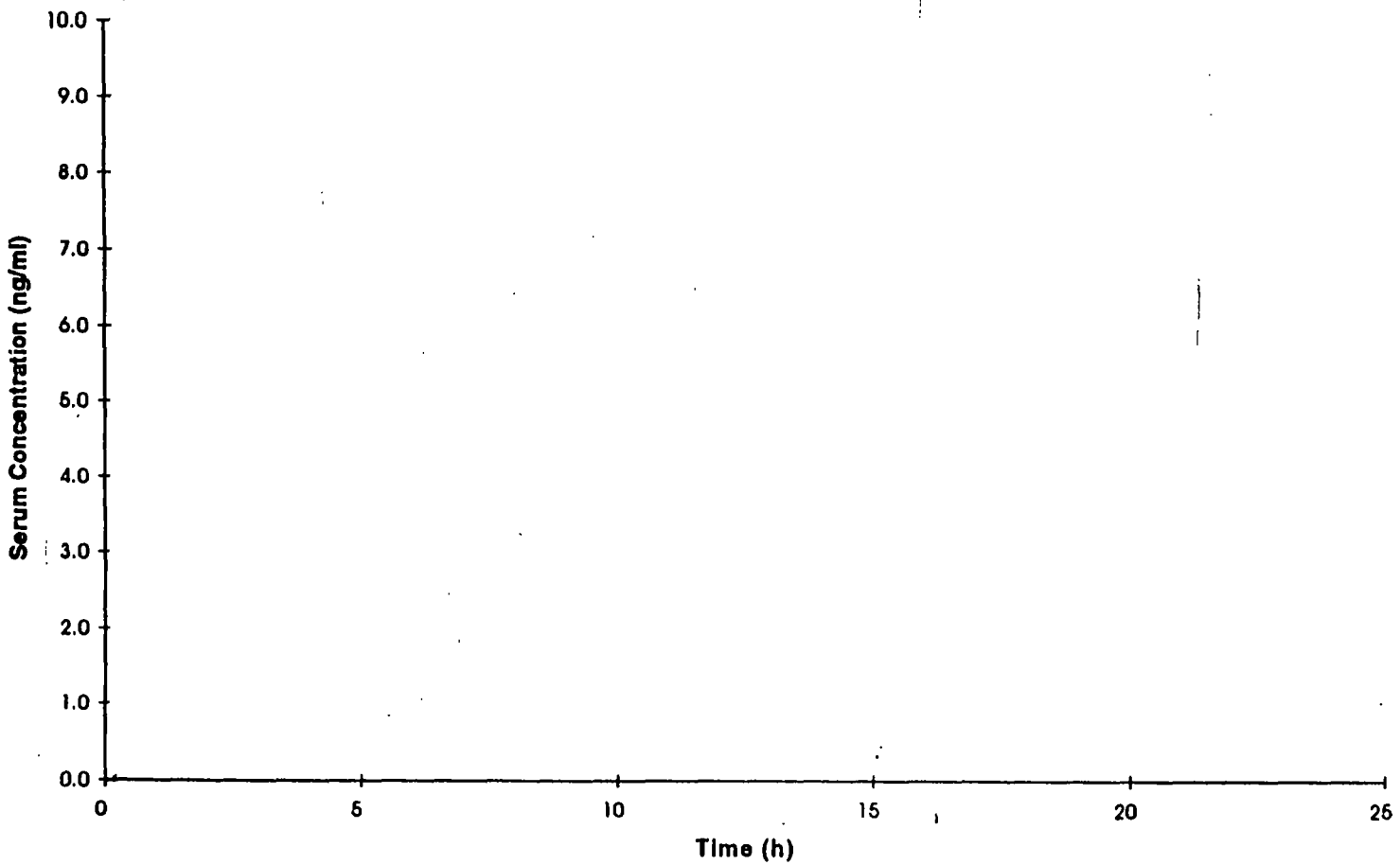
Figure 7. Serum Ziprasidone Concentrations Following Nasoenteric Administration of 20 mg Ziprasidone HCl in Suspension to the Ileal-Cecal Junction of Healthy Male Volunteers. (Ziprasidone Protocol 016)



Source Data: Appendix IV, Table 6

Study 006: (Effect of Food and Dose Proportionality at 20, 40, and 80 mg)

Study Design and Summary:

(see attachments 1 and 3)

Results:

(See attachments 3-9)

Reviewer's Comments:

1. It is not clear as to why the drug was administered with 250 mL of water in the fasting condition but with 50 mL after meals. In addition, in almost all the studies, the drug was administered with 50-60 mL of water.

2. The data clearly demonstrate that food increase both the Cmax and AUC of ziprasidone. However, the effect is much greater at the highest dose (80 mg) than at 20 and 40 mg doses (attachments 2 and 4). Overall, the AUC increased by about 1.5 to 2 fold with food at the three doses.

3. The AUC appears to increase proportionally with the increase in the dose. However, at the highest dose, the AUCs tend to increase less than proportional in all subjects (attachment 5). This observation has been consistent throughout this NDA.

4. There was a wide variation in the Cmaxs between subjects, particularly at the fasting state and there were no particular trends in terms of proportionality with the dose (attachment 6). However, with food, the Cmaxs appear to be less variable and clearly were proportional with dose.

5. It is interesting to note that there was a good correlation between the serum ziprasidone concentrations and the sedation (attachments 7 to 9). The sedation was only slightly increased as the dose increased from 20 to 80 mg, despite the increase in the ziprasidone serum levels. This suggests that sedation at one point is dependent neither on the dose nor on the serum concentration of ziprasidone which could be due to the development of tolerance. No apparent differences in the degrees of sedation were seen between fasting and fed conditions.

Conclusions:

1. Clearly food increases the absorption of ziprasidone by 1.5 to 2 folds.

2. There is a good correlation between the serum ziprasidone concentration and the sedation. This appears to be independent of the dose, possibly, due to the development of tolerance.

PROTOCOL 128-006: PHASE I STUDY TO ASSESS THE SAFETY, TOLERATION AND PHARMACOKINETICS OF CP-88,059-1 FOLLOWING ESCALATING SINGLE ORAL DOSES UNDER FASTING AND NON-FASTING CONDITIONS IN NORMAL HEALTHY MALE VOLUNTEERS

Principal Investigator: T. Hunt, M.D.

Study Publication: None

Study Dates: 9 September 1991 - 13 November 1991

Study Objective: To assess the safety and pharmacokinetics of single doses of 20, 40, and 80 mg of CP-88,059-1 (ziprasidone HCl) administered as capsules under fasting and fed conditions in ascending order, i.e., 20 mg fasting, 20 mg fed, 40 mg fasting, 40 mg fed, 80 mg fasting, 80 mg fed.

Study Design: This was an open, non-randomized, six-way crossover study of the pharmacokinetics of ziprasidone in eight healthy male subjects. Single doses of ziprasidone were administered in ascending order (20 mg → 40 mg → 80 mg); first under fasting conditions, then under fed (non-fasting) conditions at each dose level, i.e., 20 mg fasting → 20 mg fed → 40 mg fasting → 40 mg fed → 80 mg fasting → 80 mg fed. Subjects completing the study received all six doses, with at least 7 days separating each treatment day.

Evaluation Groups:

	Ziprasidone					
	20 mg Fasting	20 mg Fed	40 mg Fasting	40 mg Fed	80 mg Fasting	80 mg Fed
Entered Study	8	8	8	8	8	7
Completed Study	8	8	8	8	7	7
Evaluated for Pharmacokinetics	8	8	8	8	7	7
Assessed for Safety						
Adverse Events	8	8	8	8	8	7
Laboratory Tests	8	8	8	8	8	7
Sedation Self-Evaluations	8	8	8	8	8	7

Subjects: Healthy male volunteers ranging in age from 19 to 31 years.

Drug Administration:

Dosage Form — 20 mg CP-88,059-1 capsules (FID #CS-90-031)

Dosing — Subjects were administered single doses of ziprasidone (1 x 20 mg, 2 x 20 mg, and 4 x 20 mg) in an open fashion in the morning. Doses under fasting conditions were administered with 240 ml of water. Doses under fed conditions were administered immediately following a standard high-fat

breakfast with 50 ml of water. At least 7 days separated each treatment day.

Pharmacokinetic and Safety Evaluations: Blood samples for determination of serum ziprasidone concentrations were collected prior to and up to 72 hours after each dose of study drug. Serum concentrations were used to determine pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, half-life). Sedation was evaluated using subject self-evaluations.

Analytical Methods:

Statistical Methods: Pharmacokinetic and safety results were summarized using descriptive statistics and graphical presentations. Pharmacokinetic and sedation results were further analyzed by performing t-Tests and linear regression analyses.

Pharmacokinetic Results:

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

	Ziprasidone					
	Fasting			Fed		
Parameter	20 mg	40 mg	80 mg[a]	20 mg	40 mg	80 mg[a]
$AUC_{0-\infty}$ (ng•hr/ml)[b]	315.8 ±35	481.4 ±39	949.6 ±35	466.5 ±23	901.5 ±29	1911.2 ±29
C_{max} (ng/ml)[b]	45.6 ±36	53.6 ±52	83.5 ±38	49.5 ±15	87.2 ±29	164.8 ±20
T_{max} (hours)	4.1 ±33	4.4 ±34	6.0 ±54	5.6 ±50	6.4 ±57	6.6 ±42
K_{el} (hr^{-1})	0.148 ±44	0.102 ±28	0.111 ±49	0.182 ±20	0.171 ±21	0.186 ±13
Half-life (hours)[c]	4.7	6.8	6.2	3.8	4.1	3.7

[a]Mean data do not include subject 599-0002, who was discontinued from the study.
[b]geometric means; [c]calculated as 0.693/mean K_{el}

Safety Results:

	Number of Subjects [With/Evaluated (Discontinued)]					
	Ziprasidone					
Findings	20 mg Fasting	20 mg Fed	40 mg Fasting	40 mg Fed	80 mg Fasting	80 mg Fed
Adverse Events[a]	0/8 (0)	1/8 (0)	1/8 (0)	4/8 (0)	5/8 (1)	5/7 (0)
Clinically Significant Laboratory Test Abnormalities	0/8 (0)	0/8 (0)	0/8 (0)	0/8 (0)	0/8 (0)	0/7 (0)

[a]All adverse events were treatment-emergent, treatment-related

Summary and Conclusions: As assessed from changes in $AUC_{0-\infty}$, overall systemic exposure to ziprasidone was greater when single oral doses of 20, 40, and 80 mg were administered under fed versus fasting conditions. The effect of food on exposure increased with increasing dose. Mean $AUC_{0-\infty}$ values for the fed treatments were 48%, 87%, and 101% greater compared to the fasted treatments at the 20, 40, and 80 mg dose levels, respectively. C_{max} also demonstrated this trend at the 40 mg and 80 mg dose levels, with respective mean values for the fed treatments being 63% and 97% greater compared to the fasted treatments. These increases may be attributable to increased ziprasidone solubilization followed by increased absorption

secondary to food intake. Based on the linear regression analyses, mean $AUC_{0-\infty}$ and C_{max} values increased in a dose proportional manner under fed conditions, and in a less than proportional manner under fasting conditions. Terminal phase half-lives were consistently longer for doses given under fasting conditions. This may be attributable to dissolution rate-limited absorption under fasting conditions during the period of time over which K_{el} was estimated.

The frequency and severity of adverse events increased with increasing dose, and were generally more frequent under fed conditions at each dose level. All adverse events were of mild to moderate severity. One subject discontinued from the study after receiving ziprasidone 80 mg under fasting conditions due to treatment-related nausea and restlessness of moderate severity. The most frequently reported adverse event was somnolence, which increased with increasing dose and was greater under fed versus fasting conditions. Consistent with these results and the increases in systemic exposure, sedation increased with increasing dose, and was greater under fed versus fasting conditions. Other reported adverse events included dizziness, agitation, headache, diarrhea, nausea, vomiting, and vasodilatation. Several subjects experienced a decrease in blood pressure following single doses of ziprasidone. No serious adverse events were reported.

In summary, the administration of single doses of ziprasidone under fed conditions led to dose proportional increases in systemic exposure as compared to single doses under fasting conditions. Correspondingly, sedation increased with increasing systemic exposure to ziprasidone.

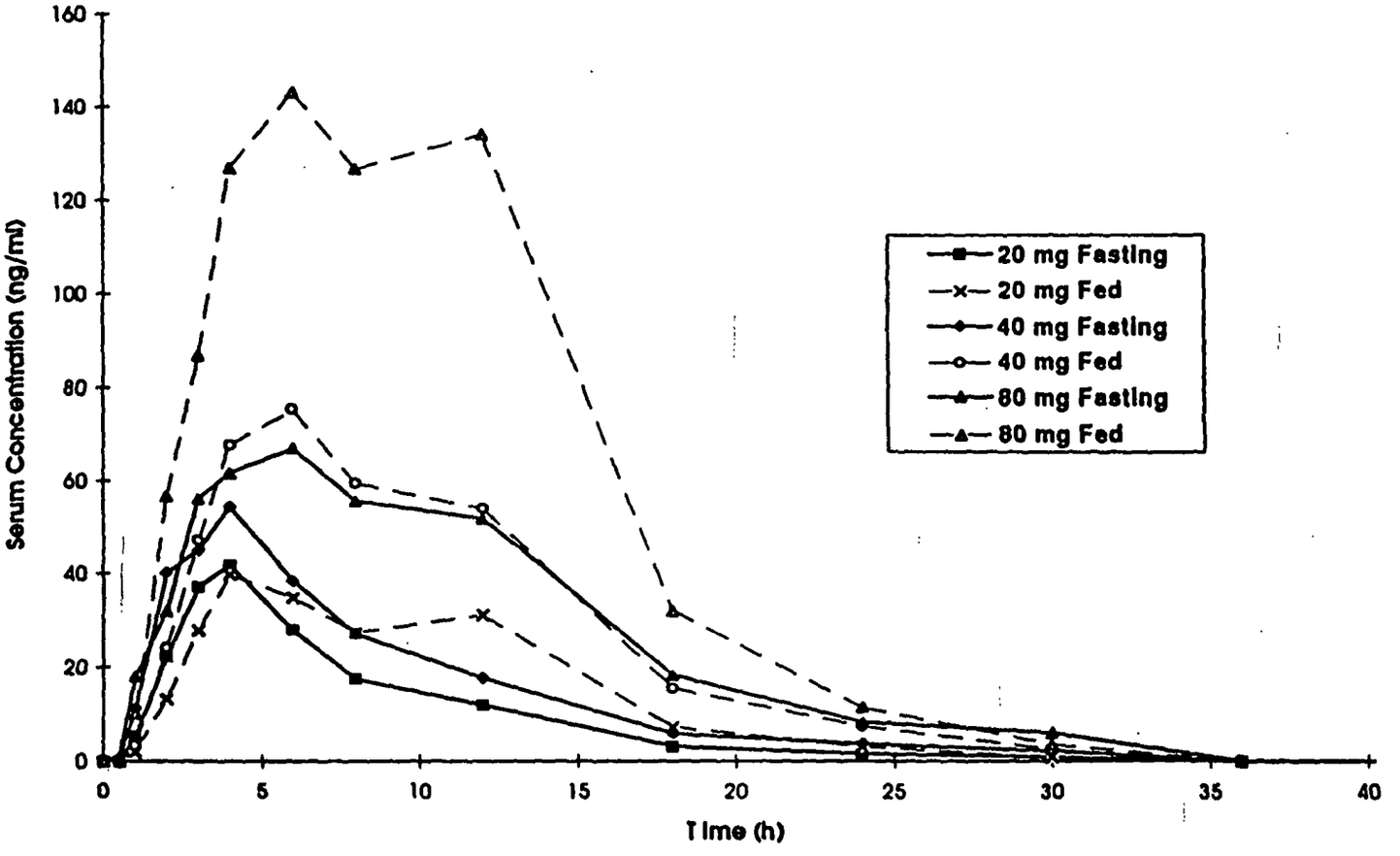


Figure 1.1 Plot of Mean Serum Ziprasidone Concentrations Versus Time Following Oral Administration of Ziprasidone HCl Capsules to Healthy Volunteers at Doses of 20, 40, and 80 mg, Under Fasting and Fed Conditions.
Ziprasidone Protocol 006
Source Data: Appendix IV, Tables 1, 2, and 3

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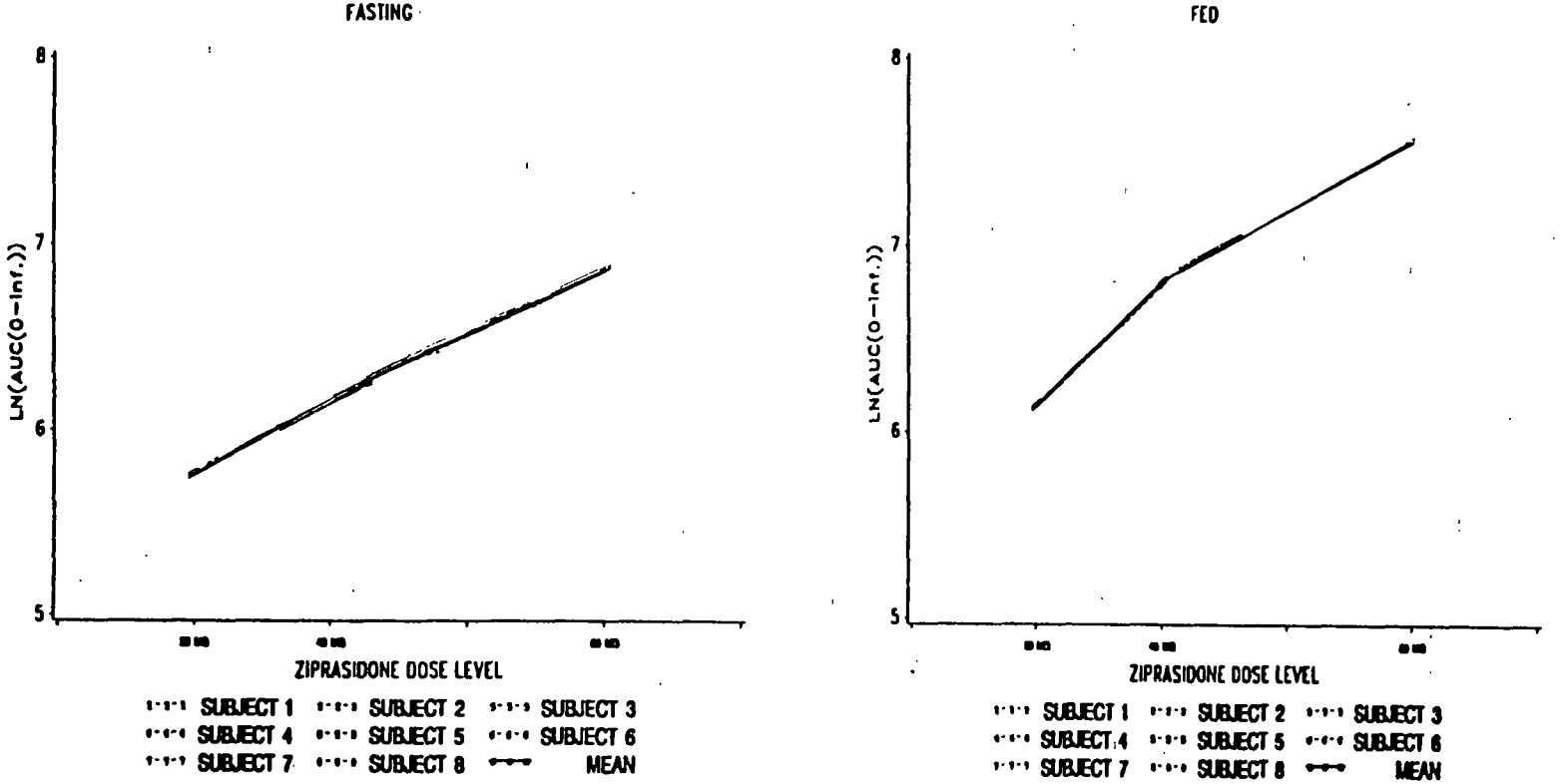
FIGURE 2
LN(AUC(0−inf.)) BY DOSE LEVEL
ZIPRASIDONE PROTOCOL 006



SOURCE DATA : APPENDIX IV TABLES 1, 2 and 3 DATE OF DATA EXTRACTION : 27JUL95 DATE OF FIGURE GENERATION : 14SEP95

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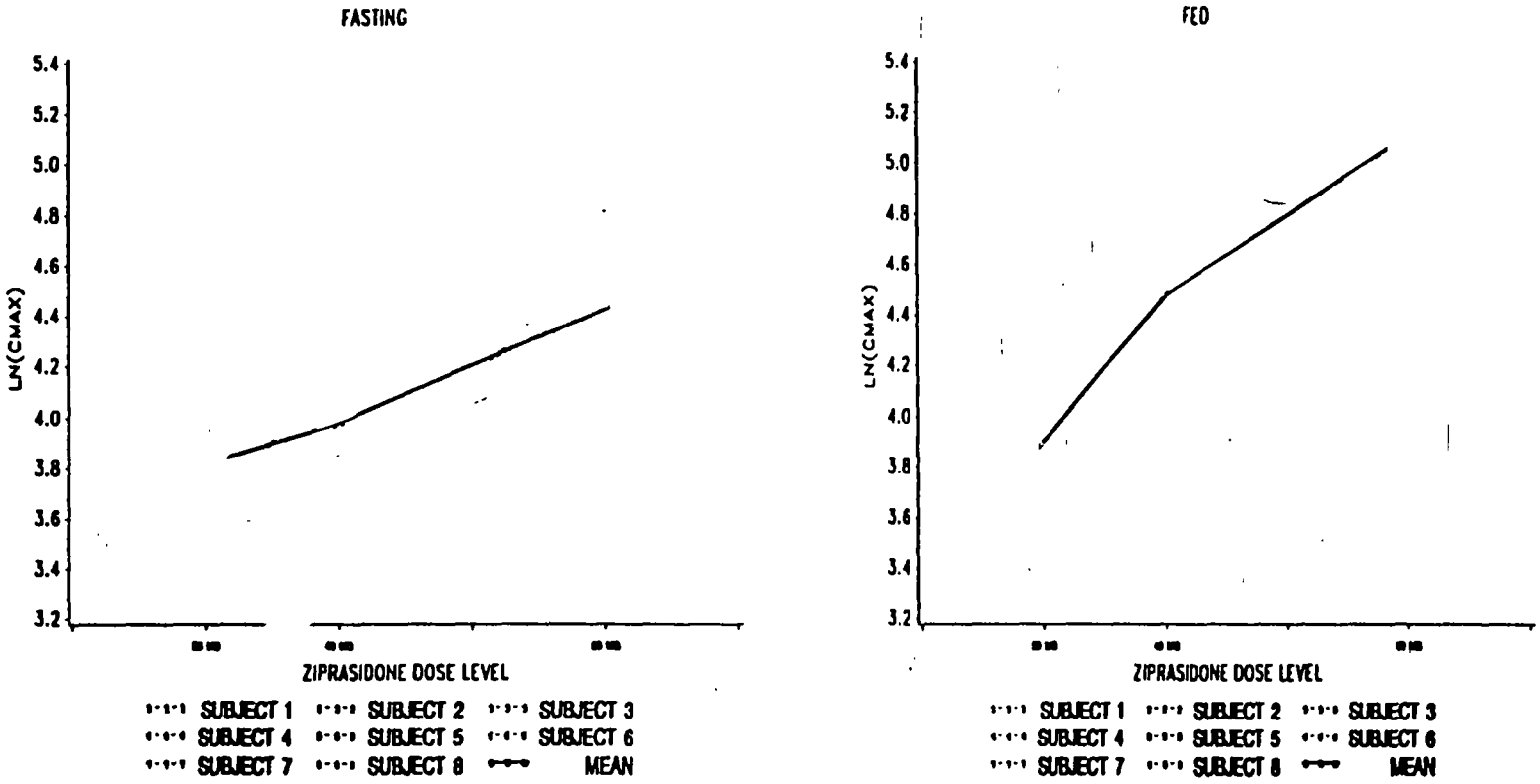
FIGURE 3
LN(CMAX(ng/ml)) BY DOSE LEVEL
ZIPRASIDONE PROTOCOL 006



SOURCE DATA : APPENDIX IV TABLES 1, 2 and 3 DATE OF DATA EXTRACTION : 27JUL95 DATE OF FIGURE GENERATION : 14SEP95

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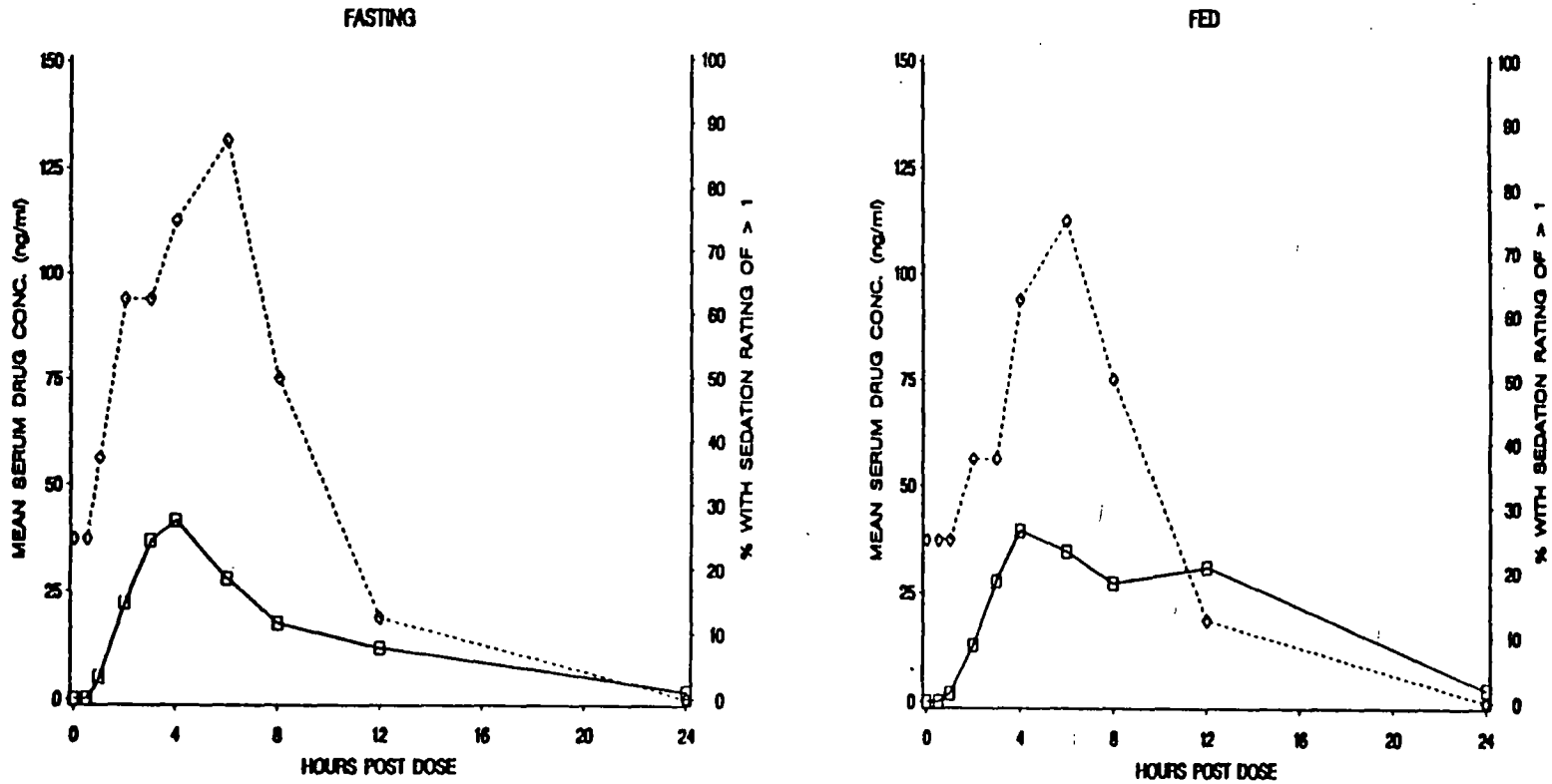
(7)

