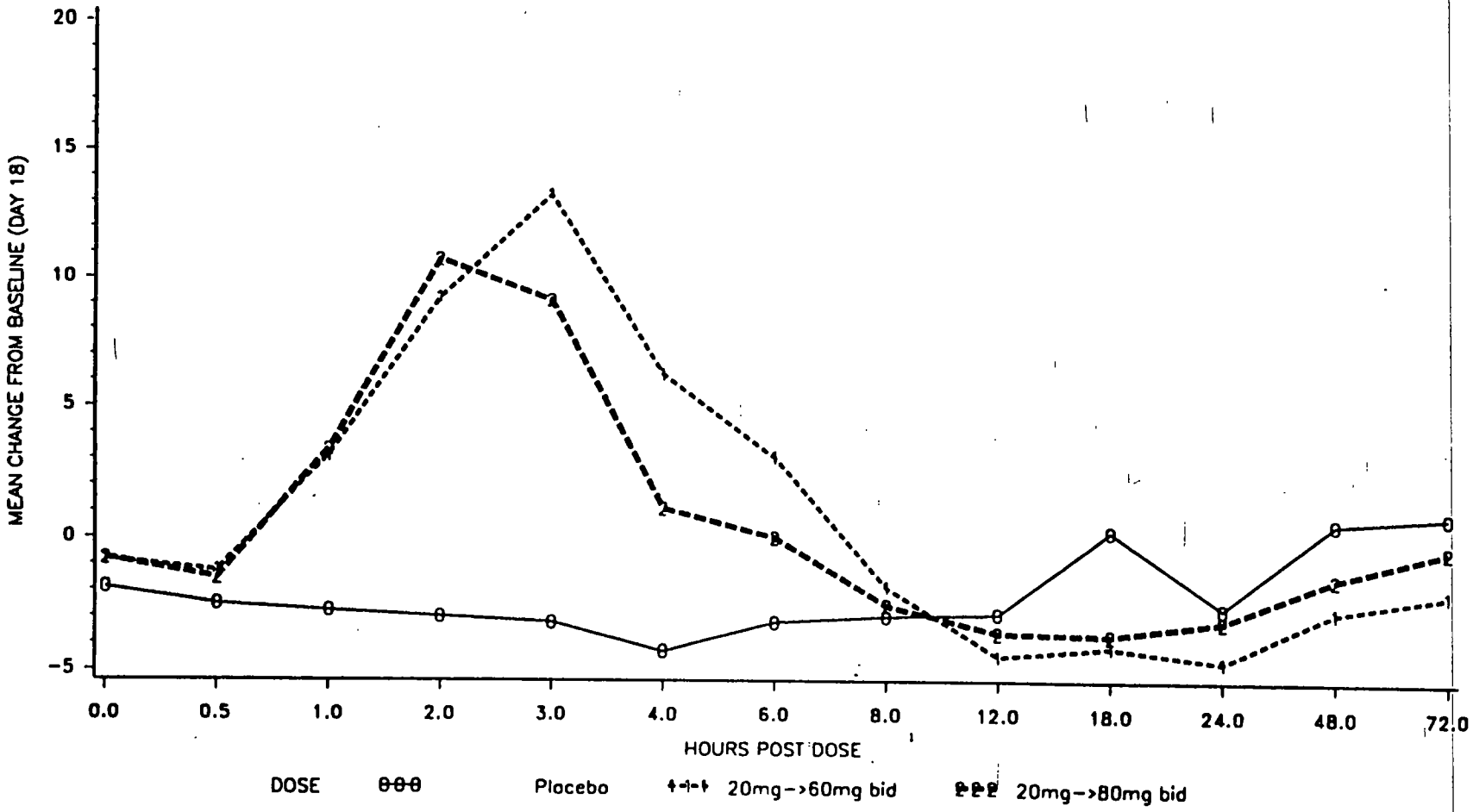
7

FIGURE 2.1
SERUM PROLACTIN (ng/ml) CHANGE FROM BASELINE ON DAY 1
ZIPRASIDONE PROTOCOL 005



Source Data : Appendix III, Table 2 Date of Data Extraction : 11JUL95 Date of Figure Generation : 12JUL95

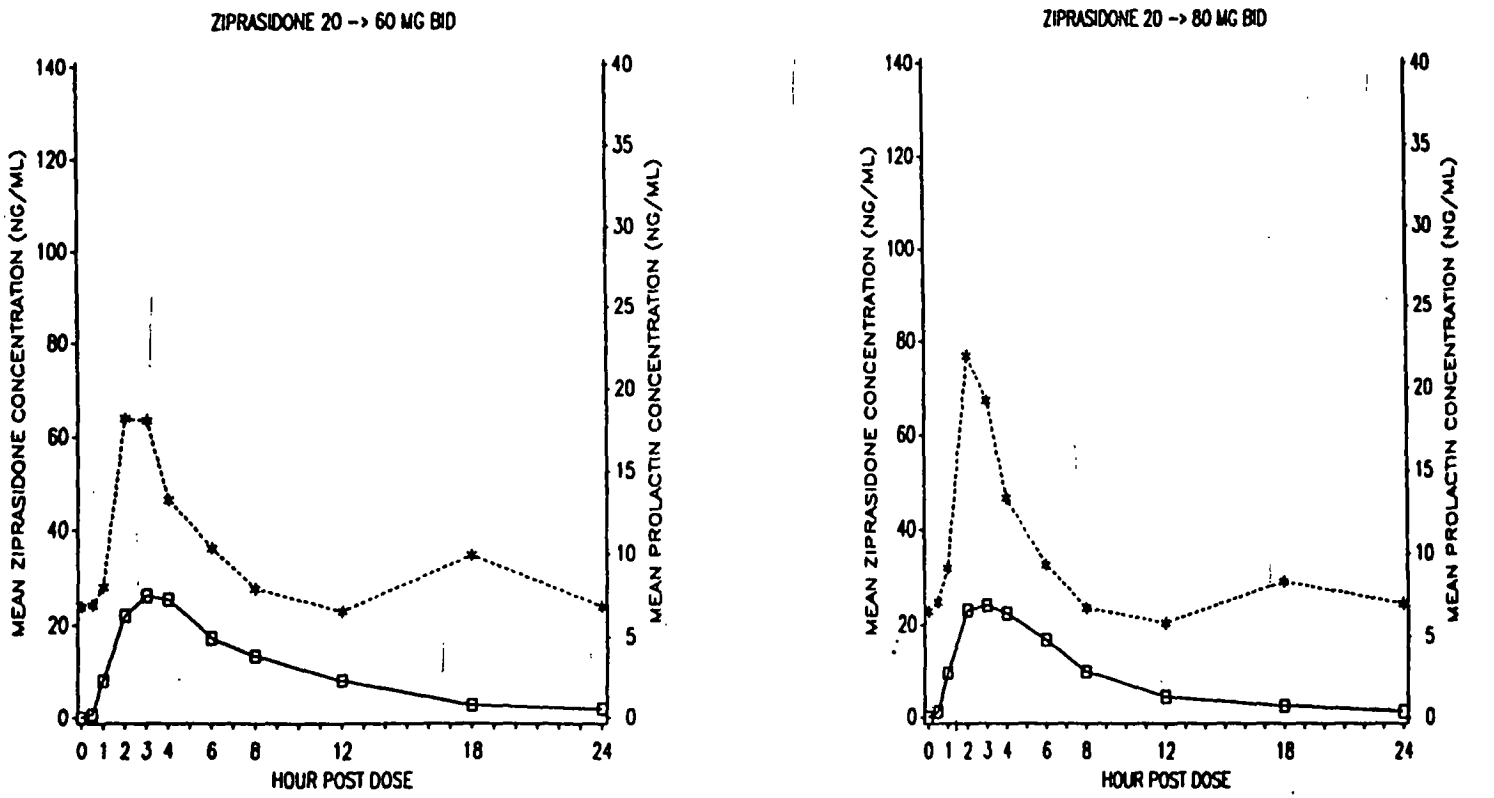
FIGURE 2.2
SERUM PROLACTIN (ng/ml) CHANGE FROM BASELINE ON DAY 18
ZIPRASIDONE PROTOCOL 005



Source Data : Appendix III, Table 2 Date of Data Extraction : 11JUL95 Date of Figure Generation : 12JUL95

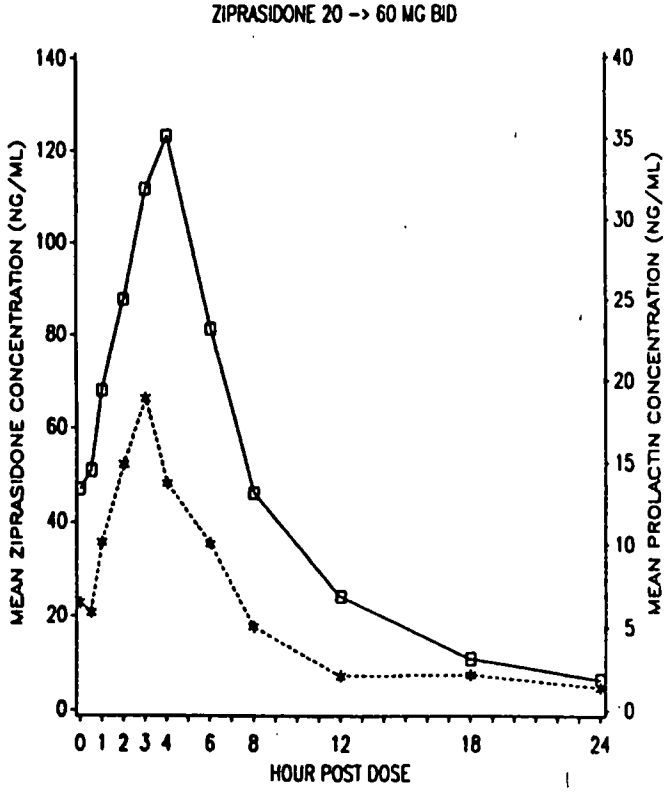
9

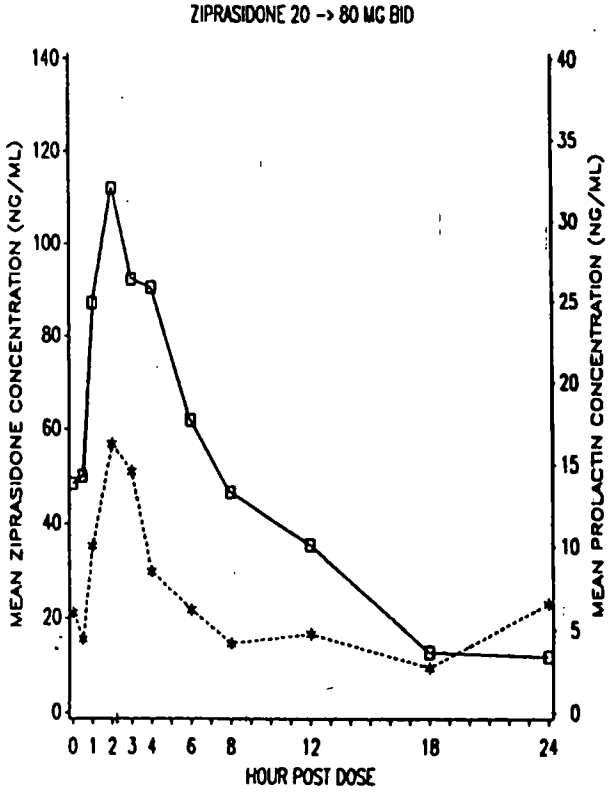
FIGURE 2.1.1
PROLACTIN AND ZIPRASIDONE MEAN CONCENTRATIONS (NG/ML) BY HOUR POST DOSE ON DAY 1
ZIPRASIDONE PROTOCOL 005



Squares represent Mean Ziprasidone Concentration (ng/ml) while Stars represent Mean Prolactin Concentration (ng/ml)
SOURCE DATA : Appendix IV, Table 1A, 1B and Appendix V, Table 1B DATE OF DATA EXTRACTION : 11JUL95 DATE OF FIGURE GENERATION : 18OCT95

