CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-825

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

NDA#	20-825
Applicant	Pfizer Inc.
Name of Drug	(ziprasidone)
Indication	Treatment of psychosis
Documents Reviewed	Vol.1.1, vols., 1.90-1.124, June 6, 1997 submission SAS database and CANDA
Medical Reviewer	Dr. Roberta Glass (HFD-120)

The following review has been discussed with the medical review team and the team leader. This review summarizes the results of statistical analyses confirmed or performed by this reviewer. In the Reviewer Evaluation and Comments Section for each study, I shall discuss the potential implications of the following four statistical issues on the interpretation of efficacy results: multiple treatment arms, dose-response relationship, multiple primary efficacy endpoints, and high dropout rates. They are evaluated and commented upon by this Reviewer and can be found within individual trial sections. The tables/figures from the sponsor are labeled as Table xS/Figure xS, and those from this reviewer's analyses are labeled as Table xR/Figure xR.

1 BACKGROUND

In March 1997, Pfizer Inc. submitted ziprasidone ( ) NDA for review. This NDA consists of three US/Canada trials (Trials 114, 115, 106), and a non-US trial (Trial 303). The medical Division (HFD-120) decided to also review an additional US trial (Trial 104) since it is a placebo-controlled trial. All five double-blind, well-controlled studies are multicenter trials (Trial 114, 34 centers; Trial 115, 51 centers; Trial 106, 17 centers; Trial 104, 17 centers; and Trial 303, 33 centers). The non-US trial (52-week) aimed at relapse prevention for hospitalized patients with chronic or subchronic schizophrenia; the other four trials (4 to 6 weeks) studied schizophrenic patients experiencing an acute exacerbation.

Clinical rating scales were used to measure aspects of therapeutic activity. They are Positive and Negative Syndrome Scale (PANSS, Appendix I), Brief Psychiatric Rating Scale (BPRS total, p.22 after signature page), BPRS core item, the Investigator Clinical Global Impressions Severity and Improvement Scales (CGI-S, CGI-I, Appendix II), etc. Each subject was to be interviewed and assessed throughout the study by the same rater for each instrument, if at all possible.

2 HISTORY OF MULTIPLE PRIMARY EFFICACY ENDPOINTS

PROTOCOL PROSPECTIVELY DEFINED MULTIPLE PRIMARY ENDPOINTS

According to the protocol, prospectively defined primary efficacy endpoints for all four short-term trials were (1) **BPRS total score** (p.22), (2) **CGI-S score** (Appendix II), and (3) **BPRS core item score** (p.22). The BPRS total score and the BPRS core item were subsets of the PANSS total scores (30 items each with scale of 1 to 7).

TWO ADDITIONAL ENDPOINTS REQUESTED BY THE AGENCY

The sponsor arranged a teleconference with Dr. Thomas Laughren, HFD-120 team Leader, on December 20, 1995 to review their proposals developed in response to recommendations outlined in the Division's "Supplementary Guidance for Preparing the Clinical Section of an NDA". The sponsor stated that Dr. Laughren requested to also display (1) **PANSS total score** (2) **PANSS negative syndrome subscale score** in the specific tabular format (by visit with p-values) suggested in the Division's Guidance document.

After this reviewer's discussion with Dr. Laughren (10/3/97), the intent of inclusion of the above two endpoints are summarized. The BPRS total measures the effect of psychiatric symptoms in general; the BPRS core item measures the effect of psychosis. These questionnaires have been available for about 40 years. The PANSS total was developed by expanding items in the BPRS total questionnaire and has been available for about 5 years. The PANSS negative syndrome subscale measures the negative symptoms. These two endpoints generally concur with the defined multiple primary efficacy endpoints in terms of treatment effect if it exists.

3 PIVOTAL STUDIES

3.1 STUDY #128-114 (6-WEEK STUDY)

3.1.1 STUDY DESCRIPTION

The treatment duration for Trial 114 was 6 weeks. The baseline period was a mandatory in-patient, single-blind, placebo washout period of 3-7 days duration. Only subjects who at baseline had (1) PANSS total score of 59, and (2) 4 (moderate) or greater on 2 or more of the core items derived from the PANSS, and (3) baseline CGI-I score of greater than 2 (not more than minimally improved) were to enter the double-blind phase. The treatment period included an obligatory in-patient, double-blind treatment duration of 14 days. An additional 28-day in-patient or out-patient, double-blind treatment period completed the study. Appropriate rating scales and safety monitoring were conducted at specific intervals throughout the study.

To detect a difference of 5 points (standard deviation of 12) in the mean change from baseline in BPRS total score between placebo and a ziprasidone group, the sponsor stated that 80 subjects per group would provide at least 80% power with two-sided α=.05. The power may decrease depending on the dropout rate.

The primary efficacy endpoints were: (1) BPRS total, (2) CGI-S, and (3) BPRS core. The secondary efficacy endpoints were PANSS total, PANSS negative, responder rates, MADRS (Montgomery-Asberg Depression Rating Scale) total score, discontinuations due to insufficient clinical response, and CGI-I. The linear model to be fitted to the primary efficacy variables included the baseline value of the response variable as a covariate. Interaction effects such as center-by-treatment and baseline-by-treatment were also investigated. In case of gross violations of linear model assumptions, methods of categorical data analysis (e.g., the Cochran-Mantel-Haenszel method stratified by baseline value and/or center) were used for the analysis of discrete and/or categorical data (e.g., CGI-S). A 'small' center was defined as a center with no subjects in one or more treatment groups. All small centers were pooled into one or more pseudo-centers. Depending on the dropout mechanism, a number of methods were adopted for the analysis of longitudinal data with dropouts.

3.1.2 REVIEWER'S SUMMARY OF THE EFFICACY RESULTS

Patient accountability is summarized in Table 1.1S. The relationships to treatment were assessed by the investigator for discontinuations due to safety-related reasons; all other cases were assigned by the sponsor. One hundred and thirty-six of the 302 (45%) subjects randomized

were prematurely discontinued from the study. The % discontinuations were 49%, 36%, and 51% in 40mg, 80 mg, and placebo groups, respectively. Eighty-two subjects (26%, 22%, and 35%) were discontinued for reasons considered to be related to treatment, with the major reason being insufficient clinical response. Fifty-four subjects (24%, 14%, and 16%) were discontinued for reasons considered to be unrelated to study drug, the majority being withdrawn consent.

Table 1.1S. Patient accountability (Table 4.1 of Vol.94), #128-114

Study Group	ziprasidone		placebo
	40 mg BID	80 mg BID	
Randomized (treated)	106	104	92
Discontinued (%)	52(49%)	37(36%)	47(51%)
Related to study drug	27(26%)	23(22%)	32(35%)
insuff. clinical response	26	16	32
adverse event	1	7	0
Unrelated to study drug	25(24%)	14(14%)	15(16%)
adverse event	1	1	1
protocol violation	3	1	1
lost to follow-up	6	2	3
not meet randomization criteria	0	3	1
withdrawn consent	15	6	8
other	0	1	1

- Time to discontinuation

The Kaplan-Meier curves for time to discontinuation for all reasons are shown in Figure 1.1S. There was a statistically significant difference in time to discontinuation over the course of the study (overall log-rank p=.031); the difference between the active treatment group and placebo was statistically significant for the 80 mg group (p=.012) but not for the 40 mg group (p=.667).

- Primary efficacy endpoints

The distributions of disease severity at baseline, as indicated by the primary endpoints, were comparable across treatment groups for all subjects. In the intent-to-treat (ITT) patients, the results of LOCF analyses shown in Table 1.2S indicated that the treatment effects for both the 40mg and 80mg arms were statistically significant at 0.05 level compared with placebo for all five primary endpoints: PANSS total (p=.048, p<.001), PANSS negative (p=.024, p=.001), BPRS total (p=.047, p<.001), BPRS core (p=.040, p<.001), and CGI-S (p=.03, p<.001). The estimated treatment effects at last observation were greater for both ziprasidone dose groups than for placebo in each of the primary efficacy variables.

The graph of mean change from baseline by duration of study participation (Figure 1.2S) showed that in general mean scores for subjects in the 80 mg group who prematurelly terminated from the study showed an improvement from baseline. The by-week change score observed cases (OC) is shown in Figure 1.3S. The by-week change score last observation carried-forward (LOCF) is shown in Figure 1.4S. The by-week treatment effect p-values for the LOCF analysis showed statistical significance as compared with placebo at all weeks for all primary efficacy endpoints.

3.1.3 REVIEWER'S EVALUATIONS AND COMMENTS

MULTIPLE TREATMENT ARMS

Trial 114 was a 3-arm study. The objective was to compare dosages of 40 mg BID and 80 mg BID of ziprasidone administered for 6 weeks with the placebo assuming monotonic dose-response relationship. The amended primary analysis method was the step-down test procedure. The primary hypothesis is the comparison between 80 mg group vs. placebo tested at a two-sided 0.05 level of significance. The 40 mg group is to be tested at 0.05 level if the 80 mg group shows statistical significance.

This step-down procedure is valid since it maintains the overall experimentwise type I error rate at 0.05 for the comparison of multiple treatment arms

DOSE-RESPONSE RELATIONSHIP

The dose-response trend was significant assuming 0 mg for placebo (Table 2R in p.17) for all primary efficacy endpoints. There was a numeric trend of dose-response between the ziprasidone groups excluding placebo.

MULTIPLE PRIMARY EFFICACY ENDPOINTS

When these efficacy endpoints were studied individually, the results of LOCF analysis showed that the changes from baseline on the protocol defined primary efficacy endpoints and the Agency requested endpoints were statistically significant for both the 40 mg ($p<.05$) and 80 mg ($p\leq.001$) (Table 3R) BID groups compared to placebo. None of the endpoints achieved statistical significance ($p>.12$) except CGI-S in the 80 mg group ($p=.028$) in the Completer analysis (Table 4R).

The differences between the LOCF and the Completer analyses seemed to be primarily attributed to early withdrawal patients. The numerical treatment effect estimates for all primary endpoints in Completer analyses were still in favor of ziprasidone though the magnitudes were smaller and the variabilities were larger than the LOCF analyses.

The medical review team requested additional analyses which excluded data obtained from This reviewer performed the ITT LOCF analyses after excluding patients enrolled by . Statistical significance (consistent with the sponsor's report submitted on 6/6/97) for the 80 mg still held, but statistical significance for the 40 mg disappeared for all five primary endpoints (PANSS total, p=.103; PANSS negative, p=.079; BPRS total, p=.097; BPRS core, p=.095; and CGI-S, p=.076).

HIGH DROPOUT RATES

The 80 mg group had the smallest early discontinuation rate (36%) compared to the 40 mg group (49%) and the placebo group (51%). The dropout rate in the 80 mg group was consistently lower during the entire double-blind treatment period (see Figure 1.1S).

Three longitudinal analyses were reported by the sponsor: (1) Wu and Bailey, Biometrics, 1989; (2) unweighted least squares; and (3) random effects model, Laird and Ware, Biometrics, 1982 to examine the robustness of their final conclusion. The treatment effect in terms of slope in the longitudinal analyses was statistically significant for all protocol defined endpoints for both dosage groups. The Agency defined endpoints also reached statistical significance except the PANSS negative syndrome subscale under the random effects model ($p=.065$ for 40 mg; $p=.1145$ for 80 mg, see Table 1.3S). The treatment effect estimates for all primary endpoints were consistently larger with the Wu-Bailey method over the random effects model. The validity of the random effects approach assumes normality of the outcome variable and that the pattern of discontinuation is missing completely at random or missing at random. The Wu and Bailey method is valid if patient discontinuation is informative. In this trial, tests of normality were reasonable for

these outcome measures. Figure 1.2S of all the primary efficacy endpoints showed that the pattern of dropouts for the placebo were primarily due to lack of efficacy (large increase in change from baseline) but less so in the 40 mg and not so (decrease in change from baseline) in the 80 mg for ziprasidone groups. The missing pattern might not be non-random and the dropout rates were high; thus, the random effects model might not be appropriate.

3.2 STUDY #128-115 (6-WEEK STUDY)

3.2.1 STUDY DESCRIPTION

The study description of Trial 115 is the same as Trial 114 except for the number of dosage arms studied. Please refer to Section 2.1.1.

3.2.2 REVIEWER'S SUMMARY OF THE EFFICACY RESULTS

Patient accountability is summarized in Table 2.1S. Two hundred seven of the 419 (49%) subjects randomized were prematurely discontinued from the study. The % discontinuations were similar among the active treatment groups, but notably higher in the placebo group (42%, 50%, 44%, 43% and 67%). One hundred twenty-four subjects (25%, 33%, 26%, 22%, and 42%) were discontinued for reasons considered to be related to treatment, with the major reason being insufficient clinical response. Eighty-three subjects (17%, 17%, 19%, 21% and 25%) were discontinued for reasons considered to be not related to study drug, the majority being withdrawn consent.