FIGURE 7.1
MEAN SERUM DRUG CONCENTRATION AND PERCENT WITH SEDATION RATING OF > 1
BY HOURS.POST DOSE AFTER 20 MG ZIPRASIDONE
ZIPRASIDONE PROTOCOL 006



SQUARES REPRESENT MEAN SERUM DRUG CONCENTRATION
DIAMONDS REPRESENT PERCENT WITH SEDATION RATING OF > 1

SOURCE DATA : Appendix III, Table 5 & Appendix IV Table 1 DATE OF DATA EXTRACTION : 27JUL95 DATE OF FIGURE GENERATION : 14SEP95

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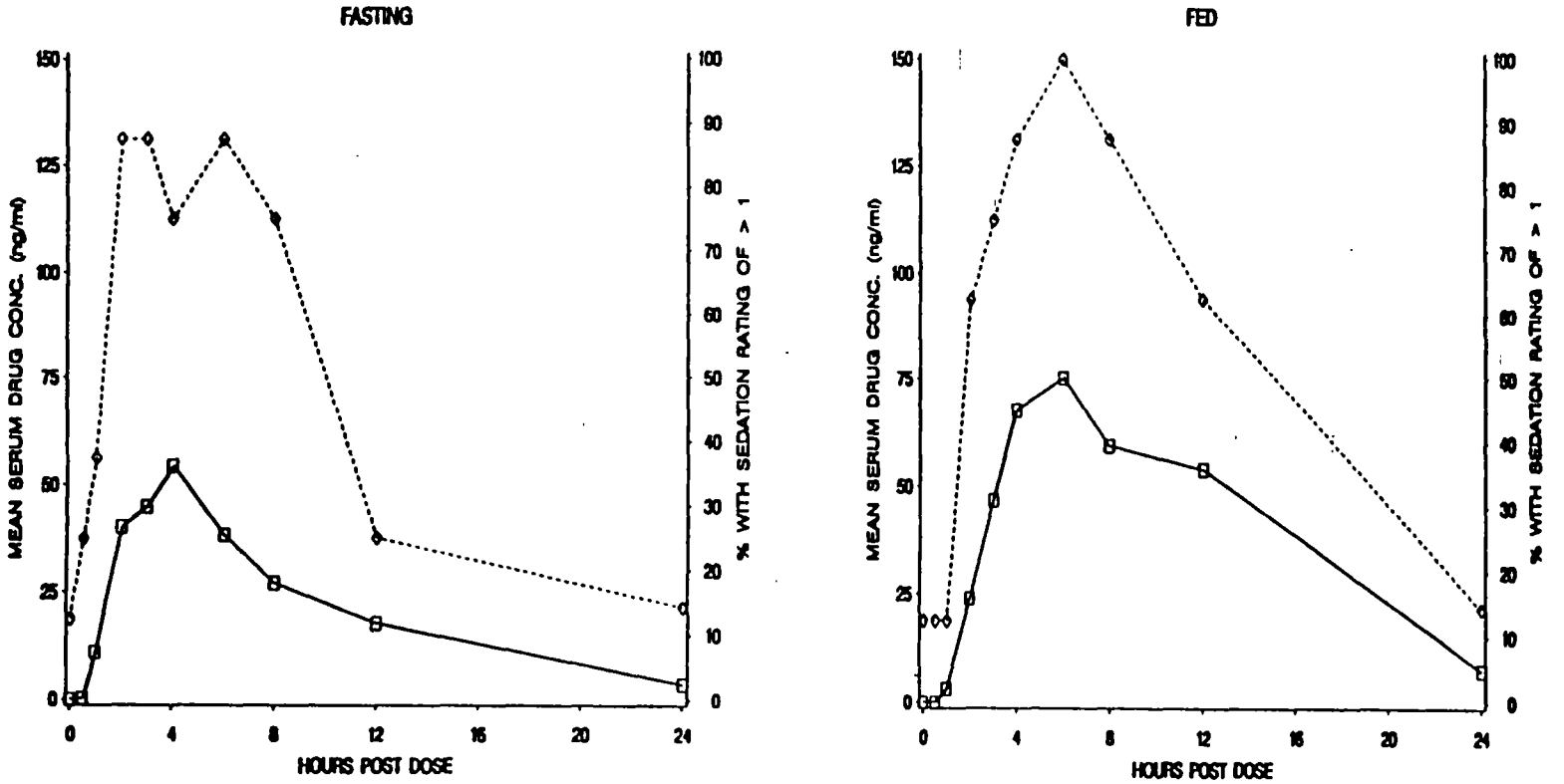
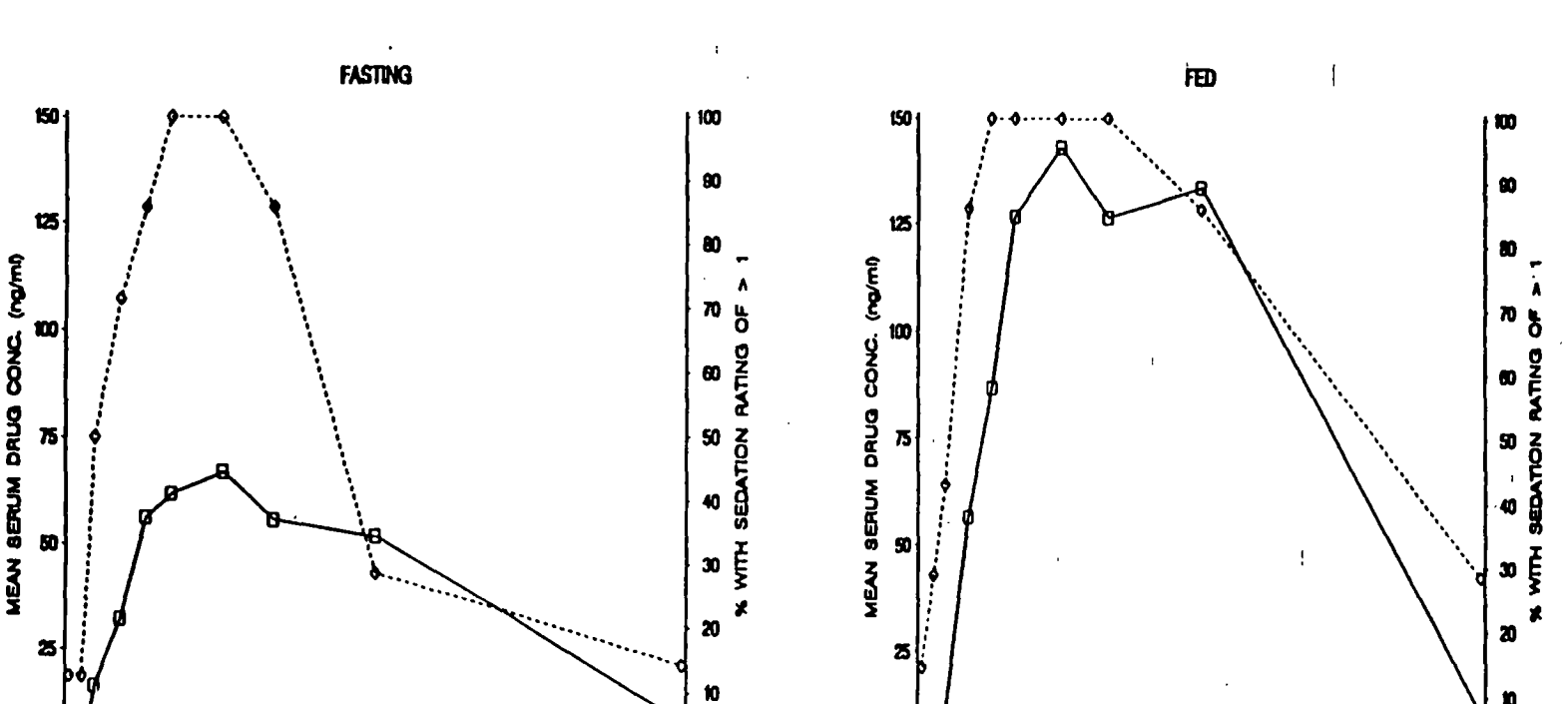
FIGURE 7.2
MEAN SERUM DRUG CONCENTRATION AND PERCENT WITH SEDATION RATING OF > 1
BY HOURS POST DOSE AFTER 40 MG ZIPRASIDONE
ZIPRASIDONE PROTOCOL 006



SQUARES REPRESENT MEAN SERUM DRUG CONCENTRATION
DIAMONDS REPRESENT PERCENT WITH SEDATION RATING OF > 1

SOURCE DATA : Appendix III, Table 5 & Appendix IV Table 2 DATE OF DATA EXTRACTION : 27JUL95 DATE OF FIGURE GENERATION : 14SEP95

FIGURE 7.3
MEAN SERUM DRUG CONCENTRATION AND PERCENT WITH SEDATION RATING OF > 1
BY HOURS POST DOSE AFTER 80 MG ZIPRASIDONE
ZIPRASIDONE PROTOCOL 006



SQUARES REPRESENT MEAN SERUM DRUG CONCENTRATION
DIAMONDS REPRESENT PERCENT WITH SEDATION RATING OF > 1

SOURCE DATA : Appendix III, Table 5 & Appendix IV Table 3 DATE OF DATA EXTRACTION : 27JUL95 DATE OF FIGURE GENERATION : 14SEP95

Study 007: (Effect of Food and Timing, 20 mg capsule, Single Dose)

Study Design and Summary:

(see attachments 1 and 3)

Results:

(See attachments 4-5)

Reviewer's Comments:

1. The results of this study are similar to other effect of food studies in which food increased both the Cmax and AUC of ziprasidone (attachments 4 and 5).

2. The effect of food was greater when the drug was administered with food than 2 hours after food consumption.

Conclusions:

This study clearly demonstrates that the drug should be taken simultaneously with food for greater effect.

PROTOCOL 128-007: PHASE I STUDY TO ASSESS THE EFFECT OF THE TIMING OF FOOD ON THE PHARMACOKINETICS OF CP-88,059-1 ADMINISTERED AS CAPSULES TO NORMAL HEALTHY MALE VOLUNTEERS

Principal Investigator: M. Lebel, Pharm.D

Study Publication: None

Study Dates: 21 April 1992 - 17 May 1992

Study Objective: The purpose of this study was to assess the effects of the timing of a standard meal on the pharmacokinetics of a single 20 mg dose of ziprasidone (CP-88,059-1).

Study Design: This was an open, three-way crossover study of the effects of the timing of food intake on the pharmacokinetics of a single 20 mg dose of ziprasidone administered to healthy male volunteers. All doses were administered as ziprasidone HCl and are expressed as the milligram equivalent of the free base of ziprasidone. Ziprasidone was to be administered under the following three conditions: after an overnight fast, with breakfast, and 2 hours after breakfast. Each subject was administered three doses with at least seven days between doses.

Evaluation Groups:

	Fasting	With Breakfast	2 Hours After Breakfast
Entered Study	10	10	9
Completed Study	9	10	9
Evaluated for Pharmacokinetics	8	8	8
Assessed for Safety			
Adverse Events	10	10	9
Laboratory Tests	10	10	9
Psychometric Testing	9	10	9

Subjects: Healthy male volunteers ranging in age from 20 to 34 years.

Drug Administration:

Dosage Form ziprasidone 20 mg capsules (FID# CS-90-031)

Dosing All subjects received single doses as ziprasidone 20 mg capsules (fasting, with breakfast, or 2 hours after breakfast) according to a computer generated randomization. Subjects received all three treatments with at least seven days between doses.

Pharmacokinetic and Safety Evaluations: Serum ziprasidone concentrations were used to estimate pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, and half-life). Subjects were monitored for adverse events and changes in laboratory test results.

Psychometric testing was done to assess the affects of ziprasidone on daytime vigilance.

Analytical Methods:

Statistical Methods: Geometric means and coefficients of variation were calculated for $AUC_{0-\infty}$ and C_{max}. Arithmetic means and coefficients of variation were calculated for T_{max} and K_{el}. Mean half-life was calculated as 0.693/mean K_{el}. Natural log-transformed $AUC_{0-\infty}$ and C_{max}, and untransformed T_{max} and K_{el} were analyzed using an ANOVA model. For $AUC_{0-\infty}$ and C_{max}, 90% confidence limits were calculated for the ratio of geometric means for each possible comparison.

Pharmacokinetic Results: (values are mean ± CV%)

	ziprasidone 20 mg		
	Fasting	With Breakfast	2 Hours After Breakfast
$AUC_{0-\infty}$ (ng•hr/ml)[a]	351.9 ± 35	597.6 ± 33	472.8 ± 32
C_{max} (ng/ml)[a]	46.1 ± 48	79.7 ± 43	68.7 ± 26
T_{max} (hours)	3.6 ± 21	4.5 ± 31	3.4 ± 27
K_{el} (hr^{-1})	0.109 ± 25	0.153 ± 18	0.138 ± 25
$T_{1/2}$ (hours)[b]	6.4	4.5	5.0

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

Safety Results:

	ziprasidone 20 mg		
	Fasting	With Breakfast	2 Hours After Breakfast
Treatment-emergent Adverse Events	10/10 (0)	10/10 (0)	9/9 (0)
Clinically Significant Laboratory Abnormalities	0/10 (0)	0/10 (0)	1/9 (0)

() Subjects discontinued

Summary and Conclusions: Administration of ziprasidone 20 mg immediately after and to a lesser extent 2 hours after a high-fat breakfast resulted in statistically significantly higher systemic exposure ($AUC_{0-\infty}$) to the compound than when administered to fasted subjects. Similar statistically significant increases for C_{max} were also observed. These increases may be attributed to enhanced ziprasidone solubilization secondary to food consumption leading to greater intestinal absorption. The lesser food effect observed following drug administration 2 hours after breakfast was consistent with the expectation that less food was present in the proximal region of the gastrointestinal tract.

Terminal phase half-lives were longer for the fasted compared to the nonfasted treatments. This observation may be attributed to the dissolution rate limited absorption associated with the fasted state that was ongoing during the period of time

over which K_{el} was characterized. Under such conditions, K_{el} would reflect the rate of in vivo dissolution in the gastrointestinal tract as opposed to the rate of elimination from the systemic circulation.

Administration of ziprasidone was associated with mild to moderate sedation in all subjects after each dose of ziprasidone. Postural hypotension and dizziness were reported by two subjects each. There were no discontinuations due to adverse events or laboratory test findings. There were no serious adverse events.

There were no apparent differences among groups for the daytime vigilance results.

In summary, the systemic exposure to ziprasidone was affected by the timing of drug administration relative to food intake. Exposure to ziprasidone, measured as mean $AUC_{0-\infty}$, was 69.8% higher when administered with breakfast, and 34.3% higher when administered 2 hours after breakfast, than when administered to fasting subjects.

Table 5.2
Summary of Statistical Analyses of Pharmacokinetic Parameters
Ziprasidone Protocol 007

Pharmacokinetic Parameter	Comparison			90% Confidence Limits
		Adjusted Geometric Means	Ratio	
AUC(0-inf) (ng*hr/ml)	With Breakfast vs. Fasting	599.02 vs. 348.57	171.8%	(153.1%, 192.9%)
	2 Hrs After Breakfast vs. Fasting	466.55 vs. 348.57	133.8%	(119.2%, 150.3%)
	2 Hrs After Breakfast vs. With Breakfast	466.55 vs. 599.02	77.9%	(69.4%, 87.4%)
Cmax (ng/ml)	With Breakfast vs. Fasting	80.60 vs. 45.94	175.5%	(138.9%, 221.7%)
	2 Hrs After Breakfast vs. Fasting	69.24 vs. 45.94	150.7%	(119.3%, 190.4%)
	2 Hrs After Breakfast vs. With Breakfast	69.24 vs. 80.60	85.9%	(68.0%, 108.5%)
		Adjusted Means	Difference	
Tmax (hr)	With Breakfast vs. Fasting	4.42 vs. 3.47	0.95	(0.12, 1.79)
	2 Hrs After Breakfast vs. Fasting	3.19 vs. 3.47	-0.29	(-1.12, 0.55)
	2 Hrs After Breakfast vs. With Breakfast	3.19 vs. 4.42	-1.24	(-2.07, -0.40)
Kel (1/hr)	With Breakfast vs. Fasting	0.1520 vs. 0.1064	0.0456	(0.0220, 0.0691)
	2 Hrs After Breakfast vs. Fasting	0.1326 vs. 0.1064	0.0262	(0.0027, 0.0497)
	2 Hrs After Breakfast vs. With Breakfast	0.1326 vs. 0.1520	-0.0193	(-0.0429, 0.0042)

Source Data: Appendix III Tables 1-4 Date of Data Extraction: 26APR95. Date of Table Generation: 28SEP95.

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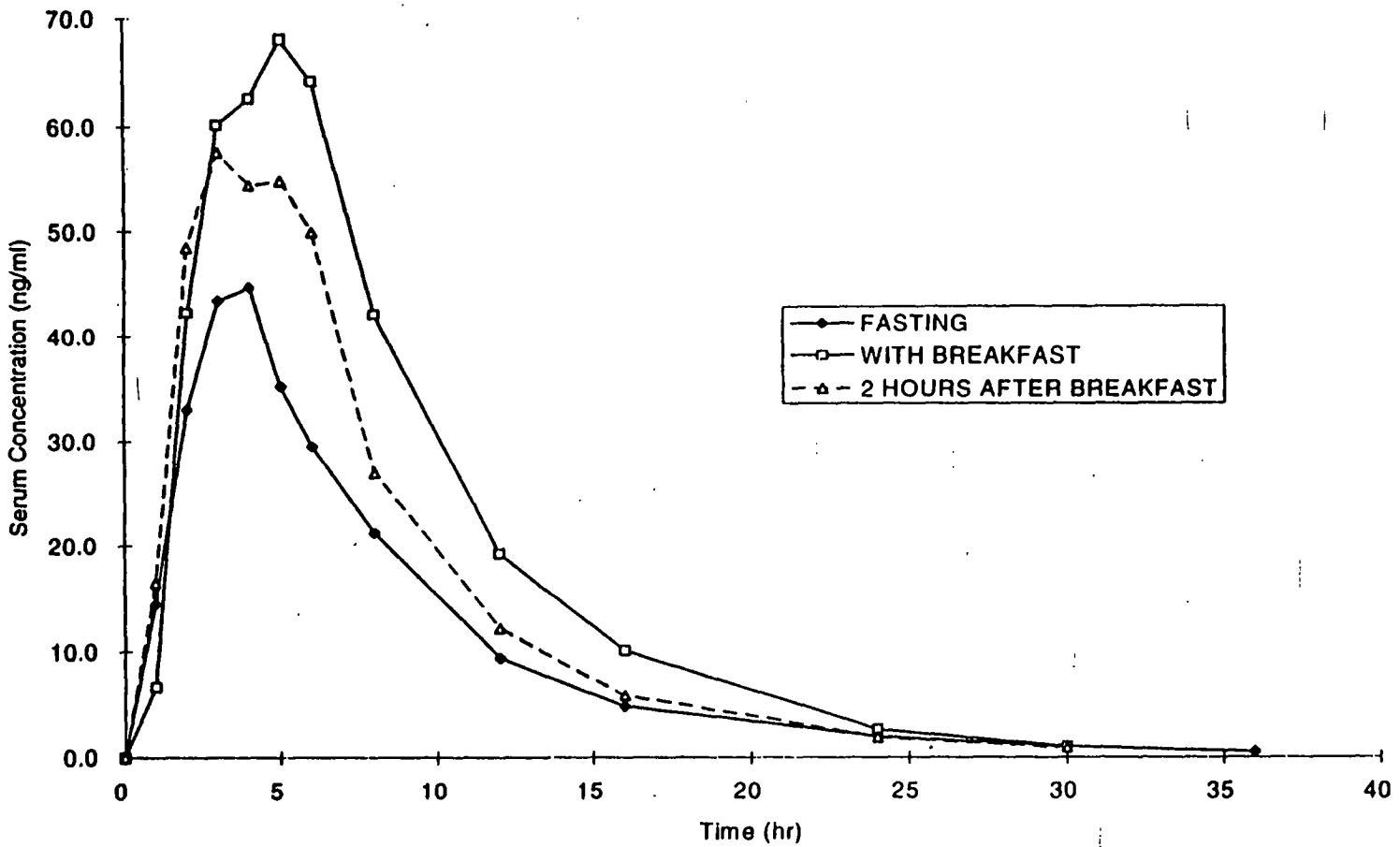
Figure 1.1 Mean Serum CP-88,059 Concentration-Time Curves Following Single Dose Administration of a 20 mg CP-88,059-1 Capsule, Under Fasting Conditions, Immediately Following, and 2-Hours After Consumption of a High-Fat Breakfast
Ziprasidone Protocol 007



Source Data: Appendix IV, Tables 1, 2, and 3

Study 036: (Effect of Food, 2 X 20 mg capsule, Single Dose)

Study Design and Summary:

(see attachments 1 and 3)

Results:

(See attachments 4-5)

Reviewer's Comments:

1. In the fed state, the drug was administered with 50 ml of water, whereas in fasting state, the drug was administered with 240 ml of water. It is not clear as to why the volume of water was not identical in both cases.

2. It is clear that the food increased the Cmax and AUC by about 2 fold (attachments 4 and 5).

3. Food also delayed the Tmax of ziprasidone by about 5 hours

4. The incidence of side effect such as somnolence and dizziness were also increased with food.

Conclusions:

This study clearly demonstrate that food increased the Cmax and AUC of ziprasidone by about 2 folds, but delays the Tmax.

PROTOCOL 128-036: PHASE I OPEN STUDY TO COMPARE THE PHARMACOKINETICS OF A 20 MG PROPOSED COMMERCIAL CAPSULE OF ZIPRASIDONE ADMINISTERED UNDER FASTING AND FED CONDITIONS IN NORMAL, HEALTHY SUBJECTS

Principal Investigator: P. Leese, M.D.

Study Publication: None

Study Dates: 4 October 1995 - 6 November 1995

Study Objective: To compare the pharmacokinetics of a 20 mg commercial capsule formulation of ziprasidone administered under fasting and fed conditions.

Study Design: This was an open, randomized, two-way crossover study comparing the pharmacokinetics of ziprasidone administered as 2 x 20 mg commercial capsules under fasting and fed conditions. Subjects received ziprasidone 2 x 20 mg capsules as single oral doses under both conditions separated by at least seven days.

Evaluation Groups:

Entered Study	12
Completed Study	12
Evaluated for Pharmacokinetics	12
Assessed for Safety	
Adverse Events	12
Laboratory Tests	0[a]

[a]Laboratory tests were performed at screening and within 24 hours prior to the first dose, unless follow-up was required.

Subjects: Healthy male and female volunteers ranging in age from 19 to 45 years.

Drug Administration:

Dosage Form: 20 mg commercial capsule (FID #QC2327)

Dosing: Subjects were administered single oral doses (2 x 20 mg) of ziprasidone in an open fashion in the morning. Doses under fasting conditions were administered with 240 ml of water. Doses under fed conditions were administered immediately following a standard breakfast with 50 ml of water.

Pharmacokinetic and Safety Evaluations: Blood samples for the determination of serum ziprasidone concentrations were collected prior to and up to 36 hours after each dose of study drug. Serum concentrations were used to estimate pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, and $T_{1/2}$). Subjects were monitored for adverse events and changes in vital signs.

Analytical Methods:

Statistical Methods: Natural log-transformed AUC_{0-t} and C_{max}, and untransformed T_{max} and K_{el} were analyzed using an ANOVA model. For AUC_{0-t} and C_{max}, 90% confidence limits were calculated for the ratio of geometric means.

Pharmacokinetic Results:

Mean ± Coefficients of Variation (%CV) of Pharmacokinetic Parameters (n=12, unless otherwise noted)

	Ziprasidone			
Parameter	Fasted		Fed	
AUC_{0-t} (ng•hr/ml)[a, b]	440	± 29	1018	± 24
$AUC_{0-\infty}$ (ng•hr/ml)[a]	496[c]	± 21	1031	± 24
C_{max} (ng/ml)[a]	50	± 44	108	± 32
T_{max} (hr)	3	± 42	8	± 41
K_{el} (1/hr)	0.093[c]	± 20	0.181	± 24
$T_{1/2}$ (hr)[d]	7.5[c]	--	3.8	--

[a]geometric mean
[b]t=time of the last pharmacokinetic blood sample with quantifiable concentrations of ziprasidone.
[c]n=10 due to the inability to estimate K_{el} for two subjects.
[d]mean $T_{1/2}$ = 0.693/mean K_{el}

Safety Results:

	Ziprasidone	
Number of Subjects With/Evaluated For:	Fasted	Fed
Adverse Events (All Causality)	7/12 (0)	12/12 (0)
Adverse Events (Treatment-emergent, treatment-related)	7/12 (0)	11/12 (0)

() subjects discontinued

Summary and Conclusions: Following postprandial administration of 2 x 20 mg commercial capsules, a positive food effect was observed in all twelve subjects. Geometric mean AUC_{0-t} and C_{max} values for the fed treatment were larger (2.3 times for AUC_{0-t} and 2.2 times for C_{max}) than those for the fasting treatment. The increased exposure to ziprasidone associated with the fed treatment may be attributed to increased ziprasidone solubilization, leading to enhanced absorption. The food effect was associated with a 5 hour increase in mean T_{max}. Terminal phase half-life values were consistently longer for the fasted treatment group. This may be due to dissolution rate-limited absorption which may occur during the period of time over which K_{el} was characterized.