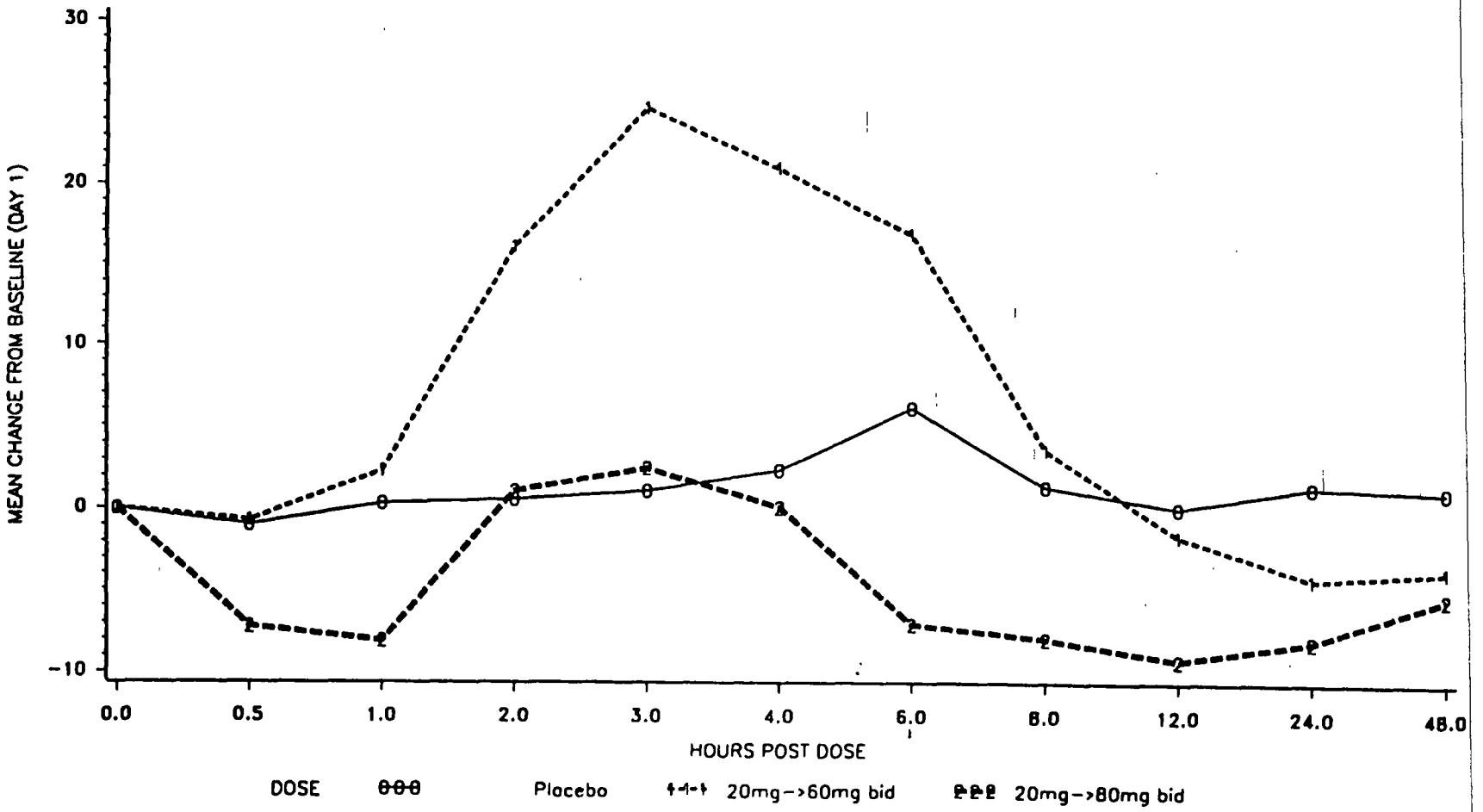
FIGURE 2.2.1
PROLACTIN AND ZIPRASIDONE MEAN CONCENTRATIONS (NG/ML) BY HOUR POST DOSE ON DAY 18
ZIPRASIDONE PROTOCOL 005





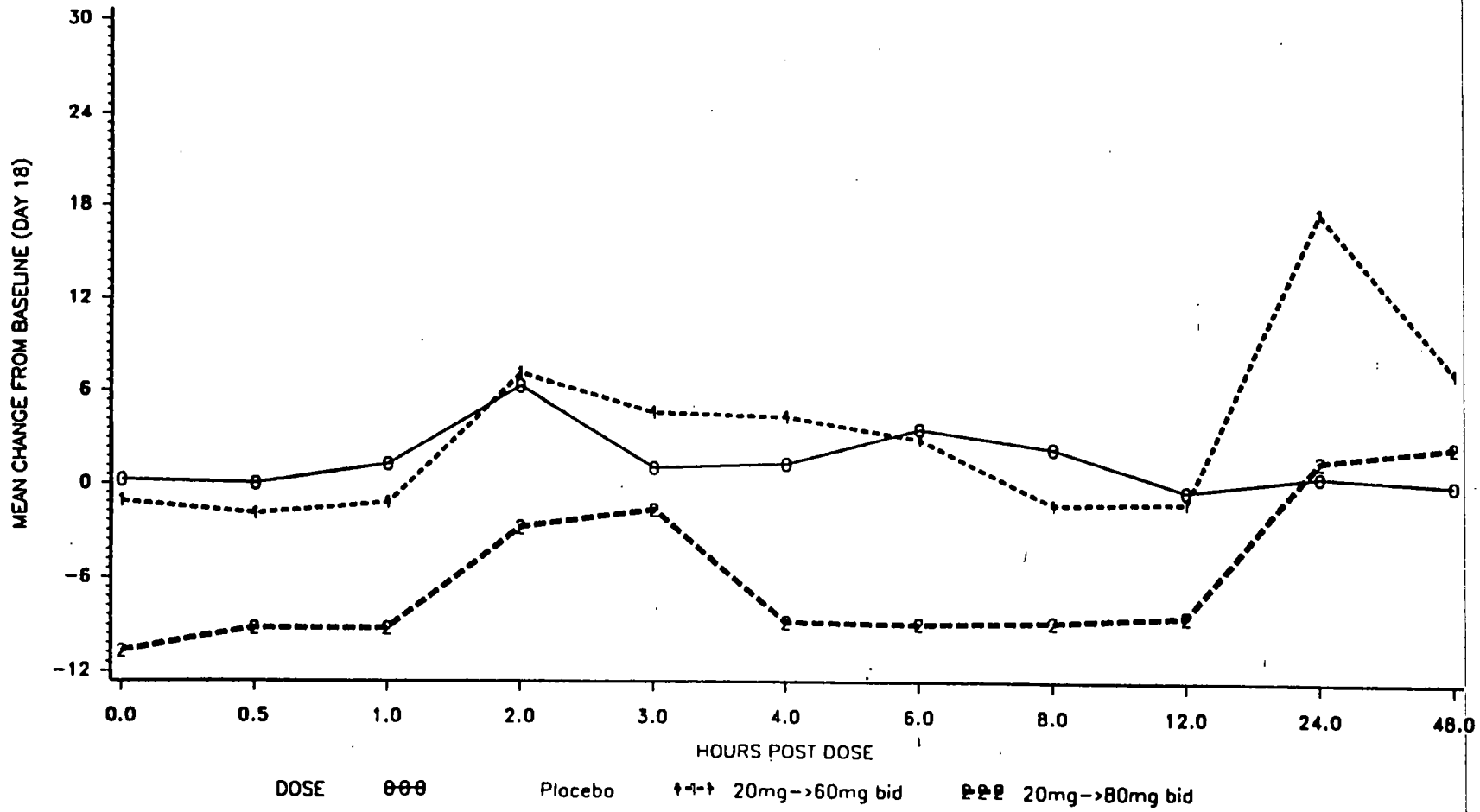
Squares represent Mean Ziprasidone Concentration (ng/ml) while Stars represent Mean Prolactin Concentration (ng/ml)
SOURCE DATA : Appendix IV, Table 1A, 1B and Appendix V, Table 1B DATE OF DATA EXTRACTION : 11JUL95 DATE OF FIGURE GENERATION : 160CT95

FIGURE 3.1
MEAN CHANGE FROM BASELINE IN SUM OF SEDATION SCORES ON DAY 1
ZIPRASIDONE PROTOCOL 005



Source Data : Appendix III, Table 3 Date of Data Extraction : 11JUL95 Date of Figure Generation : 12JUL95

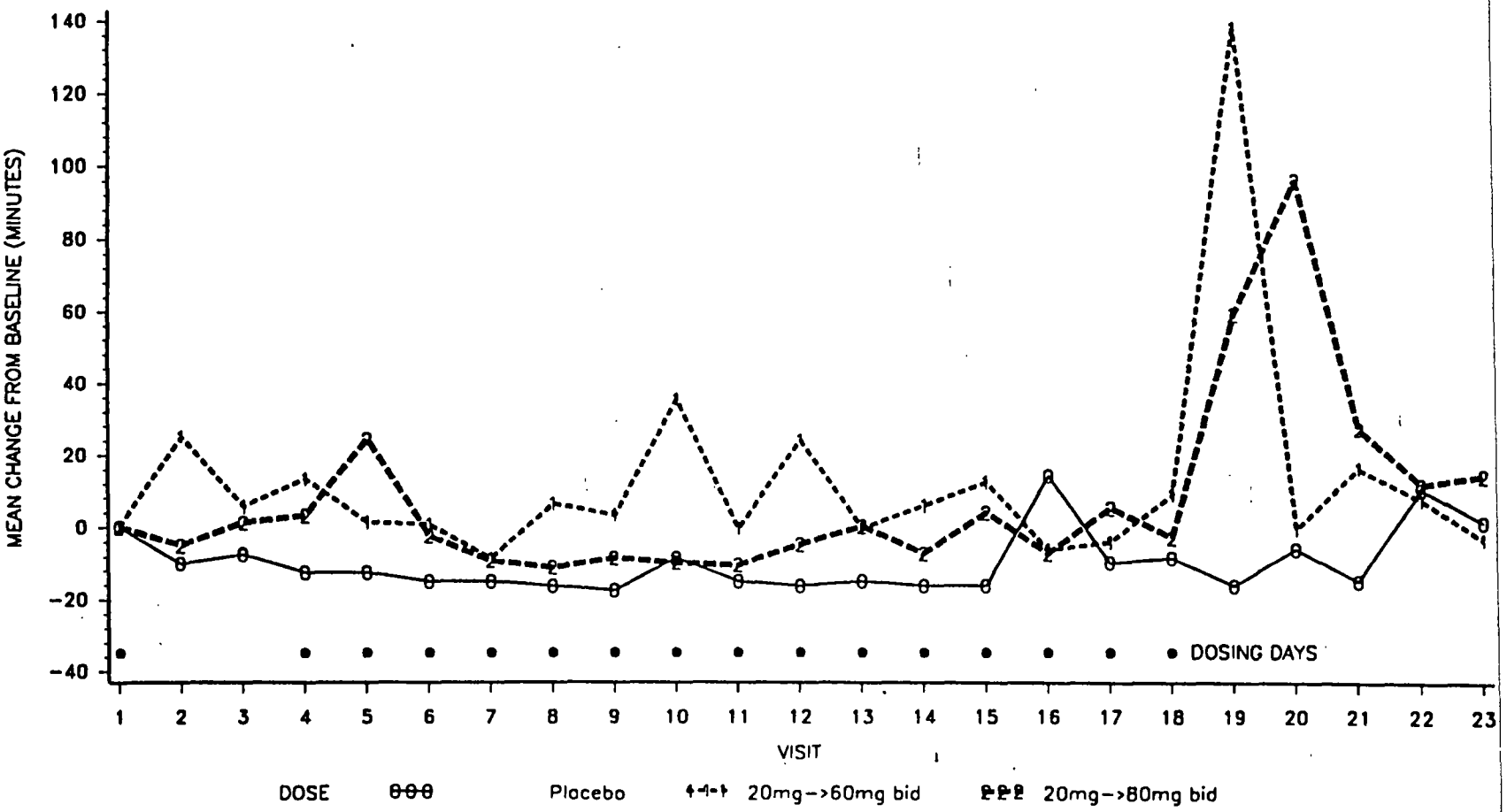
FIGURE 3.2
MEAN CHANGE FROM BASELINE IN SUM OF SEDATION SCORES ON DAY 18
ZIPRASIDONE PROTOCOL 005



Source Data : Appendix III, Table 3 Date of Data Extraction : 11JUL95 Date of Figure Generation : 12JUL95