Table 2.1S. Patient accountability (Table 4.1 of Vol.102), #128-115

Study Group	ziprasidone			haloperidol	placebo
	20mgBID	60mgBID	100mgBID		
Randomized (treated)	87	78	86	85	83
Discontinued(%)	37(42%)	39(50%)	38(44%)	37(43%)	56(67%)
Related to study drug	22(25%)	26(33%)	22(26%)	19(22%)	35(42%)
insuff. clinical resp	22	22	18	13	35
adverse event	0	2	4	6	0
lab test abnormality	0	2	0	0	0
Unrelated to study drug	15(17%)	13(17%)	16(19%)	18(21%)	21(25%)
adverse event	1	1	2	1	3
protocol violation	0	2	0	0	2
lost to follow-up	3	0	1	2	1
not met randomization	1	1	2	1	1
withdrawn consent	10	8	10	13	14
other	0	1	1	1	0

- Time to discontinuation

The Kaplan-Meier curves for time to discontinuation for all reasons are shown in Figure 2.1S. There was a statistically significant difference in time to discontinuation over the course of the study (overall log-rank p=.001); the difference between the active treatment groups and placebo was statistically significant for all active groups, p=.002, .006, .001, .002 for 20 mg, 60 mg, 100 mg, and haloperidol, respectively.

- Primary efficacy endpoints

The distributions of disease severity at baseline, as indicated by the baseline scores for all primary efficacy variables, were comparable across treatment groups for all subjects.

The dose-response trend was statistically significant for the protocol defined primary efficacy endpoints and the Agency requested endpoints: BPRS total (p=.038), CGI-S (p=.016), BPRS core (p=.025), PANSS total (p=.023) and PANSS negative (p=.030), see Table 2.2S. In the ITT patients, the results of the LOCF analyses shown in Table 2.2S indicated that the treatment effects for the 100 mg arm was statistically significant (p<.05) compared with placebo for all five primary endpoints and for the 20 mg and 60 mg arms for all but the PANSS negative subscale score: PANSS total (p=.031, p=.011, p=.012), PANSS negative (p=.121, p=.069, p=.020), BPRS total (p=.049, p=.020, p=.023), BPRS core (p=.034, p=.046, p=.009), and CGI-S (p=.030, p=.035, p=.006). The estimated treatment effects at last observation were greater than placebo for each of the three ziprasidone dose groups and in the haloperidol group for each of the primary efficacy variables. The effect of treatment in terms of mean change from baseline was also graphically presented: the by-duration of study participation (Figure 2.2S), the by-week OC (Figure 2.3S), and the by-week LOCF (Figure 2.4S) analysis. At all time points of the by-week LOCF analysis, the mean changes from baseline for all active treatment groups were greater than placebo. Statistical significance was reached for haloperidol vs. placebo for all variables at all weeks.

3.2.3 REVIEWER'S EVALUATIONS AND COMMENTS

MULTIPLE TREATMENT ARMS

Trial 115 was a 5-arm study. The primary statistical hypothesis was to test the dose-response relationship across the three ziprasidone treatment groups of over 6 weeks. The secondary objective comparing haloperidol with ziprasidone was changed to that of comparing haloperidol with placebo **after the completion of the trial.**

The overall type I error rate with respect to the primary hypothesis is controlled. This reviewer's analyses based on the original secondary objective are given in Table 1R. The mean difference was calculated as the mean change from baseline of a ziprasidone arm minus that of haloperidol. The haloperidol (active control) seemed to have a larger decrease in changes from baseline for most of the primary efficacy endpoints.

Table 1R. Mean treatment difference (Δ= ziprasidone - haloperidol), #128-115

Efficacy Endpoint	20mg		60mg		100mg		zipras. (all)	
	Δ	p-val	Δ	p-val	Δ	p-val	Δ	p-val
BPRS total	3.63	.045	2.82	.132	2.97	.106	3.14	.037
BPRS core item	1.76	.007	1.81	.007	1.42	.031	1.66	.002
CGI-S	0.41	.006	0.41	.008	0.32	.037	0.38	.002
PANSS total	7.07	.023	5.61	.083	5.83	.066	6.17	.017
PANSS -ev sym	1.09	.236	0.79	.409	0.33	.724	0.74	.335

DOSE-RESPONSE RELATIONSHIP

The significant dose-response trend seen (Table 2.2S) for all primary efficacy endpoints was mainly due to the comparison between the ziprasidone groups combined vs. placebo and there was no evidence of dose response within the ziprasidone groups (p≥.6775, Table 2R in p.17).

MULTIPLE PRIMARY EFFICACY ENDPOINTS

The LOCF analysis showed that the mean changes from baseline for the protocol defined primary efficacy endpoints and PANSS total for all three ziprasidone dosage groups were statistically

significant different (20 mg, p<.05; 60 mg, p<.05; and 100 mg, p<.023) from that of placebo. The Agency requested endpoints of PANSS negative showed mixed results. None of the endpoints achieved statistical significance in the Completer analyses.

The treatment effect estimates for the primary efficacy endpoints were only slightly smaller than 0.0 in the Completer analyses (Table 4R in p.19). The variabilities for all endpoints in the Completer analyses were 1.25 times to 1.45 times larger than those in the ITT LOCF analyses. The differences between the LOCF and the Completer analyses were primarily attributed to the effects of early withdrawals.

HIGH DROPOUT RATES

The early discontinuation rate was ≤ 50% in the ziprasidone groups (42% in 20 mg, 50% in 60 mg, and 44% in 100 mg) whereas the dropout rate in the placebo group was 1.5 times higher (67%). The shorter time to discontinuation in placebo patients was apparent after 2 weeks from trial initiation (see Figure 2.1S).

The treatment effects in terms of slope in the longitudinal analyses were statistically significant for all endpoints but BPRS core for both 20 mg and 60 mg dosage groups with the Wu-Bailey method (see Table 2.3S). Treatment effects were statistically nonsignificant for all endpoints in all ziprasidone dosage groups with the random effects model.

The sponsor explained that "The random effects model, which assumes random discontinuations, did not result in statistical significant results for the ziprasidone treatment groups for any of the variables because the random discontinuation was not met as shown in Figure 2.1S. All pairwise comparisons between the active treatment groups and placebo regarding time to discontinuation were statistically significant".

Figure 2.2S of all the primary efficacy endpoints showed that, except for the haloperidol arm, the early discontinued patients (≤ 20 days) tended to have increased changes from baseline and the later discontinued patients (≤ 35 days) tended to have no or decreased changes from baseline. However, the % of patients discontinued due to insufficient clinical response was twice as high in placebo treated patients than in ziprasidone treated patients (42% in placebo, 25% in 20 mg, 28% in 60 mg, and 21% in 100 mg). It appeared that dropout patterns in terms of change from baseline of the outcome measures were not too different among ziprasidone and placebo groups. The difference appeared to be primarily due to a different discontinuation pattern, i.e., a shorter time to discontinuation, a higher early discontinuation rate and a higher insufficient clinical response rate in the placebo treated group. Thus, the random effects model might not be appropriate.

3.3 STUDY #128-106 (4-WEEK STUDY)

3.3.1 STUDY DESCRIPTION

The treatment duration for Trial 106 was 28 days. The baseline period was a mandatory in-patient, single-blind, placebo washout period of 4-7 days duration. Only subjects who at baseline had (1) a BPRS total score of at least 37, a score of at least 4 or greater on 2 or more of the core items of the BPRS, and a score of greater than 2 on the CGI-I scale performed within 24 hours prior to the first dose of double-blind study medication were allowed to enter double-blind therapy. The treatment period included an obligatory in-patient, double-blind treatment period of 21 days. An additional 7-day in-patient or out-patient, double-blind treatment period completed the study.

The sample size was estimated assuming the placebo responder rate of BPRS total between 20% and 30%. To detect a difference of 30% in responder rate with 5% comparison-wise error rate (two-sided), approximately 40 patients per group would be required in order to achieve 80% power. Given an estimate of 20% dropout rate, the sponsor stated that approximately 50 patients per group were needed.

The primary efficacy variables were 1) BPRS total, 2) CGI-S, and 3) BPRS core. The secondary efficacy variables were responder rate (patient "response" is operationally defined as (a) a 30% decrease in the BPRS total score between baseline and final visit and (b) a score of 1 or 2 on the CGI-I at the final visit), SANS (Scale for the Assessment of Negative Symptoms) total score and global rating. The primary efficacy analysis method was the two-way ANOVA with exploration of treatment-by-center interaction at .10 level of inclusion.

3.3.2 REVIEWER'S SUMMARY OF THE EFFICACY RESULTS

Patient accountability is summarized in Table 3.1S. Sixty-three of the 139 (45%) subjects randomized were prematurely discontinued from the study. The % discontinuations were 36% in 20 mg, 49% in 60 mg, and 50% in placebo. Thirty-three subjects (25%, 21%, and 25%) were discontinued for reasons considered to be related to treatment, the major reason being insufficient clinical response. Thirty subjects (11%, 28%, and 25%) were discontinued for reasons considered to be unrelated to study drug, the majority being withdrawn consent.

Table 3.1S. Patient accountability (Table 4.1 of Vol.91), #128-106

Study Group	ziprasidone		placebo
	20 mg BID	60 mg BID	
Randomized (treated)	44	47	48
Discontinued (%)	16(36%)	23(49%)	24(50%)
Related to study drug	11(25%)	10(21%)	12(25%)
insuff. clinical resp.	11	8	12
adverse event	0	1	0
lab test abnormality	0	1	0
Unrelated to study drug	5(11%)	13(28%)	12(25%)
adverse event	1	3	0
protocol violation	2	2	2
lost to follow-up	0	1	0
withdrawn consent	1	5	9
other	1	2	1

- Time to discontinuation

The Kaplan-Meier curves for time to discontinuation for all reasons are shown in Figure 3.1S. The analysis results showed that the probability of discontinuation over the course of the study was not statistically significantly different in all ziprasidone groups compared to placebo (overall log-rank, p=.301).

- Primary efficacy endpoints

The distributions of disease severity at baseline, as indicated by the BPRS total and core items scores as well as the CGI-S scores, were comparable across treatment groups for all subjects.

Table 3.2S summarizes the treatment effects at last observation for primary efficacy variables for the ITT population. The treatment effects for the 60 mg group were statistically significant when compared with the placebo for BPRS total (p=.0220 and CGI-S (p=.039), results for the BPRS core approached significance (p=.059). The treatment effects for the 20 mg group were not significant for all three endpoints.

Figure 3.2S showes the mean change from baseline by duration of study participation (all subjects). Figure 3.3S depicted the pattern of mean change from baseline by treatment group and week (all subjects, LOCF). An initial decrease in the mean scores occurred during the first week of treatment in all treatment groups. In the remaining duration of the study, there was little further change in the placebo group. In the 20 mg group, the magnitude of the change continued to increase until week 3. In the 60 mg group, the change score indicated there was improvement in symptoms each week through week 4. In both the observed cases and LOCF analyses, the 60 mg group had the largest mean change scores at all timepoints.

3.3.3 REVIEWER'S EVALUATIONS AND COMMENTS

MULTIPLE TREATMENT ARMS

Trial 106 was specifically designed to test that 60 mg BID ziprasidone administered for 4-week is more efficacious than placebo. The comparison of 20 mg BID ziprasidone with placebo was of secondary interest. Thus, there was no issue of multiple arm adjustments.

DOSE-RESPONSE RELATIONSHIP

The dose-response trend was significant assuming 0 mg for placebo (Table 2R in p.17) for all primary efficacy endpoints. There was a small numeric dose-response trend between the ziprasidone groups.

MULTIPLE PRIMARY EFFICACY ENDPOINTS

The Protocol specified analysis for the multiple primary efficacy endpoints was two-way ANOVA with treatment and center as factors and the treatment-by-center interaction (if p<.10). However, the sponsor stated that "ANCOVA model was consistently used in efficacy analyses in all ziprasidone phase II and III studies, including Study 106". The sponsor results summarized in Table 3.2S were based on ANCOVA. Although the analysis method defined in the original protocol was two-way ANOVA, it was apparent that these clinical rating scale measurements were a function of their baseline measurements. Nonetheless, this reviewer performed the 2-way ANOVA. Treatment-by-center interaction was not statistically significant at the .10 level. The treatment effects were similar using ANCOVA and 2-way ANOVA, with larger variability for the 2-way ANOVA approach since it didn't account for the baseline covariate. For the 60 mg group, only BPRS total was statistically significant (p=.039). The BPRS core (p=.062) and the CGI-S (p=.0836) were not statistically significant. For the 20 mg group, none of the endpoints showed a significant difference from placebo. The BPRS total, but not the BPRS core or the CGI-S, consistently showed improvement from baseline in 60 mg ziprasidone compared to placebo using either 2-way ANOVA or ANCOVA analysis.

HIGH DROPOUT RATES

About half of the patients discontinued the trial early in the placebo arm (50%) and ziprasidone 60 mg arm (49%). This rate was about one-third for the 20 mg group (36%). The pattern of time to discontinuation among the three groups were not significantly different (Fig.3.1S).

Due to high but similar dropout rates for both the 60 mg group and the placebo group, and the similar patterns of time to discontinuation, the pattern of dropouts may not be informative and thus the random effect or unweighted least square approaches might be more appropriate (Wu-Bailey, 1989). The results of longitudinal analyses based on random effects or unweighted least square were non-significant for all primary endpoints for both dosage groups (Table 3.3S). Here, the focus is on the comparison between the 60 mg group and the placebo group. The treatment effect estimates were similar either using the ITT LOCF or the Completer analyses but the variability was larger with the ITT LOCF analysis (see Tables 3R and 4R).