No subjects discontinued from the study, and no serious adverse events were reported. The incidence of adverse events was greater following administration of ziprasidone under fed versus fasting conditions. Somnolence of mild to moderate severity was the most frequently reported adverse event in both treatment groups, with more subjects experiencing somnolence following ziprasidone administration

under the fed versus fasting state. The severity of somnolence also increased, with a greater number of moderate occurrences following ziprasidone administration under fed versus fasting conditions. Following dosing under fed conditions, 4 subjects experienced mild to moderate abdominal pain, three subjects had mild dizziness, and three subjects had mild orthostatic dizziness. Other adverse events in both treatment groups were isolated and of mild to moderate severity. All treatment-emergent adverse events were considered treatment-related except for one instance each of mild orthostatic dizziness and mild dizziness which occurred prior to dosing under fed conditions.

In summary, administration of a single dose of 2 x 20 mg commercial capsules of ziprasidone under fed conditions resulted in an approximately two-fold increase in systemic exposure as compared to administration under fasting conditions. There was a higher incidence of adverse events, particularly those affecting the nervous system, following administration of ziprasidone under fed versus fasting conditions in this study.

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Table 5.2
Summary of Statistical Analyses of Pharmacokinetic Parameters (AUC, Cmax, Tmax, and Kel)
Ziprasidone Protocol 036

Pharmacokinetic Parameter	Fed	Fasted		90% Confidence Limits
	Geometric Means		Ratio	
AUC (0-t) (ng.hr/ml)	1018	440	231.6%	(209.2%, 256.5%)
Cmax (ng/ml)	108	50	218.3%	(182.0%, 261.7%)
	Means		Difference	
Tmax (hr)	8	3	5	(3.4, 6.9)
	Adjusted Means		Difference	
Kel (1/hr)	0.181	0.086	0.095	(0.079, 0.111)

Adjusted means are displayed for Kel because of the unequal number of subjects in each sequence.
Source Data: Appendix III Tables 1-4 Date of Data Extraction: 23MAY96. Date of Table Generation: 24MAY96.

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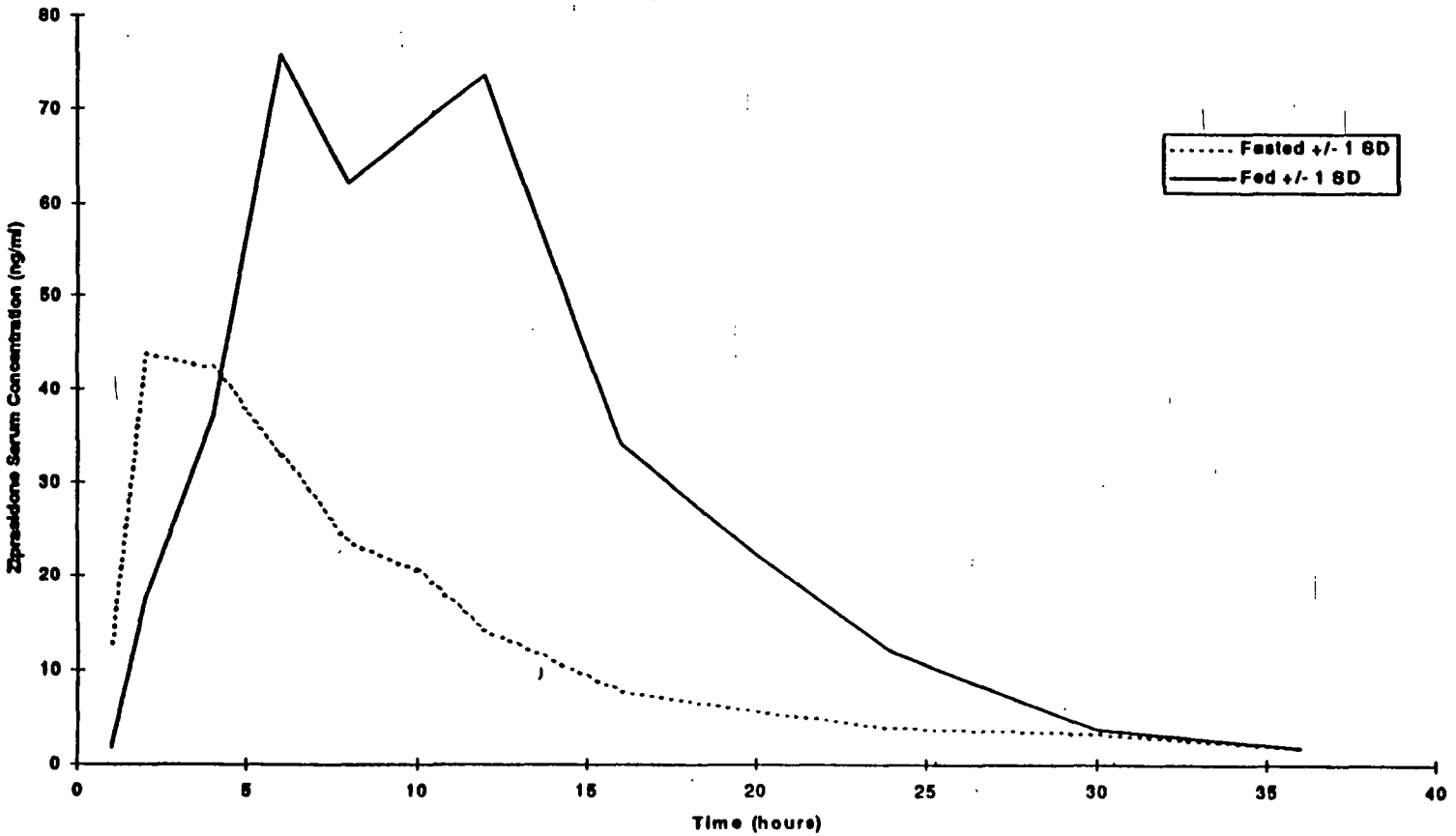
Figure 1. Mean Serum Ziprasidone Concentrations Versus Time Following Oral Administration of a 20 mg Commercial Capsule of Ziprasidone (FID #QC2327) to Normal, Healthy Subjects Under Fasting and Fed Conditions

Ziprasidone Protocol 036



Source Data: Appendix IV, Tables 1 and 2

Table 2.3.5

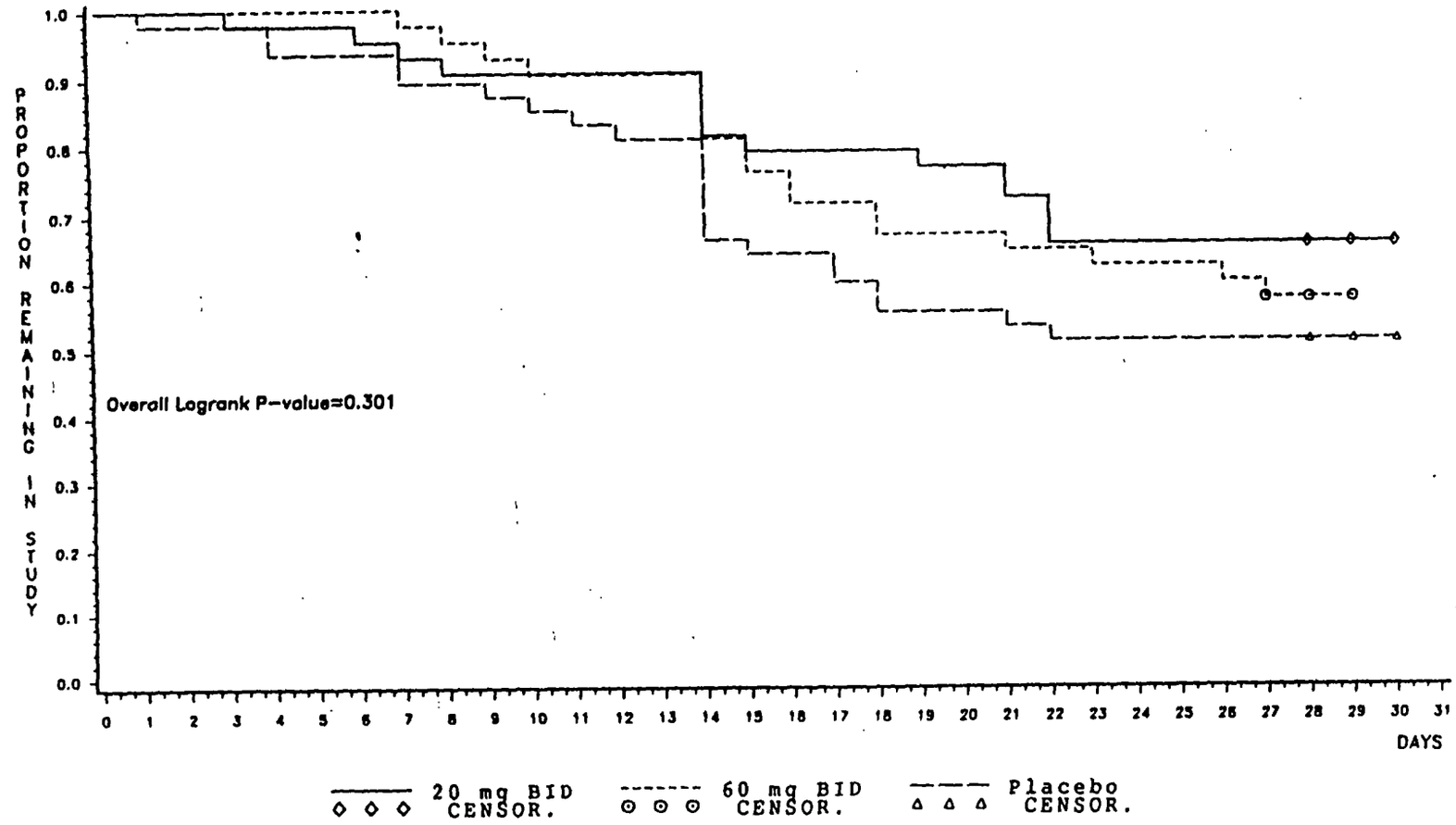
Variable	Treatment Comparison	Method*	Treatment Effect	P-Value	95% Confidence Limit Lower	Upper
BPRSd Core	20 mg BID vs Placebo	Wu-Bailey(1)	-0.2210	0.1532	-0.5241	0.0822
		UWLS(2)	-0.3773	0.0938	-0.8185	0.0640
		Random(3)	-0.1460	0.3337	-0.4419	0.1500
	60 mg BID vs Placebo	Wu-Bailey(1)	-0.2630	0.0965	-0.5732	0.0471
		UWLS(2)	-0.4728	0.0347	-0.9117	-0.0339
		Random(3)	-0.1255	0.4120	-0.4254	0.1743
	100 mg BID vs Placebo	Wu-Bailey(1)	-0.3402	0.0279	-0.6435	-0.0368
		UWLS(2)	-0.3939	0.0691	-0.8186	0.0308
		Random(3)	-0.2099	0.1607	-0.5031	0.0834
	Haloperidaol vs Placebo	Wu-Bailey(1)	-0.6155	0.0001	-0.9218	-0.3091
		UWLS(2)	-0.9777	0.0000	-1.4020	-0.5535
		Random(3)	-0.5048	0.0008	-0.8011	-0.2085
CGI Severity	20 mg BID vs Placebo	Wu-Bailey(1)	-0.0822	0.0187	-0.1508	-0.0137
		UWLS(2)	-0.1185	0.0173	-0.2161	-0.0210
		Random(3)	-0.0663	0.0630	-0.1361	0.0036
	60 mg BID vs Placebo	Wu-Bailey(1)	-0.0784	0.0279	-0.1482	-0.0085
		UWLS(2)	-0.1245	0.0119	-0.2215	-0.0275
		Random(3)	-0.0457	0.2056	-0.1165	0.0251
	100 mg BID vs Placebo	Wu-Bailey(1)	-0.0965	0.0058	-0.1650	-0.0280
		UWLS(2)	-0.1240	0.0104	-0.2188	-0.0291
		Random(3)	-0.0517	0.1434	-0.1210	0.0176
	Haloperidaol vs Placebo	Wu-Bailey(1)	-0.1564	0.0000	-0.2256	-0.0872
		UWLS(2)	-0.2267	0.0000	-0.3215	-0.1319
		Random(3)	-0.1367	0.0001	-0.2067	-0.0667

* Methods are: (1) Wu and Bailey, Biometrics, 1989; (2) Unweighted Least Squares;
(3) Random Effects Model, Laird and Ware, Biometrics,1982.

Source Data: Appendix V Table 15, 16. Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

Figure 3.1.5

Figure 1
Kaplan–Meier Curves for Time–to–Discontinuation for All Reasons
By Treatment Group – All Subjects
Ziprasidone Protocol 106



Source Data: Table 4.2 and Appendix III Table 25 Date of Data Extraction: 28AUG95 Date of Figure Generation: 08MAY96

Table 3.2S

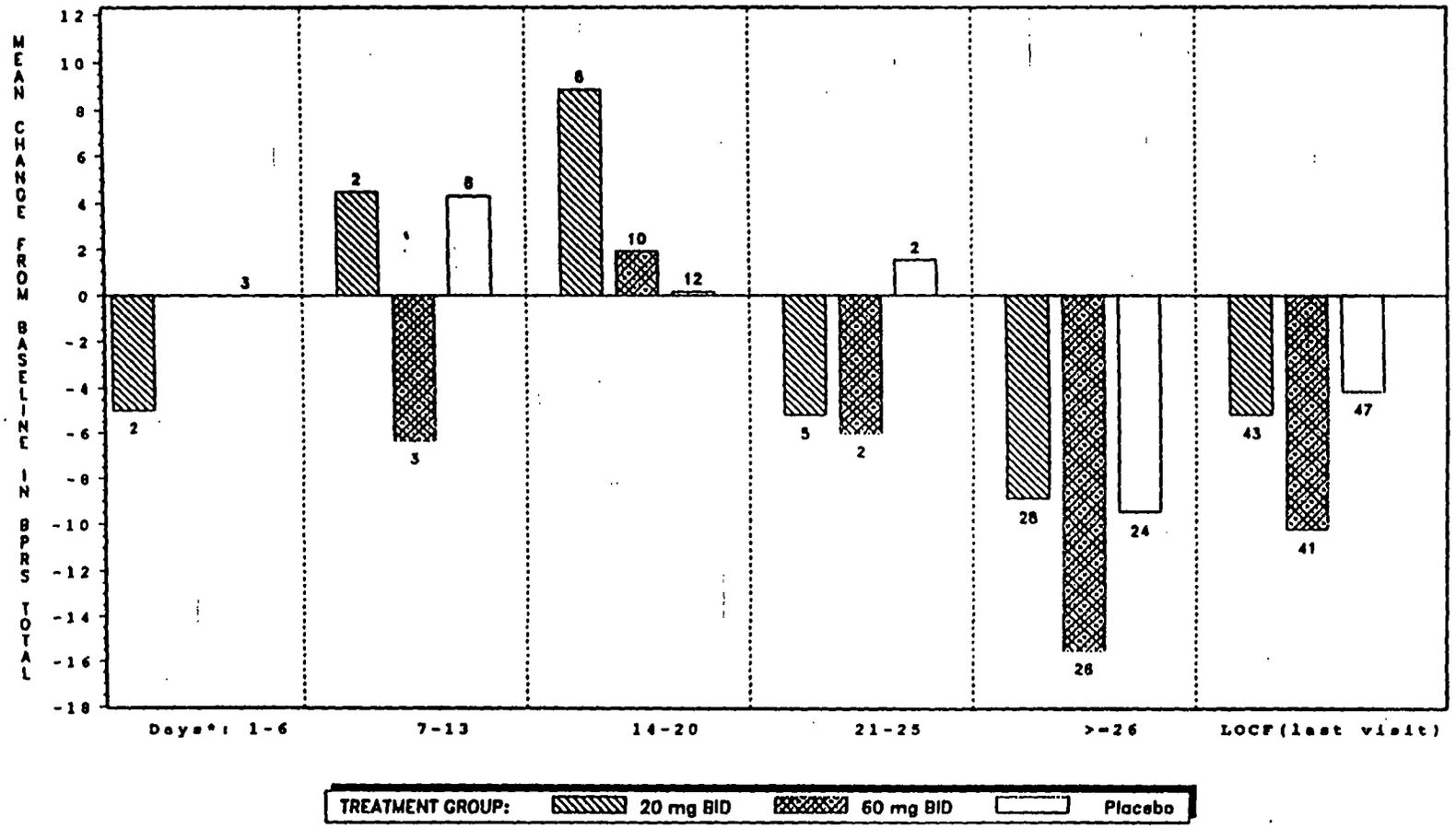
Table 5.1.10
Treatment Effects at Last Observation for Primary Efficacy Variables - All Subjects
Ziprasidone Protocol 106

Variable	Treatment Comparison	Estimated Treatment Effect*	P-Value**	Lower 95% Confidence Limit**	Upper 95% Confidence Limit**
BPRS Total	20 mg BID vs Pbo	-1.10	0.657	-6.01	3.80
	60 mg BID vs Pbo	-5.81	0.022	-10.77	-0.86
	Zipras. vs Pbo	-3.46	0.108	-7.68	0.77
BPRS Core	20 mg BID vs Pbo	-0.37	0.677	-2.10	1.37
	60 mg BID vs Pbo	-1.68	0.059	-3.43	0.06
	Zipras. vs Pbo	-1.02	0.176	-2.51	0.47
CGI Severity	20 mg BID vs Pbo	-0.25	0.209	-0.65	0.14
	60 mg BID vs Pbo	-0.42	0.039	-0.82	-0.02
	Zipras. vs Pbo	-0.34	0.053	-0.68	0.00

*Estimates of treatment effects (e.g. for treated group - placebo) are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and fixed effect terms for center and treatment.
**The p-values and 95% confidence intervals are derived from the respective t-tests. (Refer to Appendix III Tables 20.1.2, 21.1.2 and 22.1.2)
Source Data: Appendix V Tables 15,16. Date of Data Extraction: 15DEC95. Date of Table Generation: 15JAN96.

Figure 3.25

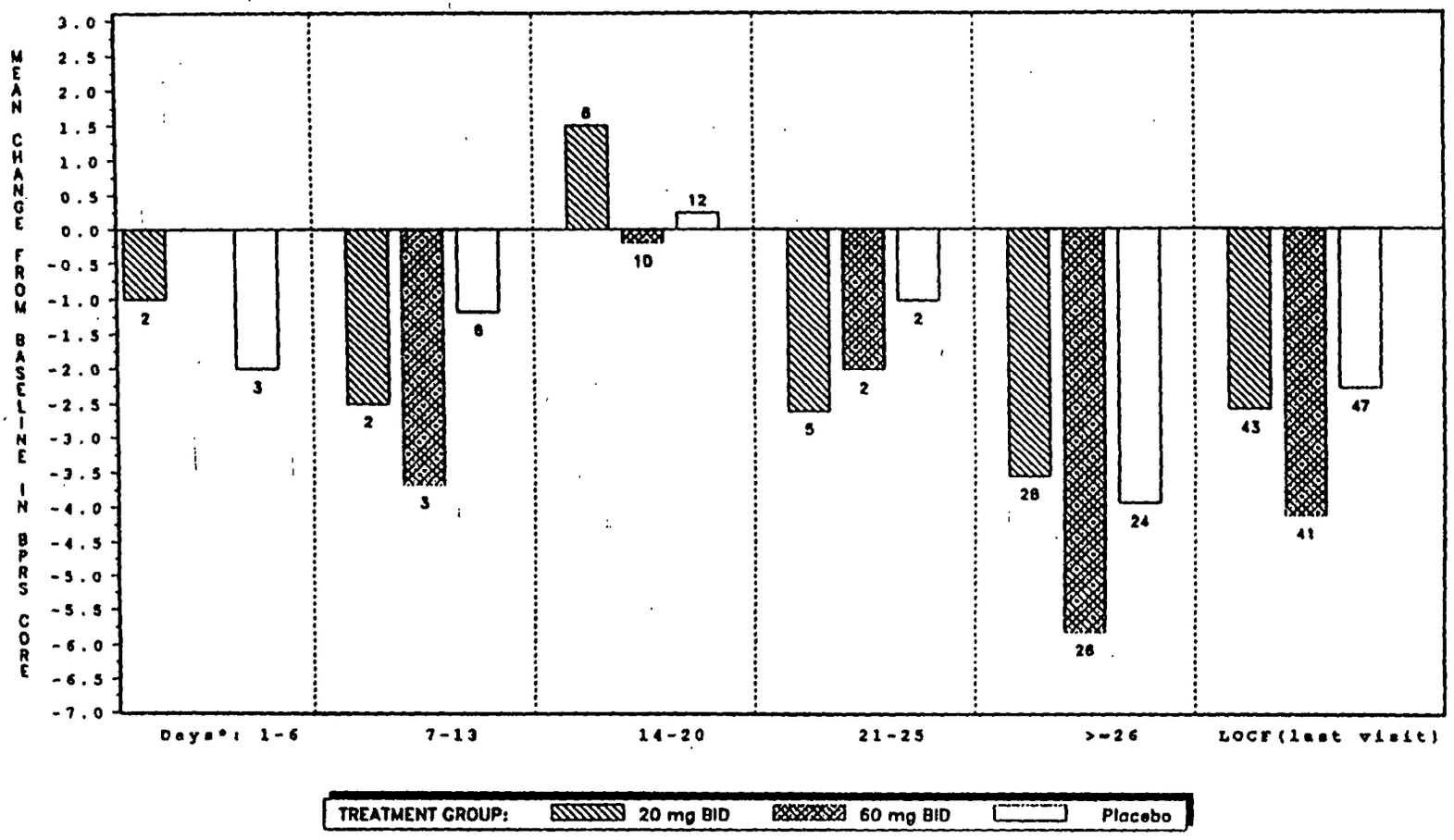
Figure 2.1
BPRS Total Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 106



*Duration of Participation (in Days).
Source Data: Appendix III Tables 25, and Appendix V Table 15 Date of Data Extraction: 28AUG95 Date of Figure Generation: 08MAY96

Figure 3.2.S

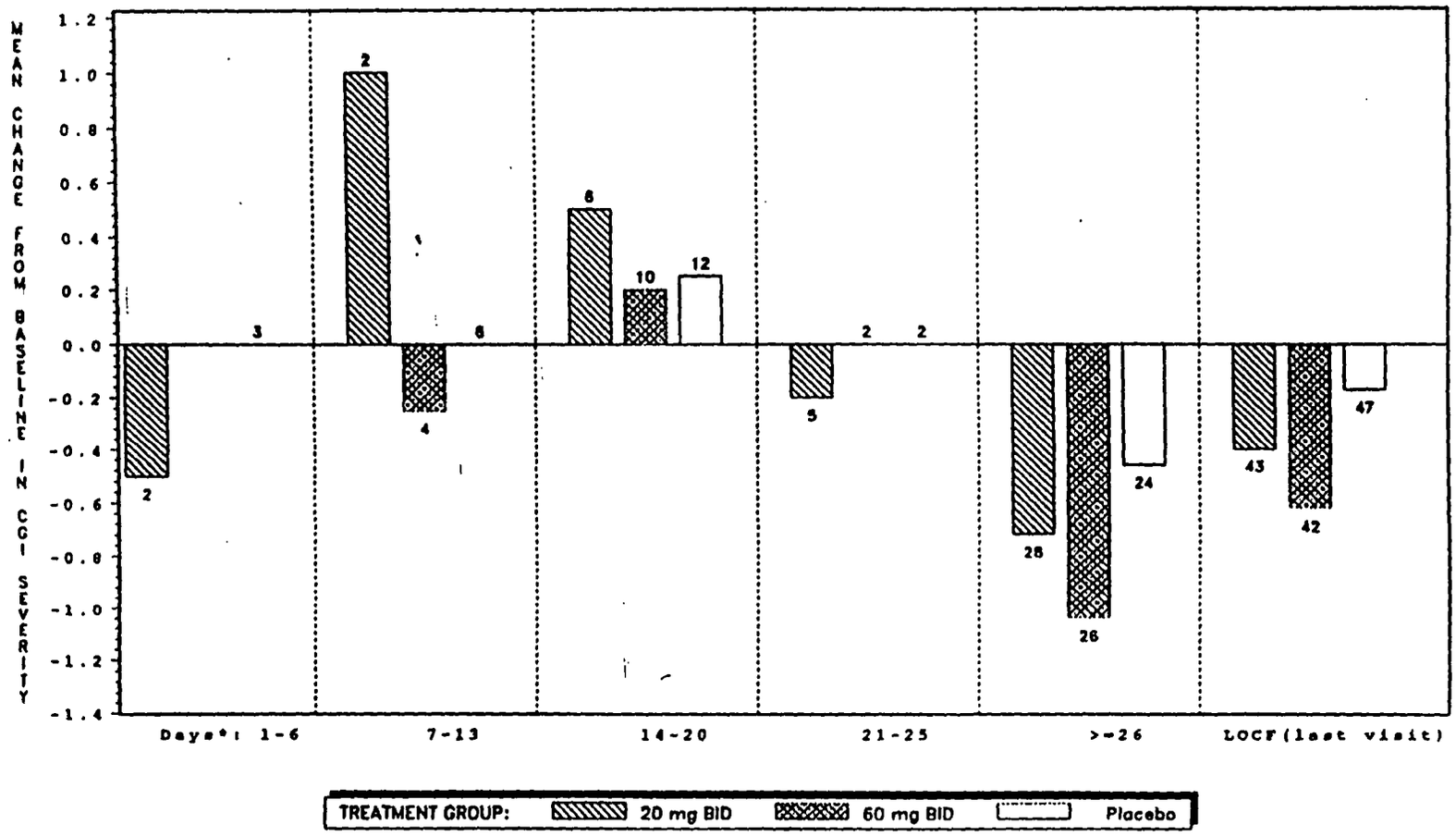
Figure 2.2
BPRS Core Items Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 106



*Duration of Participation (In Days).
Source Data: Appendix III Tables 25 and Appendix V Table 15 Date of Data Extraction: 28AUG95 Date of Figure Generation: 08MAY96