13

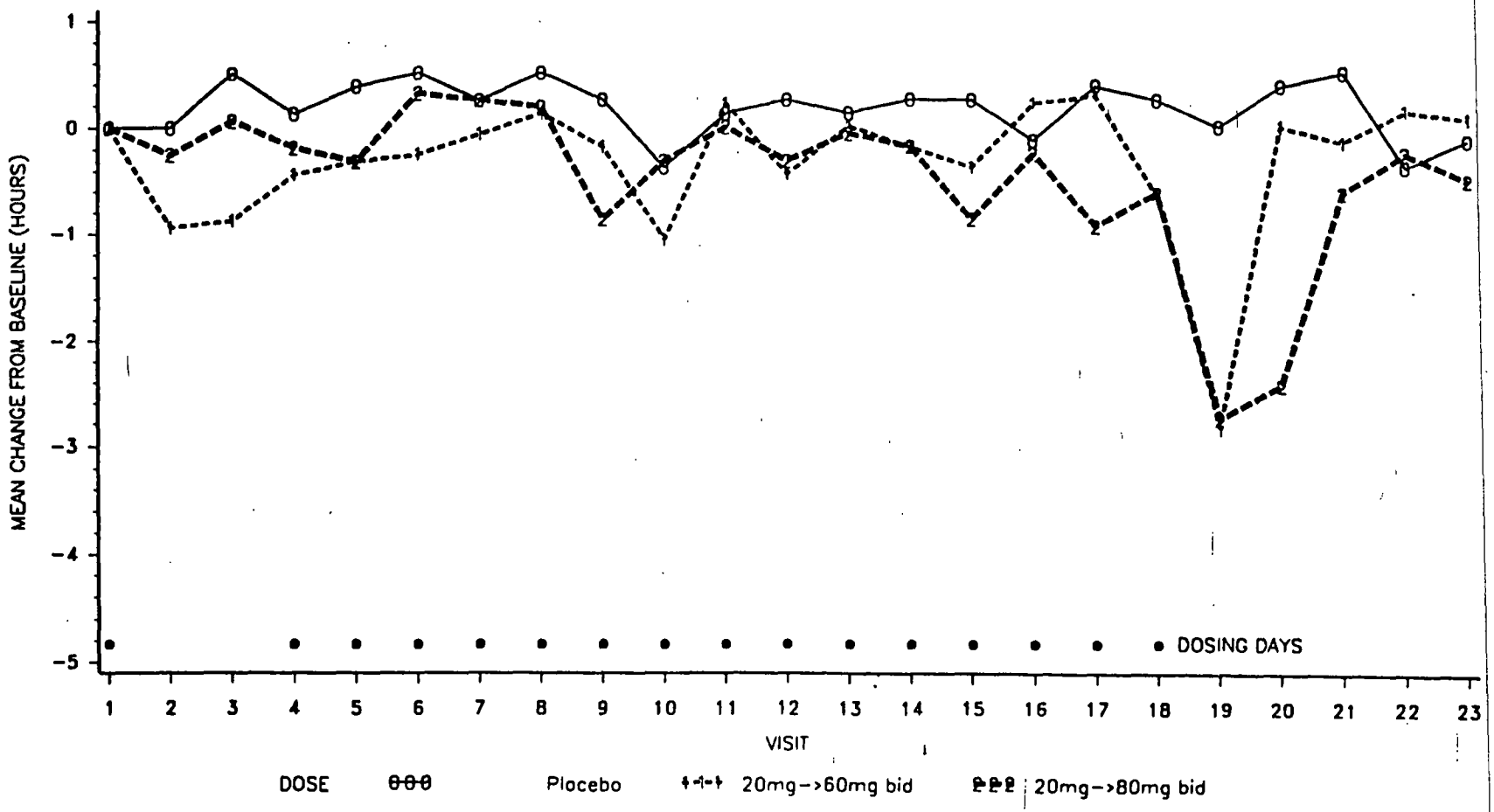
FIGURE 4.1
RESULTS OF SLEEP PROFILE – CHANGE FROM BASELINE FOR 'MINUTES TO FALL ASLEEP'
ZIPRASIDONE PROTOCOL 005



Source Data : Appendix III, Table 4 Date of Data Extraction : 11JUL95 Date of Figure Generation : 12JUL95

14

FIGURE 4.2
RESULTS OF SLEEP PROFILE – CHANGE FROM BASELINE FOR 'HOURS OF SLEEP'
ZIPRASIDONE PROTOCOL 005



Source Data : Appendix III, Table 5 Date of Data Extraction : 11JUL95 Date of Figure Generation : 12JUL95

Study 013 (Multiple Dose, 5, 20, 40 and 60 mg)

Study Design and Summary:

(see attachments 1-5)

Results:

(See attachments 6-11)

Reviewer's Comments:

1. From the data shown in attachments 6 the ratios of dose normalized mean AUCs on day 18 are not constant as shown below:

Dose (mg)	AUC (ng.h/ml)	AUC/Dose	Expected AUC (Based on 5 mg)	% Difference (based on 5 mg)
5	110	21.8		
20	259	12.95	109 X 4 = 436	-40.6
40	658	16.45	109 X 8 = 872	-24.5%
60	1027	17.11	109 X 12 = 1308	-21.4

   If the drug follows a linear kinetic, all ratios should be constant.

2. It is not clear as to why the mean half-life increased from 3.2 h on day 1 to 10.0 h on day 18 as the dose increased from 5 to 60 mg, respectively. If the sponsor is claiming dose proportionality (linear PK) of the drug, the half life should relatively remain constant. No convincing explanations were given by the sponsor. It should also be noted that the drug appears to be detected in serum up to 24 hours at 5 and 20 mg doses and up to 48 hours at 40 and 60 mg doses (attachment 11). The sponsor did not give any explanation on these observations which could be due to the assay limitations. In addition, the sponsor did not include the SD or the CV (%) in the summary table for the half-lives (see attachment 6).

3. It should also be noted that there is a high variability in the data as demonstrated by the large values of CV (%) and the SD (attachment 6).

4. Steady state attained within two day.

5. Only males were used.

Conclusions:

1. Overall, it appears that there is a trend for proportional increase in the AUC and Cmax with dose.

2. The marked increase in the half-life with dose is inconsistent with the claim for linear PK.

3. There is a high variability in the data and it is not clear from this study as if it is inherent to the drug or due to the assay limitations.

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PROTOCOL 128-013: PHASE I MULTIPLE DOSE, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF ORAL CP-88,059-1 UNDER NON-FASTING CONDITIONS IN NORMAL MALE VOLUNTEERS

Principal Investigator: G. Apseloff, M.D.

Study Publication: Miceli, J., Hansen, R., Johnson, A., Wilner, K. Single and multiple dose pharmacokinetics of ziprasidone in healthy males [poster]. 10th Annual Meeting of the American Association of Pharmaceutical Scientists; 1995 November 8; Miami Beach, Florida.

Study Dates: 17 November 1992 - 1 July 1993

Study Objective: To assess the safety and pharmacokinetics of multiple doses of CP-88,059-1 (ziprasidone HCl) under fed conditions.

Study Design: This was a double-blind, multiple dose, placebo-controlled study evaluating the safety and pharmacokinetics of ziprasidone HCl in 39 normal, healthy, male subjects. Ziprasidone or placebo was administered orally, twice daily for 16 days (washout period on days 2-3) under fed conditions and four dose levels of ziprasidone (5 mg BID; 20 mg BID; 20 mg BID, titrated to 40 mg BID; and 20 mg BID, titrated to 60 mg BID) were examined. All doses are expressed as mg equivalents of free base.

Evaluation Groups:

	Ziprasidone				
	5 mg BID	20 mg BID	20→40 mg BID	20→60 mg BID	Placebo
Entered Study	6	8	8	7	10
Completed Study	6	6	6	6	6
Evaluated for Pharmacokinetics	6	6	6	6	0
Evaluated for Pharmacodynamics	6	8	8	7	10
Assessed for Safety					
Adverse Events	6	8	8	7	10
Laboratory Tests	6	8	8	7	10
Simpson-Angus Rating Scale (EPS)	6	8	8	7	10
Akathisia	6	8	8	7	10
Abnormal Involuntary Movements (AIMS)	6	8	8	7	10
Sedation Self-Evaluations	6	8	8	7	10
Sleep Profile Self-Evaluations	6	8	8	7	10

Subjects: Healthy male volunteers ranging in age from 18 to 45 years.

Drug Administration:

Dosage Form

Drug	Lot Number	FID Number	Potency	Formulation
CP-88,059-1	ED-G-013-192	CS-90-028	5 mg	Capsules
CP-88,059-1	ED-G-014-192	CS-90-031	20 mg	Capsules
Placebo	ED-G-012-192	BK-87-007	–	Capsules

Dosing: Subjects received ziprasidone or placebo twice daily 12 hours apart for 14 days with only morning doses on days 1 and 18 and no drug administered on days 2-3. All subjects were administered placebo, BID, in single-blind fashion beginning with evening dosing on day 18 and stopped with a morning dose on day 20. The subjects consumed a standard breakfast and dinner over a 20 minute period with study medication being given immediately after with 50 ml of water.

Pharmacokinetic, Pharmacodynamic, and Safety Evaluations: Blood samples for determination of serum ziprasidone concentrations were collected prior to and up to 72 hours after dosing on days 1 and 18, and just prior to the morning dose on days 5-17. Serum concentrations were used to determine pharmacokinetic parameters ($AUC_{(0-12)}$, $AUC_{(0-\infty)}$, C_{max}, T_{max}, K_{el}, and $T_{1/2}$). Serum prolactin concentrations were measured on days 1, 5-17, and up to 72 hours postdose on day 18. Subjects were assessed for extrapyramidal side effects (Simpson-Angus rating scale), akathisia (Barnes scale), abnormal involuntary movements (AIMS) at various time points throughout the study. Subjects completed evaluations of sedation and sleep throughout the study.

Analytical Methods: Serum concentrations of ziprasidone were determined by high performance liquid chromatography (HPLC) involving liquid-liquid extraction with detection by atmospheric pressure ionization mass spectrometry (API-MS). The assay had a dynamic range of 0.5 to 50.0 ng/ml.

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

Pharmacokinetic Results:

Mean ± Coefficients of Variation (%CV) of Pharmacokinetic Parameters

	Ziprasidone							
	5 mg BID		20 mg BID		20→40 mg BID		20→60 mg BID	
	mean	CV%	mean	CV%	mean	CV%	mean	CV%
	DAY 1							
$AUC_{(0-12)}$[a] (ng•hr/ml)	73.7	25	175.7	76	314.6	53	215.0	36
C_{max}[a] (ng/ml)	12.2	34	26.6	71	60.0	56	34.3	38
T_{max} (hr)	5.0	22	4.8	27	3.8	48	4.0	42
K_{el} (hr^{-1})	0.220	22	0.143	34	0.172	20	0.161	25
$T_{1/2}$[c] (hr)	3.2	-	4.8	-	4.0	-	4.3	-
	DAY 18							
$AUC_{(0-12)}$[a] (ng•hr/ml)	109.8	43	259.2	82	658.0	51	1027.9	43
R[b]	1.49	26	1.48	46	-	-	-	-
C_{max}[a] (ng/ml)	14.8	45	44.6	108	118.6	68	139.4	58
T_{max} (hr)	5.2	26	3.8	58	3.7	22	4.7	32
K_{el} (hr_{-1})	0.175	31	0.145	19	0.079	51	0.069	72
$T_{1/2}$[c] (hr)	4.0	-	4.8	-	8.8	-	10.0	-

[a] = Geometric means

[b] = Accumulation ratio; calculated as $AUC_{(0-12)Day\ 18}/AUC_{(0-12)Day\ 1}$.

[c] = Calculated as 0.693/mean K_{el}.