3.4 STUDY #128-104 (4-WEEK STUDY)

3.4.1 STUDY DESCRIPTION

The study description of Trial 104 is the same as Trial 106 except for the number of dosage arms studied. Please refer to Section 2.3.1.

3.4.2 REVIEWER'S SUMMARY OF THE EFFICACY RESULTS

Patient accountability is summarized in Table 4.1S. Ninety-seven of the 200 (48.5%) subjects randomized were prematurely discontinued from the study. The % discontinuations were 36%, 53%, 58%, and 46% for 5 mg, 20 mg, 40 mg BID ziprasidone groups and placebo, respectively. Sixty-one subjects (23%, 29%, 35%, and 34%) were discontinued for reasons considered to be related to treatment, the major reason being insufficient clinical response. Thirty-six subjects (13%, 24%, 23%, and 12%) were discontinued for reasons considered to be not related to study drug, the majority being withdrawn consent.

Table 4.1S. Patient accountability (Table 4.1 of Vol.120), #128-104

Study Group	ziprasidone			placebo
	5 mg BID	20 mg BID	40 mg BID	
Randomized (treated)	47	55	48	50
Discontinued (%)	17(36%)	29(53%)	28(58%)	23(46%)
Related to study drug	11(23%)	16(29%)	17(35%)	17(34%)
insuff. clinical resp.	11	16	15	16
adverse event	0	0	2	1
Unrelated to study drug	6(13%)	13(24%)	11(23%)	6(12%)
adverse event	2	0	0	1
lab test abnormality	0	1	0	0
protocol violation	3	5	5	0
withdrawn consent	0	7	5	4
other	1	0	1	1

- Time to discontinuation

The Kaplan-Meier curves for time to discontinuation for all reasons are shown in Figure 5.1S. There was no significant difference in time to discontinuation patterns between all ziprasidone and placebo groups.

- Primary efficacy endpoints

The distributions of disease severity at baseline, as indicated by the BPRS total and core as well as the CGI-S scores, were comparable across treatment groups. Table 4.2S summarized the

treatment effects at last observation for primary efficacy variables for the ITT population. None of the estimated treatment effects of ziprasidone relative to the placebo were statistically significant in the ITT LOCF analyses.

Figure 4.2S showed the mean change from baseline by duration of study participation (all subjects). Those subjects who were discontinued earlier did generally not improve. The sponsor noted that "over half the discontinuations occurred during the first two weeks of treatment, so a substantial number of subjects in the last visit analyses had less than half of the planned course of treatment".

3.4.3 REVIEWER'S EVALUATIONS AND COMMENTS

MULTIPLE TREATMENT ARMS

Trial 104 was designed to test that ziprasidone administered for 4 weeks at 5 mg, 20 mg, and 40 mg BID, is more efficacious than placebo.

No multiple comparison adjustment was proposed by the sponsor. Three comparisons were made: 5 mg vs. placebo, 20 mg vs. placebo, and 40 mg vs. placebo. Since none of the three primary efficacy endpoints reached statistical significance at two-sided .05 level either based on the ITT LOCF or the Completer analyses, the multiple adjustments became a moot issue.

DOSE-RESPONSE RELATIONSHIP

There was no dose-response trend either including or excluding placebo (Table 2R in p.17) with respect to any of the primary efficacy endpoints.

MULTIPLE PRIMARY EFFICACY ENDPOINTS

This is also a moot issue.

results were similar based on the ITT LOCF analyses.

HIGH DROPOUT RATES

The early discontinuation rates were about one third to three-fifths: 36% in 5 mg, 53% in 20 mg, 58% in 40 mg, and 46% in placebo. Rates of discontinuation due to insufficient clinical response were similar among all groups. The pattern of time to discontinuation was not significantly different among all groups. Neither ITT LOCF nor Completer analyses showed evidence of a treatment effect with any dose.

3.5 STUDY #128-303 (52-WEEK STUDY)

3.5.1 STUDY DESCRIPTION

After a three day single-blind placebo run-in, subjects were randomized to receive ziprasidone 20 mg BID (n=76), 40 mg BID (n=72), 80 mg BID (n=71) or placebo BID (n=75) double-blind for up to 52 weeks.

Assuming that 60% of placebo patients would relapse within one year, to detect a 50% relapse improvement within one year for ziprasidone treatment, i.e., 30% relapse, the standard likelihood ratio yielded a sample size of 53 patients per group in order to achieve 90% power at 5% level of significance. Taking into account a 10% discontinuation rate within one year for

reasons other than relapse, and that all patients who had not relapsed at the end of one year would be discontinued at that time, the sponsor's simulation study showed that 60 patients per group would provide adequate power after allowing for these features of the design. The computation assumed that times to relapse follow an exponential distribution.

The primary efficacy measure was "the time to impending psychotic relapse (used for sample size estimation), together with the proportion of patients fulfilling the relapse criteria over the duration of the study". The operational definition of an impending psychotic relapse is "a CGI improvement score of 6 (much worse) or more or a score of 6 (severe) or more on either of the PANSS items p7 (hostility) or G8 (uncooperativeness) on two successive days." Other efficacy measures included PANSS total, CGI ratings, Global Assessment of Functioning (GAF) scales, and BPRS total. Time to discontinuation was analyzed using the logrank test or, if necessary, the Cox proportional hazards model will be used. In general, ANCOVA will be used for other endpoints. Interaction terms will be tested at 0.1 level of inclusion. When the assumptions of ANCOVA are violated, Cochran-Mantel-Haenszel (CMH) methods (stratified by baseline value using RIDIT scoring) would be used. Small centers may be pooled on a geographical basis.

3.5.2 REVIEWER'S SUMMARY OF THE EFFICACY RESULTS

Patient accountability is summarized in Table 5.1S. One hundred and eighty-two of the 294 (62%) subjects randomized were prematurely discontinued from the study. The % discontinuations were 55%, 57%, 54%, and 81% for 20 mg, 40 mg, 80 mg BID ziprasidone groups and placebo, respectively. One hundred and sixteen subjects (43%, 39%, 38%, and 67%) were discontinued for reasons considered to be related to treatment, the major reason being insufficient clinical response. Forty-four subjects (12%, 18%, 16%, and 15%) were discontinued for reasons considered to be unrelated to study drug.

Table 5.1S. Patient accountability (Table 4.1 of Vol.112), #128-303

Study Group	ziprasidone			placebo
	20 mg BID	40 mg BID	80 mgBID	
Randomized (treated)	76	72	71	75
Discontinued (%)	42(55%)	41(57%)	38(54%)	61(81%)
Related to study drug	33(43%)	28(39%)	27(38%)	50(67%)
insuff. clinical resp	27	22	24	43
adverse event	6	6	1	6
lab test abnormality	0	0	2	1
Unrelated to study drug	9(12%)	13(18%)	11(16%)	11(15%)
adverse event	1	1	4	5
lab test abnormality	0	1	0	0
lost to follow-up	0	1	0	0
withdrawn consent	4	5	5	1
special safety test	0	0	0	1
other	4	5	2	4

- Time to discontinuation

The Kaplan-Meier curves for time to discontinuation for all reasons are shown in Figure 5.1S. The analysis results showed that the probability of discontinuation over the course of the study was statistically significantly lower in all ziprasidone groups compared to placebo (overall log-rank $p<.001$). The relative risk of discontinuation was similar in all ziprasidone treatment groups. The

test of linearity showed no statistically significant difference between the three active treatment groups (p=.652).

All 294 ITT patients were white. The majority (73%) were males aged 18-76 years; females aged 23-82 years. The subjects in this study were chronically ill with a long history of schizophrenia. There were no notable imbalances across treatment groups in either the past or present medical history.

- Primary efficacy endpoints

In the ITT patients, the results of LOCF analyses shown in Table 5.2S indicated that the rate of relapse for the whole study duration was lower in the 40 mg ziprasidone group compared to placebo and was also lower in the other two ziprasidone groups compared to placebo: 36%, 30.6%, 33.8%, and 57.3% for 20 mg, 40 mg, 80 mg, and placebo, respectively. The relative risk of relapse in each of the ziprasidone groups compared to placebo was similar: .481 in 20 mg, .414 in 80 mg, and .411 in 80 mg groups. The phenomena were captured in the Kaplan-Meier curves (Figure 5.2S). Analysis including placebo showed that there was a statistically significant dose-response trend (p=.002, Table 5.2S). However, this was primarily due to the comparison between the ziprasidone groups combined vs. the placebo group (p<.001) and there was no dose-response trend for the ziprasidone groups (p=.595).

- Other efficacy endpoints

For clinical ratings scales, the reductions from baseline in mean score for the PANSS total and PANSS-derived variables were greater in the ziprasidone treatment groups than in placebo. The most marked differences were seen after week-16, when the improvement in the ziprasidone groups mean scores continued in contrast to no further changes or a general worsening of the mean score in the placebo group. In all cases, the week-52 observed cases analysis indicated a greater mean improvement from baseline in the ziprasidone groups compared to placebo; see Table 5.3S.

3.5.3 REVIEWER'S EVALUATIONS AND COMMENTS

MULTIPLE TREATMENT ARMS

Trial 303 was a 4-arm study. The primary statistical hypothesis was to test 40 mg BID of ziprasidone is superior to placebo in preventing relapse in chronic schizophrenia. Other arm comparisons or dose-response exploration were secondary objectives. Thus, there was no issue of multiple arm adjustments.

DOSE-RESPONSE RELATIONSHIP

In Table 5.2S, the sponsor used contrasts (0, -1, 0, 1) corresponding to (placebo, 20 mg, 40 mg and 80 mg) for dose response test for linear effect among the ziprasidone groups. The contrasts should exclude the placebo group. My analysis excluding placebo also showed no dose-response trend for the ziprasidone groups (p=.612).

MULTIPLE PRIMARY EFFICACY ENDPOINTS

The primary efficacy endpoint defined in the protocol was the time to relapse together with the proportion of relapse over the duration of the study and the primary statistical hypothesis of interest was the comparison between 40 mg ziprasidone vs. placebo. Time to relapse (p=.001) and proportion of relapse (p=.0015) were each significant at 0.025 using the most conservative Bonferroni adjustment.

HIGH DROPOUT RATES

This was a 52-week trial. The early discontinuation rates were about half for the ziprasidone groups (55% in 20 mg, 57% in 40 mg, and 54% in 80 mg) and 81% for the placebo group. The majority of the early withdrawals were due to insufficient clinical response 57% in placebo, 35% in 20 mg, 31% in 40 mg, and 34% in 80 mg. The pattern of time to discontinuation was significantly different among the four groups (overall log-rank, p<.001).

There was only 20% patients left at the end of the trial for the placebo group. The median time to relapse was 20.5 weeks (95% CI: 10.8 weeks to 36.7 weeks) in the placebo group but none of the treatment groups reached the median time to relapse during the 52-week study. The treatment effect in terms of risk ratio was statistically significant between all dosage groups vs. placebo.

4 OVERALL REVIEWER'S EVALUATION SUMMARY

The efficacy results of the four placebo-controlled studies reviewed are summarized in Table 3R (p.18) for the ITT LOCF analyses and in Table 4R (p.19) for the Completer analyses. The results of subgroup analyses by gender can be found in Table 5R (male) and Table 6R(female).

MULTIPLE TREATMENT ARMS

The primary statistical hypothesis was specific and adjustments needed were properly documented for all trials except Trials 104. Study 104 does not provide statistical evidence of treatment effect or dose-response trend.

DOSE-RESPONSE RELATIONSHIP

This reviewer checked the monotonic dose-response assumption for all four Trials. Table 2R (p. 17) summarizes the results of dose-response analyses using linear contrast with coefficients derived from a linear orthogonal polynomial. In Trials 114, 115, and 106, my analyses including the placebo group show a significant dose-response relationship for all primary efficacy endpoints. However, a dose-response trend cannot be concluded over the ziprasidone dosages.

MULTIPLE PRIMARY EFFICACY ENDPOINTS

Significant improvement from baseline was shown in protocol defined endpoints for all dosage groups in Trials 114, 115 and for 60 mg BID group in Trial 106 (marginal significance for BPRS core, p=.059) based on the ITT LOCF analysis. The longitudinal analyses of Wu and Bailey (1989) assuming informative dropouts also showed significant treatment effect for all three primary endpoints in Trial 114; for BPRS total and CGI-S but not BPRS core in Trial 115. The longitudinal analyses of random effects approach or unweighted least square approach assuming random dropouts failed to show significant treatment effect for all three primary endpoints in Trial 106. Note the assessment of whether the dropout pattern was informative or not was based on the method proposed by Wu-Bailey (1989). None of the three primary efficacy endpoints reached statistical significance at two-sided 0.05 level either based on the ITT LOCF or the Completer analyses in Study 104. Study 303 showed that patients treated with ziprasidone 40 mg BID appeared to have a significantly longer time to relapse (p=.001) and small % of relapse (p=.0015).