Figure 3.2.5

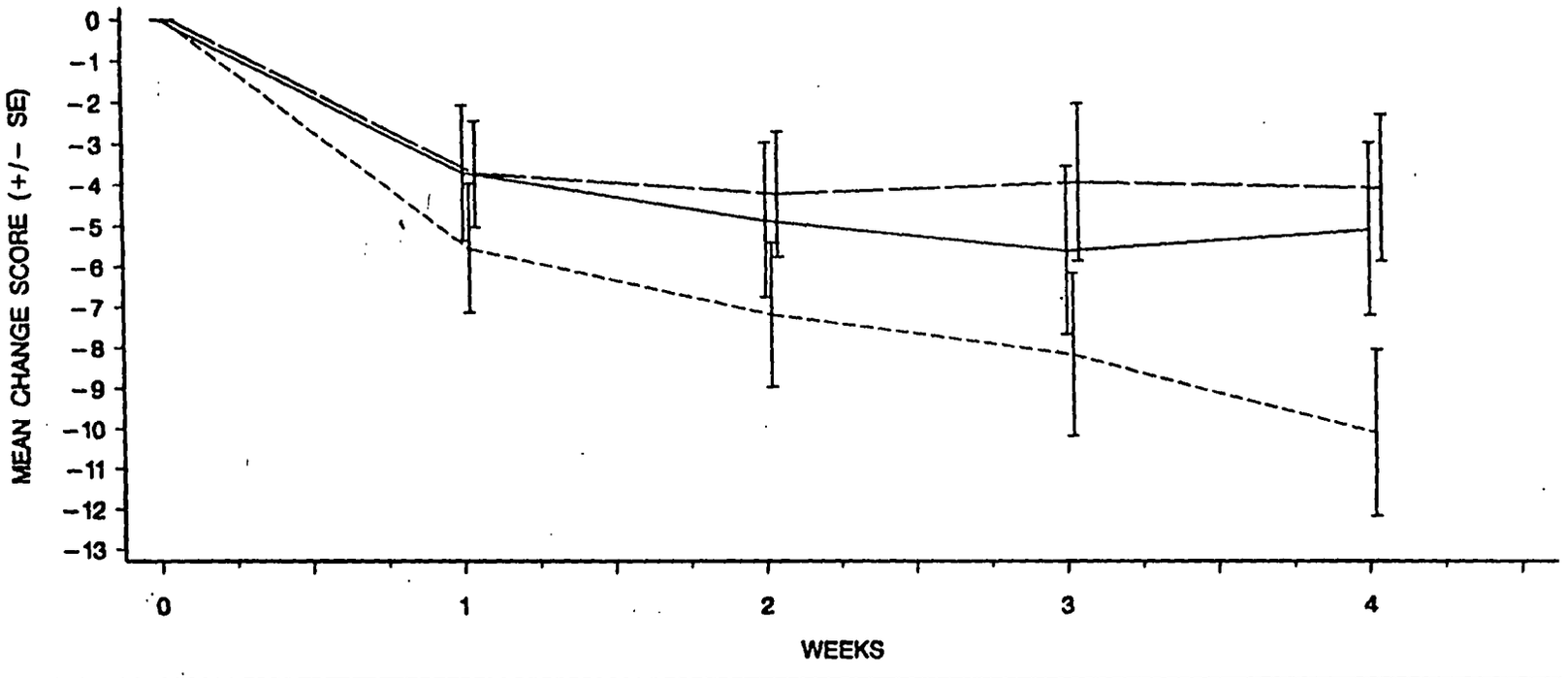
Figure 2.3
CGI Severity Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 106



*Duration of Participation (in Days).
Source Data: Appendix III Tables 25 and Appendix V Table 16 Date of Data Extraction: 28AUG95 Date of Figure Generation: 08MAY96

Figure 3.35

Figure 3.1
BPRS Total Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 106

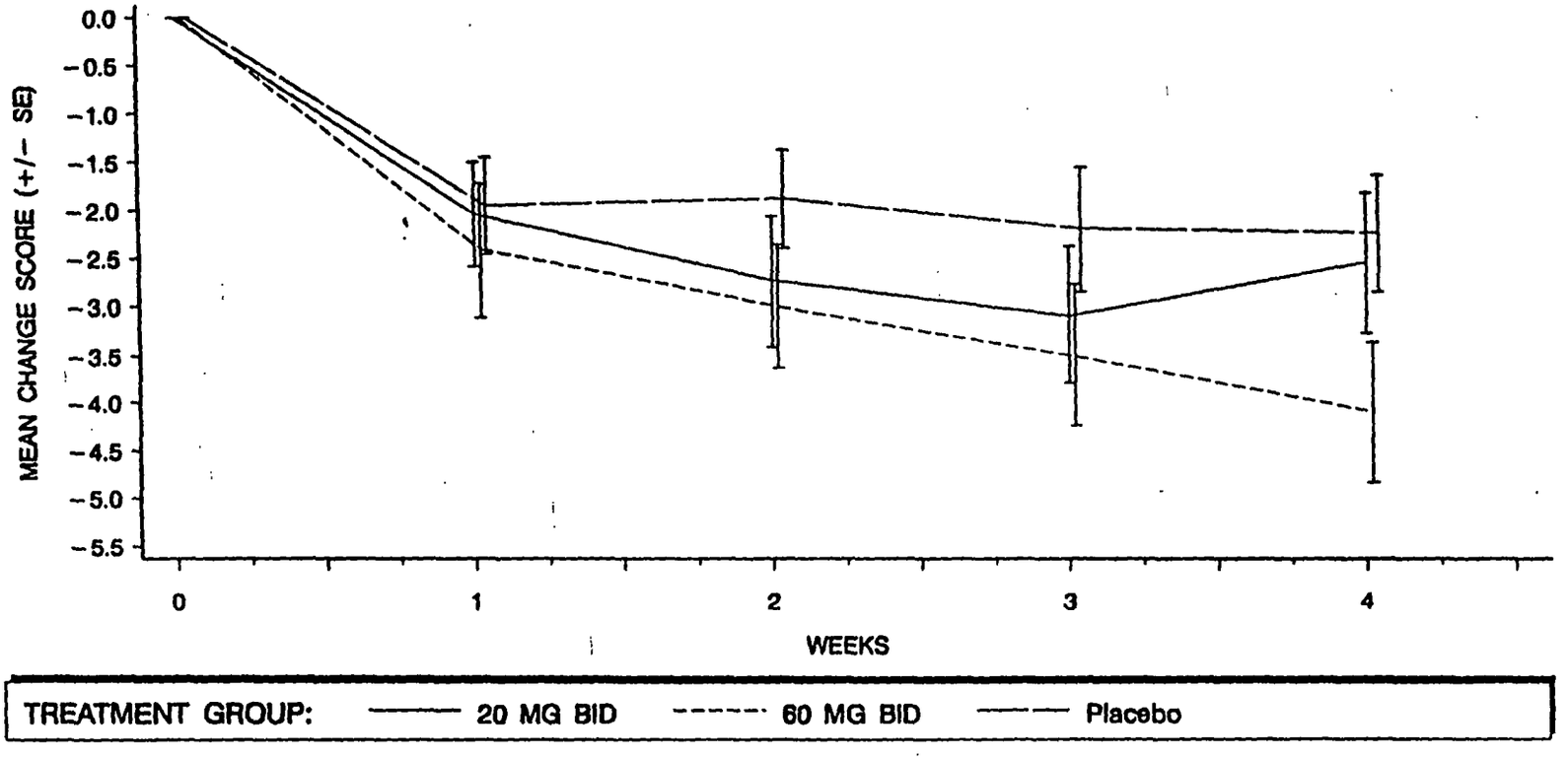


20 mg BID 43 43 43 43 43
60 mg BID 41 41 41 41 41
Placebo 47 47 47 47 47

Source Data: Appendix III Table 2.10 Date of Data Extraction: 15DEC95. Date of Table Generation: 08MAY96.

Figure 3.3S

Figure 3.2
BPRS Core Items Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 106

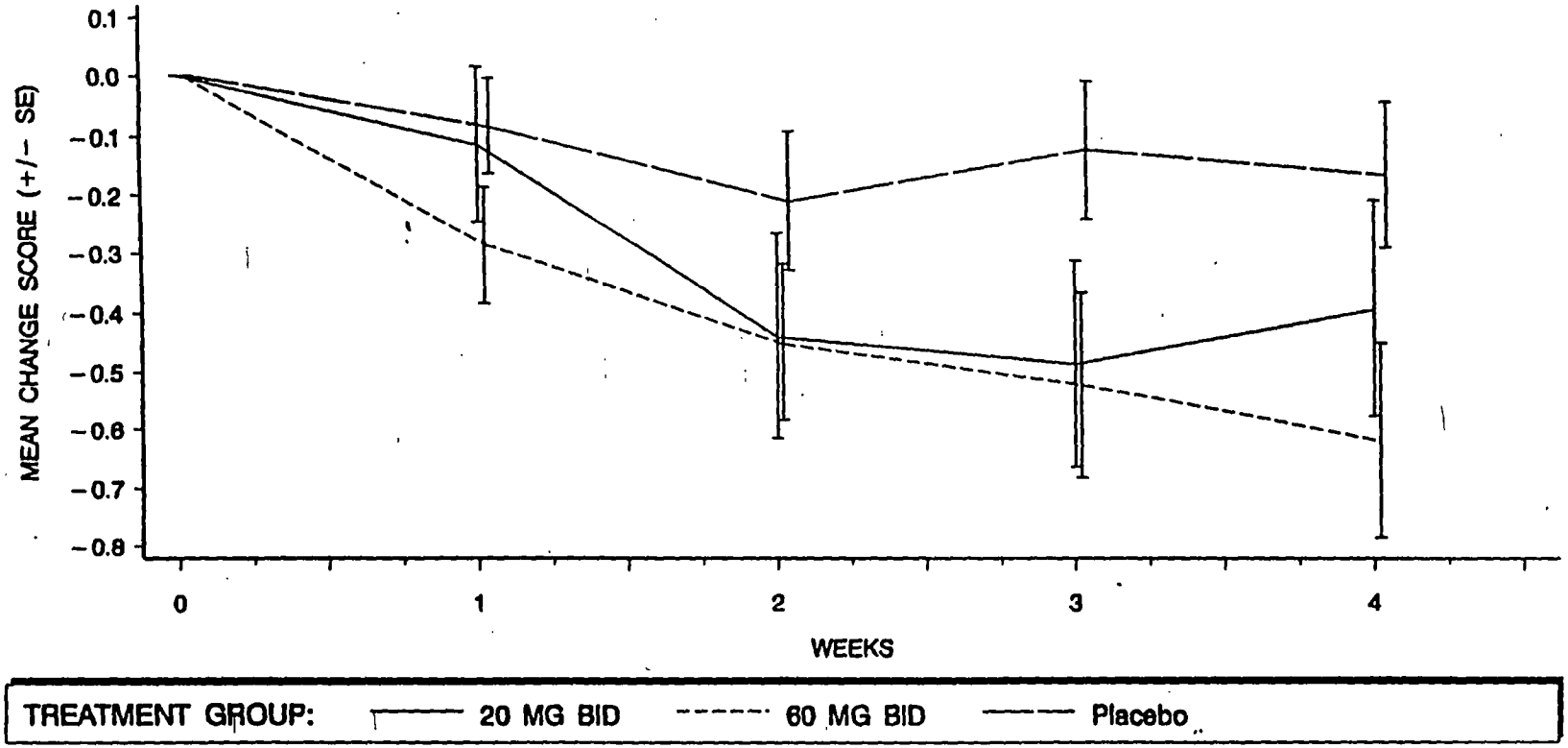


20 mg BID 43 43 43 43 43
60 mg BID 41 41 41 41 41
Placebo 47 47 47 47 47

Source Data: Appendix III Table 3.10 Date of Data Extraction: 28JUL95. Date of Table Generation: 08MAY96.

Figure 3.3 S

Figure 3.3
CGI Severity Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 106



20 mg BID 43 43 43 43 43
60 mg BID 42 42 42 42 42
Placebo 47 47 47 47 47

Source Data: Appendix III Table 4.10 Date of Data Extraction: 28JUL95. Date of Table Generation: 08MAY96.

Table 3.3.5

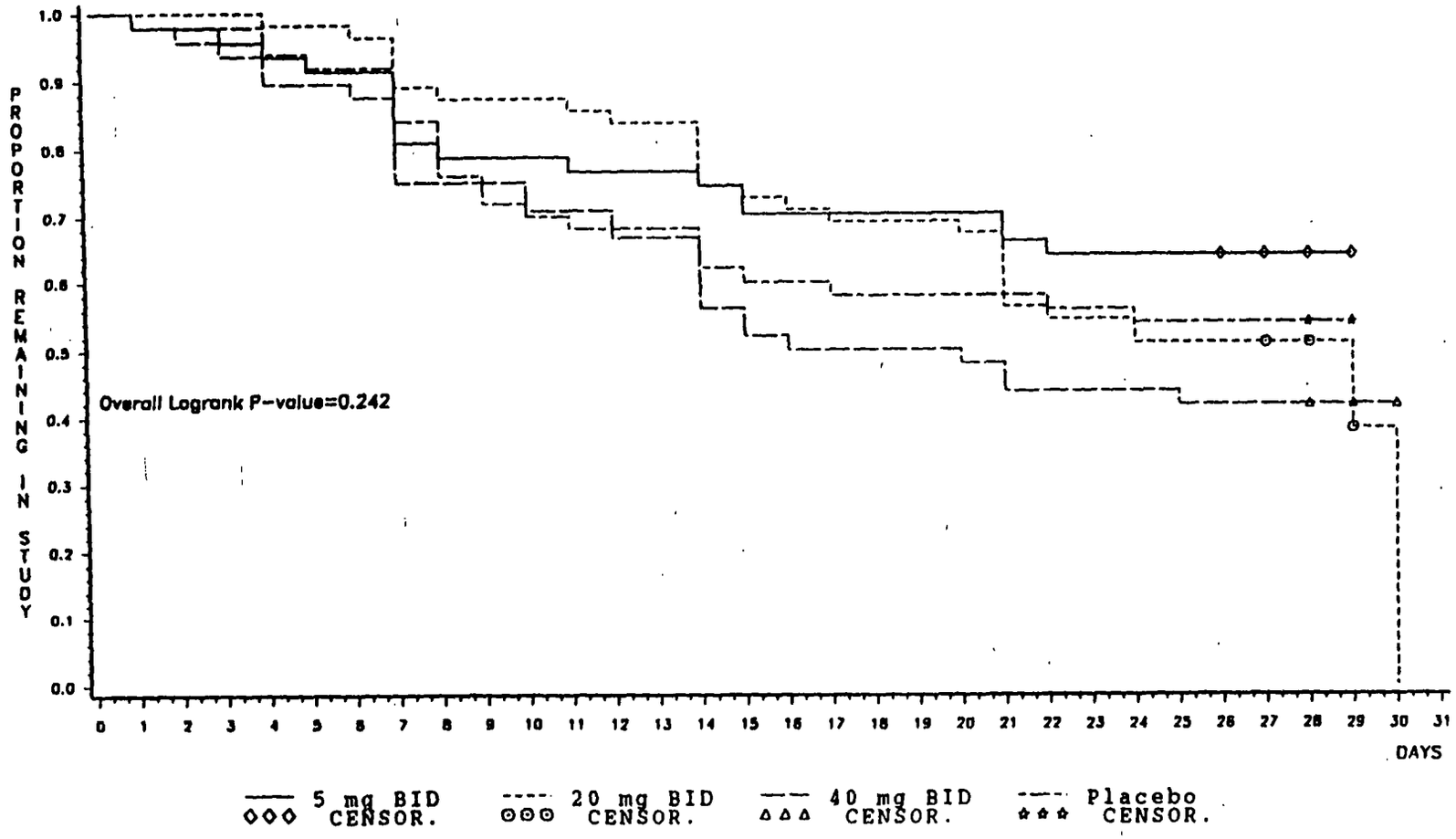
Appendix IIIA Table 9
Longitudinal Analysis of Treatment Effects - All Subjects, Observed Cases
Ziprasidone Protocol 106

Variable	Treatment Comparison	Method*	Treatment Effect	P-Value	95% Confidence Limit Lower	Upper
BPRS Total	20 mg BID vs placebo	Wu-Bailey(1)	-0.609	0.433	-2.131	0.914
		UWLS(2)	-0.367	0.757	-2.693	1.960
		Random(3)	-0.173	0.827	-1.731	1.385
	60 mg BID vs placebo	Wu-Bailey(1)	-1.971	0.013	-3.520	-0.421
		UWLS(2)	-2.054	0.066	-4.242	0.134
		Random(3)	-1.399	0.082	-2.977	0.180
BPRS Core Items	20 mg BID vs placebo	Wu-Bailey(1)	-0.067	0.802	-0.592	0.457
		UWLS(2)	0.167	0.706	-0.703	1.038
		Random(3)	0.044	0.872	-0.495	0.584
	60 mg BID vs placebo	Wu-Bailey(1)	-0.538	0.049	-1.074	-0.003
		UWLS(2)	-0.398	0.337	-1.210	0.414
		Random(3)	-0.385	0.167	-0.932	0.162
CGI Severity	20 mg BID vs placebo	Wu-Bailey(1)	-0.105	0.100	-0.229	0.020
		UWLS(2)	-0.055	0.572	-0.244	0.135
		Random(3)	-0.086	0.183	-0.213	0.041
	60 mg BID vs placebo	Wu-Bailey(1)	-0.159	0.014	-0.285	-0.032
		UWLS(2)	-0.139	0.131	-0.319	0.041
		Random(3)	-0.125	0.056	-0.254	0.003

* Methods are: (1) Wu and Bailey, Biometrics,1989; (2) Unweighted Least Squares; (3) Random Effects Model, Laird and Ware, Biometrics, 1982.
Source Data : Appendix V Tables 15 and 16.Date of Data Extraction : 15DEC95.Date of Table Generation : 08OCT96.

Figure 4.15

Figure 1
Kaplan–Meier Curves for Time–to–Discontinuation for All Reasons
All Randomized Subjects By Treatment Group
Ziprasidone Protocol 104



Source Data: Table 4.2 and Appendix III Table 24 Date of Data Extraction: 28AUG95 Date of Figure Generation: 090CT96

Table 4.2 S

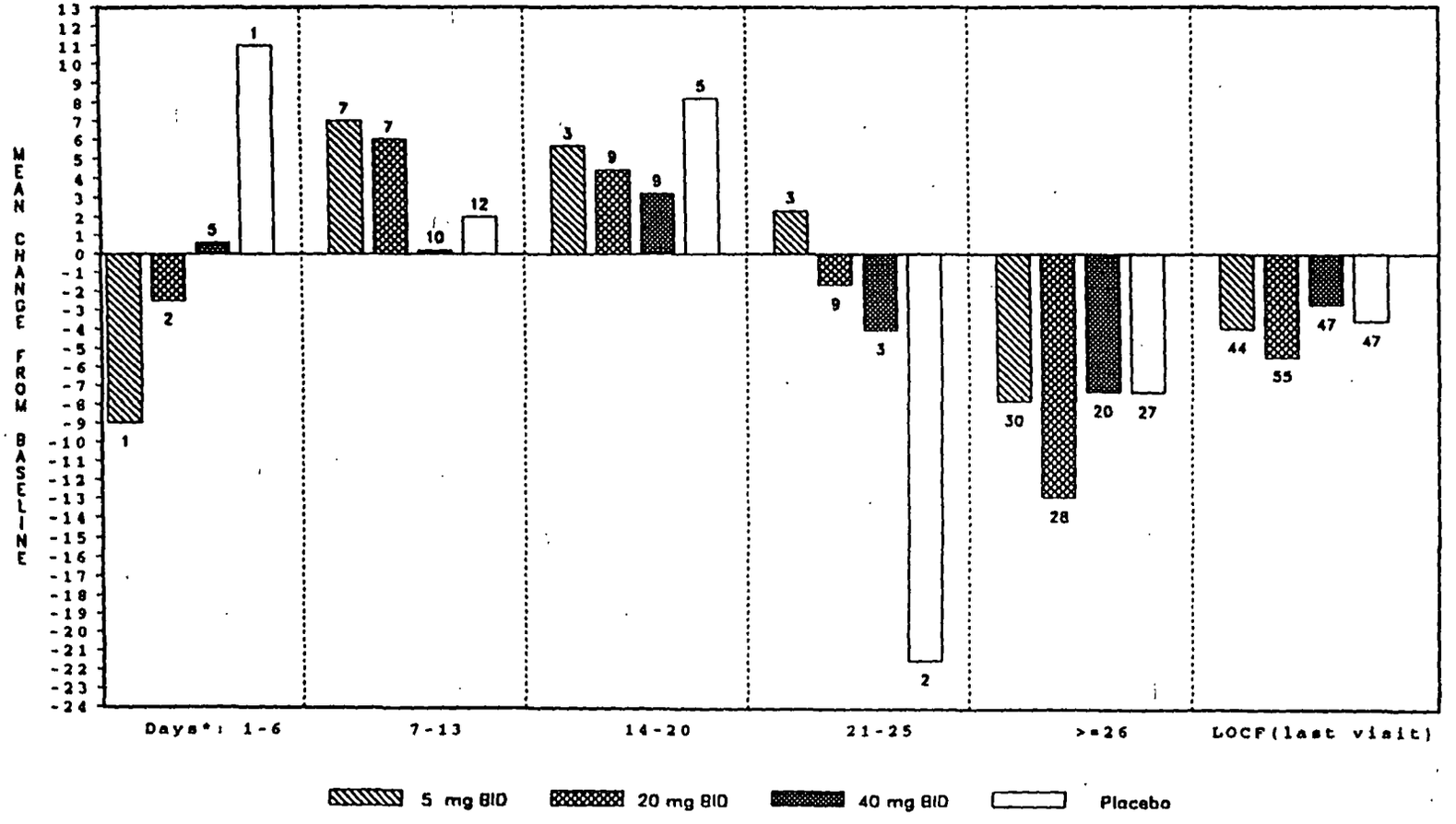
Table 5.1.10
Treatment Effects at Last Observation for Primary Efficacy Variables - All Subjects
Ziprasidone Protocol 104

Variable	Treatment Comparison	Estimated Treatment Effect*	P-Value**	Lower 95% Confidence Limit**	Upper 95% Confidence Limit**
BPRS Total	5 mg BID vs Pbo	-0.20	0.926	-4.55	4.14
	20 mg BID vs Pbo	-1.95	0.354	-6.08	2.19
	40 mg BID vs Pbo	1.36	0.535	-2.94	5.65
	Zipras. vs Pbo	-0.26	0.881	-3.76	3.23
BPRS Core	5 mg BID vs Pbo	0.28	0.742	-1.41	1.97
	20 mg BID vs Pbo	-0.26	0.751	-1.86	1.35
	40 mg BID vs Pbo	0.87	0.301	-0.79	2.53
	Zipras. vs Pbo	0.30	0.664	-1.06	1.66
CGI Severity	5 mg BID vs Pbo	0.32	0.076	-0.03	0.68
	20 mg BID vs Pbo	0.04	0.827	-0.31	0.38
	40 mg BID vs Pbo	0.22	0.233	-0.14	0.57
	Zipras. vs Pbo	0.19	0.192	-0.10	0.48

*Estimates of treatment effects for treated group minus placebo are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and fixed effect terms for center and treatment.
**The p-values and 95% confidence intervals are derived from the respective t-tests.
Source Data: Appendix V Tables 16,17. Date of Data Extraction: 17JUL95. Date of Table Generation: 11OCT96.

Figure 4.2S

Figure 2.1
BPRS Total Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 104

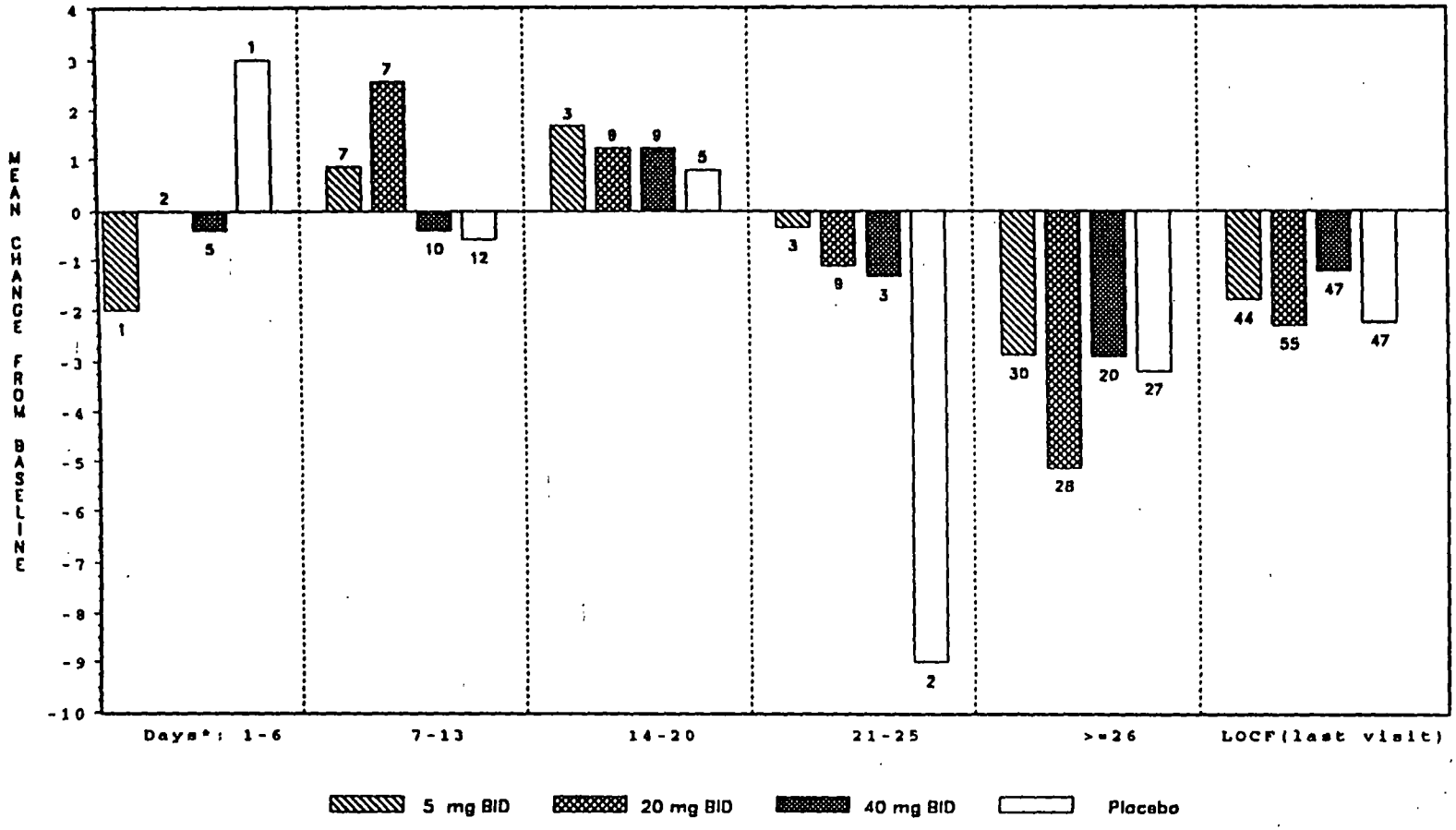


* Duration of Participation (In Days).