Pharmacodynamic Results:

Serum Prolactin Concentrations

	Mean (ng/ml) ± Standard Deviation			
	Day 1		Day 18	
Treatment Group	Baseline (ng/ml)	Maximum Change (ng/ml)	Change from Day 1 Baseline: Predose (ng/ml)	Maximum Change from Day 1 Baseline (ng/ml)
Ziprasidone 5 mg BID	10.47	11.10	3.15	7.77
Ziprasidone 20 mg BID	12.14	24.00	-0.95	10.50
Ziprasidone 20→40 mg BID	9.88	27.68	5.62	28.87
Ziprasidone 20→60 mg BID	9.63	20.93	11.70	20.38
Placebo	9.91	5.28	1.23	5.90

Safety Results:

	Number of Subjects [With/Evaluated (Discontinued)]				
	Ziprasidone				
Findings	5 mg BID	20 mg BID	20→40 mg BID	20→60 mg BID	Placebo
Adverse Events (All Causality)	4/6 (0)	7/8 (2)	8/8 (2)	6/7 (1)	6/10 (2)
Adverse Events (Treatment-emergent, Treatment-related)	4/6 (0)	5/8 (2)	7/8 (1)	4/7 (0)	2/10 (0)
Clinically Significant Laboratory Test Abnormalities	2/6 (0)	6/8 (0)	5/8 (0)	4/7 (0)	5/10 (0)
Simpson-Angus Determinations[a]	0/6 (0)	3/8 (0)	5/8 (0)	1/7 (0)	0/10 (0)
AIMS Determinations[a]	0/6 (0)	0/8 (0)	0/8 (0)	0/7 (0)	0/10 (0)
Akathisia Determinations[a]	0/6 (0)	0/8 (0)	0/8 (0)	0/7 (0)	0/10 (0)

a = greater than or equal to 1 on rating scale

Summary and Conclusions: Over the 5 to 60 mg BID dose range, systemic exposure following 14 days of multiple dosing increased with dose. The relationship between dose and overall exposure at steady-state appeared dose proportional from 20 to 60 mg based on dose adjusted mean $AUC_{(0-12)}$ values. Dose adjusted $AUC_{(0-12)}$ values for the 5 mg dose level appeared disproportionally greater in comparison to values for the higher doses. Except for two subjects at the 20 and 40 mg dose levels who had markedly higher exposures at their respective dose levels, the steady-state dose adjusted C_{max} appeared dose proportional from 5 to 60 mg.

In general, multiple dose administration led to increased variability compared to day 1. This was inferred from increases in coefficients of variation for C_{max} and $AUC_{(0-12)}$ between days 1 and 18. No relationship between dose and pharmacokinetic variability was observed. Except for the 20 mg dose group, individual steady-state C_{max} values ranged approximately 3- to 7-fold. For the 20 mg group, steady-state C_{max} values were highly variable, ranging approximately 20-fold.

At the higher dose levels (40 and 60 mg), longer terminal phase half-lives were observed at steady-state (9 to 10 versus 4 to 5 hours). The longer half-lives are attributed to the ability to characterize the additional dispositional phase following multiple dosing and not to a dose dependent decrease in oral clearance.

At the 5 and 20 mg dose levels the observed accumulation was greater than the predicted by 30% and 24%, respectively. This discrepancy may, in part, be an artifact owing to an underestimation of $AUC_{(0-\tau)}$ on day 1 because of the inability to characterize an additional dispostional phase (as discussed above).

At all dose levels, a lag-time of approximately 0.5 to 1 hour was observed.

Mean maximum observed serum concentrations of ziprasidone and prolactin occurred 4 to 6 hours after the morning dose on day 1 for the 5 mg BID group and 3 to 5 hours after the morning dose on day 1 for the 20 mg BID group, 20→40 mg BID group, and 20→60 mg BID group. Ziprasidone T_{max} was 5.0, 4.8, 3.8, and 4.0 hours in the four treatment groups, respectively. Following the morning dose on day 18, mean maximum observed serum ziprasidone and prolactin concentrations occurred 4 to 6 hours after the morning dose for the 5 mg BID group and the 20→60 mg BID group and 2 to 4 hours after in the 20 mg BID and 20→40 mg BID groups. The comparison between day 1 and day 18 mean prolactin and mean ziprasidone concentrations indicates on day 1, increasing ziprasidone concentrations correlated with increasing prolactin concentrations; however, on day 18, there seems to be some evidence of tolerance upon repetitive dosing in that higher ziprasidone concentrations are not matched by proportionally higher prolactin concentrations.

Subject 501-0006 in the placebo group had the only serious adverse event reported (subject hospitalized for the treatment of severe cellulitis and severe skin ulcers which began prior to study initiation). Two subjects in the 20 mg BID group, four subjects in the 20→40 mg BID group, and three subjects in the 20→60 mg BID group, reported severe adverse events including headache, orthostatic hypotension, somnolence, Epstein-Barr virus, agitation, chest pain, euphoria, pharyngitis, dizziness, syncope,

nausea, hallucinations and insomnia. Two subjects in the placebo group reported severe adverse events including bilateral foot cellulitis, ulcerations and dyspepsia. The most frequently occurring adverse event reported among the five treatment groups was headache, generally mild to moderate in severity. Two subjects in the 20 mg BID group and one subject in the 20→40 mg BID group discontinued the study for treatment-related reasons (postural hypotension). One subject each in the 20→40 mg BID group and 20→60 mg BID group and four subjects in the placebo group were discontinued for reasons not related to study drug. One subject in the 20→40 mg BID group and one subject in the 20→60 mg BID group discontinued after a 3-fold increase in SGPT above the upper limit of normal, subsequently attributed to infection with the Epstein-Barr virus.

Following the administration of ziprasidone to all groups except the 5 mg BID dose group on day 1, mean sedation scores rose and peaked between 3 and 4 hours after dosing. This also correlated with T_{max}, as the three treatment groups had a T_{max} between 3 and 5 hours. Mean sedation scores in the 5 mg BID and placebo groups on day 1 did not exhibit the same pattern. Following the administration of ziprasidone on day 18, the only notable increase in sedation relative to the placebo group was in the 20→60 mg BID group, starting after 1 hour and peaking at 6 hours after dosing.

The average number of minutes to fall asleep appeared relatively stable across all five groups for days 1 through 18. On day 19, however, the mean number of minutes to fall asleep increased in the 20 mg BID, 20→40 mg BID and 20→60 mg BID groups, returning to normal for all groups by day 21. Consistent with this pattern, the mean number of hours of sleep reported was fairly stable on days 1 through 18, but decreased in the same groups on day 19.

Nine subjects (three subjects from the 20 mg BID dosing group, five subjects from the 20→40 mg BID dosing group and 1 subject from the 20→60 mg BID dosing group) had one or more abnormal extrapyramidal symptoms, all of which were mild. Two subjects in the 20→40 mg BID group reported tremor. There were no positive AIMS or Barnes akathisia scores noted for any subject.

For the mean change from baseline in supine diastolic blood pressure, a difference between the 20 mg BID group and the other treatment groups was apparent between days 10 and 18, with the 20 mg BID group exhibiting a greater decrease in the mean change from baseline versus the other four treatment groups compared to placebo. One subject in the 20 mg BID group had an ECG on day 10 with the finding by the investigator to be premature atrial contraction that was repeated and determined to be not clinically significant. One subject in the 20→60 mg BID group had an ECG on day -11 with the finding by the investigator to be a left axis deviation that was not clinically significant. No other ECG abnormalities were observed.

In conclusion, over the 5 to 60 mg BID dose range, systemic exposure following 14 days of multiple dosing increased with dose. The administration of multiple doses of ziprasidone in the fed state were associated with symptoms which are consistent with the pharmacologic properties of this compound.

Attachment 6

6

Table 5.1.1 Summary of Pharmacokinetic Parameters Following Single (Day 1) and Multiple (bid) Dose Administration of Ziprasidone HCl to Healthy Male Volunteers for 14.5 Days (Days 4 to 18)
Ziprasidone Protocol 013

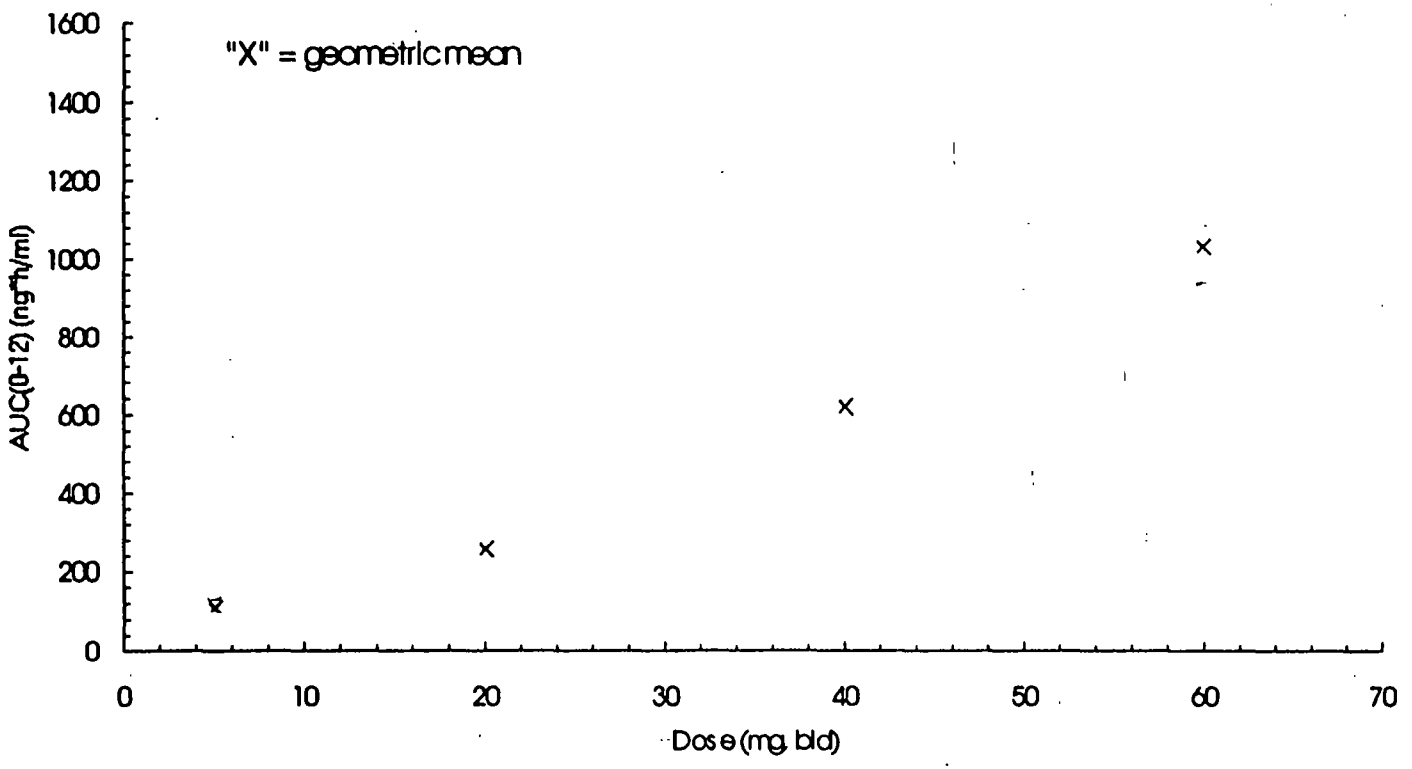
		AUC(0-12) (ng•h/ml) Day 1	AUC(0-12) (ng•h/ml) Day 18	R[a] Day 18	Cmax (ng/ml) Day 1	Cmax (ng/ml) Day 18	Tmax (h) Day 1	Tmax (h) Day 18	Kel (h^{-1}) Day 1	Kel (h^{-1}) Day 18	T1/2[b] (h) Day 1	T1/2[b] (h) Day 18
5 mg	MEAN[c]	73.7	109.8	1.49	12.2	14.8	5.0	5.2	0.220	0.175	3.2	4.0
	SD	18.7	46.7	0.39	4.1	6.7	1.1	1.3	0.048	0.054	--	--
	CV%	25	43	26	34	45	22	26	22	31	--	--
20 mg	MEAN[c]	175.7	259.2	1.48	26.6	44.6	4.8	3.8	0.143	0.145	4.8	4.8
	SD	134.0	213.3	0.67	18.9	48.1	1.3	2.2	0.049	0.027	--	--
	CV%	76	82	46	71	108	27	58	34	19	--	--
40 mg[d]	MEAN[c]	314.6	658.0	--	60.0	118.6	3.8	3.7	0.172	0.079	4.0	8.8
	SD	166.8	334.6	--	33.8	80.1	1.8	0.8	0.034	0.040	--	--
	CV%	53	51	--	56	68	48	22	20	51	--	--
60 mg[e]	MEAN[c]	215.0	1027.9	--	34.3	139.4	4.0	4.7	0.161	0.069	4.3	10.0
	SD	77.1	446.8	--	13.1	81.2	1.7	1.5	0.040	0.049	--	--
	CV%	36	43	--	38	58	42	32	25	72	--	--

[a] = Accumulation ratio; calculated as $AUC(0\text{-}12)_{Day\ 18}/AUC(0\text{-}12)_{Day\ 1}$.
[b] = Calculated as 0.693/mean Kel.
[c] = Geometric mean and standard deviation for AUC(0-12), AUC(0-∞), Cmax, and R; arithmetic mean and standard deviation for all other parameters except T1/2.
[d] = Dosing and titration schedule: subjects received 20 mg bid for the first three days of multiple dosing and 40 mg bid for the remaining 11 days.
[e] = Dosing and titration schedule: subjects received 20 mg bid for the first 3 days of multiple dosing, 40 mg bid for the next 3 days then 60 mg bid for the remaining 8 days.