The Agency requested endpoints showed mixed results: PANSS total showed improvement from baseline in both Trials 114 and 115; PANSS negative showed improvement for both 40 mg and 80 mg BID ziprasidone groups in Trial 114, and for 100 mg but not for 20 mg and 60 mg BID ziprasidone groups in Trial 115.

HIGH DROPOUT RATES

All five trials had moderate to high premature discontinuation rates: 36% to 51% in Trial 114; 42% to 67% in Trial 115; 36% to 50% in Trial 106; 36% to 58% in Trial 104; and 54% to 81% in Trial 303. Since Trial 104 failed to show a treatment effect or dose-response trend, it was excluded for further comments.

In Trial 114, the dropouts in the placebo group primarily had a large increase from baseline, less so in 40 mg and a decrease from baseline in 80 mg ziprasidone groups with respect to all primary efficacy endpoints.

In Trial 115, the dropout patterns in terms of change from baseline were not very different among three ziprasidone dose groups and placebo. They were primarily due to shorter time to discontinuation, higher early discontinuation rate and higher insufficient clinical response rate in the placebo group.

In Trial 106, the patterns of dropouts for both 60 mg ziprasidone and placebo were similar. Both LOCF and Completer analyses showed significant treatment effect in BPRS total and CGI-S but not BPRS core. However, the longitudinal analyses using the random effects approach or unweighted least squares approach assuming random dropouts failed to show a significant treatment effect for all three primary endpoints in Trial 106.

In Trial 303, the pattern of time to discontinuation was significantly different among the four groups. By the end of the Trial (52 week), about 50% of the patients remained in the study in each of ziprasidone dose groups and only 20% of the patients in placebo. The treatment effects in terms of risk ratio and % of relapse were statistically significant for all dosage groups compared to placebo.

5 CONCLUSION

In the short-term studies for the acute exacerbation of schizophrenia and schizoaffective disorder patients, the effect of ziprasidone was apparent. Clearly, 40 mg, 80 mg in Trial 114, and 20 mg, 60 mg, 100 mg in Trial 115 and 60 mg in Trial 106 were significantly more effective than placebo in decreasing change from baseline on BPRS total, CGI-S, and BPRS core (marginal significance in Trial 106), the protocol defined multiple primary efficacy variables. The Agency requested efficacy variables showed mixed results: PANSS total was significant for Trials 114 and 115; PANSS negative syndrome was significant for 100 mg but not 20 mg or 60 mg ziprasidone in Trial 115 using the ITT LOCF analyses. Due to high dropouts (ranges from %) , the pattern seen in the Completer analyses differed from the ITT LOCF analyses for Trial 114. The difference was due most likely to lack of efficacy in the placebo group. For Trial 115, the difference between ziprasidone treatment groups and placebo was primarily due to different discontinuation pattern, higher early discontinuation rate and higher insufficient clinical response rate in the placebo treated group. Both Trials 114 and 115 seemed to suggest that the dropout pattern was informative. Trial 106, on the other hand, showed similar and high dropout rates and a similar pattern of time to discontinuation for both the 60 mg ziprasidone and the placebo groups. It seemed to suggest that the dropout pattern was random and results of the random effects or unweighted least square approach failed to show improvement from baseline for all three primary efficacy endpoints.

For some reason, Trial 104 did not show any treatment effect in any primary endpoint for any ziprasidone dose group.

In the long term study (Trial 303), ziprasidone clearly showed a significantly longer time to relapse than placebo. In addition, the reported five primary efficacy endpoints used in the short

term study were all significant at 0.05 for all dosage arms but PANSS negative (neg. sym) in 40 mg group (p=.073) when compared to placebo.

Sue-Jane Wang
Mathematical Statistician

Concur: Dr. Sahlroot 11/7/97

Dr. Chi 11/24/97

cc:
NDA # 20-825
HFD120/Dr. Leber
HFD120/Dr. Laughren
HFD120/Dr. Mosholder
HFD120/Dr. Glass
HFD120/Mr. Purvis
HFD120/Mr. Hardemann
HFD344/Dr. Barton
HFD710/Dr. Chi
HFD710/Dr. Sahlroot
HFD710/Dr. Wang
HFD710/Chron

This review consists of 19 pages of text, 14 Sponsor Tables, 15 Sponsor Figures, 6 Reviewer Tables, and 2 Appendices with a total of 55 pages.

Table 2R. Summary of dose response relationship on the primary efficacy endpoints (ITT LOCF analysis)

Study	BPRS total score Δ (C.I.) p-val	BPRS core items Δ (C.I.) p-val	CGI-Severity Δ (C.I.) p-val	PANSS total score Δ (C.I.) p-val	PANSS -ve subscale Δ (C.I.) p-val
114					
All*	-4.6(-7.4, -1.9) .0009	-1.6(-2.5,-0.7) .0006	-0.4(-0.6,-0.2) .0001	-7.9(-12.6,-3.2) .0010	-1.8(-3.1,-0.6) .0030
zipra**	-2.3(-4.9, 0.3) .0769	-0.8(-1.6,0.03) .0850	-0.2(-0.4,0.01) .0594	-4.1(-8.5, 0.3) .0717	-0.7(-1.9, 0.5) .2003
115					
All	-2.8(-5.3,-0.2) .0380	-1.1(-2.0,-0.1) .0252	-0.3(-0.5,-0.1) .0157	-5.2(-9.6,-0.7) .0231	-1.5(-2.8,-0.2) .0294
zipra	-0.2(-2.8, 2.4) .8608	-0.2(-1.1, 0.8) .7016	-0.04(-0.3,0.2) .6775	-0.2(-4.6, 4.2) .9178	-0.3(-1.6, 1.1) .7121
106					
All	-4.3(-7.9,0.7) .0171	-1.2(-2.5,0.0) .0504	-0.3(-0.6,0.0) .0488		
zipra	-2.8(-6.6,1.0) .1320	-0.8(-2.1,0.5) .2412	-0.1(-0.4,0.2) .2412		
104					
All	0.8(-2.4,4.1) .6035	0.6(-0.7,1.9) .3398	0.0(-0.3,0.3) .7470		
zipra	1.1(-1.8,4.0) .4419	0.5(-0.7,1.7) .4098	-0.1(-0.3,0.1) .6149		

* Dose response testing across all dosage groups and placebo, assuming 0 mg for the placebo group.
** Dose response testing within ziprasidone dosage groups.

Table 3R. Summary of difference in changes from baseline between ziprasidone and placebo on primary efficacy endpoints*

Study Arm (n)	BPRS total score Δ (C.I.) p-val	BPRS core items Δ (C.I.) p-val	CGI-Severity Δ (C.I.) p-val	PANSS total score Δ (C.I.) p-val	PANSS neg subscale Δ (C.I.) p-val
114					
40 (104)	-3.9(-7.7, -.05) .047	-1.3(-2.6,-.06) .040	-.3(-.6,-.03) .030	-6.7(-13.3,-.07) .048	-2.0(-3.8,-0.3) .024
80 (103)	-7.2(-11, -3.3) .000	-2.5(-3.8,-1.2) .000	-.6(-.9,-.3) .000	-12.5(-19,-5.9) .000	-3.1(-4.9,-1.3) .001
115					
dose-resp	-2.8(-5.3,-0.2) .038	-1.1(-2.0,-0.1) .025	-.3(-0.5,-0.1) .016	-5.2(-9.6,-0.7) .023	-1.5(-2.8,-0.2) .030
20 (86)	-3.6(-7.2,-0.0) .049	-1.4(-2.7,-0.1) .034	-.3(-0.6,-0.0) .030	-6.8(-12.9,-0.6) .031	-1.4(-3.3, 0.4) .121
60 (76)	-4.4(-8.1,-0.7) .020	-1.4(-2.7,-0.0) .046	-.3(-0.6,-0.0) .035	-8.2(-14.6,-1.9) .011	-1.8(-3.6, 0.1) .069
100 (82)	-4.2(-7.9,-0.6) .023	-1.7(-3.0,-0.4) .009	-.4(-0.7,-0.1) .006	-8.0(-14.3,-1.7) .012	-2.2(-4.1,-0.4) .020
Halop (80)	-7.2(-10.8,-3.6) .000	-3.2(-4.5,-1.9) .000	-.8(-1.1,-0.4) .000	-13.8(-20.1,-7.6) .000	-2.5(-4.4,-0.7) .008
106					
20 (43)	-1.1(-6.0,3.8) .657	-0.4(-2.1,1.4) .677	-0.3(-0.7, 0.1).209		
60 (41)	-5.8(-10.8,-0.9) .022	-1.7(-3.4,0.1) .059	-0.4(-0.8,-0.0).039		
104					
5 (44)	-0.2(-4.6,4.1) .926	0.3(-1.4,2.0) .742	0.3(-0.0,0.7) .076		
20 (55)	-2.0(-6.1,2.2) .354	-0.3(-1.9,1.4) .751	0.0(-0.3,0.4) .827		
40 (47)	-1.4(-2.9,5.7) . 535	0.9(-.79, 2.5) .301	0.2(-0.1,0.6) .233		

* ITT LOCF analysis

Table 4R. Summary of difference in changes from baseline between ziprasidone and placebo on primary efficacy endpoints*

Study Arm (n)	BPRS total score Δ (C.I.)	p-val	BPRS core items Δ (C.I.)	p-val	CGI-Severity Δ (C.I.)	p-val	PANSS total score Δ (C.I.)	p-val	PANSS neg subscale Δ (C.I.)	p-val
114										
40 (104)	-2.8(-6.8, 1.2)	.175	-1.0(-2.5,0.5)	.171	-0.2(-.6, 0.1)	.216	-5.4(-12.3,1.5)	.122	-1.2(-3.2,0.7)	.214
80 (103)	-1.5(-5.3, 2.3)	.441	-1.0(-2.4,0.4)	.153	-0.4(-.7,-0.0)	.028	-3.2(-9.7,3.4)	.342	-0.5(-2.4,1.3)	.572
115										
dose-resp	0.7(-2.4,3.8)	.669	-0.4(-1.7,0.8)	.506	-0.1(-0.4,0.2)	.496	-0.4(-5.8,4.9)	.876	-0.5(-2.2,1.1)	.523
20 (86)	-0.8(-5.3,3.7)	.717	0.0(-1.8,1.8)	.985	-0.1(-0.5,0.3)	.703	-2.2(-9.9,5.6)	.585	-0.7(-3.1,1.7)	.553
60 (76)	-0.7(-5.5,4.0)	.757	-0.2(-2.1,1.7)	.819	-0.1(-0.6,0.3)	.582	-3.0(-11.1,5.2)	.473	-1.5(-4.0,1.0)	.244
100 (82)	0.8(-3.8,5.3)	.741	-0.5(-2.3,1.3)	.578	-0.1(-0.6,0.3)	.508	-0.8(-8.6,7.1)	.850	-0.7(-3.1,1.8)	.591
Halop (80)	-2.1(-6.6,2.4)	.363	-1.4(-3.3,0.4)	.119	-0.4(-0.8,.03)	.066	-5.3(-13.2,2.6)	.187	-0.7(-3.2,1.7)	.562
106										
20 (43)	0.9(-4.6, 6.3)	.747	0.6(-1.7,2.9)	.619	-0.3(-0.8, 0.3)	.330				
60 (41)	-6.8(-12.5,-1.2)	.018	-2.0(-4.4,0.4)	.096	-0.6(-1.1,-0.1)	.033				
104										
5 (44)	-1.2(-6.3, 3.9)	.647	-0.8(-2.9, 1.5)	.501	0.2(-0.3,0.7)	.335				
20 (55)	-5.6(-10.9,-0.3)	.039	-2.7(-5.0,-0.5)	.018	-0.3(-0.8,0.3)	.307				
40 (47)	-1.0(-6.8, 4.7)	.723	-1.3(-3.8, 1.2)	.308	0.2(-0.4,0.7)	.597				

* Completer Analyis

Table 5R. Summary of difference in changes from baseline between ziprasidone and placebo on primary efficacy endpoints (male)*

Study Arm (n)	BPRS total score Δ (S.E.)	p-val	BPRS core items Δ (S.E.)	p-val	CGI-Severity Δ (S.E.)	p-val	PANSS total score Δ (S.E.)	p-val	PANSS neg subscale Δ (S.E.)	p-val
114										
40 (74)	-3.8(2.2)	.083	-1.4(0.8)	.057	-0.3(0.2)	.060	-6.6(3.9)	.091	-2.3(1.0)	.031
80 (76)	-7.7(2.2)	<.001	-2.7(0.8)	<.001	-0.5(0.2)	.002	-13.1(3.9)	.001	-3.5(1.1)	.001
115										
20 (52)	-3.7(2.2)	.098	-1.6(0.8)	.050	-0.4(0.2)	.047	-6.0(3.7)	.105	-0.2(1.1)	.866
60 (55)	-3.6(2.2)	.107	-1.5(0.8)	.051	-0.4(0.2)	.049	-6.4(3.7)	.083	-0.6(3.7)	.569
100 (53)	-3.9(2.2)	.078	-1.9(0.8)	.016	-0.5(0.2)	.008	-6.3(3.7)	.092	-1.0(1.1)	.328
Halop (52)	-7.5(2.1)	<.001	-3.2(0.8)	<.001	-0.8(0.2)	<.001	-13.3(3.6)	<.001	-2.0(1.0)	.058
106										
20 (29)	-0.08(2.8)	.978	0.06(1.0)	.951	-0.2(0.2)	.340				
60 (34)	-4.10(2.6)	.117	-1.0(0.9)	.287	-0.2(0.2)	.320				
104										
5 (41)	-0.7(2.3)	.766	0.2(0.9)	.850	0.3(0.2)	.118				
20 (52)	-1.9(2.2)	.389	-0.3(0.9)	.767	0.05(0.2)	.778				
40 (38)	0.6(2.3)	.798	0.5(0.9)	.587	0.2(0.2)	.232				

* ITT LOCF analysis.