Source Data: Appendix III Table 28 and Appendix V Table 15 Date of Data Extraction: 28AUG95 Date of Figure Generation: 09OCT96

Figure 4.2.5

Figure 2.2
BPRS Core Items Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 104

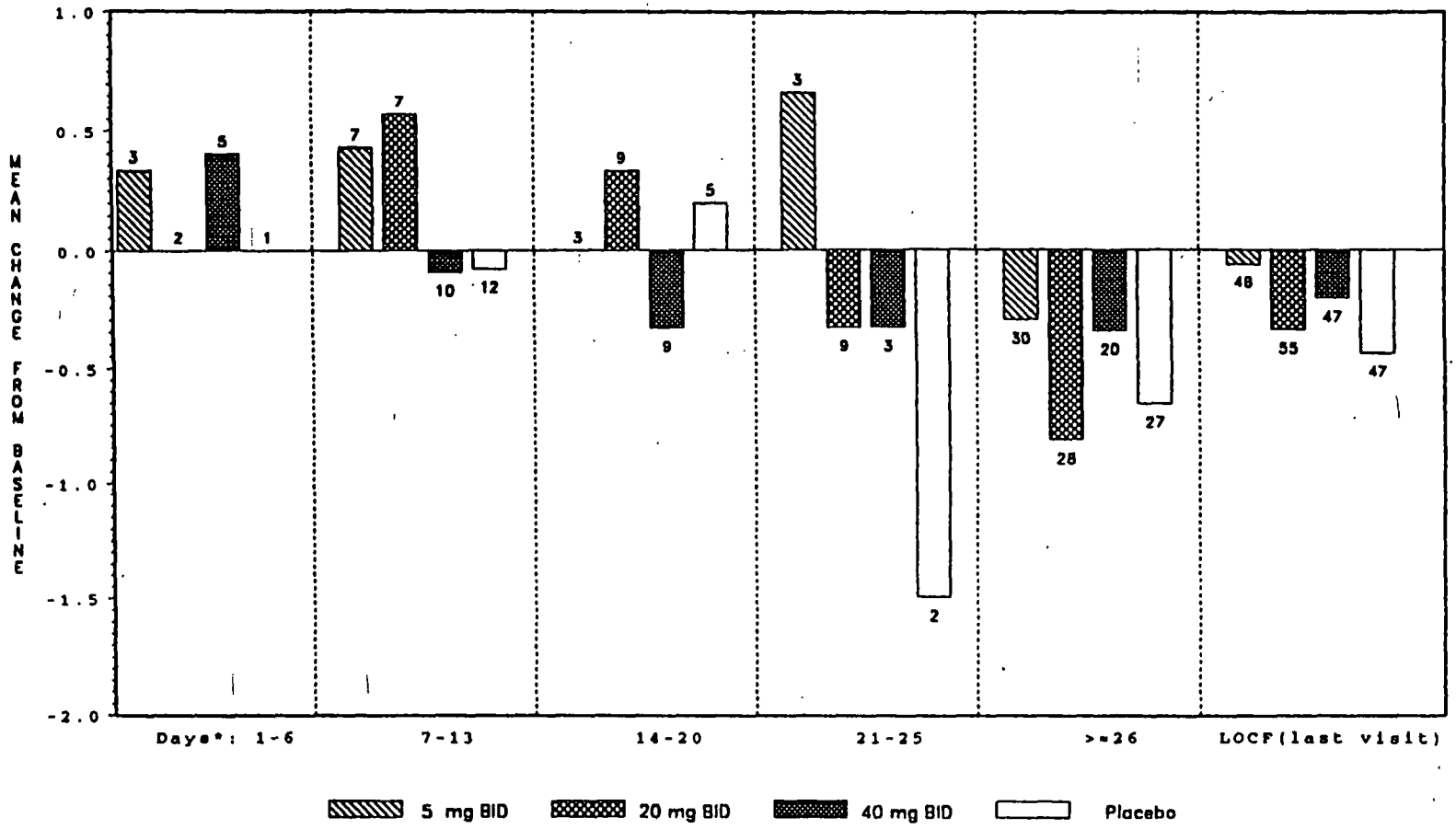


* Duration of Participation (in Days).

Source Data: Appendix III Table 28 and Appendix V Table 15 Date of Data Extraction: 28AUG95 Date of Figure Generation: 09OCT96

Figure 4.25

Figure 2.3
CGI Severity Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 104

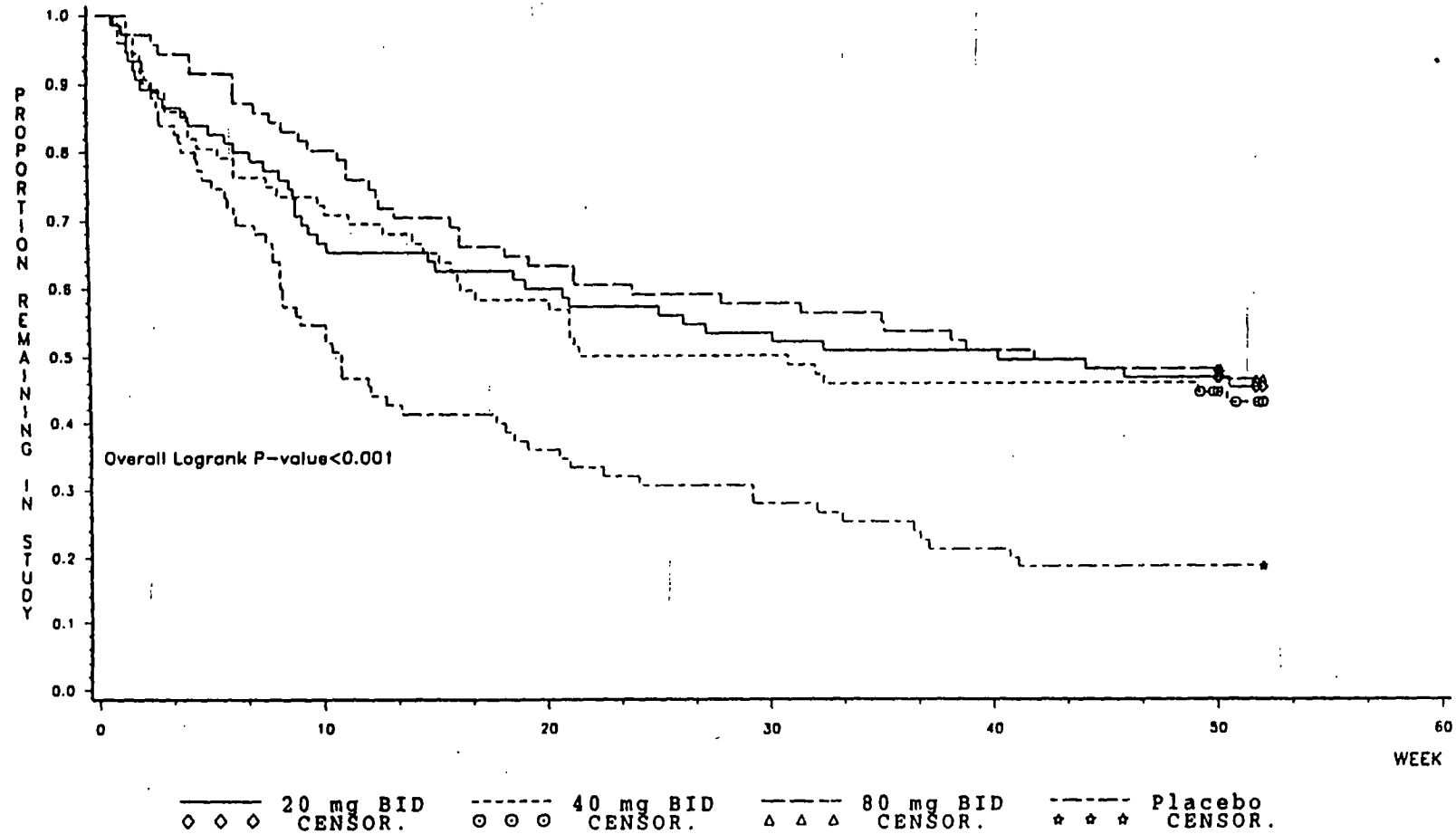


* Duration of Participation (In Days).

Source Data: Appendix III Table 28 and Appendix V Table 16 Date of Data Extraction: 28AUG95 Date of Figure Generation: 09OCT96

Figure 5.15

Figure 1.3
Kaplan–Meier Curves for Time–to–Discontinuation for All Reasons by Treatment Group
All Subjects
Ziprasidone Protocol 303



Source Data: Appendix III Table 27 Date of Data Extraction: 06JAN97 Date of Figure Generation: 06JAN97

Table 5.2.5

Table 5.1.2
Analysis of Time-to-Relapse - All Subjects
Ziprasidone Protocol 303

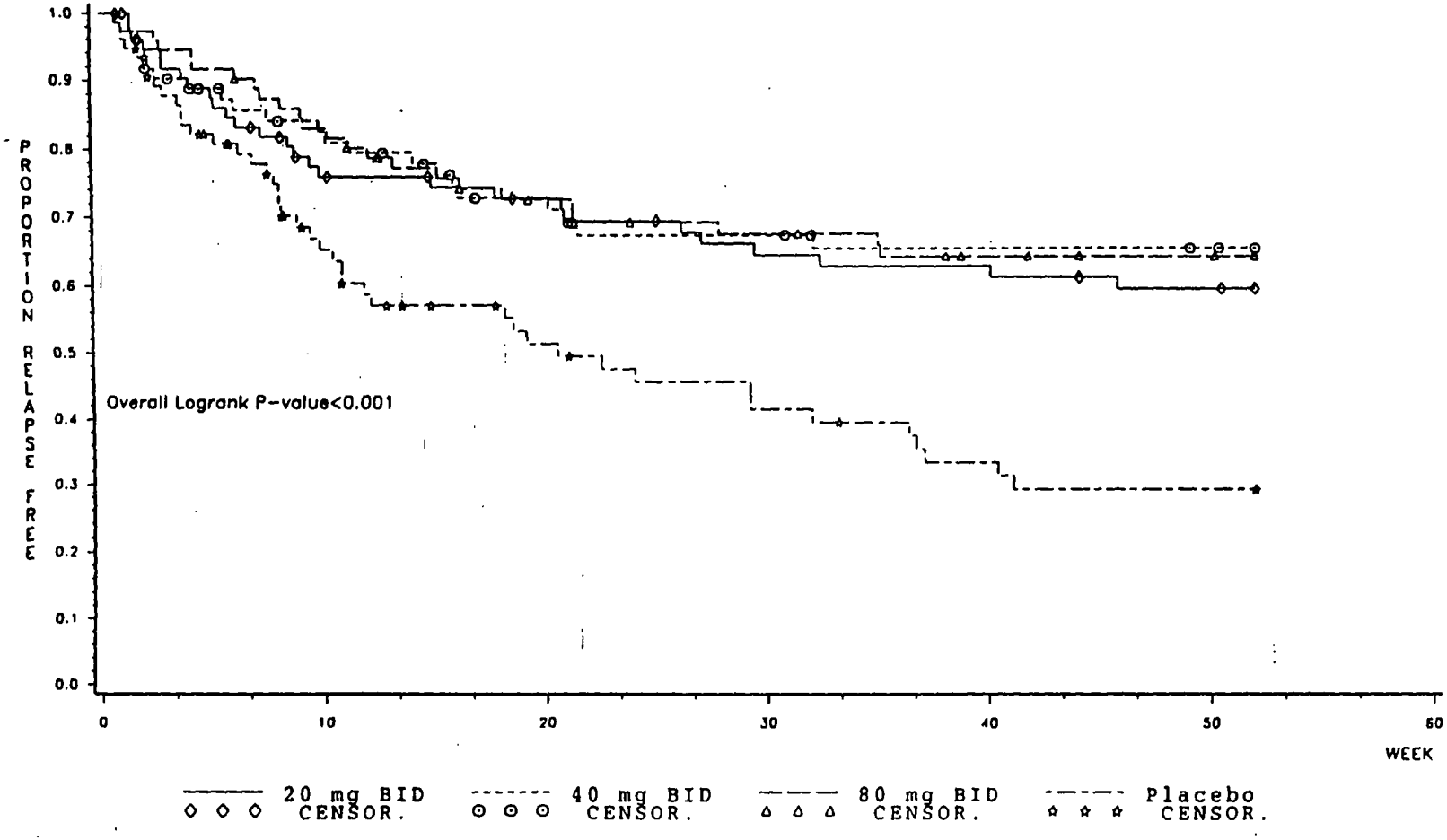
Treatment Group	N	Cumulative Incidence(%) of Relapse* <=28 weeks	Cumulative Incidence(%) of Relapse* <=52 weeks	Probability of Relapse** <=28 weeks	Probability of Relapse** <=52 weeks	Relative Risk	95% Confidence Limits Lower	95% Confidence Limits Upper	P-Value***
Ziprasidone									
20 mg BID	75	23 (30.7)	27 (36.0)	0.339	0.405	0.481	0.296	0.781	0.003
40 mg BID	72	21 (29.2)	22 (30.6)	0.326	0.346	0.414	0.247	0.693	0.001
80 mg BID	71	22 (31.0)	24 (33.8)	0.324	0.358	0.411	0.249	0.680	0.001
Placebo	75	35 (46.7)	43 (57.3)	0.545	0.708				
Overall									<0.001
Dose Response									0.002
Zip. vs Placebo									<0.001
Linear Among Zip.									0.595

*. Percent to number of patients at baseline
** Estimates of probability of relapse at <=28 weeks or <=52 weeks are based on the Kaplan-Meier product-limit method
***The p-values for comparing each treatment with placebo and for overall are derived from a Cox regression model that includes a contrast variable for each treatment group versus placebo. The p-value for dose response is based on Cox regression model using the actual dosage levels (0 mg for placebo). The dose response is further tested for Ziprasidone groups combined versus placebo using model contrasts (-3, 1, 1, 1) and for linear effect among the Ziprasidone groups using contrasts (0, -1, 0, 1).

Source Data. Appendix III Table 27. Date of Data Extraction: 06JAN97 Date of Table Generation 06FEB97.

Figure 5.2S

Figure 1.1
Kaplan-Meier Curves for Time-to-Relapse by Treatment Group
All Subjects
Ziprasidone Protocol 303



Source Data: Appendix III Table 27 Date of Data Extraction: 06JAN97 Date of Figure Generation: 06JAN97

Table 5.35

Table 5.1.27
Treatment Effects at Last Observation for Selected Efficacy Variables - All Subjects
Ziprasidone Protocol 303

Variable	Treatment Comparison	Estimated Treatment Effect*	P-Value**	Lower 95% Confidence Limit**	Upper 95% Confidence Limit**
PANSS Total	20 mg BID vs Pbo	-12.69	0.001	-19.88	-5.50
	40 mg BID vs Pbo	-11.57	0.002	-18.79	-4.35
	80 mg BID vs Pbo	-15.57	<0.001	-22.80	-8.35
	Zipras. vs Pbo	-13.28	<0.001	-19.15	-7.41
PANSS Negative	20 mg BID vs Pbo	-3.44	<0.001	-5.19	-1.70
	40 mg BID vs Pbo	-2.27	0.012	-4.03	-0.51
	80 mg BID vs Pbo	-3.97	<0.001	-5.72	-2.22
	Zipras. vs Pbo	-3.23	<0.001	-4.65	-1.80
PANSS Negative (Neg. Sym.)	20 mg BID vs Pbo	-3.27	0.009	-5.70	-0.84
	40 mg BID vs Pbo	-2.28	0.073	-4.77	0.21
	80 mg BID vs Pbo	-3.83	0.002	-6.19	-1.47
	Zipras. vs Pbo	-3.13	0.002	-5.06	-1.19
CGI Severity	20 mg BID vs Pbo	-0.59	0.001	-0.95	-0.23
	40 mg BID vs Pbo	-0.76	<0.001	-1.12	-0.40
	80 mg BID vs Pbo	-0.74	<0.001	-1.11	-0.38
	Zipras. vs Pbo	-0.70	<0.001	-0.99	-0.40
CGI Improvement	20 mg BID vs Pbo	-0.86	0.001	-1.38	-0.34
	40 mg BID vs Pbo	-0.93	0.001	-1.45	-0.41
	80 mg BID vs Pbo	-1.05	<0.001	-1.57	-0.53
	Zipras. vs Pbo	-0.95	<0.001	-1.37	-0.52

*Estimates of treatment effects (e.g. for treated group - placebo) are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and fixed effect terms for center and treatment.
**The p-values and 95% confidence intervals are derived from the respective t-tests. (Refer to Appendix III Tables 18.2, 19.2, 20.2, 21.2, 22.2, 23.2, 24.2, and 25.2)
Source Data: Appendix V Tables 15, 16, and 17. Date of Data Extraction: 06JAN97. Date of Table Generation: 25FEB97

Table 5.3 S

Table 5.1.27
Treatment Effects at Last Observation for Selected Efficacy Variables - All Subjects
Ziprasidone Protocol 303

Variable	Treatment Comparison	Estimated Treatment Effect*	P-Value**	Lower 95% Confidence Limit**	Upper 95% Confidence Limit**
BPRSd Total	20 mg BID vs Pbo	-7.36	0.001	-11.70	-3.01
	40 mg BID vs Pbo	-6.99	0.002	-11.35	-2.62
	80 mg BID vs Pbo	-8.85	<0.001	-13.21	-4.49
	Zipras. vs Pbo	-7.73	<0.001	-11.28	-4.18
BPRSd Core Items	20 mg BID vs Pbo	-1.39	0.043	-2.73	-0.05
	40 mg BID vs Pbo	-1.86	0.007	-3.21	-0.51
	80 mg BID vs Pbo	-2.07	0.003	-3.41	-0.72
	Zipras. vs Pbo	-1.77	0.002	-2.87	-0.68
GAF Scale	20 mg BID vs Pbo	6.91	0.003	2.33	11.50
	40 mg BID vs Pbo	7.90	0.001	3.29	12.52
	80 mg BID vs Pbo	8.34	<0.001	3.73	12.96
	Zipras. vs Pbo	7.72	<0.001	3.97	11.47

*Estimates of treatment effects (e.g. for treated group - placebo) are based on least squares means (LSMEANS) derived from an ANCOVA model with baseline response as covariate and fixed effect terms for center and treatment.
**The p-values and 95% confidence intervals are derived from the respective t-tests. (Refer to Appendix III Tables 18.2, 19.2, 20.2, 21.2, 22.2, 23.2, 24.2, and 25.2)
Source Data: Appendix V Tables 15, 16, and 17. Date of Data Extraction: 06JAN97. Date of Table Generation: 25FEB97.

Study 031: (BE of 1 X 20 mg Commercial vs Research Capsules, single dose)

Study Design and Summary:

(see attachments 1 and 3)

Results:

(See attachments 4-6)

Reviewer's Comments:

1. This is partially failed BE study since the 90% CI for the Cmax ranged from 72% to 101%, whereas for the AUC ranged from 92% to 103% (attachments 4).

2. The mean and individual Cmaxs and AUCs were consistently higher in almost all subjects following the research capsules than the commercial capsules (attachments 5 and 6).

3. The Tmax for the commercial capsules was delayed by about 3 hours compared the research capsule.

4. The variability in the data was similar following both treatments.

Conclusions:

1. In this study, the BE criteria were not met since the 90% CI for the Cmax was 72% to 101% which is outside the currently required limits (80% to 125%).

2. The blood level of ziprasidone was constantly higher after the research capsules compared to the commercial capsules.

PROTOCOL 128-031: PHASE I OPEN STUDY TO COMPARE THE PHARMACOKINETICS OF ZIPRASIDONE ADMINISTERED AS ONE 20 MG PROPOSED COMMERCIAL CAPSULE AND ONE 20 MG RESEARCH CAPSULE ADMINISTERED UNDER FED CONDITIONS IN NORMAL, HEALTHY VOLUNTEERS

Principal Investigator: T. Hunt, M.D.

Study Publication: None

Study Dates: 6 February 1995 - 4 March 1995

Study Objective: To compare the pharmacokinetics of a single oral dose of ziprasidone 20 mg administered as one proposed commercial capsule and as one research capsule, both under fed conditions.

Study Design: This was an open, randomized, two-way crossover study comparing the pharmacokinetics of ziprasidone administered as one proposed 20 mg commercial capsule and one 20 mg research capsule, both under fed conditions. Subjects completing the study received both formulations as single oral doses separated by at least seven days.

Evaluation Groups:

Entered Study	23
Completed Study	22
Evaluated for Pharmacokinetics	22
Assessed for Safety	
Adverse Events	23
Laboratory Tests	10[a]

[a]The number of subjects reflects the number of female subjects who had serum pregnancy tests performed within 6 days after the last dosing day, during the second treatment period. Other laboratory tests were performed at screening and prior to the first day of dosing.

Subjects: Healthy male and female volunteers ranging in age from 18 to 42 years.

Drug Administration:

Dosage Form	20 mg proposed commercial capsule (FID #QC2213) 20 mg research capsule (FID #CS-90-031)
Dosing	Subjects were administered single 20 mg doses of ziprasidone as either the proposed commercial capsule or the research capsule on the first treatment day following a standard breakfast. After a washout period of at least seven days, subjects received the alternate treatment. All doses were administered with 50 ml of water.

Pharmacokinetic and Safety Evaluations: Blood samples for the determination of serum ziprasidone concentrations were collected prior to and up to 36 hours after each dose of study drug. Serum concentrations were used to determine pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, T_{max}, K_{el}, and $T_{1/2}$). Subjects were monitored for adverse events.

Analytical Methods:

Statistical Methods: Natural log-transformed $AUC_{0-\infty}$ and C_{max}, and untransformed T_{max} and K_{el} were analyzed using an ANOVA model. For $AUC_{0-\infty}$ and C_{max}, 90% confidence limits were calculated for the ratio of geometric means.

Pharmacokinetic Results:
Mean ± Coefficients of Variation (%CV) of Pharmacokinetic Parameters (n=22)

	Ziprasidone				
Parameter	20 mg research capsule		20 mg proposed commercial capsule		90% Confidence Limits
$AUC_{0-\infty}$ (ng•hr/ml)[a]	518[b]	± 24	504	± 17	(92.5%, 102.6%)
C_{max} (ng/ml)[a]	54	± 43	46	± 31	(72.0%, 101.3%)
T_{max} (hr)	7	± 53	10	± 45	(2, 5)
K_{el} (hr^{-1})	0.157[c]	± 15	0.160	± 20	(-0.011, 0.017)
$T_{1/2}$ (hr)[d]	4.4[c]	–	4.3	–	–

[a]geometric mean
[b]$AUC_{0-Tlast}$ reported for one subject due to the inability to estimate K_{el}.
[c]n=21 due to the inability to estimate K_{el} for one subject.
[d]mean $T_{1/2}$ = ln(2)/mean K_{el}

Safety Results:

	Ziprasidone	
	20 mg research capsule	20 mg proposed commercial capsule
Adverse Events (All Causality)	9/23 (0)	7/22 (0)
Adverse Events (Treatment-emergent, treatment-related)	9/23 (0)	6/22 (0)

() subjects discontinued

Summary and Conclusions: The extent of exposure to ziprasidone, as measured by $AUC_{0-\infty}$, was similar after administration of either the proposed 20 mg commercial capsule or the 20 mg research capsule under fed conditions. The relative bioavailability of the proposed commercial capsule was 97%. The 90% confidence limits for the ratio of mean $AUC_{0-\infty}$ fell within the required 80% to 125% range. Mean C_{max} for the proposed commercial capsule was 15% lower than the mean C_{max} observed following administration of the research capsule. The 90% confidence limits

for the ratio of mean C_{max} were 72.0% and 101.3%, which fell outside the 80% to 125% range. There were no apparent gender differences for either $AUC_{0-\infty}$ or C_{max}.

Mean T_{max} was 3 hours later for the proposed commercial capsule. Mean terminal phase half-lives were similar for both formulations.

One subject discontinued from the study for non-treatment-related reasons (personal conflict). Following administration of the research capsule, the most frequently reported adverse event was mild to moderate somnolence. Other adverse events following dosing with the research capsule were isolated and of mild severity. All events were considered treatment-related except one case of mild headache. Isolated incidences of somnolence, headache, abnormal dreams, and abnormal thinking occurred following administration of the proposed commercial capsule, all of mild to moderate severity. All events were considered treatment-related except two cases of mild headache. No serious adverse events were reported.

In summary, based on $AUC_{0-\infty}$ and C_{max}, the 20 mg proposed commercial capsule was not bioequivalent to the 20 mg research capsule in this study. There were few adverse events and no serious adverse events reported.

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Table 5.2
Summary of Statistical Analyses of Pharmacokinetic Parameters (AUC, Cmax, Tmax, and Kel)
Ziprasidone Protocol 031

Pharmacokinetic Parameter	Comm. Cap.	Res. Cap.		90% Confidence Limits
	Geometric Means		Ratio	
AUC (0-inf) (ng.hr/ml)	504	518	97.4%	(92.5%, 102.6%)
Cmax (ng/ml)	46	54	85.4%	(72.0%, 101.3%)
	Means		Difference	
Tmax (hr)	10	7	3	(2, 5)
	Adjusted Means		Difference	
Kel (1/hr)	0.160	0.157	0.003	(-0.011, 0.017)

Adjusted means are displayed for Kel because of the unequal number of subjects in each sequence.
Source Data: Appendix III Tables 1-4 Date of Data Extraction: 23SEP95. Date of Table Generation: 23SEP95.