Source Data: Appendix IV, Tables 1 - 4

Attachment 7

Figure 1.16 Steady-State AUC(0-12) Values Versus Dose Following Twice Daily Administration of 5, 20, 40[a], and 60[b] mg Ziprasidone HCl to Healthy Male Volunteers for 14 Days
Ziprasidone Protocol 013

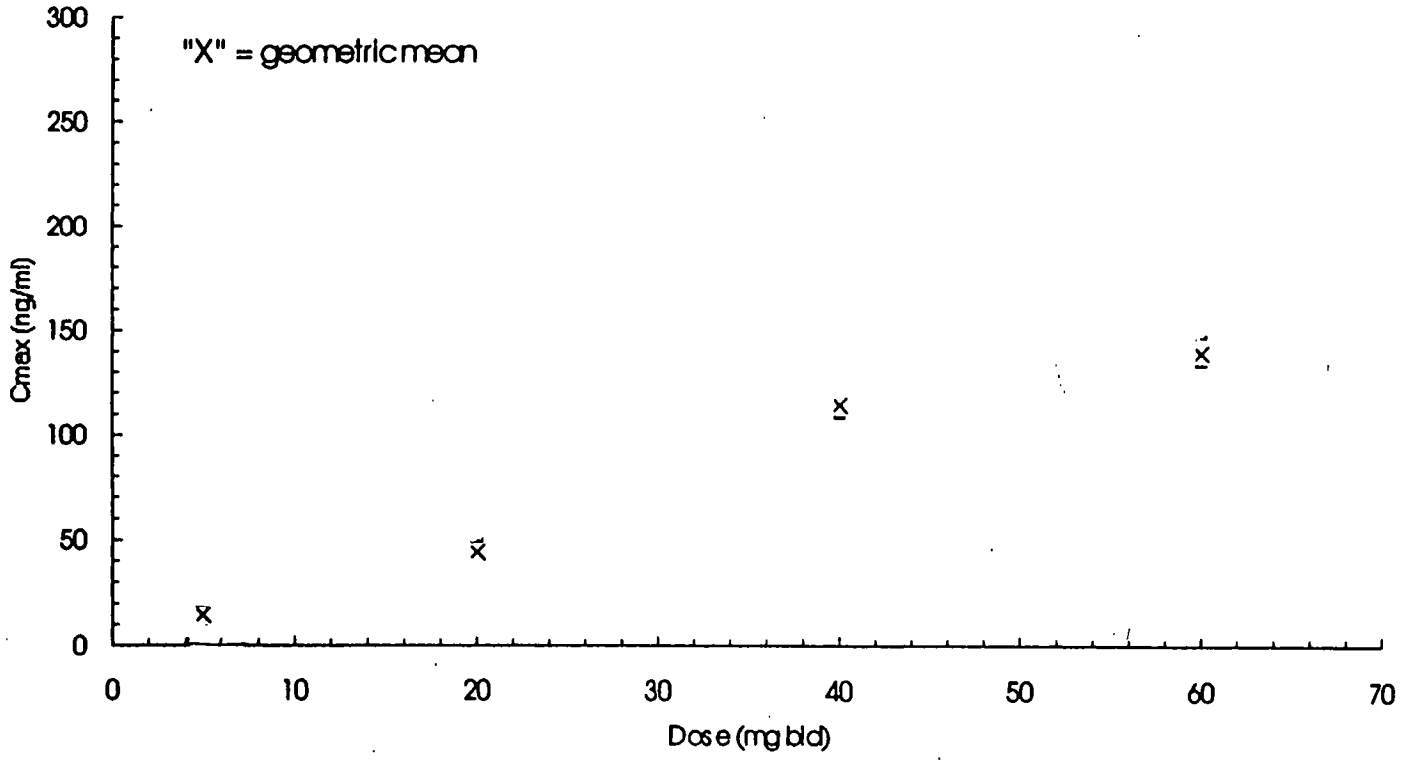


a = Dosing and titration schedule: subjects received 20 mg bid for the first three days of multiple dosing and 40 mg bid for the remaining 11.5 days.
b = Dosing and Titration schedule: subjects received 20 mg bid for the first 3 days of multiple dosing, 40 mg bid for the next 3 days then 60 mg bid for the remaining 8.5 days.

Source Data: Appendix IV, Tables 1 - 4

Attachment 8

Figure 1.17 Steady-State Cmax Values Versus Dose Following Twice Daily Administration of 5, 20, 40[a], and 60[b] mg Ziprasidone HCl to Healthy Male Volunteers for 14 Days
Ziprasidone Protocol 013

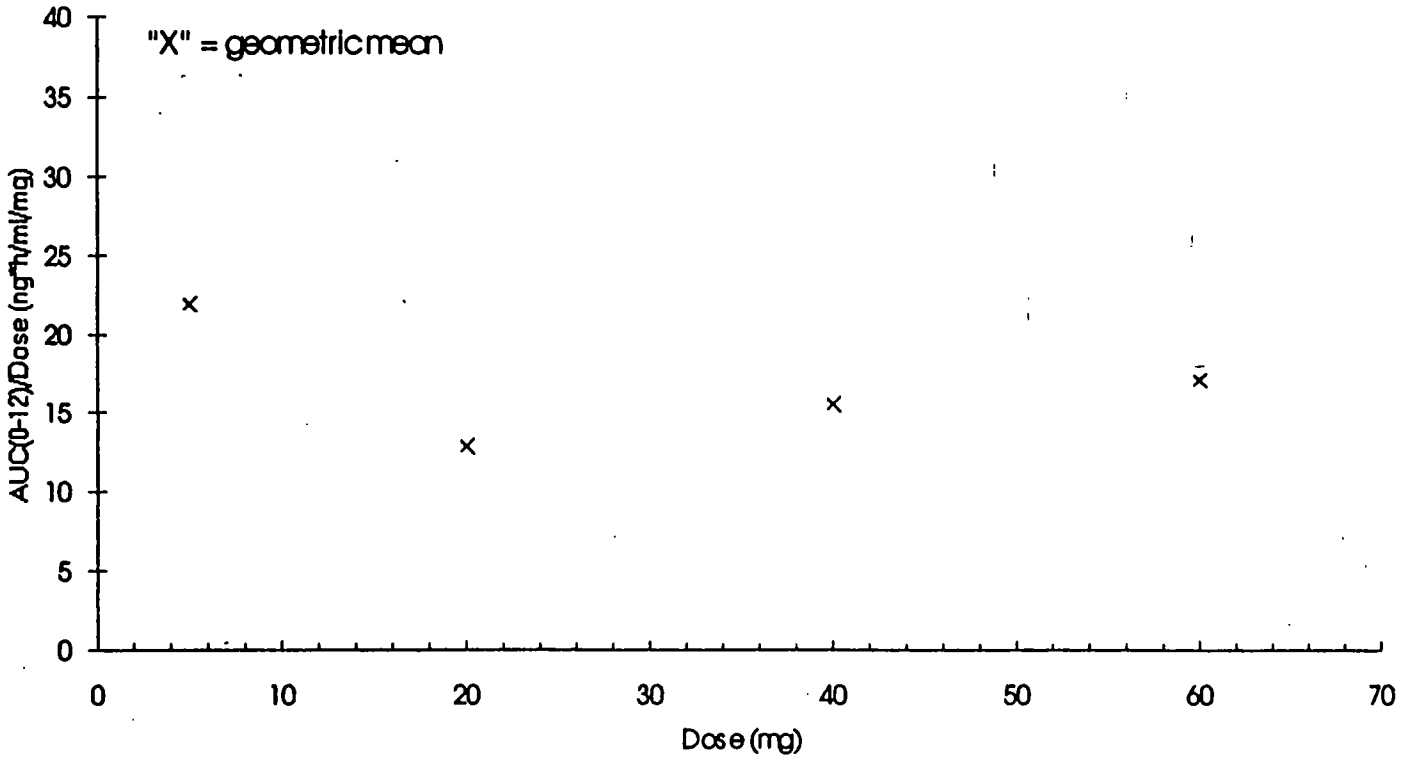


[a] = Dosing and titration schedule: subjects received 20 mg bid for the first three days of multiple dosing and 40 mg bid for the remaining 11.5 days.
[b] = Dosing and titration schedule: subjects received 20 mg bid for the first 3 days of multiple dosing, 40 mg bid for the next 3 days then 60 mg bid for the remaining 8.5 days.

Source Data: Appendix IV, Tables 1 - 4

Attachment 9

Figure 1.18 Steady-State Dose Normalized AUC(0-12) Values Versus Dose Following Twice Daily Administration of 5, 20, 40[a], and 60[b] mg Ziprasidone HCl to Healthy Male Volunteers for 14 Days
Ziprasidone Protocol 013



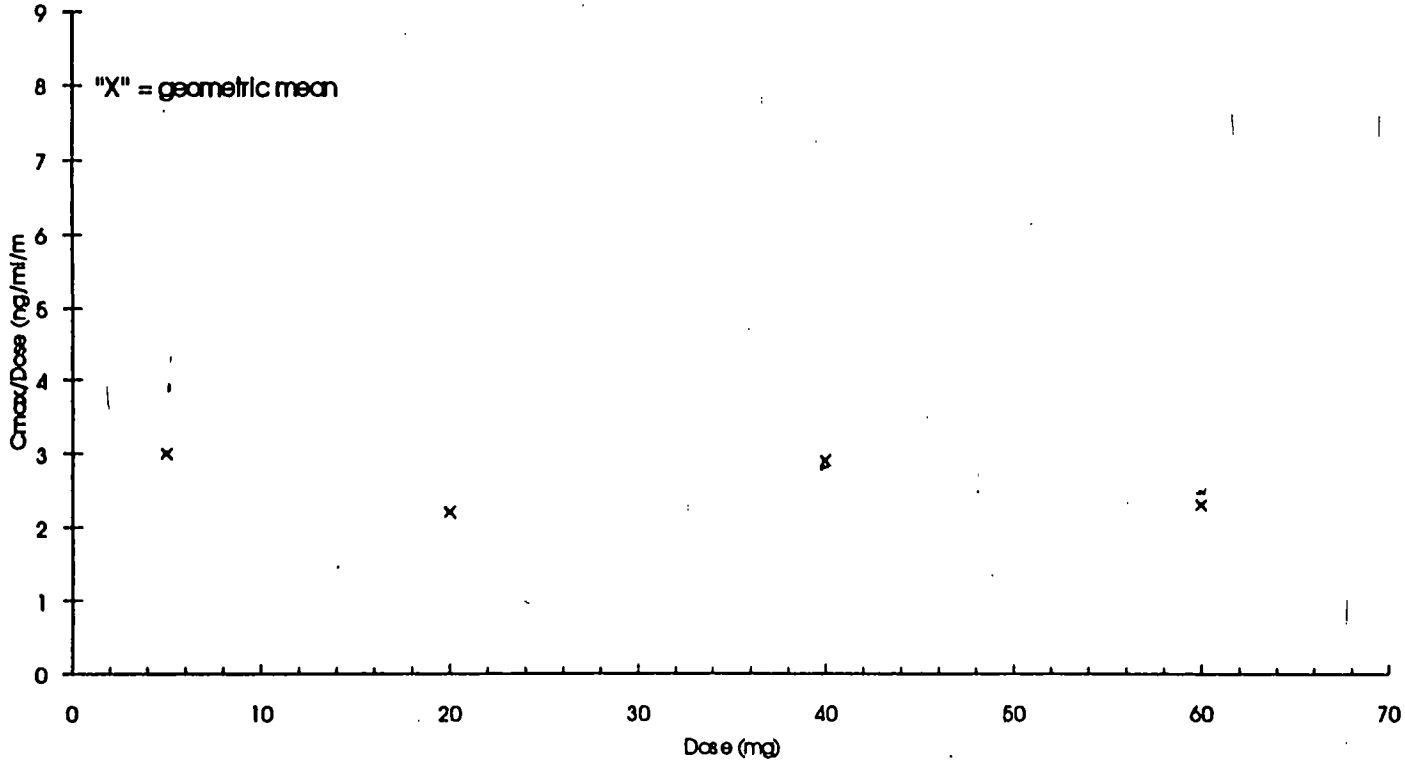
[a] = Dosing and titration schedule: subjects received 20 mg bid for the first three days of multiple dosing and 40 mg bid for the remaining 11.5 days.
[b] = Dosing and titration schedule: subjects received 20 mg bid for the first 3 days of multiple dosing, 40 mg bid for the next 3 days then 60 mg bid for the remaining 8.5 days.