Table 6R. Summary of difference in changes from baseline between ziprasidone and placebo on primary efficacy endpoints (female)*

Study Arm (n)	BPRS total score Δ (S.E.)	p-val	BPRS core items Δ (S.E.)	p-val	CGI-Severity Δ (S.E.)	p-val	PANSS total score Δ (S.E.)	p-val	PANSS neg subscale Δ (S.E.)	p-val
114										
40 (30)	-8.7(4.9)	.079	-1.7(1.6)	.279	-0.4(0.3)	.193	-12.6(7.9)	.116	-3.0(2.0)	.144
80 (27)	-10.2(4.9)	.041	-2.7(1.6)	.095	-1.0(0.3)	.003	-17.2(7.9)	.034	-3.8(2.0)	.069
115										
20 (34)	-3.5(3.8)	.349	-0.8(1.4)	.587	-0.3(0.3)	.286	-6.8(6.7)	.311	-2.4(2.0)	.222
60 (21)	-5.3(4.4)	.229	-0.6(1.6)	.737	-0.2(0.3)	.536	-9.3(7.8)	.236	-2.9(2.3)	.206
100 (30)	-3.7(3.9)	.339	-1.2(1.4)	.404	-0.07(0.3)	.807	-8.5(6.9)	.221	-2.9(2.0)	.164
Halop (28)	-8.9(4.0)	.028	-3.8(1.5)	.011	-0.8(0.3)	.012	-16.8(7.0)	.019	-3.3(2.1)	.117
106										
20 (14)	-3.7(7.4)	.619	-2.5(2.7)	.364	-0.5(0.6)	.389				
60 (8)	-14.8(7.4)	.063	-5.9(2.8)	.052	-1.5(0.6)	.027				
104										
5 (5)	11.9(10.6)	.292	3.1(2.9)	.307	1.5(0.5)	.019				
20 (3)	0.5(10.9)	.965	0.2(2.6)	.943	-0.05(0.6)	.930				
40 (9)	5.3(8.5)	.554	2.1(2.0)	.313	0.2(0.5)	.687				

* ITT LOCF analysis.

Explanation of the primary efficacy endpoints derived from PANSS total (see Appendix I)

- Brief Psychiatric Rating Scale total score (BPRS total): PANSS p2-p7, n1-n2, and g1-g10 (see Appendix I),
- CGI-Severity Score (CGI-S), (see Appendix II),
- BPRS core items score (BPRS core) - 4 items (PANSS p2: conceptual disorganization, p3: hallucinatory behavior, p6: suspiciousness, and p9: unusual thought content).

BPRS total score contains 18 items, six from positive subscales, two from negative subscales, 10 from general psychopathology subscales.

BPRS core item score consists of 4 items all from positive subscales.

Comments: There is one item (conceptual disorganization) common to the BPRS total score and the BPRS core item scores.

PANSS negative syndrome subscale score contains 7 items.

Comments: There are two items (blunted affect and emotional withdrawal) common to the BPRS total score and the PANSS negative syndrome subscale score.

The BPRS total score questionnaire has been available for about 40 years, which measures the psychiatric symptoms in general. The BPRS core measures symptoms specific to psychosis.
The PANSS total score questionnaire was expanded from the BPRS total score questionnaire and has been available for about 5 years per conversation with Dr. Laughren.
The PANSS negative syndrome subscale score measures specifically the negative symptoms.

Appendix I

POSITIVE AND NEGATIVE SYNDROME SCALE FOR SCHIZOPHRENI

Instructions : Circle the appropriate rating for each item following the semi-structured clinical interview. Refer to the Rating Manual for item definitions, description of anchoring points and scoring procedure.

1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate severe, 6 = severe, 7 = extreme

1) POSITIVE SUBSCALE

P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganization	1	2	3	4	5	6	7
P3	Hallucinatory behavior	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7

Subtotal [| |]

2) NEGATIVE SUBSCALE

N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity and flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7

Subtotal [| |]

3) GENERAL PSYCHOPATHOLOGY SUBSCALE

G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerism and posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgement and insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

Subtotal [| |]

Total PANSS score (this is the sum of the 3 subtotals) [| |]

PROTOCOL #128-114

Appendix II

APPENDIX IV

PLEASE USE A CHECK MARK (X) WHERE APPLICABLE AND BE SURE TO INITIAL AND DATE ALL CORRECTIONS

☐ NOT DONE

CLINICAL GLOBAL IMPRESSION (CGI)

INSTRUCTIONS: Indicate only one response for the question by placing a cross (X) in the appropriate numbered box. Use two vertical lines (II) through old answer and initial/date when making corrections.

SEVERITY OF ILLNESS:

Considering your total clinical experience with this patient population, how mentally ill is the patient at this time?

- [0] NOT ASSESSED
- [1] Normal, not at all ill
- [2] Borderline mentally ill
- [3] Mildly ill
- [4] Moderately ill
- [5] Markedly ill
- [6] Severely ill
- [7] Among the most extremely ill

GLOBAL IMPROVEMENT:

Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment.

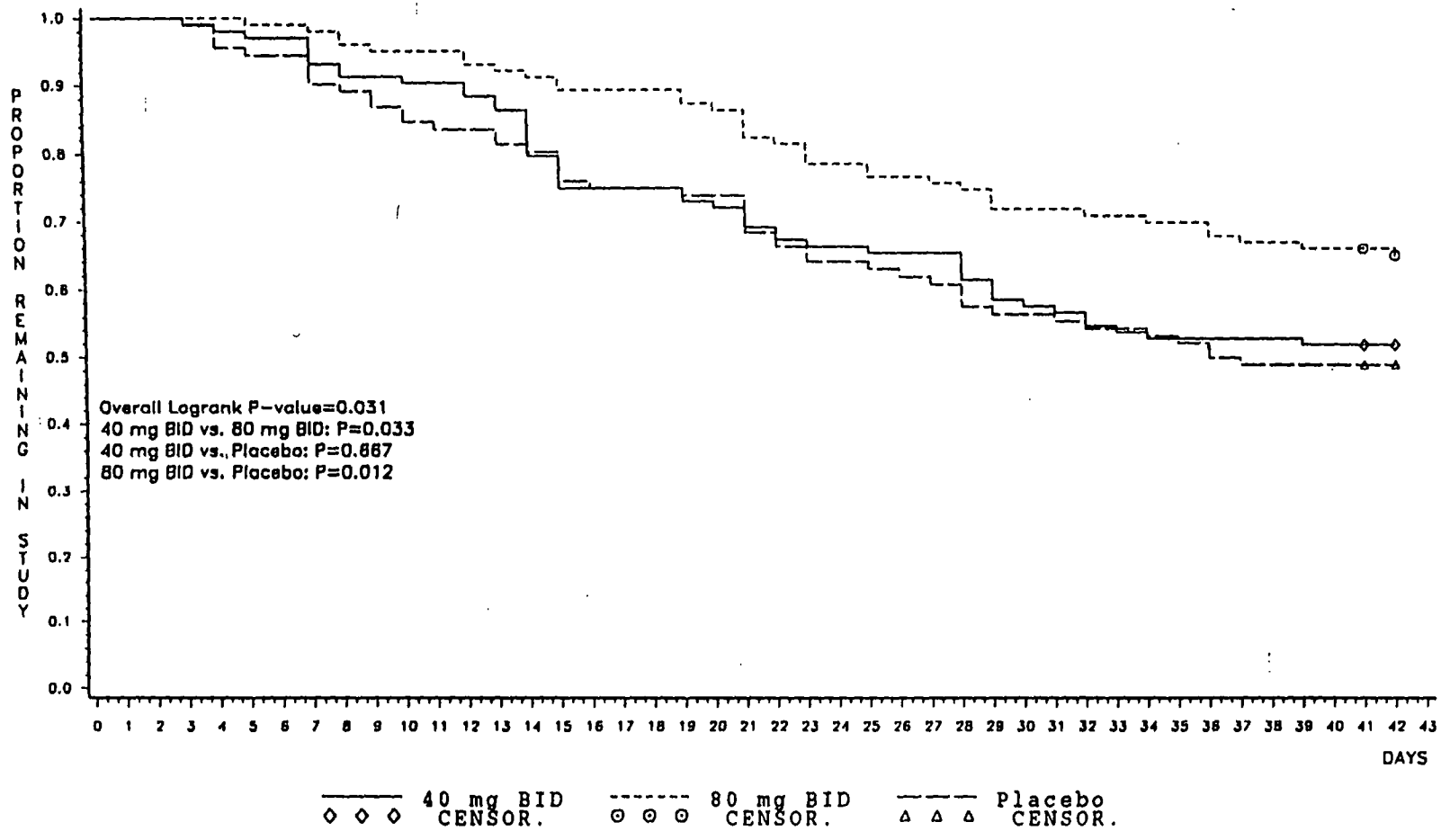
Compared to his/her condition at admission to the project (study), how much has he/she changed?

- [0] NOT ASSESSED
- [1] Very much improved
- [2] Much improved
- [3] Minimally improved
- [4] No change
- [5] Minimally worse
- [6] Much worse
- [7] Very much worse

TIME DONE (24 hour clock): _____ RATER: _____

Figure 1.1S

Figure 1
Kaplan–Meier Curves for Time–to–Discontinuation for All Reasons
By Treatment Group – All Subjects
Ziprasidone Protocol 114



Source Data: Table 4.2 and Appendix III Table 28 Date of Data Extraction: 29MAR96 Date of Figure Generation: 13SEP96

Table 1.2

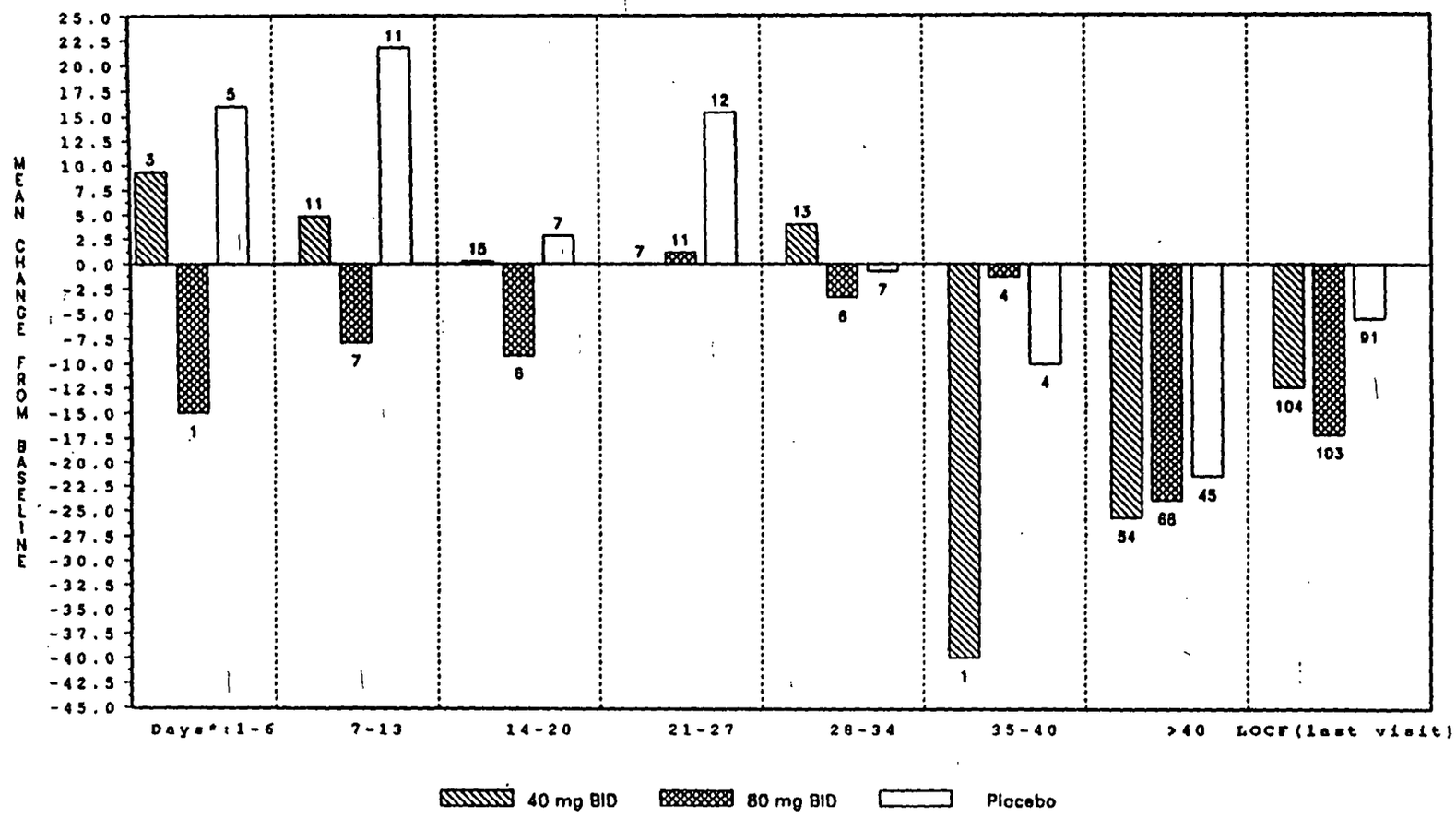
Table 5.1.16
Treatment Effects at Last Observation for Primary Efficacy Variables - All Subjects
Ziprasidone Protocol 114