(5)

Table 5.1.1 Summary of Pharmacokinetic Parameters for Ziprasidone Following Administration of a Single 20 mg Commercial Capsule and a Single 20 mg Research Capsule of Ziprasidone to Normal, Healthy Volunteers under Fed Conditions. Ziprasidone Protocol 031

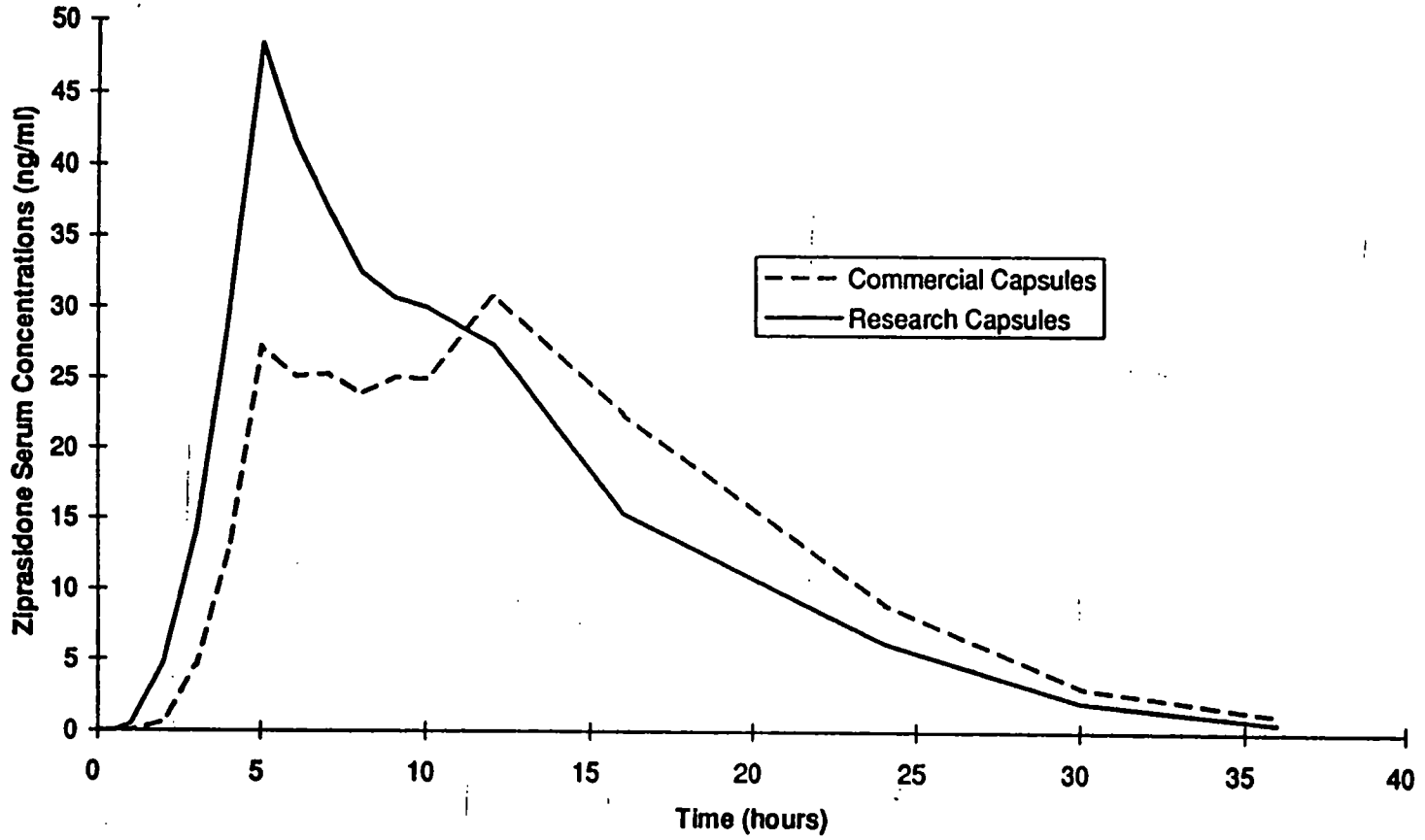
Treatment		Gender	AUC (0-∞)[a]	Cmax[a]	Tmax	Kel	T1/2[b]
20 mg Research Capsule FID #CS-90-031	Mean	M	526	54	7	0.162	4.3
	S.D.	M	115	16	4	0.026	--
	% CV	M	22	29	51	16	--
	Mean	F	508	53	7	0.149	4.6
	S.D.	F	137	30	4	0.020	--
	% CV	F	27	57	59	13	--
	Mean	M&F	518	54	7	0.157	4.4
	S.D.	M&F	123	23	4	0.024	--
	% CV	M&F	24	43	53	15	--
20 mg Commercial Capsule FID #QC2213	Mean	M	512	46	10	0.163	4.2
	S.D.	M	82	14	4	0.035	--
	% CV	M	16	30	40	22	--
	Mean	F	495	45	11	0.156	4.5
	S.D.	F	95	15	6	0.029	--
	% CV	F	19	33	52	18	--
	Mean	M&F	504	46	10	0.160	4.3
	S.D.	M&F	86	14	5	0.032	--
	% CV	M&F	17	31	45	20	--

[a] Geometric Means and Standard Deviations are reported for AUC(0-∞) and Cmax.
[b] Calculated as ln(2)/mean Kel.

Source Data: Appendix IV, Tables 1 and 2

6

Figure 1.1 Mean Serum Ziprasidone Concentrations vs Time Following Oral Administration of a Single 20 mg Commercial Capsule and a Single 20 mg Research Capsule of Ziprasidone to Normal, Healthy Volunteers under Fed Conditions.
Ziprasidone Protocol 031



Source Data: Appendix IV, Tables 1 and 2

Study 035: Study Design and Summary (AM vs PM for Commercial and Research Capsules):

(see attachments 1-3)

Results:

(See attachments 4-10)

Reviewer's Comments:

1. The commercial and research capsules are bioequivalent (attachment 4). The 90% CI for the AUC0-12 were 92% to 114% and for the Cmax was 80% to 124% (attachment 5).

2. In general, the AUC0-12 h at AM is being constantly higher than the AUC0-12 h at PM for both commercial and research capsules (attachment 6). The variability in the data appears to be greater in the evening than in the morning. However, this does not appear to be of clinical significance.

3. No difference in the PK between female and males (attachment 6-8).

4. No difference in the prolactin serum levels between the formulations nor between genders (attachments 9 and 10).

Conclusions:

1. The two formulations are bioequivalent based on the CI for the AUC0-12h and the Cmax which were within the required 90% CI limits (80 to 125%).

2. There is no difference in the data between the dosing schedules (AM vs PM) or between gender.

PROTOCOL 128-035: PHASE I OPEN, MULTIPLE DOSE, ORAL STUDY TO COMPARE THE MORNING AND EVENING PHARMACOKINETICS OF ZIPRASIDONE ADMINISTERED AS A 20 MG PROPOSED COMMERCIAL CAPSULE AND AS A 20 MG RESEARCH CAPSULE IN NORMAL, HEALTHY SUBJECTS

Principal Investigator: T. Hunt, M.D.

Study Publication: None

Study Dates: 28-August-95 - 29-September-95

Study Objective: To compare the morning and evening steady-state pharmacokinetics of a 20 mg proposed commercial capsule and a 20 mg research capsule in normal, healthy subjects.

Study Design: This was an open, randomized, two-way crossover study consisting of two (2) five-day treatment periods (days 1-5 and days 6-10) with no washout between treatment periods. Ziprasidone was administered as 1 x 20 mg proposed commercial capsule or 1 x 20 mg research capsule twice daily for 5 days for each treatment sequence. Subjects were randomized to the Group A sequence (proposed commercial capsule → research capsule) or Group B sequence (research capsule → proposed commercial capsule). Each subject received both formulations in the fed state.

Evaluation Groups:

	Commercial Capsule	Research Capsule
Entered Study	12	12
Completed Study	12	12
Evaluated for Pharmacokinetics	12	12
Assessed for Safety		
Adverse Events	12	12
Laboratory Tests*	0	0

*Laboratory tests were done only at screening and prior to dosing.

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

Drug Administration:

Dosage Form: ziprasidone proposed commercial capsule
20 mg FID #QC2327

ziprasidone research capsule
20 mg FID #CS-90-031

Dosing: Both dosages were each administered BID for 5 days. Group A received 1 x 20 mg proposed commercial capsule BID on days 1-5 then 1 x 20 mg research capsule BID on days 6-10. Group B received 1 x 20 mg research capsule BID on days 1-5 then 1 x 20 mg proposed commercial capsule BID on days 6-10.

Pharmacokinetic, Pharmacodynamic, and Safety Evaluations: Serum for ziprasidone pharmacokinetics was collected prior to and up to 12 hours after morning and evening dosing on day 5 of each treatment leg. Additional serum samples were obtained prior to morning dosing on day 1 and just prior to and 12 hours following morning dosing on days 2-4 and 7-9. Serum prolactin concentrations were measured from the samples obtained for the quantification of ziprasidone at baseline and on day 5 of the commercial capsule leg retrospectively. Subjects were monitored for adverse events, and changes in vital signs.

Analytical Methods:

Statistical Methods: Natural log-transformed AUC and C_{max} and untransformed T_{max} were analyzed using an ANOVA model. For AUC and C_{max}, the anti-log (exponent) of the difference and the confidence limits were taken to estimate the ratio between the formulations and their 90% confidence intervals.

Pharmacokinetic Results:

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

	20 mg Commercial Capsule	20 mg Research Capsule
AUC_{0-24} (ng•hr/ml)[a]	826 ± 28	886 ± 25
$AUC_{0-12a.m.}$ (ng•hr/ml)[a]	486 ± 22	476 ± 32
$AUC_{0-12p.m.}$ (ng•hr/ml)[a]	324 ± 49	401 ± 25
$C_{max\ a.m.}$ (ng/ml)[a]	72 ± 13	73 ± 41
$C_{max\ p.m.}$ (ng/ml)[a]	52 ± 39	54 ± 32
$T_{max\ a.m.}$ (hours)	7 ± 48	5 ± 40
$T_{max\ p.m.}$ (hours)	6 ± 81	7 ± 46

[a] geometric mean

Pharmacodynamic Results:

Mean Serum Prolactin Concentrations (ng/ml)

	Male			Female		
Hours Post Dose	N	Mean	SD[a]	N	Mean	SD[a]
Baseline	7	22.0	17.7	5	11.2	3.3
0[b]	7	29.7	23.2	5	42.2	31.3
24	7	30.0	17.4	5	44.1	13.1

[a] Standard deviation

[b] Pre-dose, occurring on the morning of the fifth day of commercial capsule dosing

Safety Results:

Findings	Ziprasidone 20 mg Commercial Capsule	Ziprasidone 20 mg Research Capsule
Adverse Events (All Causality)	8/12 (0)	11/12 (0)
Adverse Events (Treatment Emergent, Treatment Related)	8/12 (0)	11/12 (0)

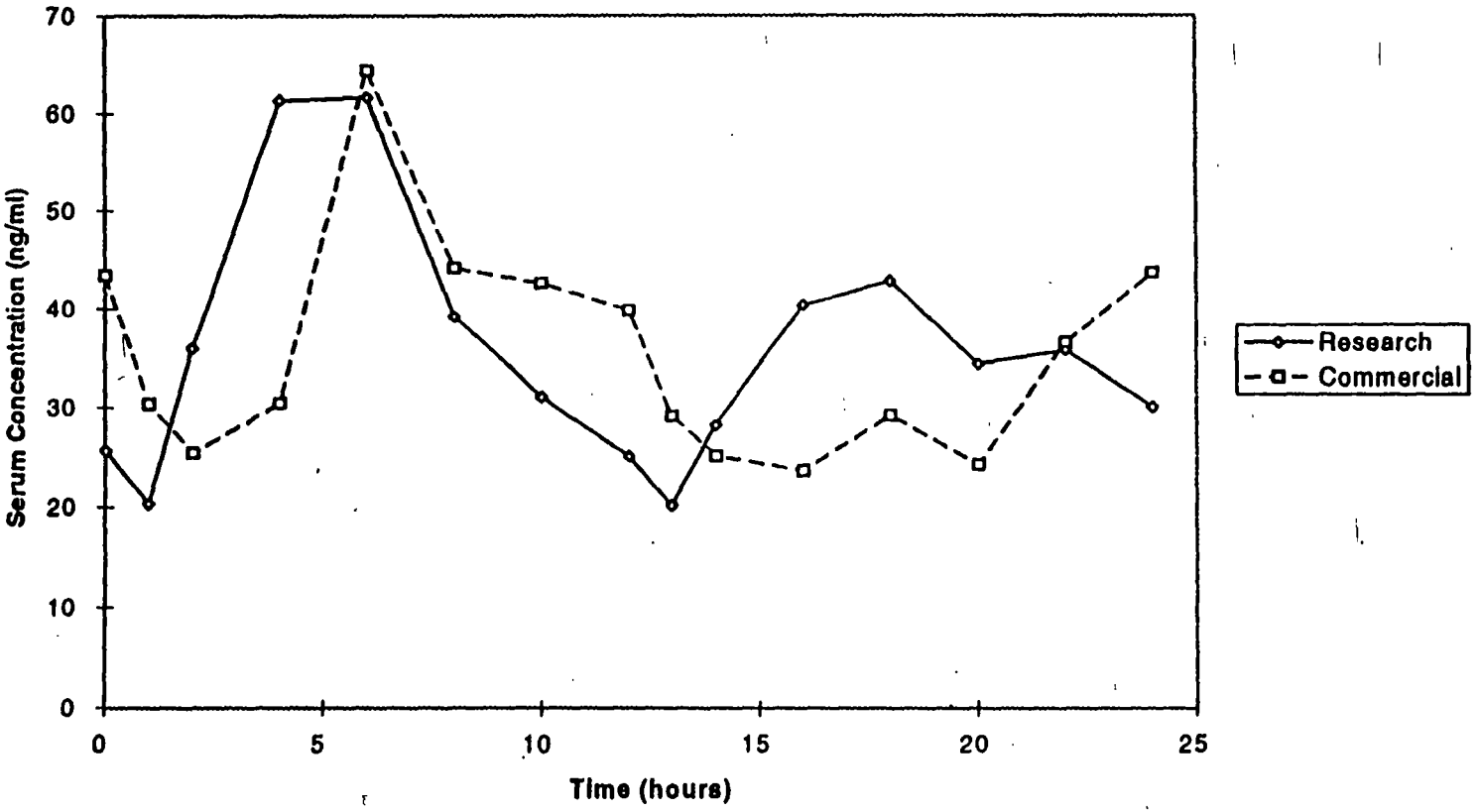
() subjects discontinued

Summary and Conclusions: Using the morning dose pharmacokinetic data as the basis for establishing bioequivalence between the two formulations, the 20 mg commercial capsules were considered to be bioequivalent to the 20 mg research capsules. The 90% confidence limits on the ratios of the $AUC_{0\text{-}12a.m.}$ (91.8%, 113.7%) and $C_{max\ a.m.}$ (80.3%, 123.7%) were within the 80% to 125% range. For the commercial formulation, evening mean AUC and C_{max} values were less than their respective morning values, with mean decreases ranging from 28% to 33%. A comparison of the evening pharmacokinetic parameters between the two formulations fell outside the 80% to 125% range, but the 90% confidence limits on the ratio of the $AUC_{0\text{-}24}$ (84.8%, 102.4%) were within the 80% to 125% range. There did not appear to be any significant differences between male and female subjects.

The results of the serum prolactin concentration data suggest that modest elevations in prolactin concentrations persist in female subjects while on ziprasidone treatment.

Adverse events were experienced by 8 of 12 subjects receiving ziprasidone 20 mg proposed commercial capsules, and 11 of 12 subjects receiving ziprasidone 20 mg research capsules. The majority of adverse events were considered related to treatment and all were of mild severity. The predominant adverse events in both treatment groups were those of the nervous system, primarily somnolence and agitation. There were no serious adverse events.

Figure 1. Mean Serum Ziprasidone Concentrations Versus Time on Day Five Following Twice Daily Administration 20 mg Ziprasidone using Research or Commercial Capsules
Ziprasidone Protocol 035



Source Data: Appendix IV, Tables 1 and 2

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Table 5.2.1 Page 1 of 1
Summary of Statistical Analyses of AM Pharmacokinetic Parameters (AUC(0-12), Cmax(0-12), and Tmax(0-12))
Ziprasidone Protocol 035

Pharmacokinetic Parameter	Comm. Cap.	Res. Cap.		90% Confidence Limits
	Geometric Means		Ratio	
AUC(0-12) (ng.hr/ml)	486.4	476.0	102.2%	(91.8%, 113.7%)
Cmax(0-12) (ng/ml)	72.3	72.6	99.7%	(80.3%, 123.7%)
	Means		Difference	
Tmax(0-12) (hr)	6.5	5.0	1.5	(-0.6, 3.6)

Source Data: Appendix III, Tables 1-3 Date of Data Extraction: 22MAY96. Date of Table Generation: 22MAY96.

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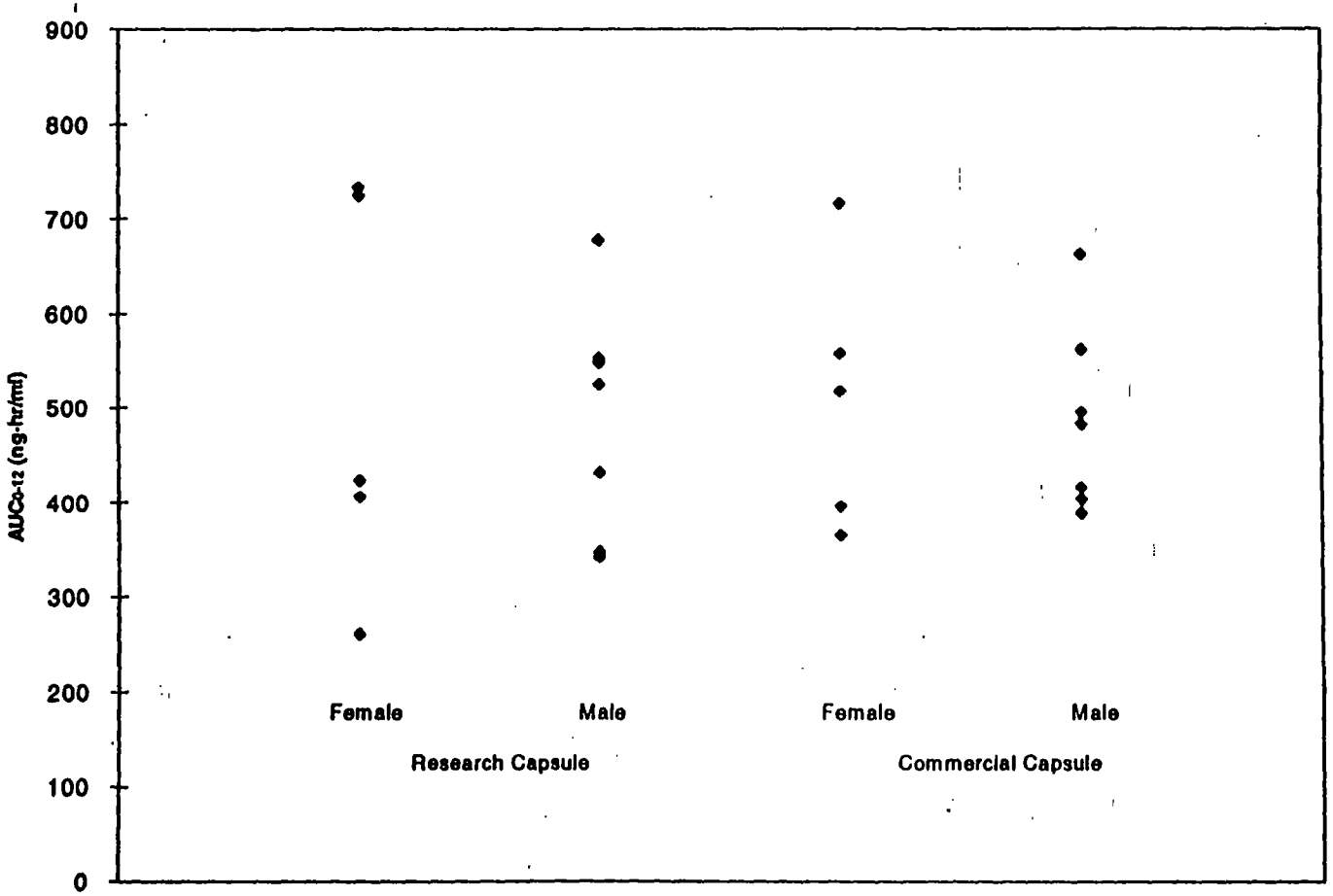
Table 5.1.1 Summary of Pharmacokinetic Parameters Following Multiple Dose Administration of 20 mg Commercial Capsules and 20 mg Research Capsules
Ziprasidone Protocol 035

Treatment	Gender		$AUC_{0\text{-}24}$* (ng•hr/ml)	$AUC_{0\text{-}12a.m.}$* (ng•hr/ml)	$AUC_{0\text{-}12p.m.}$* (ng•hr/ml)	$C_{max\,a.m.}$* (ng/ml)	$C_{max\,p.m.}$* (ng/ml)	$T_{max\,a.m.}$ (hr)	$T_{max\,p.m.}$ (hr)
Commercial Capsules	M(N=7)	Mean	785	480	292	69	44	7	8
		S.D.	247	93	167	10	18	2	4
		CV%	31	19	57	15	41	33	55
Commercial Capsules	F (N=5)	Mean	886	496	374	77	66	6	4
		S.D.	203	135	135	7	16	4	6
		CV%	23	27	36	9	24	71	138
Research Capsules	M(N=7)	Mean	849	477	367	79	56	4	7
		S.D.	197	122	99	28	24	1	3
		CV%	23	26	27	36	42	32	52
Research Capsules	F (N=5)	Mean	941	475	453	64	52	6	8
		S.D.	207	74	31	7	2	2	3
		CV%	22	16	7	11	4	41	43
Commercial Capsules	M&F (N=12)	Mean	826	486	324	72	52	7	6
		S.D.	229	106	160	10	20	3	5
		CV%	28	22	49	13	39	48	81
Research Capsules	M&F (N=12)	Mean	886	476	401	73	54	5	7
		S.D.	217	154	99	30	18	2	3
		CV%	25	32	25	41	32	40	46

*Geometric Mean and Standard Deviation

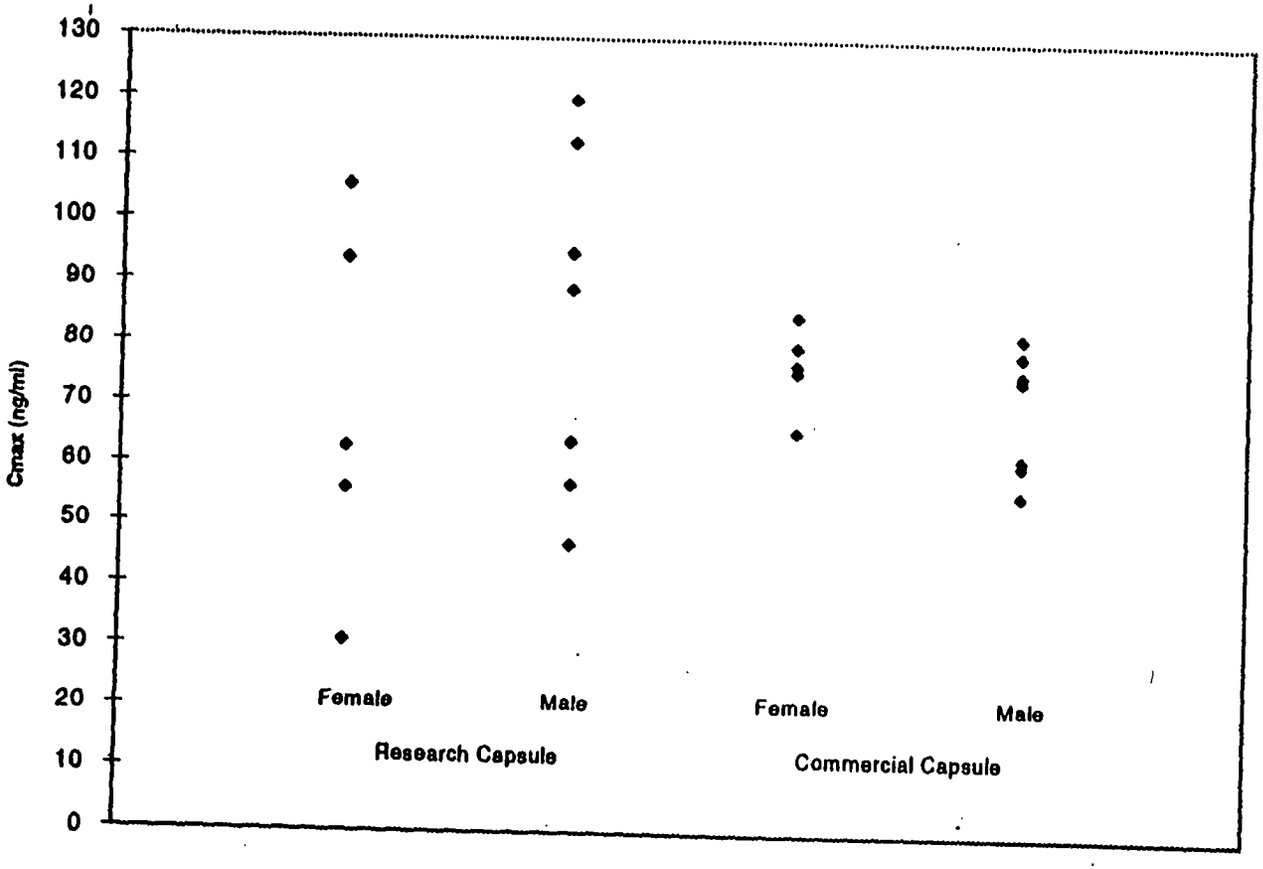
Source Data: Appendix IV, Tables 1 and 2

Figure 6. Comparison of Individual $AUC_{0\text{-}12a.m.}$ Values by Gender Following Administration of 1 x 20 mg Research Capsule and 1 x 20 mg Commercial Capsule
Ziprasidone Protocol 035



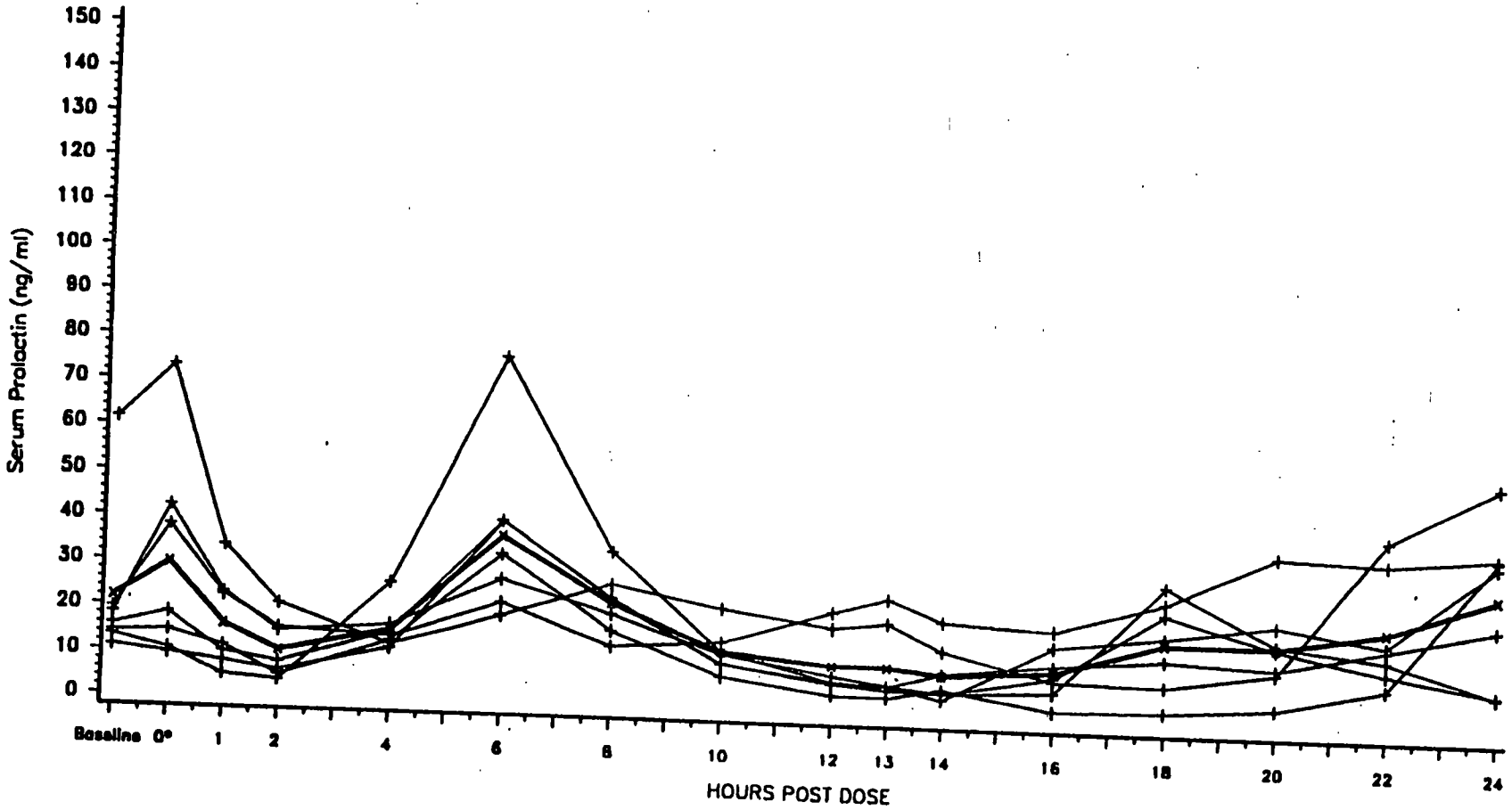
Source Data: Appendix IV, Tables 1 and 2