Source Data: Appendix IV, Tables 1 - 4

Attachment 6

10

Figure 1.19 Steady-State Dose Normalized Cmax Values Versus Dose Following Twice Daily Administration of 5, 20, 40[a], and 60[b] mg Ziprasidone HCl to Healthy Male Volunteers for 14 Days
Ziprasidone Protocol 013



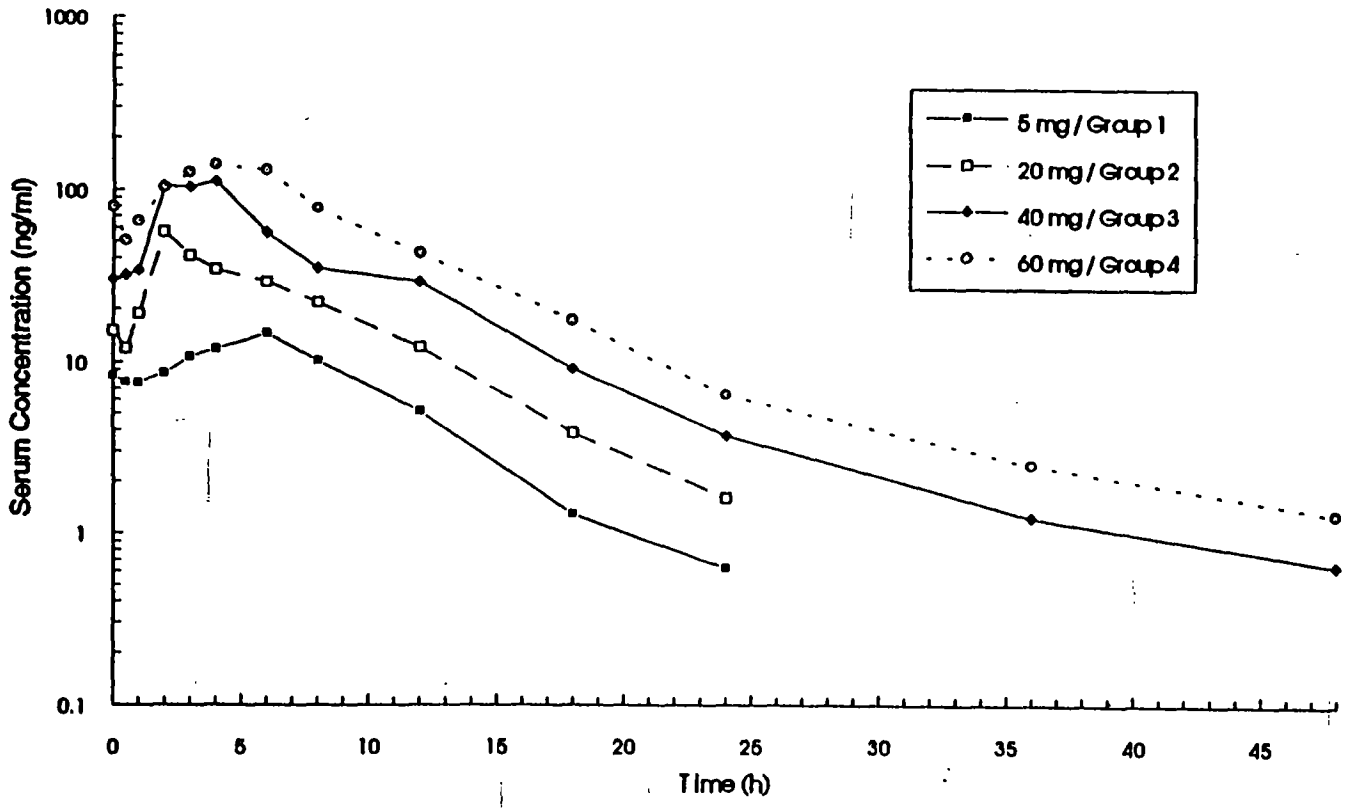
a = Dosing and titration schedule: subjects received 20 mg bid for the first three days of multiple dosing and 40 mg bid for the remaining 11.5 days.
b = Dosing and titration schedule: subjects received 20 mg bid for the first 3 days of multiple dosing, 40 mg bid for the next 3 days then 60 mg bid for the remaining 8.5 days.

Source Data: Appendix IV, Tables 1 - 4

Attachment #1

11

Figure 1.2 Mean Steady State Serum Ziprasidone Concentrations Following Administration of 5, 20, 40[a], and 60[b] mg Ziprasidone HCl BID to Healthy Male Volunteers for 14 Days - Day 18
Ziprasidone Protocol 013



[a] = Dosing and titration schedule: subjects received 20 mg bid for the first three days of multiple dosing and 40 mg bid for the remaining 11.5 days.
[b] = Dosing and titration schedule: subjects received 20 mg bid for the first 3 days of multiple dosing, 40 mg bid for the next 3 days then 60 mg bid for the remaining 8.5 days.
Source Data: Appendix IV, Tables 1 -4

Study 044 (Single Doses of 5, 10, and 20 mg in Children and Adolescents With Tourett's Syndrome-Interim Report)

Study Design and Summary:

(see attachments 1-3)

Results:

(See attachments 4-8)

Reviewer's Comments:

The data clearly shows that both the AUC and Cmax were slightly increased as the dose increased from 5 to 20 mg in all subjects (attachments 4-6). The reasons for the lack of dose proportionality are not clear. However, it is interesting to note that when the doses were normalized for body weight, the relationship with AUCs and Cmaxs becomes more linear, but scattered (attachments 7 and 8). It should be noted that the drug was administered as a suspension of 40 mg/ml in this study.

Conclusions:

It is not clear as to why there is no dose proportionality in this patients population.

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Study 010: (Absolute BA):

Study Design and Summary:

(see attachments 1-3)

Results:

(See attachments 4-5)

Reviewer's Comments:

1. The sponsor did not give a rationale as to why the drug was not administered after the same oral and IV dose. The drug has previously been given IV up to 40 mg as 30 minute infusion (study # 032) which was relatively tolerable up to 20 mg. In the current study the drug was administered as 20 mg PO and 5 mg IV infusion over 60 minutes.

2. It is not clear as to why the mean half life was calculated using the mean elimination rate constant (i.e. 0.693/mean Kel) rather than from individual half-lives (attachment 4). In general, the half life tends to be slightly shorter after IV (~3 h) than oral administration (~4 h).

3. Although, the blood was collected up to 36 hours after PO and IV dosing, the drug appears to be detected up to 16 hours after the IV and up to 24 hours after the oral administration (attachment 5). There were no comments from the sponsor.

4. Based on this data, the mean absolute bioavailability of the drug is approximately 60% ranging from 38 to 74% (attachment 4).

Conclusions:

1. The absolute bioavailability of the drug is approximately 60%.

2. The bioavailability would have been more accurate if determined after the same oral and IV dose.

PROTOCOL 128-010: PHASE I STUDY TO DETERMINE THE ABSOLUTE BIOAVAILABILITY OF CP-88,059-1 IN NORMAL, HEALTHY MALE VOLUNTEERS

Principal Investigator: T. Hunt, M.D., Ph.D.

Study Publication: None

Study Dates: 5 January 1993 - 24 January 1993

Study Objectives: 1) Determine the absolute bioavailability of ziprasidone HCl (CP-88,059-1). 2) Evaluate the relationship between changes in serum prolactin concentrations and serum ziprasidone concentrations.

Study Design: This was an open, randomized, two-way crossover study of the pharmacokinetics of ziprasidone in 12 healthy male volunteers. Ziprasidone was administered intravenously (5 mg over 1 hour) and orally (20 mg capsule). Each subject received a single dose of ziprasidone on each of two study days with at least 7 days between doses. All doses were administered under nonfasting conditions.

Evaluation Groups:

Entered Study	12
Completed Study	12
Evaluated for Pharmacokinetics	12
Evaluated for Pharmacodynamics	12
Assessed for Safety	12
Adverse Events	12
Laboratory Tests	12

Subjects: Healthy male volunteers ranging in age from 19 to 43 years

Drug Administration:

Dosage Form	0.05 mg/ml intravenous solution (FID# G00070AA) 20 mg capsule (FID# CS-90-031)
Dosing	Single doses of 5 mg (i.v) or 20 mg (oral) were administered on days 1 and 8 under nonfasting conditions. Capsules were administered with 50 ml of water. The intravenous solution was infused over a 60 minute period.

Pharmacokinetic and Safety Evaluations: Blood samples were collected immediately prior to each drug administration (time zero) and up to 36 hours after the start of infusion or oral dosing for the determination of serum ziprasidone concentrations. Serum concentrations were used to estimate terminal phase rate constant (K_{el}), area under the curve from time zero to infinity ($AUC_{0-\infty}$), maximum observed concentration (C_{max}), first occurrence of C_{max} (T_{max}), oral bioavailability (F),

steady-state volume of distribution (V_{dss}), and systemic clearance (CL). Serum prolactin concentrations were determined in samples collected at the same time as the pharmacokinetic samples up to 24 hours after drug administration. Sedation was evaluated using subject self-evaluations.

Analytical Methods:

Statistical Methods: Pharmacokinetic, pharmacodynamic, and safety results were summarized using descriptive statistics and graphs. Concentration - response plots were used to examine the relationships of serum prolactin concentrations and sedation scores to serum ziprasidone concentrations.

Pharmacokinetic Results:

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

	Ziprasidone			
Parameter	5 mg intravenous infusion		20 mg oral capsules	
$AUC_{0-\infty}$ (ng•hr/ml)[a]	99.8	± 20	232.2	± 16
C_{max} (ng/ml)[a]	34.6	± 24	28.2	± 26
T_{max} (hours)	1.01	± 5.0	5.1	± 26
K_{el} (hr^{-1})	0.250	± 17	0.177	± 16
$T_{1/2}$ (hours)[b]	2.8	--	3.9	--
F (%)	--	--	58	± 16
V_{dss} (L/kg)	2.3	± 23	--	--
CL (ml/min/kg)	11.7	± 10	--	--

[a] Geometric mean

[b] Mean $T_{1/2}$ = 0.693/mean K_{el}

Pharmacodynamic Results:

Serum Prolactin Concentrations (ng/ml) (Mean ± Standard Deviation)(n=12)

	Ziprasidone			
	5 mg intravenous infusion		20 mg oral capsules	
Baseline	13.24[a]	± 3.97	14.98	± 10.35
Maximum	63.75	± 22.89	37.84	± 16.99
Hours post dose	0.75		5	

[a] n = 11

Safety Results:

	Ziprasidone	
	5 mg intravenous infusion	20 mg oral capsules
Adverse Events	9/12 (0)	7/12 (0)
Abnormal Laboratory Tests	0/12 (0)	0/12 (0)

() subjects discontinued

Summary and Conclusions: Mean absolute bioavailability of ziprasidone administered as a 20 mg capsule with food was 58%. Mean V_{dss} was 2.3 L/kg and mean systemic CL was 11.7 ml/min/kg. Serum ziprasidone concentrations approximately 12 ng/ml and higher were associated with increased serum prolactin concentrations.

The most frequently reported adverse event was postural hypotension. Five of 12 subjects had postural hypotension following the 20 mg capsule, and 7 of 12 after the intravenous infusion. All cases of postural hypotension were mild except for one subject following the 20 mg capsule who had moderate postural hypotension. Other reported adverse events included headache, asthenia, nausea, and dizziness. There were no serious adverse events reported for this study.

Ziprasidone was also associated with sedation, although the increase in sedation scores lagged behind the increase in serum ziprasidone concentrations by about 1/2 hour following the intravenously infused ziprasidone, and by approximately 2 hours following the 20 mg ziprasidone capsule.