Variable	Treatment Comparison	Estimated Treatment Effect*	P-Value**	Lower 95% Confidence Limit**	Upper 95% Confidence Limit**
PANSS Total	40 mg BID vs Pbo	-6.66	0.048	-13.26	-0.07
	80 mg BID vs Pbo	-12.45	0.000	-19.05	-5.86
	Zipras. vs Pbo	-9.56	0.001	-15.34	-3.77
PANSS Negative	40 mg BID vs Pbo	-2.03	0.024	-3.79	-0.27
	80 mg BID vs Pbo	-3.09	0.001	-4.85	-1.34
	Zipras. vs Pbo	-2.56	0.001	-4.10	-1.02
BPRSd Total	40 mg BID vs Pbo	-3.87	0.047	-7.70	-0.05
	80 mg BID vs Pbo	-7.15	0.000	-10.97	-3.33
	Zipras. vs Pbo	-5.51	0.001	-8.87	-2.16
BPRSd Core	40 mg BID vs Pbo	-1.34	0.040	-2.62	-0.06
	80 mg BID vs Pbo	-2.47	0.000	-3.75	-1.19
	Zipras. vs Pbo	-1.91	0.001	-3.03	-0.78
CGI Severity	40 mg BID vs Pbo	-0.31	0.030	-0.60	-0.03
	80 mg BID vs Pbo	-0.60	0.000	-0.88	-0.32
	Zipras. vs Pbo	-0.46	0.000	-0.70	-0.21

*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 17.1.2, 18.1.2, 19.1.2, 20.1.2 and 21.1.2)
Source Data: Appendix V Tables 15,16. Date of Data Extraction: 29MAR96. Date of Table Generation: 02APR96.

Figure 1.2 S

Figure 2.1
PANSS Total Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 114



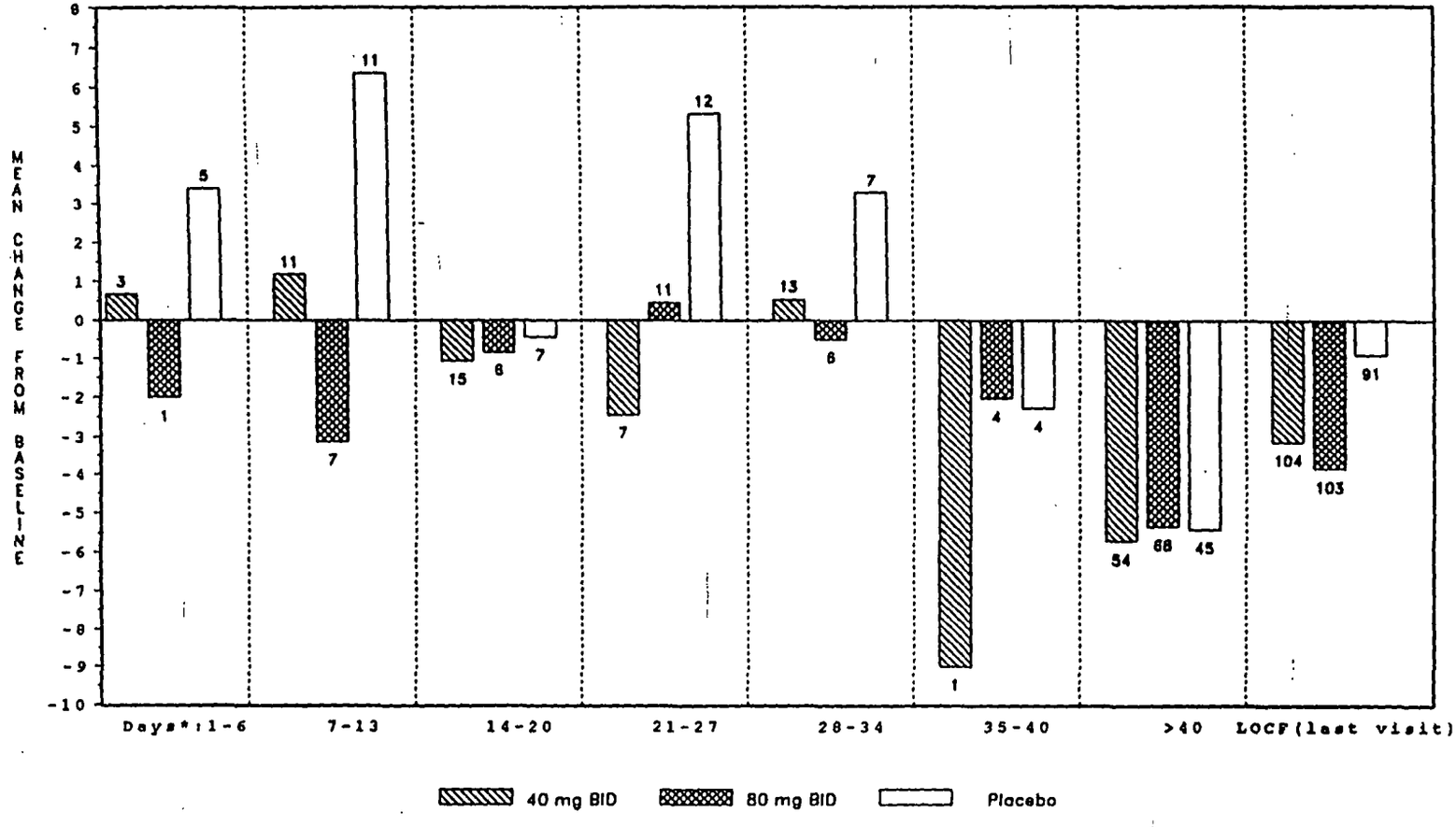
* Duration of Participation (in Days).

Source Data: Appendix III Table 29 and Appendix V Table 15 Date of Data Extraction: 29MAR96 Date of Figure Generation: 19APR96

PAGE 132

Figure 1.25

Figure 2.2
PANSS Negative Subscale Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 114

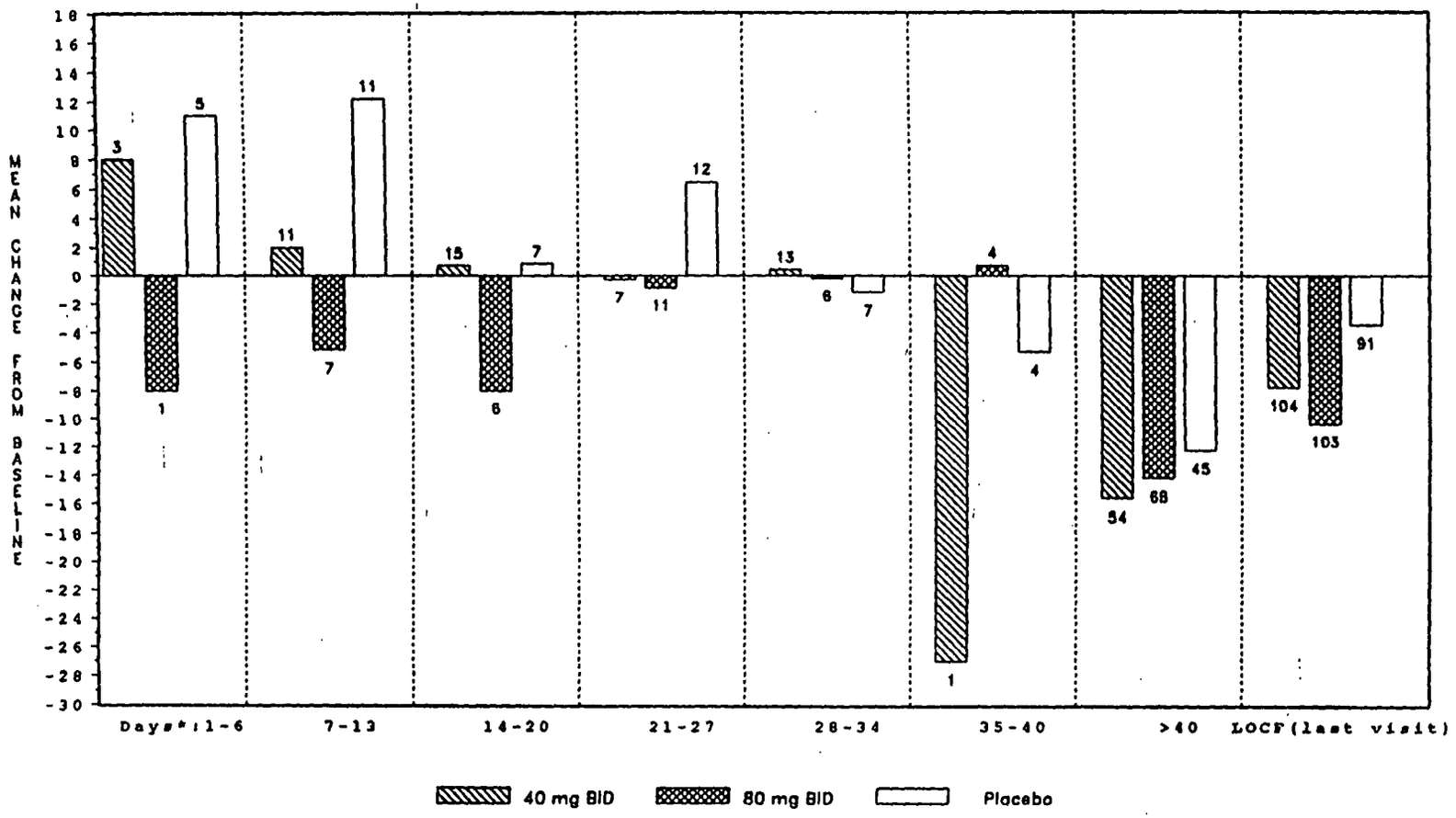


* Duration of Participation (In Days).

Source Data: Appendix III Table 29 and Appendix V Table 15 Date of Data Extraction: 29MAR96 Date of Figure Generation: 19APR96

Figure 1.25

Figure 2.3
BPRSd Total Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 114



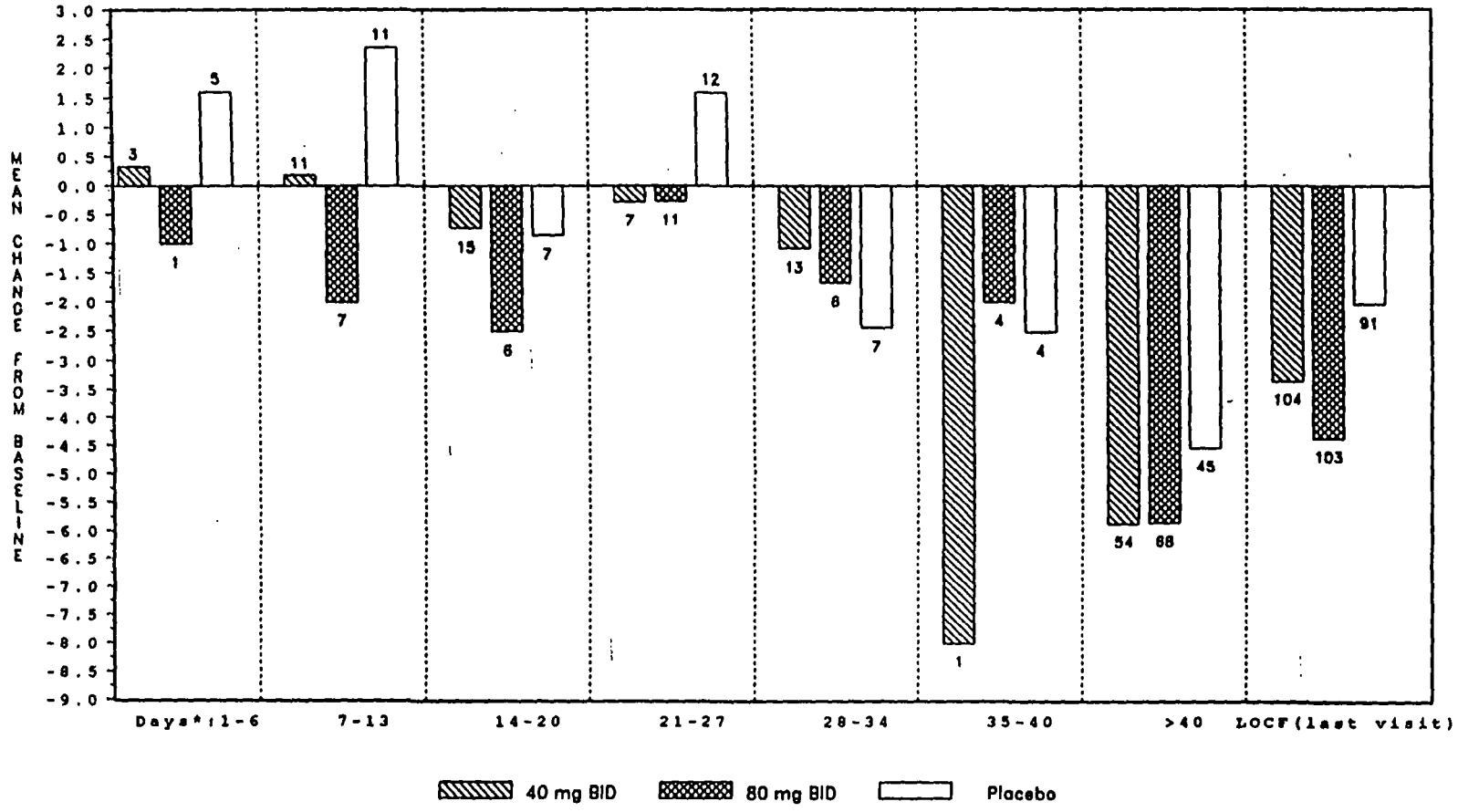
* Duration of Participation (in Days).