Figure 7. Comparison of Individual C_{max}a.m. Values by Gender Following Administration of 1 x 20 mg Research Capsule and 1 x 20 mg Commercial Capsule
Ziprasidone Protocol 035



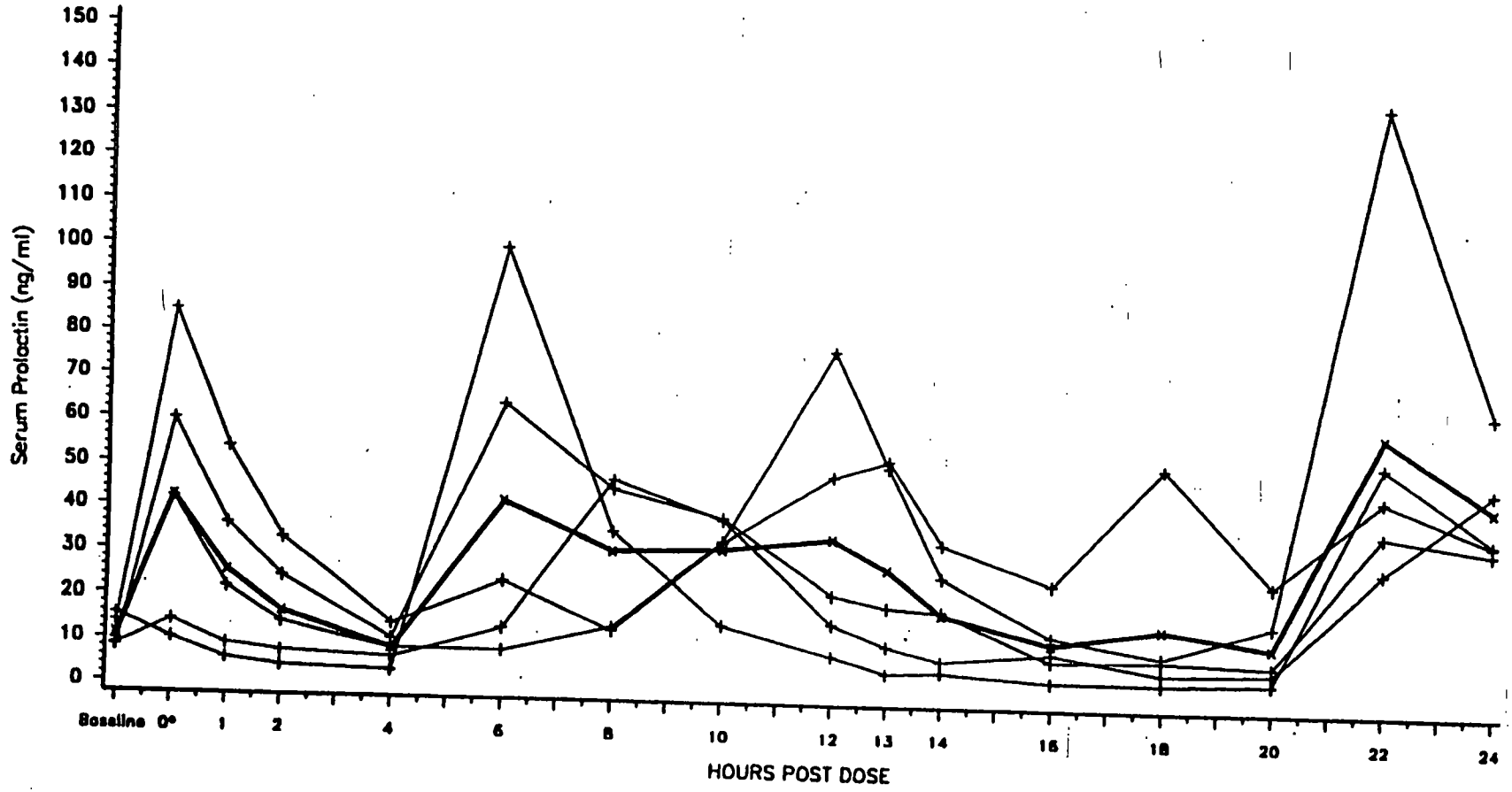
Source Data: Appendix IV, Tables 1 and 2

FIGURE 8.1
SERUM PROLACTIN (ng/ml): Commercial Cap. – Male Subjects
ZIPRASIDONE PROTOCOL 035



Mean value represented by thicker line.
* Pre-Dose, occurring on the fifth day of Commercial Capsule dosing.
Source Data : Appendix III, Table 12 and Appendix V, Table 11 Date of Data Extraction : 24OCT96 Date of Figure Generation : 19NOV96

FIGURE 8.2
SERUM PROLACTIN (ng/ml): Commercial Cap. – Female Subjects
ZIPRASIDONE PROTOCOL 035



Mean value represented by thicker line.
* Pre-Dose, occurring on the fifth day of Commercial Capsule dosing.
Source Data : Appendix III, Table 12 and Appendix V, Table 11 Date of Data Extraction : 24OCT96 Date of Figure Generation : 19NOV96

21. Study 040 (BE of 2 X 20 mg vs 1 X 40 Commercial Capsules, Multiple dose)

Study Design and Summary:

(see attachments 1 and 4)

Results:

(See attachments 5-13)

Reviewer's Comments:

1. The BE was partially failed since the 90% CI for the AUC was slightly outside the range (78% to 102%) whereas for the Cmax ranged from 82% to 104% (attachments 5).

2. There was no particular trend (i.e., treatment effect) in the Cmax and AUC values with respect to treatment days (attachments 6-9).

3. There was some variability among the treatments (attachment 10).

4. Overall, the serum trough levels after the 1 X 40 mg is higher than after the 2 X 20 mg dose (attachment 11).

5. There was relatively good correlation between the saliva and serum ziprasidone concentration (attachment 12). In addition, the saliva/serum ratios were highly variable (~0.02% to ~2.25%) with no particular pattern or trend to be higher or lower than 1%, the unbound drug fraction (attachment 13). However, it is not clear as to why some of the ratios were much higher than the unbound drug fraction. This observation suggests that the drug excreted and/or secreted by the salivary glands via active transport mechanisms.

6. As expected, the urinary excretion data for the parent drug and its major metabolites sulfone and sulfoxide were similar to those found in the mass balance study.

Conclusions:

1. In this study, the BE criteria were not met since the 90% CI for the AUC was 78% to 102% which is slightly outside the currently required limits (80% to 125%).

2. The serum trough levels of ziprasidone was constantly higher after the 1 X 40 mg capsules compared to the 2 X 20 mg capsules.

PROTOCOL 128-040: PHASE I OPEN, MULTIPLE DOSE, ORAL STUDY TO COMPARE THE PHARMACOKINETICS OF ZIPRASIDONE ADMINISTERED AS A 40 MG PROPOSED COMMERCIAL CAPSULE AND AS TWO, 20 MG COMMERCIAL CAPSULES IN NORMAL, HEALTHY SUBJECTS

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

Study Publication: None

Study Dates: 6 March 1996 - 7 May 1996

Study Objective: To assess the safety, toleration and steady-state pharmacokinetics of a 40 mg proposed commercial capsule vs two 20 mg commercial capsules of CP 88,059-1 (ziprasidone HCl).

Study Design: This was an open, randomized, two-treatment, three period crossover study of the steady-state pharmacokinetics of ziprasidone HCl administered orally, twice daily as 1 x 40 mg commercial capsule and as 2 x 20 mg commercial capsules in three (3) three-day treatment periods in the same subjects. Half of the subjects received the 1 x 40 mg proposed commercial capsule (treatment A) on two occasions and 2 x 20 mg commercial capsules (treatment B) on one occasion; the other half of the subjects received the 2 x 20 mg capsules on two occasions and the proposed 1 x 40 mg commercial capsule on one occasion. To avoid potential toleration problems, subjects were titrated from 20 mg BID to 40 mg BID over a three day period, before starting the randomized treatment regimen. All doses are expressed as mg equivalents of ziprasidone free base. Both ziprasidone capsule formulations were administered in an open fashion in the fed state.

Evaluation Groups:

	Titration: 20 mg Commercial Capsule BID	1 x 40 mg Proposed Commercial Capsule BID	2 x 20 mg Commercial Capsule BID
Entered Study	19	17	19
Completed Study	19	15	15
Evaluated for Pharmacokinetics	0	13	13
Assessed for Safety			
Adverse Events	19	17	19
Laboratory Tests[a]	1	0	0

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

Subjects: Healthy male and female volunteers ranging in age from 18 to 43 years.

Drug Administration:

Dosage Form

Drug	Lot Number	FID Number	Potency	Formulation
CP-88,059-1	N5155	QC2214	40 mg	proposed commercial capsules
CP-88,059-1	N5056	QC2327	20 mg	commercial capsules

Dosing: Subjects received 1 x 40 mg proposed commercial capsules BID and 2 x 20 mg commercial capsules BID in three (3) three-day treatment periods, with no washout between treatments. Subjects received the ziprasidone capsules according to one of two treatment sequences. In Sequence 1, subjects received the 1 x 40 mg proposed commercial capsule (Treatment A) on one occasion and 2 x 20 mg commercial capsule (Treatment B) on two occasions. In Sequence 2 subjects received 2 x 20 mg commercial capsules (Treatment B) on one occasion and 1 x 40 mg proposed commercial capsule (Treatment A) on two occasions. To avoid potential toleration problems, all subjects had a three day titration period during which they received 1 x 20 mg commercial capsule BID before starting the randomized treatment sequence. All dosages were administered BID, 12 hours apart in the fed state.

Pharmacokinetic, Pharmacodynamic and Safety Evaluations: Blood samples for the determination of serum ziprasidone concentrations were collected prior to and up to 12 hours after dosing on days 6, 9 and 12. Serum concentrations were used to determine pharmacokinetic parameters $AUC_{0\text{-}12}$, C_{max} and T_{max}. Additional serum samples were obtained prior to morning dosing on days 1, 4, 5, 7, 8, 10 and 11, and were also collected prior to lunch and dinner on day 10 to coincide with the saliva collection. Urine samples were collected from just prior to morning dose to 12 hours post dose on day 10 dose for assessment of ziprasidone and the BITP (benzisothiazolil piperazine) sulfoxide and sulfone metabolite excretion. Saliva samples were obtained on day 10 just prior to the consumption of breakfast, lunch and dinner. Quantitative information obtained from urine and saliva collections was correlated with systemic exposures of serum ziprasidone concentrations. Subjects were monitored for adverse events and changes in vital signs.

Analytical Methods:

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

Pharmacokinetic Results:

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

Group 1[b]	Day 6	Day 9	Day 12
$AUC_{0\text{-}12}$[a] (ng•hr/ml)	838 ± 30	968 ± 39	983 ± 39
C_{max} [a](ng/ml)	123 ± 23	125 ± 29	121 ± 41
T_{max} (hr)	6 ± 27	8 ± 35	7 ± 41
Group 2[c]	Day 6	Day 9	Day 12
$AUC_{0\text{-}12}$[a] (ng•hr/ml)	870 ± 13	851 ± 45	767 ± 37
C_{max} [a](ng/ml)	120 ± 23	106 ± 41	99 ± 39
T_{max} (hr)	4 ± 96	3 ±105	9 ± 37

[a] geometric means and standard deviations are reported for $AUC_{0\text{-}12}$ and C_{max}

[b] 1 x 40 mg proposed commercial capsule→2 x 20 mg commercial capsules→2 x 20 mg commercial capsules.

[c] 2 x 20 mg commercial capsules→1 x 40 mg proposed commercial capsule→1 x 40 mg proposed commercial capsule

Safety Results:

	Number of Subjects [With/Evaluated (Discontinued)] Ziprasidone		
Findings	1 x 20 mg BID Titration	1 x 40 mg Proposed Commercial Capsule BID	2 x 20 mg Commercial Capsules BID
Adverse Events (All Causality)	15/19 (0)	15/17 (2)	18/19 (4)
Adverse Events (Treatment-emergent, Treatment-related)	15/19 (0)	15/17 (2)	18/19 (4)
Clinically Significant Laboratory Test Abnormalities	0/1 (0)*	NA	NA

*Laboratory tests were performed only at screening and prior to dosing, unless follow-up was required. Subject 599-0013 had a follow-up urinalysis done on day 3 due to elevated specific gravity at screening.

Summary and Conclusions:

The relative bioavailability of the 40 mg proposed commercial capsule as measured by AUC_{0-12} was 89.3% with a 90% confidence interval slightly outside bioequivalence acceptance limits (78.4%, 101.7%). The ratio of adjusted mean C_{max} values comparing the 40 mg proposed commercial capsule and the 20 mg commercial capsules was 92.5% with a 90% confidence interval within bioequivalence acceptance limits (82.2%, 104.2%). Based on visual inspection, steady-state systemic exposures to ziprasidone were attained by Day 6. Systemic exposure for the one woman participating in the study was comparable to the male subjects.

Mean T_{max} values ranged from 3 to 9 hours hours across all treatments, with no statistically significant difference in T_{max} observed between treatments.

Urine concentrations were highest for ziprasidone (range ng/ml), followed by BITP sulfone (range ng/ml) and BITP-sulfoxide (range ng/ml). Over the 12 hour collection period, 1.04% of the dose was excreted as unchanged drug, 0.95 % as BITP-sulfone, and 0.05% as BITP-sulfoxide. Salivary concentrations at predose, 4 hours and 10 hours postdose increased with increasing serum ziprasidone concentration, but were more variable than serum concentrations with saliva CV% values ranging from approximately 90% to 150% versus 40% to 60% for serum. The mean salivary to serum concentration ratios expressed in percent in predose, 4 and 10 hour postdose samples were 0.84%, 0.88%, and 0.94%, respectively. The ratios appeared independent of serum ziprasidone concentrations except at serum concentrations above 110 ng/ml where ratios typically exceeded 1% and were moderately higher than the ziprasidone free fraction of ziprasidone observed in serum.

Two subjects discontinued the study while receiving 1 x 40 mg proposed commercial capsule BID and four subjects discontinued while receiving 2 x 20 mg commercial capsules BID, all due to treatment related adverse events. While receiving 1 x 40 mg BID, one subject discontinued the study due to moderate anxiety and one subject

discontinued due to moderate depressed mood. While receiving 2 x 20 mg capsules BID, one subject discontinued the study due to moderate neck muscle spasms, one subject discontinued due to moderate anxiety and mild dyspnea, one subject discontinued due to mild anxiety, blurred vision, restlessness and moderate extra pyramidal reaction and one subject discontinued due to moderate auditory disturbance, depressed mood, visual disturbance and anxiety. The majority of subjects in all treatment groups experienced adverse events, predominantly somnolence. Other commonly reported adverse events included insomnia, anxiety, agitation and headache. All adverse events were of mild to moderate severity, and all were considered by the investigator to be related to treatment with the study drug except 1 case of back pain, accidental injury, and of syncope. No serious adverse events were reported.

In summary, based on the lower limit of the 90% confidence interval for $AUC_{0\text{-}12}$, the 40 mg proposed commercial capsule was not bioequivalent to the 20 mg commercial capsule in this study. The majority of subjects in all treatment groups experienced adverse events, primarily somnolence. There were no serious adverse events.

(5) 59

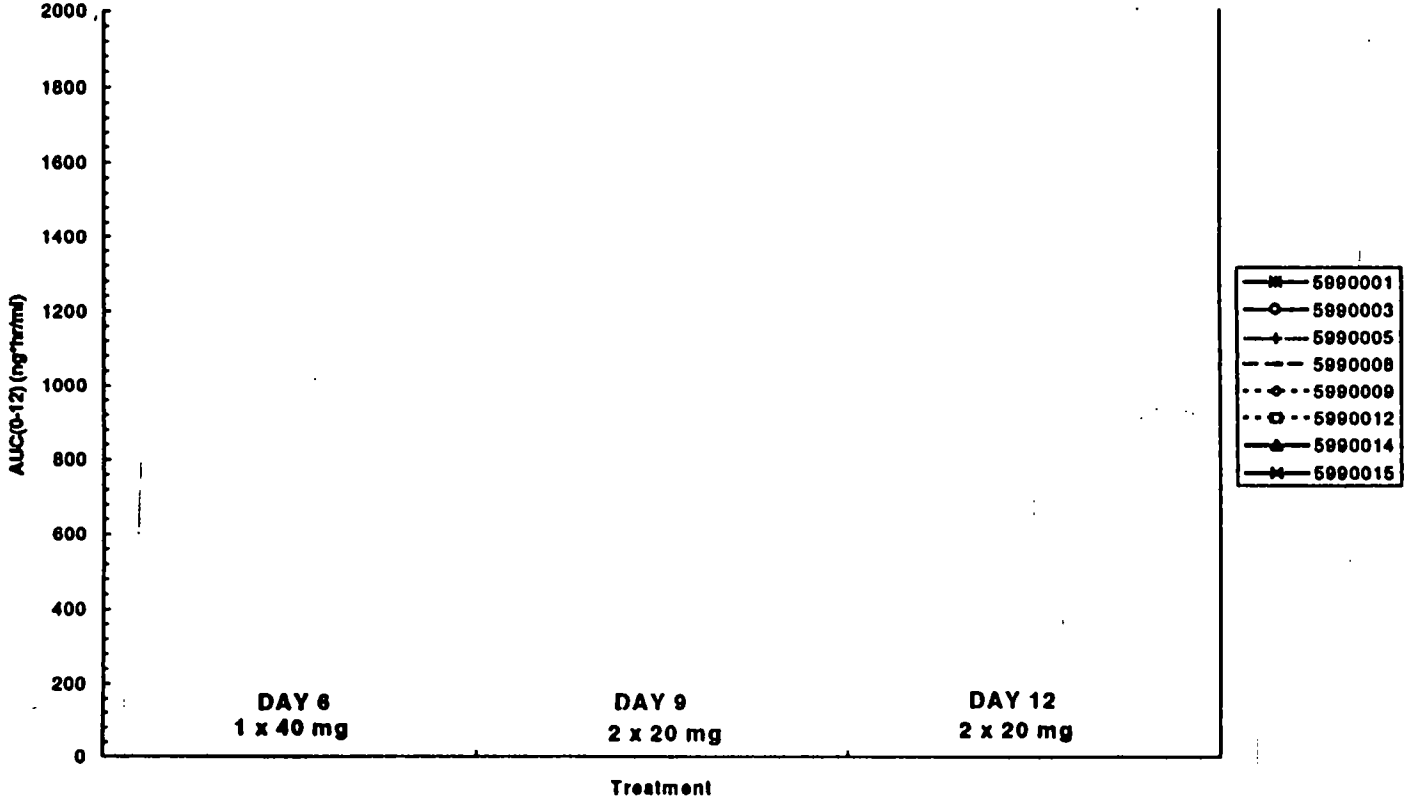
5

Table 5.2
Summary of Statistical Analyses of Pharmacokinetic Parameters (AUC(0-12), Cmax, and Tmax)
Ziprasidone Protocol 040

Pharmacokinetic Parameter	Comparison			90% Confidence Limits
		Adjusted Geometric Means	Ratio	
AUC(0-12) (ng.hr/ml)	1 x 40 mg vs. 2 x 20 mg	828.3 vs. 927.5	89.3%	(78.4%, 101.7%)
Cmax (ng/ml)	1 x 40 mg vs. 2 x 20 mg	110.8 vs. 119.7	92.5%	(82.2%, 104.2%)
		Adjusted Means	Difference	
Tmax (hr)	1 x 40 mg vs. 2 x 20 mg	6.2 vs. 6.1	0.1	(-1.7, 1.9)

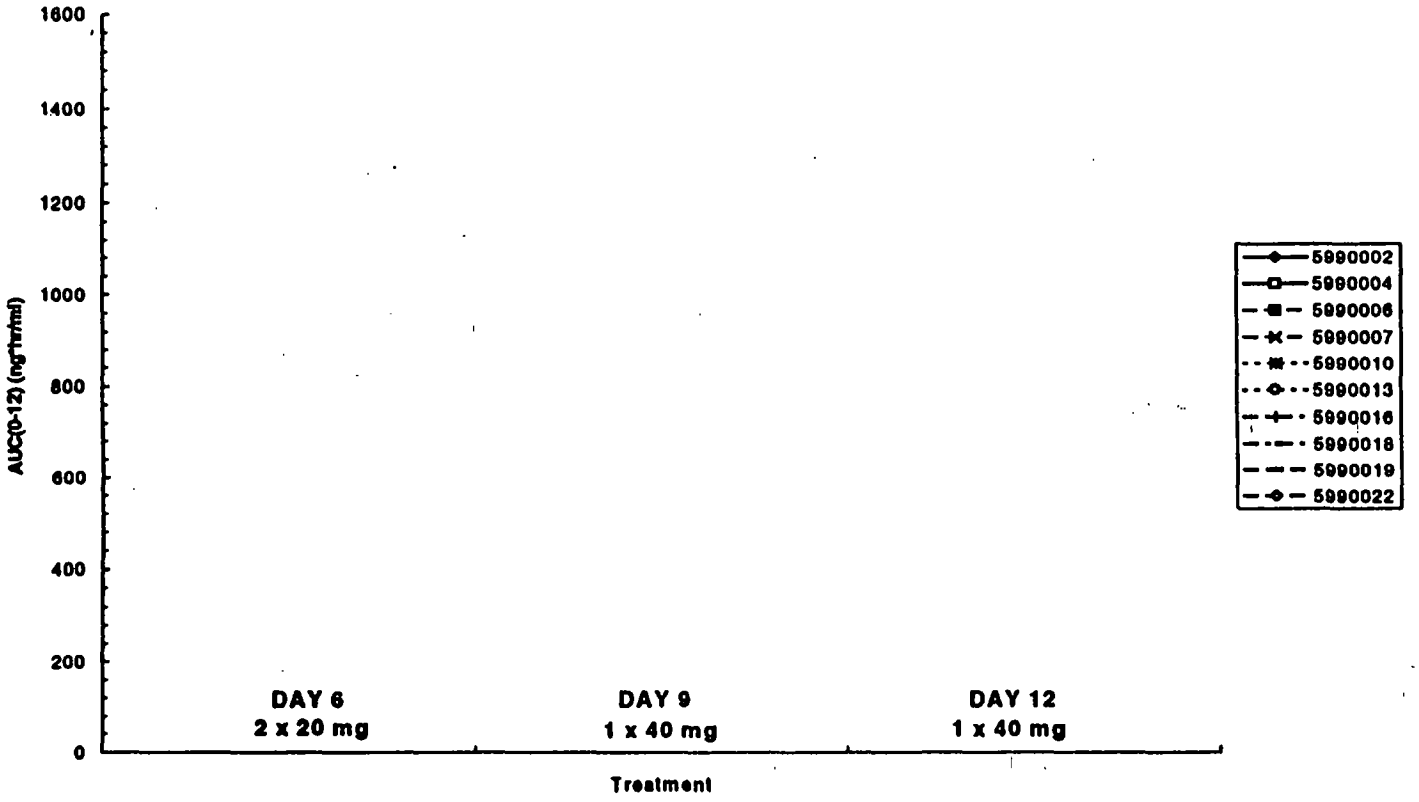
Source Data: Appendix III, Tables 1-3. Date of Data Extraction: 25JUL96 Date of Table Generation: 06AUG96

Figure 1.1 Ziprasidone AUC(0-12) Values in Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules - Group 1
Ziprasidone Protocol 040



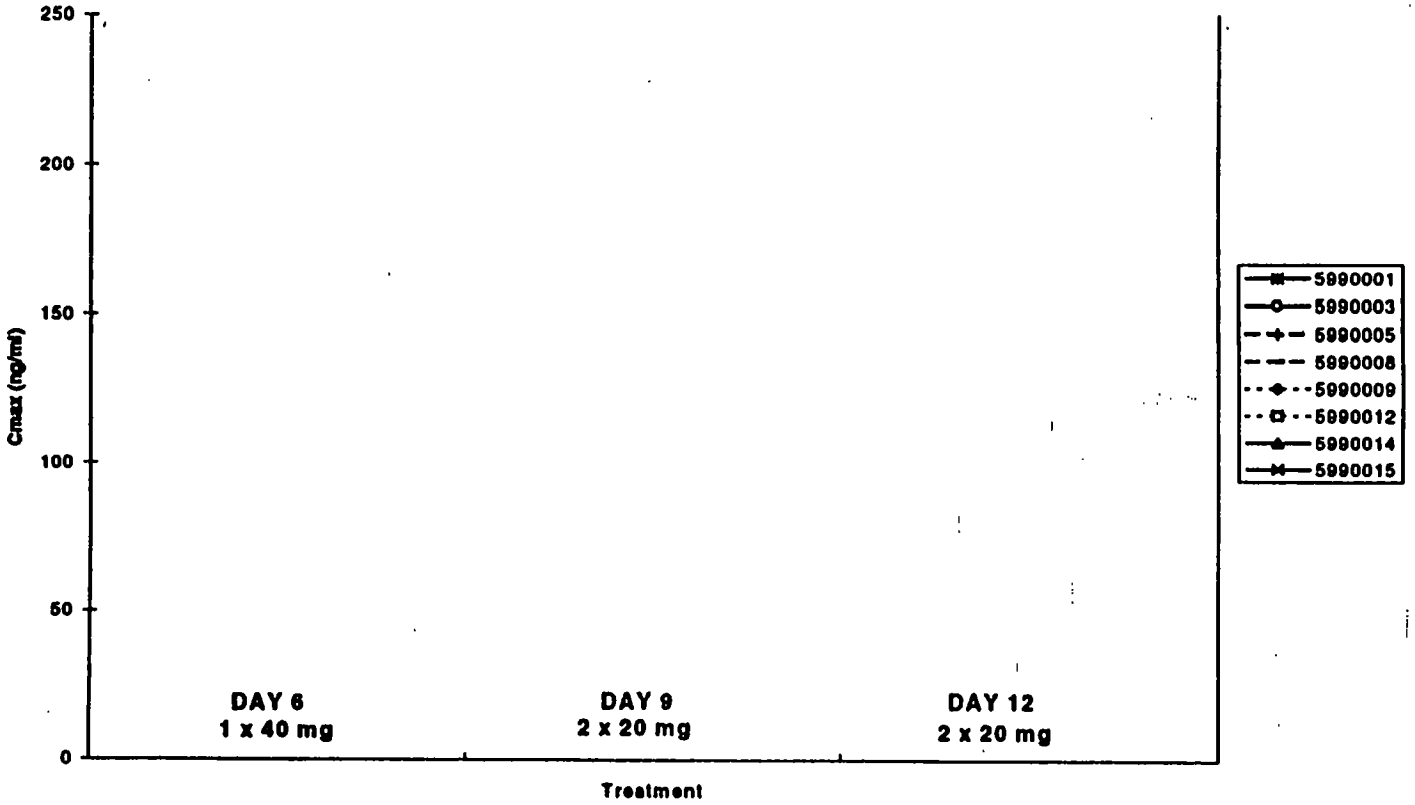
Source Data: Appendix IV, Tables 1 - 3

Figure 1.2 Ziprasidone AUC(0-12) Values In Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules - Group 2
Ziprasidone Protocol 040