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Table 5.1 Individual and Mean Ziprasidone Pharmacokinetic Parameters Following Single Dose Administration of Ziprasidone HCl Orally (20 mg Capsule) and as a 5 mg Intravenous Infusion Delivered Over 1-Hour, to Healthy Male Volunteers in the Fed State.
Ziprasidone Protocol 010

20 mg Capsule - Oral Route

Patient	Sequence[a]	Body Weight (kg)	AUC(0-∞) (ng•h/ml)	Cmax (ng/ml)	Tmax (h)	Kel (h^{-1})	T1/2 (h)	F (%)
599-0001	B→A	79.6						
599-0002	A→B	76.9						
599-0003	A→B	76.9						
599-0004	B→A	87.8						
599-0005	A→B	79.2						
599-0006	B→A	65.6						
599-0007	A→B	64.7						
599-0008	B→A	70.1						
599-0009	A→B	62.9						
599-0010	B→A	76.0						
599-0011	A→B	64.3						
599-0012	B→A	71.9						
MEAN[b]		73.0	232.2	28.2	5.1	0.177	3.9[c]	58
SD		7.4	37.0	7.3	1.3	0.028	--	0.09
CV%		10	16	26	26	16	--	16

5 mg Infusion Over 1 Hour - Intravenous Route

Patient	Sequence[a]	AUC(0-∞) (ng•h/ml)	Cmax (ng/ml)	Tmax (h)	Kel (h^{-1})	T1/2 (h)	CL (ml/min/kg)	Vdss (L/kg)
599-0001	B→A							
599-0002	A→B							
599-0003	A→B							
599-0004	B→A							
599-0005	A→B							
599-0006	B→A							
599-0007	A→B							
599-0008	B→A							
599-0009	A→B							
599-0010	B→A							
599-0011	A→B							
599-0012	B→A							
MEAN[b]		99.8	34.6	1.01	0.250	2.8[c]	11.7	2.3
SD		19.7	8.1	0.05	0.042	--	1.9	0.5
CV%		20	24	5	17	--	10	23

[a] = Treatment sequence: Oral route, A; Intravenous route, B.

[b] = Geometric mean and standard deviation for AUC(0-∞), Cmax, and F; arithmetic mean and standard deviation for all other parameters except T1/2.

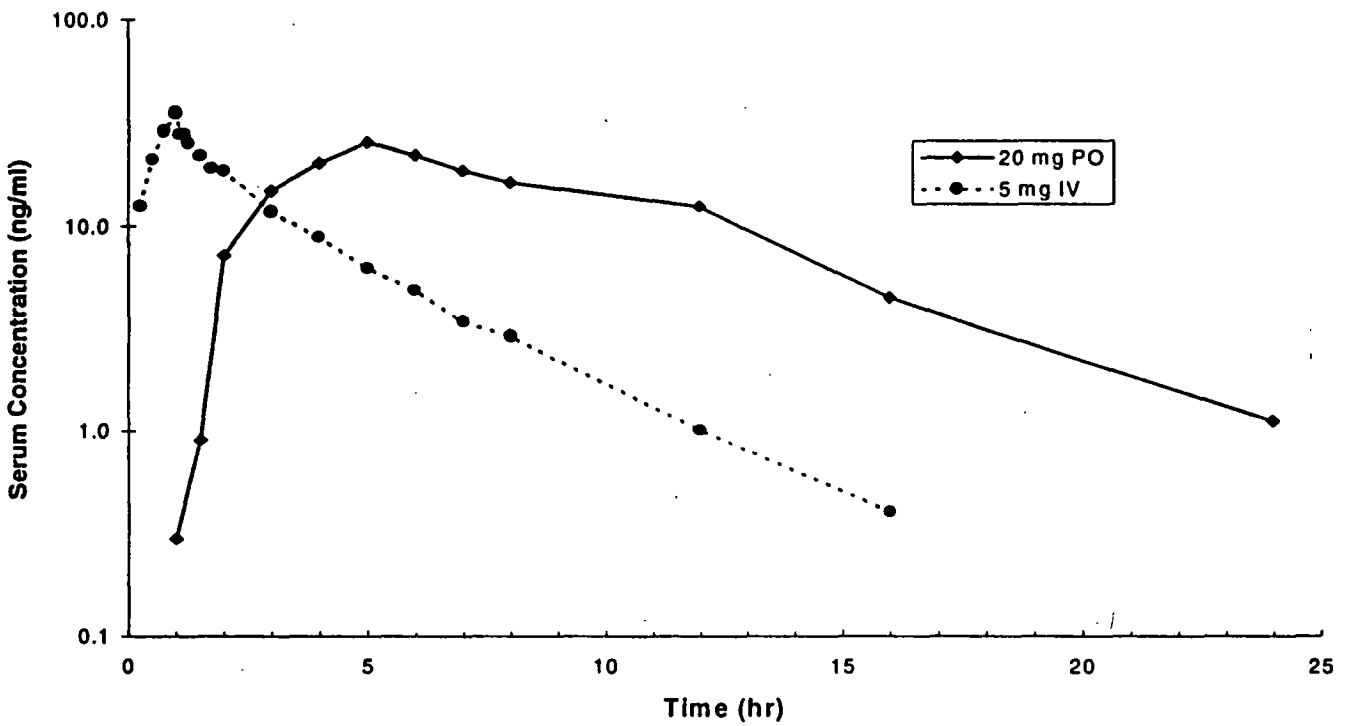
[c] = Calculated as 0.693/mean Kel.

Source Data: Appendix IV, Tables 1 and 2

(5)

(5)

Figure 1.1 Mean Serum Ziprasidone Concentrations VS Time Following Oral Administration of a 20 mg Ziprasidone HCl Capsule and Following Intravenous Administration of 5 mg Ziprasidone HCl Over 1 Hour To Healthy Male Volunteers
Ziprasidone Protocol 010



Source Data: Appendix IV, Tables 1 and 2

Study 016: (Intubation- Capsule, IV, Solution or Suspension into the Duodenum and Ileal/Cecal Junction at 20 mg Single Dose)

Study Design and Summary:

(see attachments 1 and 3)

Results:

(See attachments 4-8)

Reviewer's Comments:

1. This was a part of the formulation development study to compare the bioavailability (BA) of the drug from different absorption sites throughout the GI tract.

2. The drug was administered after overnight fasting in all arms of the study except after the capsules. Therefore, the comparison with the capsules may not be valid since the food increases the BA of the drug.

3. Overall, when the drug was administered as suspension, the BA was lowest compared to other treatments (attachments 4 -6). However, there were only two subjects who received the suspension treatments in which one is consistently a high absorber and the other is consistently a low absorber (attachments 7 and 8).

4. The BA for the capsule was comparable to that of solution instilled into the duodenum (43% vs 45%). Again, the BA of the drug after the capsule could have been increased as a result of the food effect.

Conclusions:

1. This is an interesting study which suggests that the absorption of the drug is highest from the duodenum site compared to the distal region of the GI tract. The reason for this could be related to either the availability of surface area for absorption and/or the absorption mechanism at these regions.

2. The order of ziprasidone absorption is as follows: solution (duodenum), capsule (fed), solution (ileal/cecal), suspension (duodenum) and suspension (ileal/cecal).

PROTOCOL 128-016: PHASE I PILOT STUDY TO COMPARE THE PHARMACOKINETICS OF A SINGLE DOSE OF CP-88,059 ADMINISTERED ORALLY, INTRAVENOUSLY OR BY INTUBATION TO THE DUODENUM AND ILEAL/CECAL JUNCTION IN NORMAL, HEALTHY MALE VOLUNTEERS

Principal Investigator: J. Scavone, Pharm.D.

Study Publication: None

Study Dates: 19 June 1993 - 20 January 1994

Study Objective: The objective of this pilot study was to assess the pharmacokinetics of ziprasidone (CP-88,059) when given to normal, healthy volunteers: orally, infused into the duodenum or at the ileal/cecal junction, and infused intravenously.

Study Design: This was an open, randomized, six-way crossover pilot study comparing the pharmacokinetics of 20 mg ziprasidone administered as an oral capsule (fed conditions), by intravenous infusion (fasting conditions), and by infusion into the duodenum and ileal/cecal junction as a solution or as a suspension (fasting conditions). Subjects received formulations as single doses separated by at least 7 days. The two nasoenteric infusion treatment legs were added by amendment (016E) to the protocol (016). Only two subjects participated in those treatment legs.

Evaluation Groups:

Number of Subjects	Capsule -Oral	Solution-IV Infusion	Solution-Nasoenteric Infusion (duodenum)	Solution-Nasoenteric Infusion (ileal/cecal junction)	Suspension-Nasoenteric Infusion (duodenum)	Suspension-Nasoenteric Infusion (ileal/cecal junction)
Randomized	6	7	6	5	2	2
Completed	5	5	6	5	2	2
Discontinued*	1	2	0	0	0	0
Analyzed for Pharmacokinetics	6	7	6	5	2	2
Analyzed for Safety						
Adverse Events	6	7	6	5	2	2
Laboratory Data**	0	1	0	0	1	0

*Discontinuations appear in last completed treatment leg; all discontinuations occurred during washout prior to next treatment leg

**Laboratory tests were performed at screening only, unless follow-up was required

Subjects: Normal, healthy male volunteers ranging in age from 19-40 years.

Drug Administration:

Dosage Form
ziprasidone HCl 20 mg capsule (FID# CS-90-031)
ziprasidone HCl 40 mg powder (FID# G00396AA)
vehicle (powder) for suspension (FID# G00397AA)
ziprasidone HCl 0.05 mg/ml solution (FID# G00070AA)

Dosing

Subjects were administered single 20 mg doses as an oral capsule (fed), as a solution and by intravenous infusion (fasted), as a solution by nasoenteric infusion to the duodenum and ileal/cecal junction (fasted), and as a suspension by nasoenteric infusion to the duodenum and ileal/cecal junction (fasted). Ziprasidone HCl powder was used to prepare the suspension. Each dose was to be separated by at least 7 days

Pharmacokinetic and Safety Evaluations: Serum concentrations were used to estimate the area under the serum concentration curve ($AUC_{0-\infty}$), maximum observed concentration (C_{max}), time to C_{max} (T_{max}), terminal phase rate constant (K_{el}), elimination half-life ($T_{1/2}$), bioavailability, volume of distribution at steady-state (Vdss), and systemic clearance (CL). Subjects were monitored for adverse events.

Analytical Methods:

Statistical Methods: Geometric mean and standard deviation were calculated for $AUC_{0-\infty}$, C_{max}, and bioavailability. Arithmetic mean and standard deviation were calculated for all other parameters except $T_{1/2}$.

Pharmacokinetic Results:

	Treatment Legs (Subjects Evaluated)					
Pharmacokinetic Parameters	Oral Capsule (6)	Intravenous Infusion (7)	Duodenum-Solution (6)	Duodenum-Suspension (2)[c]	Ileal/Cecal - Solution (5)	Ileal/Cecal - Suspension (2)[c]
Bioavailability(%)[a]	43 (41)	-	45 (40)	19	30 (60)	8
$AUC_{0-\infty}$ (ng•h/ml)[a]	356.6 (51)	816.2 (16)	373.8 (48)	127.2	240.1 (68)	51.4
C_{max} (ng/ml)[a]	39.6 (42)	297.0 (19)	124.9 (60)	18.3	60.2 (65)	7.1
T_{max} (h)[a]	5.0 (33)	0.93 (13)	0.67 (39)	5.0	0.85 (16)	1.3
K_{el} (h^{-1})[a]	0.209 (37)	0.192 (26)	0.216 (25)	0.254	0.209 (41)	-
$T_{1/2}$ (h)[b]	3.3	3.6	3.2	2.7	3.3	-
CL (ml/min/kg)[a]	-	5.74 (21)	-	-	-	-
Vdss (L/kg)[a]	-	1.08 (28)	-	-	-	-

[a]Geometric Mean (CV%) for Bioavailability, $AUC_{0-\infty}$, C_{max}; Arithmetic Mean (CV%) for T_{max}, K_{el}, Cl, and Vdss

[b]Calculated as 0.693/mean K_{el}

[c]N of 2, Arithmetic Mean for all parameters

Safety Results:

	Number of Subjects (With/Evaluated (Discontinued)) Ziprasidone 20 mg					
	Oral Capsule	Intravenous Infusion	Duodenum-Solution	Duodenum-Suspension	Ileal/Cecal - Solution	Ileal/Cecal - Suspension
Findings						
Adverse Events (All Causality)	5/6(0)	7/7(0)	3/6(0)	1/2(0)	3/5(0)	1/2(0)
Adverse Events (Treatment-related, treatment-emergent)	5/6(0)	7/7(0)	3/6(0)	0/2(0)	2/5(0)	1/2(0)
Abnormal Laboratory Tests[a]	-	0/1(0)	-	0/1(0)	-	-

[a]Laboratory tests were performed at screening only, unless follow-up was required

Summary and Conclusions: When delivered as a solution, ziprasidone was rapidly absorbed at both the duodenum and ileal/cecal junction. Bioavailability of the duodenal solution (mean value 45%) was similar to that obtained with the oral capsule (mean value 43%). Bioavailability of the solution delivered to the ileal/cecal junction (mean value 30%) was lower perhaps due to capacity limited absorption at the distal region of the small intestine or simply less intestinal exposure. Mean systemic clearance (serum) of ziprasidone administered by intravenous infusion was 5.84 ml/min/kg and mean Vdss was 1.11 L/kg.