Source Data: Appendix III Table 29 and Appendix V Table 15 Date of Data Extraction: 29MAR96 Date of Figure Generation: 19APR96

PAGE 134

Figure 1.2S

Figure 2.4
BPRSd Core Items Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 114



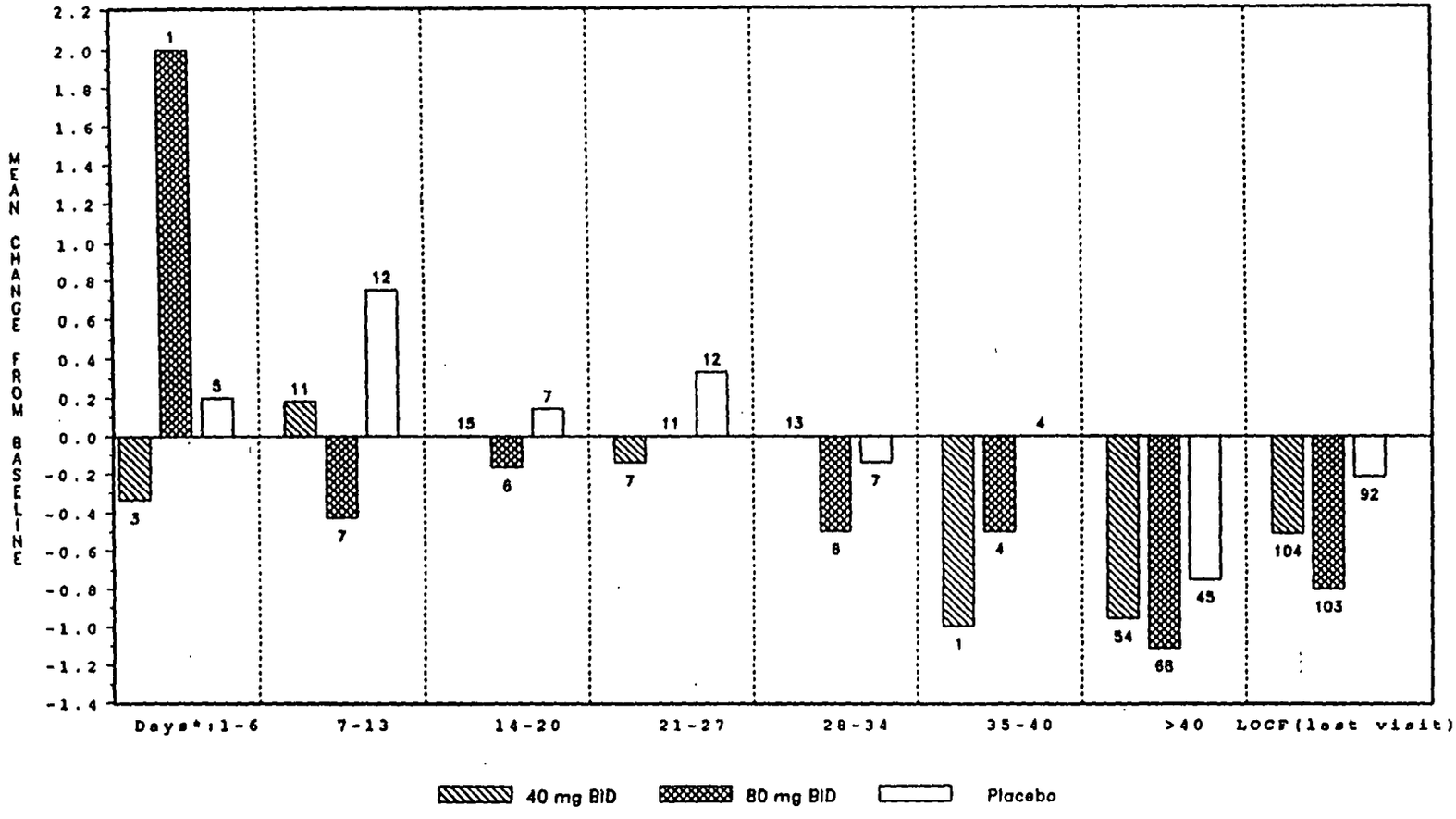
* Duration of Participation (In Days).

Source Data: Appendix III Table 29 and Appendix V Table 15 Date of Data Extraction: 29MAR96 Date of Figure Generation: 19APR96

PAGE 135

Figure 1.2 S

Figure 2.5
CGI Severity Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 114



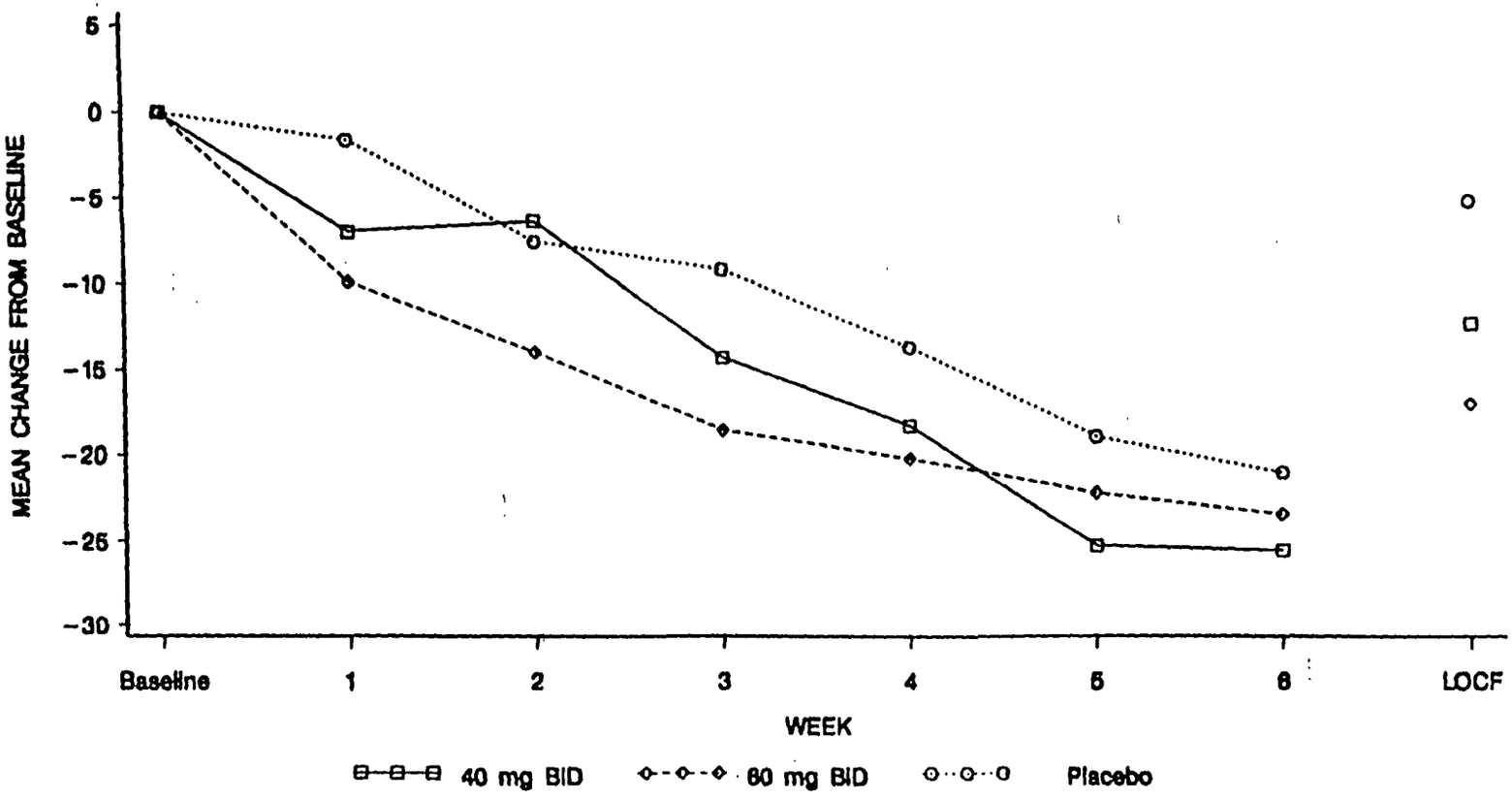
* Duration of Participation (in Days).

Source Data: Appendix III Table 29 and Appendix V Table 16 Date of Data Extraction: 29MAR96 Date of Figure Generation: 19APR96

PAGE 136

Figure 1.35

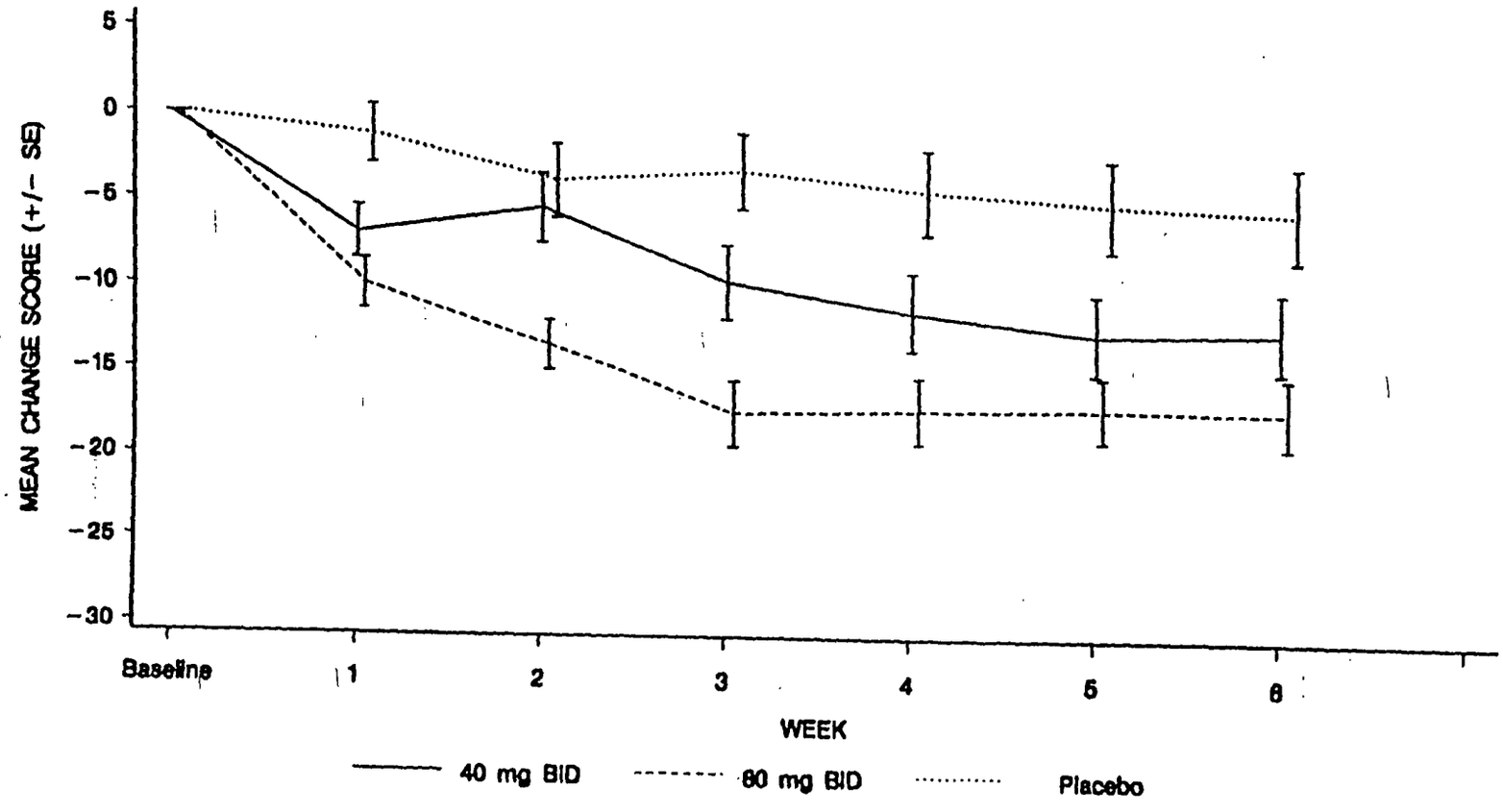
Figure 3.1
PANSS Total Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, Observed Cases
Ziprasidone Protocol 114



Source Data: Table 5.1.1 Date of Data Extraction: 29MAR96. Date of Table Generation: 05APR96.