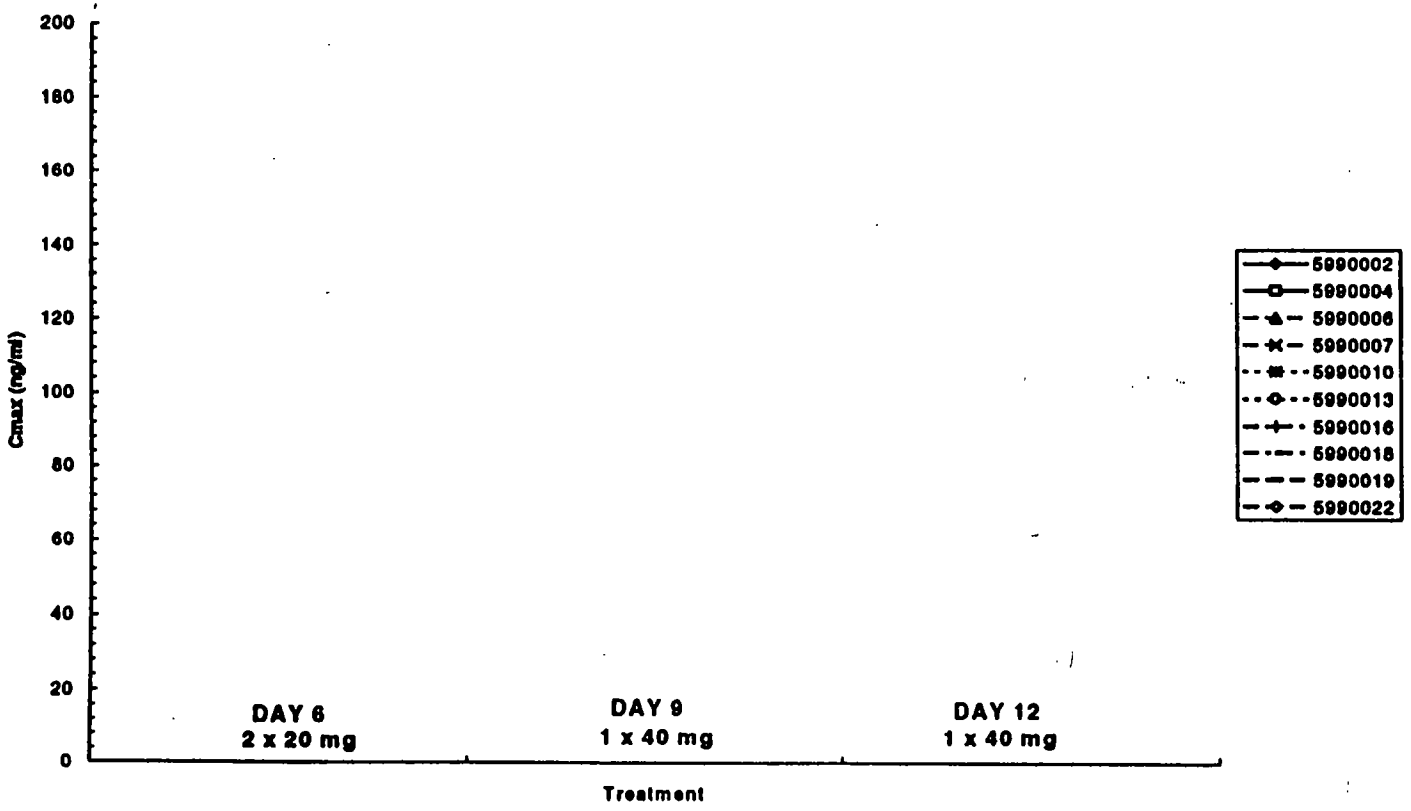
Source Data: Appendix IV, Tables 1 - 3

Figure 1.3 Ziprasidone Cmax Values in Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules - Group 1
Ziprasidone Protocol 040



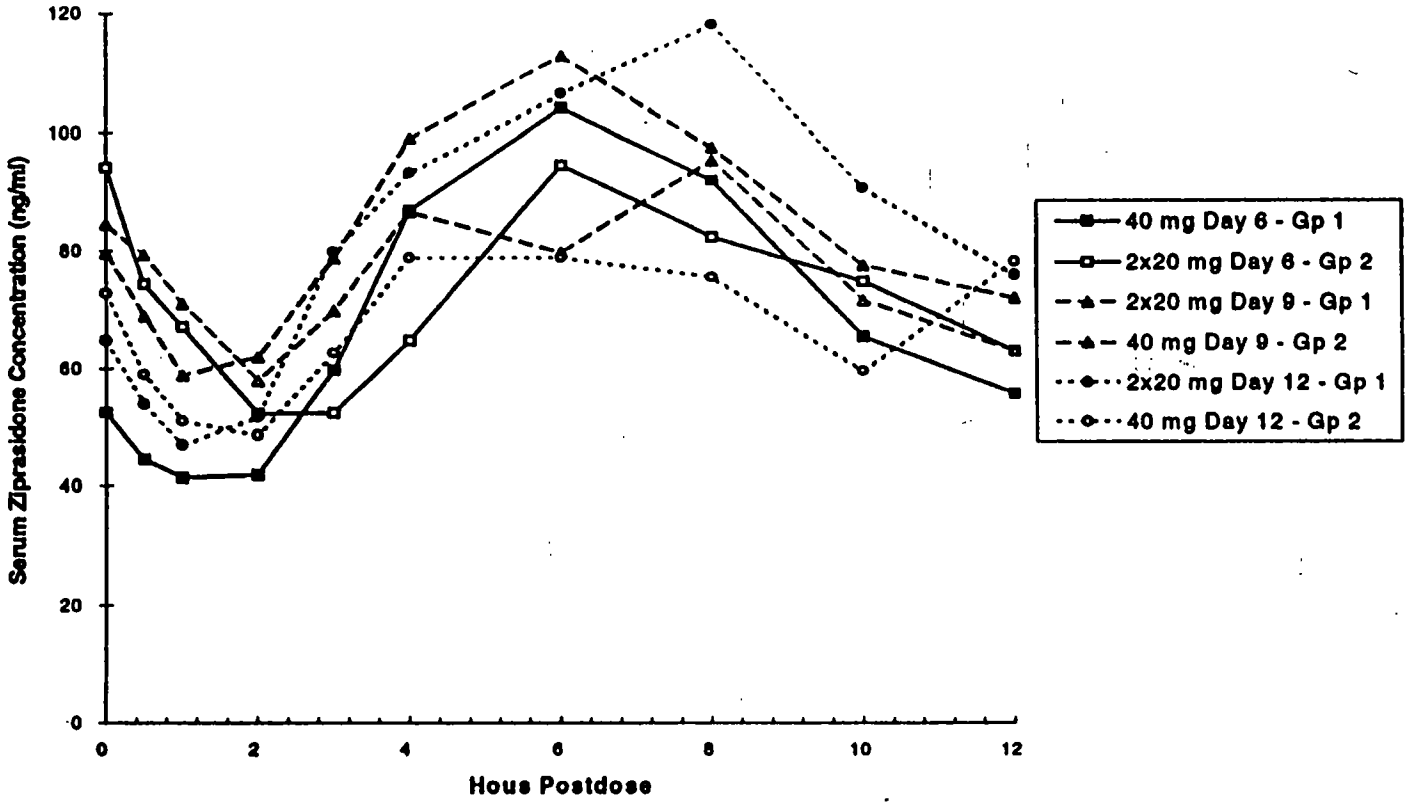
Source Data: Appendix IV, Tables 1 - 3

Figure 1.4 Ziprasidone Cmax Values In Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules - Group 2
Ziprasidone Protocol 040



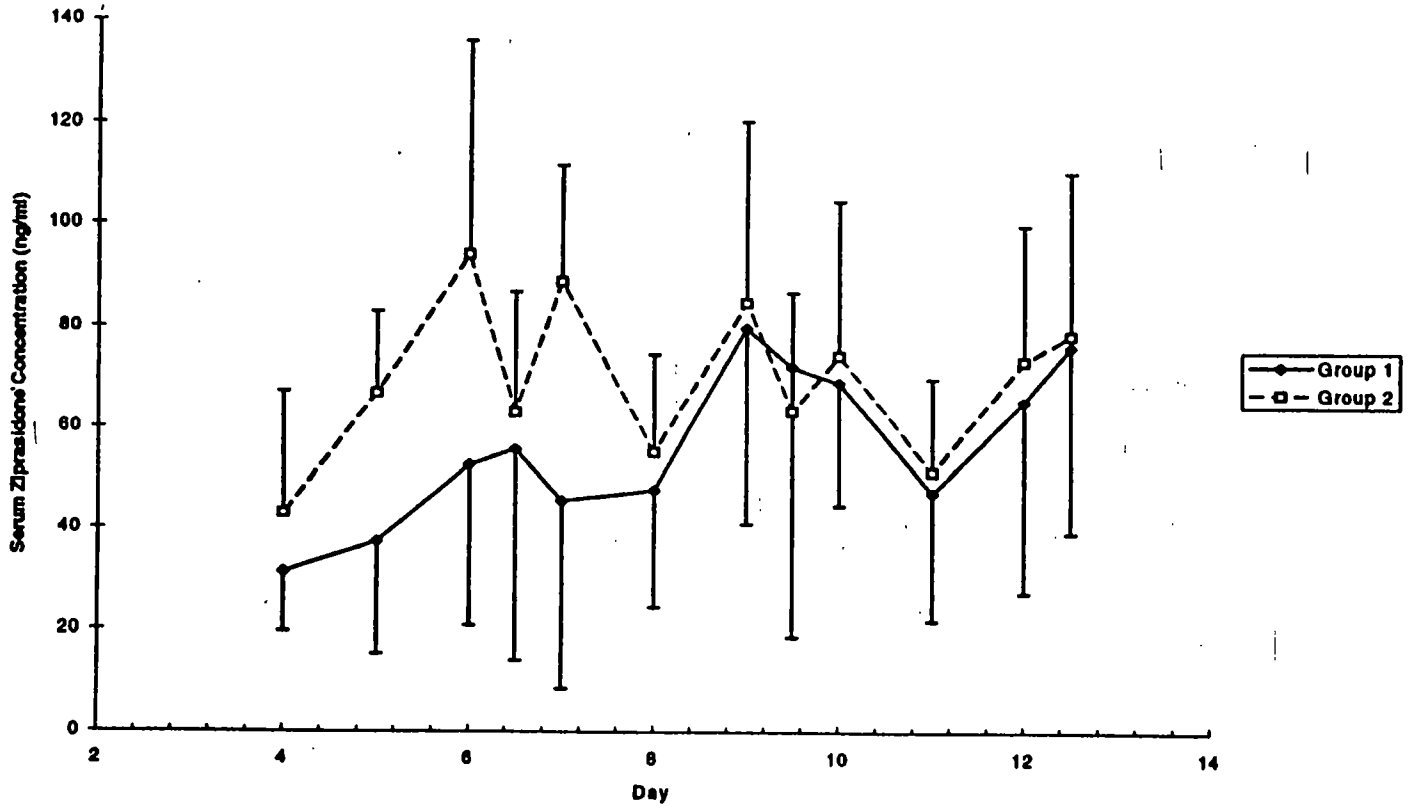
Source Data: Appendix IV, Tables 1 - 3

Figure 4.1 Mean Serum Ziprasidone Concentrations on Days 6, 9 and 12 In Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules
Ziprasidone Protocol 040



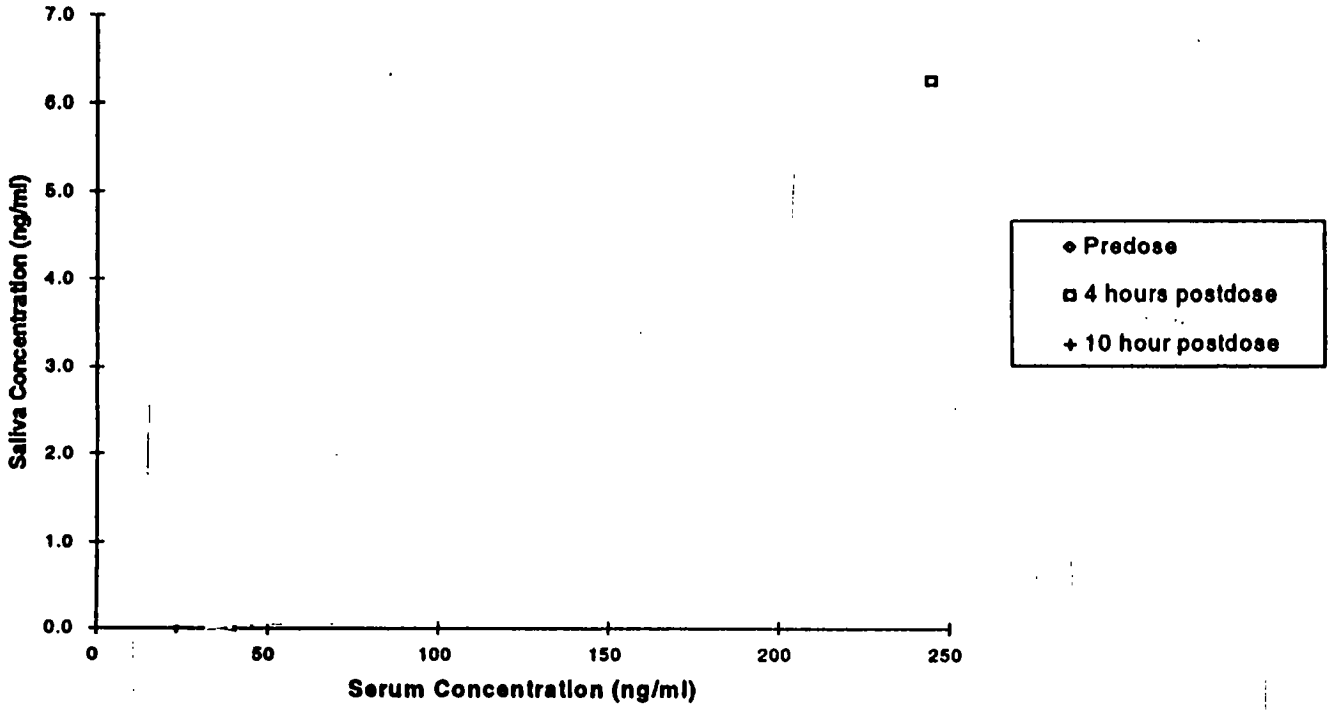
Source Data: Appendix IV, Tables 1 - 3

Figure 4.8 Mean Trough Serum Ziprasidone Concentrations on Days 4 Through 12 in Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules
Ziprasidone Protocol 040



Source Data: Appendix IV, Table 4

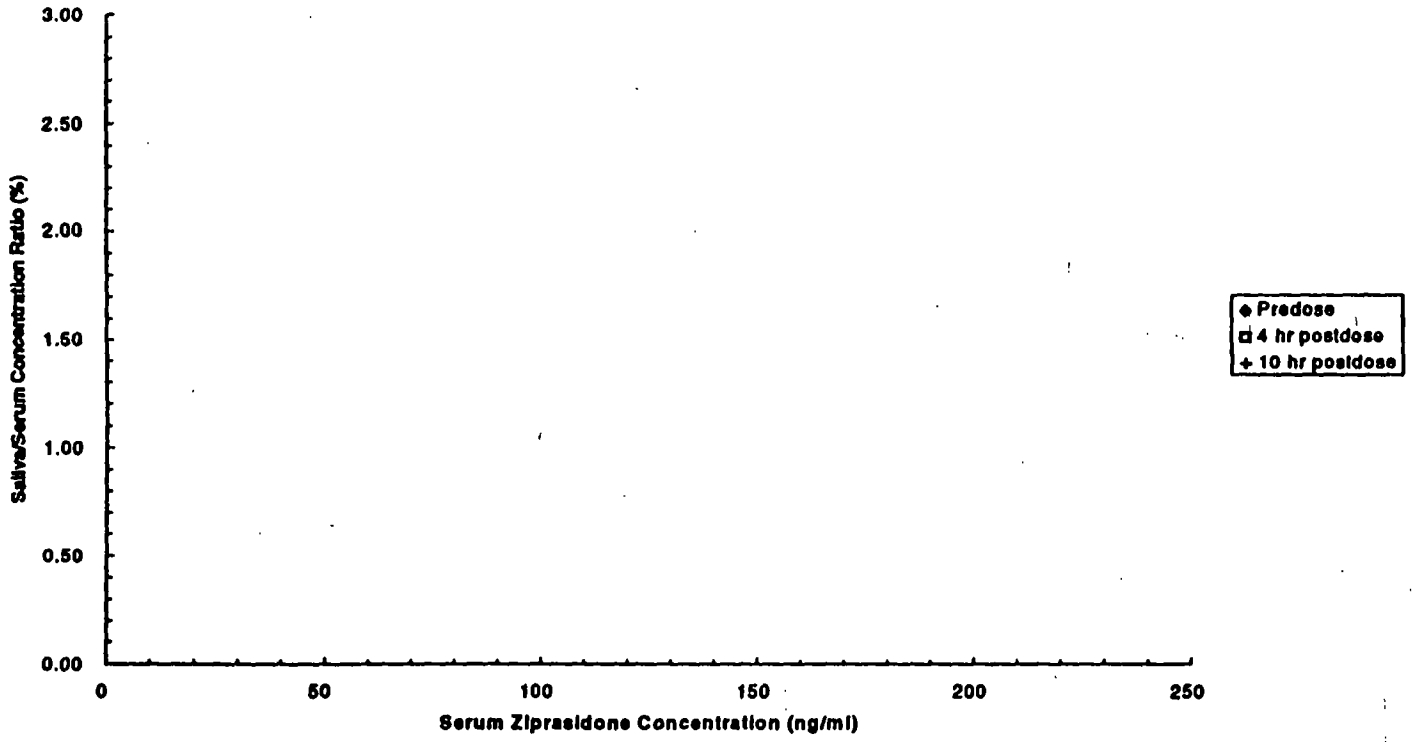
Figure 4.11 Ziprasidone Saliva Concentration Versus Serum Concentration in Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules
Ziprasidone Protocol 040



Source Data: Appendix IV, Table 5

13

Figure 4.12 Ziprasidone Saliva to Serum Concentration Ratio Versus Serum Concentration in Subjects Receiving 40 mg Ziprasidone HCl BID Using 2 x 20 mg Capsules or 40 mg Capsules
Ziprasidone Protocol 040



Source Data: Appendix IV, Table 5

Study 047 (1 X 40 mg vs 2 X 20 mg Capsules)

Study Design and Summary: (see attachments 1-3)

Results:

(See attachments 4-12)

Reviewer's Comments:

1. This is a repeat BE study since in the previous study (#128-040) the 90% CI for the AUC was 78% to 102% and for the Cmax was 82% to 104%. Thus, it did not meet the BE criteria.

2. The mean relative bioavailability of the 40 mg capsule compared to 2 X 20 mg capsules was 92.5% based on AUC (attachment 4).

3. The 90% CI for the AUC0-12 was 84% to 102%) and for the Cmax was 81% to 104% (attachment 4).

4. There was wide spread in the data between subjects as shown in attachments 5-8. It is noteworthy that after 1 X 40 mg dose on day 9, there is a consistent drop in both the AUCs and the Cmaxs in all subjects (attachments 5 and 7). However, after 2 X 20 mg dose also on day 9, there was a reverse trend in both the AUCs and Cmaxs which were consistently greater than day 6 and day 12 (attachments 6 and 8). These observations are clearly shown in attachments 9 and 10 where the overall mean values for both the AUCs and Cmaxs are plotted against each dosing day.

5. In general, it appears that the serum drug levels are consistently higher following the 2 X 20 mg than the 1 X 40 mg dosing (attachments 11 and 12). Attachment 12 clearly shows that in group 1 the serum level was consistently higher after 2 X 20 mg from days 4-6 and dropped when dosing was switched to 1 X 40 mg on day 7. This observation was in the reversed order for group 2 who on day 7 switched from 1 X40 mg to 2 X 20 mg.

Conclusions:

1. The two formulations were bioequivalent since the AUC and Cmax 90% CI were within the required limits (80% to 125%).

2. In general, the AUCs and Cmaxs are higher after 2 X 20 mg than after 1 X 40 mg.

PROTOCOL 128-047: PHASE I OPEN, MULTIPLE DOSE, ORAL STUDY TO COMPARE THE PHARMACOKINETICS OF ZIPRASIDONE ADMINISTERED AS A 40 MG PROPOSED COMMERCIAL CAPSULE AND AS TWO, 20 MG COMMERCIAL CAPSULES IN NORMAL, HEALTHY SUBJECTS

Principal Investigators: A. Laurent, M.D.

Study Publication: None

Study Dates: 8 July 1996 - 12 August 1996

Study Objective: To compare the steady-state pharmacokinetics of a 40 mg proposed commercial capsule and two 20 mg commercial capsules of ziprasidone in normal, healthy subjects using a three-period, repeated measure study design.

Study Design: This was an open, randomized, two-treatment, three period crossover study to evaluate the steady-state pharmacokinetics of ziprasidone in the same subjects. The study consisted of three (3) three-day periods. Half of the subjects were randomized to receive the 1 x 40 mg proposed commercial capsule for two periods and the 2 x 20 mg commercial capsules for one period. The other half of the subjects were randomized to receive the 2 x 20 mg capsules for two periods and the 1 x 40 mg capsule for one period. To avoid potential toleration problems, subjects were titrated from 20 mg BID to 40 mg BID at the beginning of the study. Subjects received 1 x 20 mg capsules BID for three days prior to receiving 40 mg BID. There was no washout between treatments.

Evaluation Groups:

	20 mg Commercial Capsule, BID Titration	40 mg Proposed Commercial Capsule, BID	2 x 20 mg Commercial Capsules, BID
Entered Study	26	24	25
Completed Study	25	24	23
Evaluated for Pharmacokinetics	0	23	23
Assessed for Safety			
Adverse Events	26	24	25
Laboratory Tests[a]	0	1[b]	0

[a]Laboratory tests were performed only at screening and prior to the first dose, unless follow-up was required.
[b]One male subject had an additional urinalysis performed during the study.

Subjects: Healthy male and female volunteers ranging in age from 19 to 45 years.

Drug Administration:

Dosage Form 20 mg commercial capsule (FID #QC2327)
40 mg proposed commercial capsule (FID #QC2214)

Dosing

Subjects were administered oral doses of ziprasidone in the morning and evening for 11 days (20 mg BID on days 1-3; 40 mg BID on days 4-11), and a single 40 mg dose in the morning on day 12. Doses were administered with 50 ml of water under fed conditions immediately following breakfast or dinner.

Pharmacokinetic and Safety Evaluations: Blood samples for the determination of serum ziprasidone concentrations were collected just prior to and up to 12 hours following the morning dose on days 6, 9, and 12. Additional serum samples were obtained prior to morning dosing on days 1, 4, 5, 7, 8, 10, and 11. Serum concentrations were used to estimate pharmacokinetic parameters (AUC_{0-12}, C_{max}, and T_{max}). Subjects were monitored for adverse events.

Analytical Methods:

Statistical Methods: Natural log-transformed AUC_{0-12} and C_{max}, and untransformed T_{max} were analyzed using an ANOVA model. For AUC_{0-12} and C_{max}, 90% confidence limits were calculated for the ratio of geometric means. Unless otherwise noted, mean values are arithmetic.

Pharmacokinetic Results:

Means and Coefficients of Variation (%CV) of Pharmacokinetic Parameters

Parameter	1 x 40 mg Capsule						2 x 20 mg Capsules					
	Day 6		Day 9		Day 12		Day 6		Day 9		Day 12	
Group 1[a] (n = 12)												
AUC_{0-12} (ng•hr/ml)[b]	--		819	(44)	927	(26)	964	(32)	--		--	
C_{max} (ng/ml)[b]	--		112	(51)	119	(32)	139	(36)	--		--	
T_{max} (hr)	--		6.3	(50)	4.7	(57)	5.3	(65)	--		--	
Group 2[c] (n = 11)												
AUC_{0-12} (ng•hr/ml)[b]	790	(47)	--		--		--		901	(45)	773	(47)
C_{max} (ng/ml)[b]	111	(52)	--		--		--		109	(50)	93	(56)
T_{max} (hr)	5.6	(46)	--		--		--		5.5	(36)	7.6	(28)

[a] received sequence 2 per protocol: 2 x 20 mg → 1 x 40 mg → 1 x 40 mg
[b] geometric mean
[c] received sequence 1 per protocol: 1 x 40 mg → 2 x 20 mg → 2 x 20 mg

Summary of Statistical Analyses of AUC_{0-12} and C_{max} (n = 23)

Parameter	Comparison	Ratio*	90% Confidence Limits
AUC_{0-12} (ng•hr/ml)	1 x 40 mg vs 2 x 20 mg	92.5%	(83.6%, 102.4%)
C_{max} (ng/ml)	1 x 40 mg vs 2 x 20 mg	91.7%	(80.8%, 103.9%)

*ratio of adjusted geometric means