Based on data obtained from 2 subjects, the pharmacokinetics of ziprasidone delivered as a suspension differed markedly from the pharmacokinetics of ziprasidone administered as a solution. Systemic exposure was reduced as reflected in lower C_{max} and AUC_{0-} values and thus, marked reductions were also seen in bioavailability of ziprasidone administered as a suspension to the duodenum or to the ileal/cecal junction relative to any of the other formulations. These results coupled with the similarity of the bioavailability values obtained for the oral capsule delivered in the fed state and the duodenal solution highlight the importance of food as a solubilization enhancer for ziprasidone.

Although all subjects in the study experienced adverse events, the majority of events reported were mild or moderate treatment-related somnolence. There was one instance of mild treatment-related postural hypotension during intravenous infusion of ziprasidone. No subjects discontinued the study because of these events. Three subjects discontinued the study because of inability to tolerate the nasoenteric tube used in some of the treatment legs. No serious adverse events were reported during the study.

Table 5.1 Summary of Pharmacokinetic Parameters in Healthy Male Volunteers Following Administration of 20 mg Ziprasidone HCl in Solution and Suspension to the Duodenum and Ileal-Cecal Junction, in Solution Intravenously and Orally Using a Capsule
(Ziprasidone Protocol 016)

Treatment	(N)	Bioavailability (%)	AUC(0-∞) (ng•h/ml)	Cmax (ng/ml)	Tmax (h)	Kel (h^{-1})	T1/2[b] (h)	Cl (ml/min/kg)	Vdss (L/kg)
INTRAVENOUS									
MEAN[a]	7	--	816.2	297.0	0.93	0.192	3.6[b]	5.74	1.08
SD		--	133.6	55.4	0.12	0.050	--	1.21	0.30
CV%		--	16	19	13	26	--	21	28
CAPSULE									
MEAN[a]	6	43	356.6	39.6	5.0	0.209	3.3[b]	--	--
SD		18	180.5	16.5	1.7	0.077	--		
CV%		41	51	42	33	37	--		
DUODENUM (SOLUTION)									
MEAN[a]	6	45	373.8	124.9	0.67	0.216	3.2[b]		
SD		18	181.0	74.7	0.26	0.053	--		
CV%		40	48	60	39	25	--		
DUODENUM SUSPENSION[c]									
MEAN	2	19	127.2	18.3	5.0	0.254	2.7[b]	--	--
SD		--	--	--	--	--	--		
CV%		--	--	--	--	--	--		

[a] = Geometric mean and standard deviation for AUC(0-∞), Cmax, and F; arithmetic mean and standard deviation for all other parameters except T1/2.
[b] = Calculated as 0.693/mean Kel.
[c] = N of 2; arithmetic mean for all parameters.

Source Data: Appendix IV, Tables 1-6

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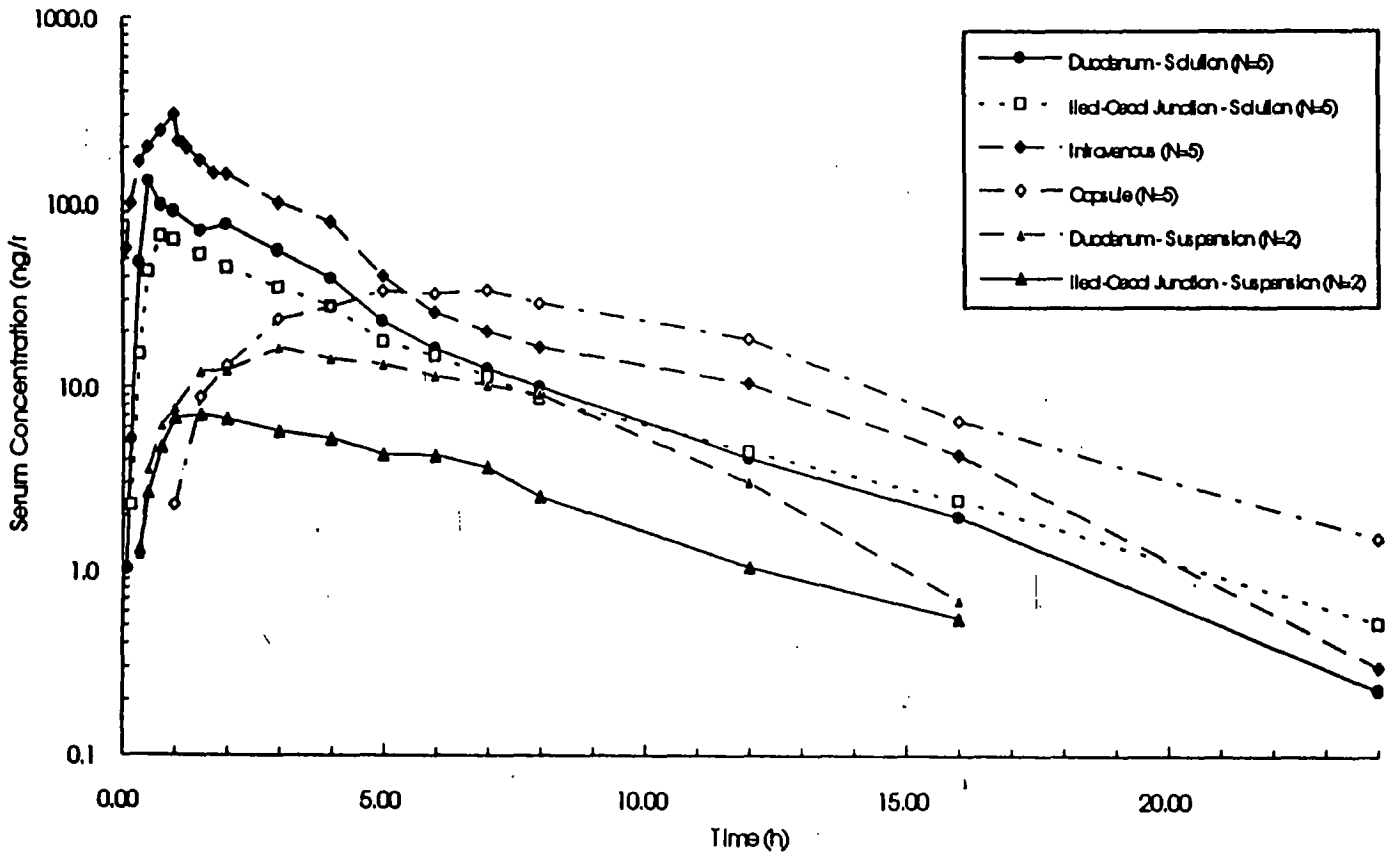
Table 5.1 Summary of Pharmacokinetic Parameters in Healthy Male Volunteers Following Administration of 20 mg Ziprasidone HCl in Solution and Suspension to the Duodenum and Ileal-Cecal Junction, in Solution Intravenously and Orally Using a Capsule
(Cont'd) (Ziprasidone Protocol 016)

Treatment	(N)	Bioavailability (%)	AUC(0-∞) (ng•h/ml)	Cmax (ng/ml)	Tmax (h)	Kel (h^{-1})	T1/2[b] (h)	Cl (ml/min/kg)	Vdss (L/kg)
ILEAL-CECAL (SOLUTION)									
MEAN[a]	5	30	240.1	60.2	0.85	0.209	3.3	--	--
SD		18	163.3	39.3	0.14	0.085	--		
CV%		60	68	65	16	41	--		
ILEAL-CECAL (SUSPENSION)[c]									
MEAN	2	8	51.4	7.1	1.3	--	--	--	--
SD		--	--	--					
CV%		--	--	--					

[a] = Geometric mean and standard deviation for AUC(0-∞), Cmax, and F; arithmetic mean and standard deviation for all other parameters except T1/2.
[b] = Calculated as 0.693/mean Kel.
[c] = N of 2; arithmetic mean for all parameters.

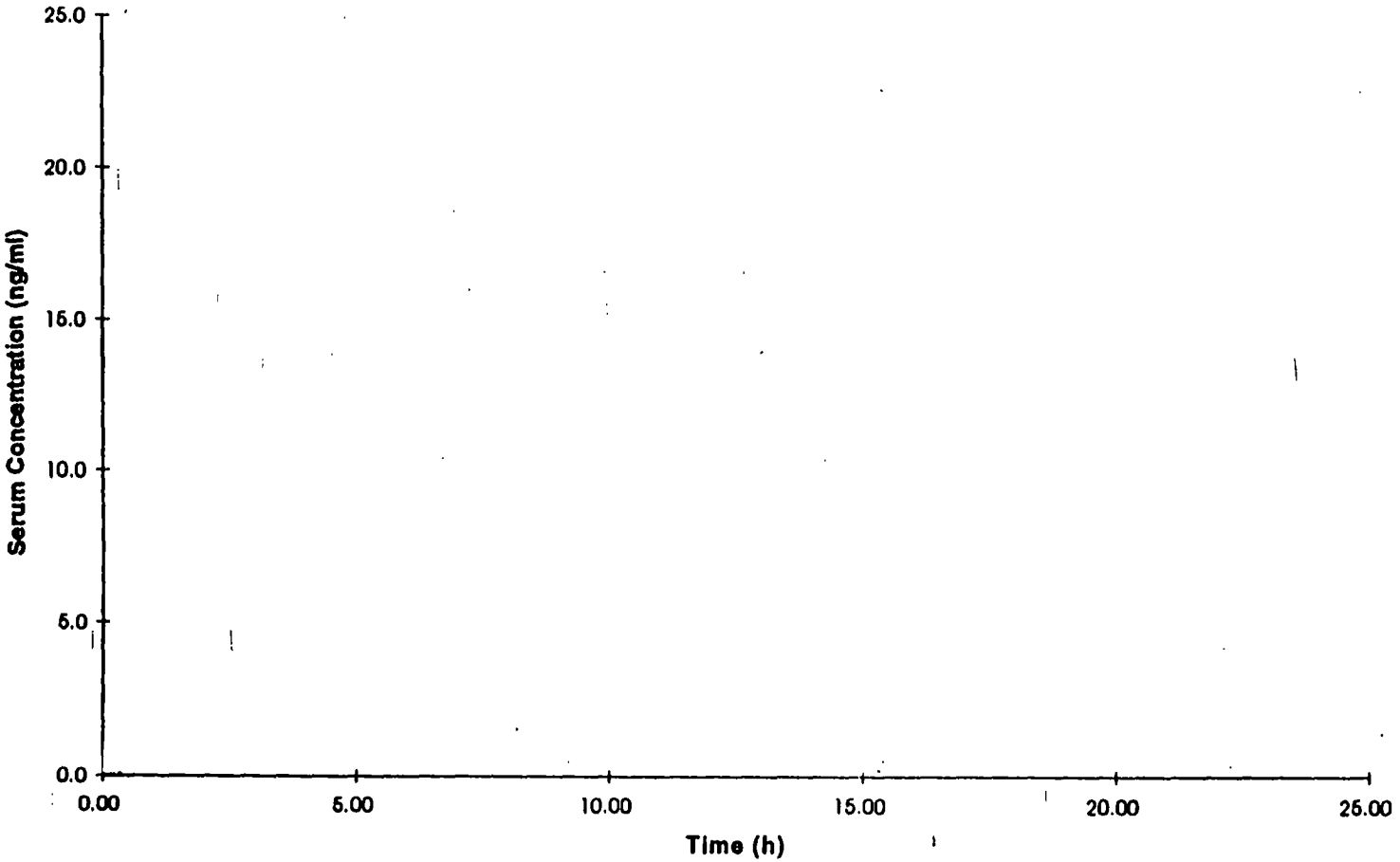
Source Data: Appendix IV, Tables 1-6

Figure 1. Mean Serum Concentrations Following Administration of 20 mg Ziprasidone HCl to Healthy Male Volunteers in Solution and Suspension via Nasoenteric Intubation to the Duodenum and Ileal-Cecal Junction, in Solution Intravenously and Orally Using a Capsule
(Ziprasidone Protocol 016)



Source Data: Appendix IV, Tables 1-6

Figure 5. Serum Ziprasidone Concentrations Following Nasoenteric Administration of 20 mg Ziprasidone HCl in Suspension to the Duodenum of Healthy Male Volunteers.
(Ziprasidone Protocol 016)



Source Data: Appendix IV, Table 4