Figure 1.45

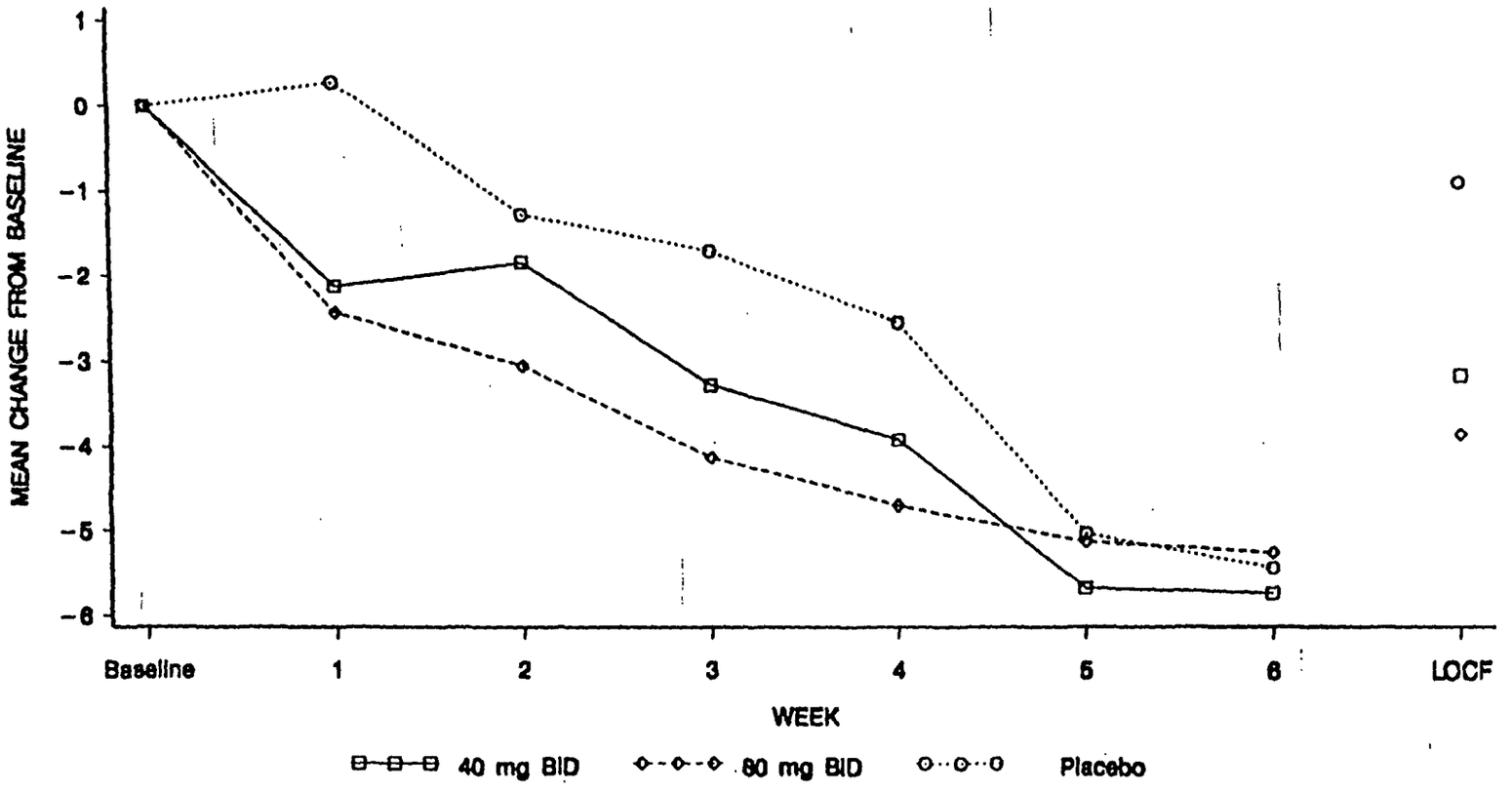
Figure 3.2
PANSS Total Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 114



Source Data: Appendix III Table 2.10 Date of Data Extraction: 29MAR96. Date of Table Generation: 05APR96.

Figure 1.3.5

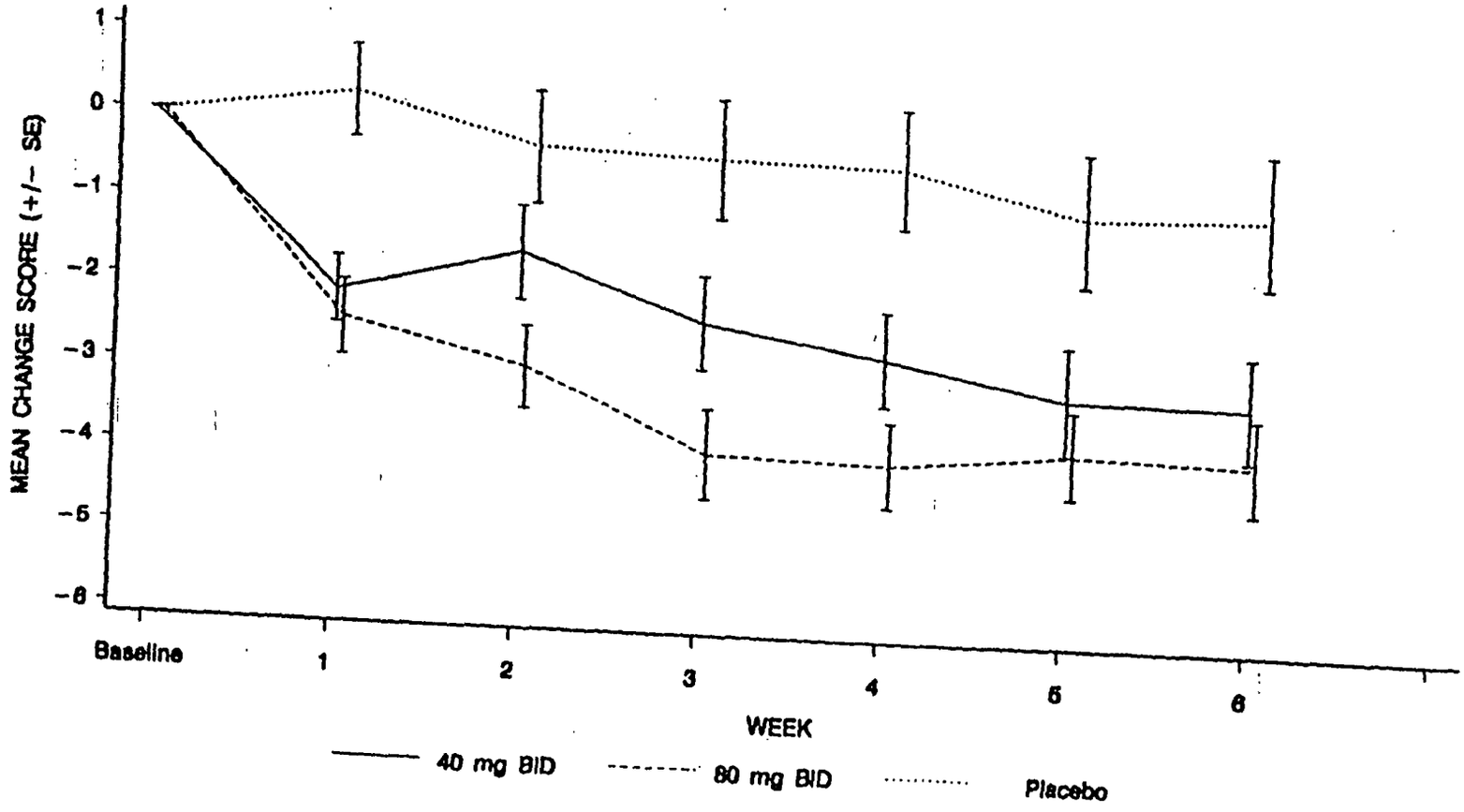
Figure 3.3
PANSS Negative Subscale Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, Observed Cases
Ziprasidone Protocol 114



Source Data: Table 5.1.4 Date of Data Extraction: 29MAR96. Date of Table Generation: 05APR96.

Figure 1.45

Figure 3.4
PANSS Negative Subscale Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 114

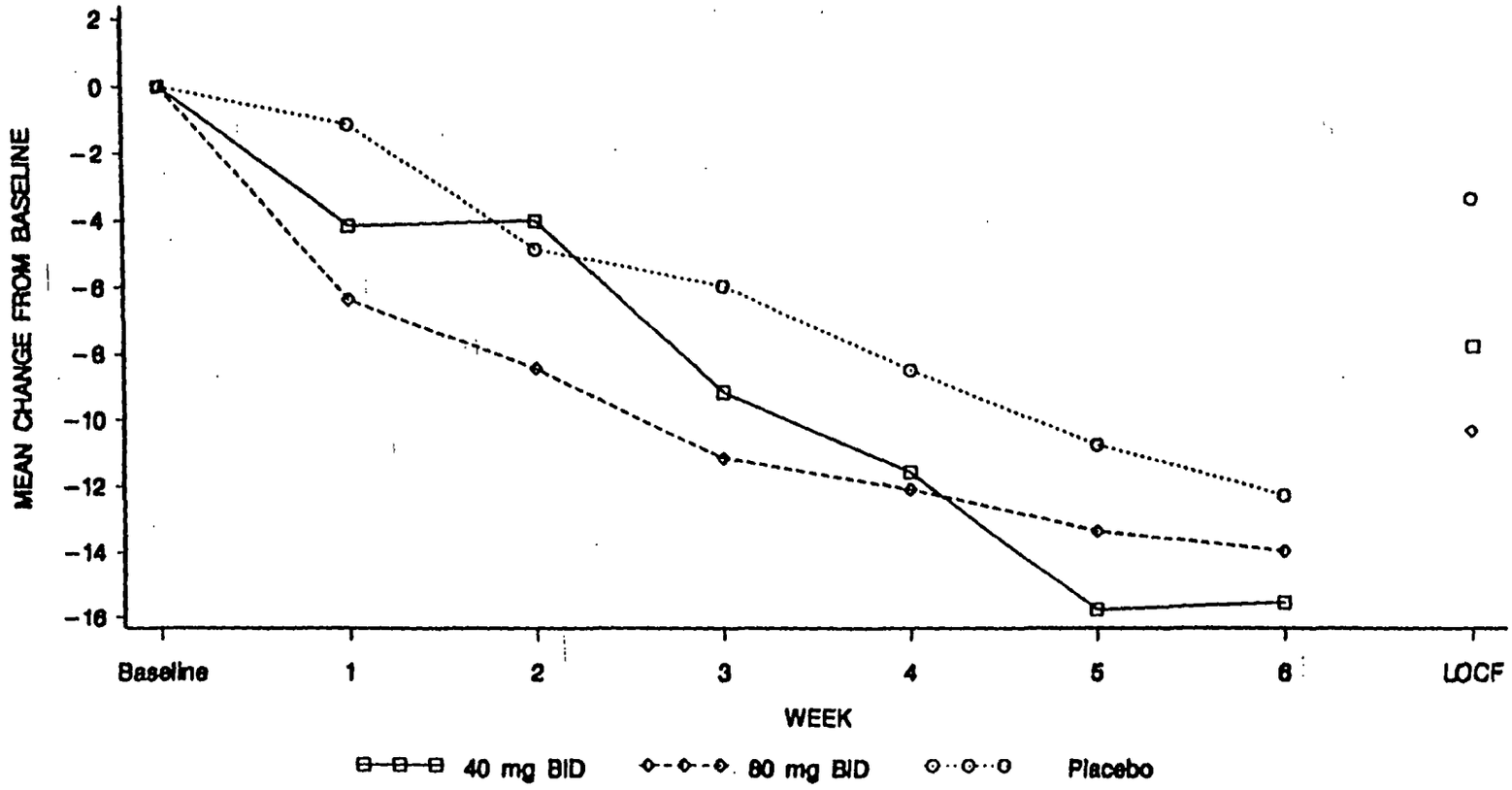


Source Data: Appendix III Table 3.10 Date of Data Extraction: 29MAR96. Date of Table Generation: 05APR96.

PAGE 140

Figure 1.3 S

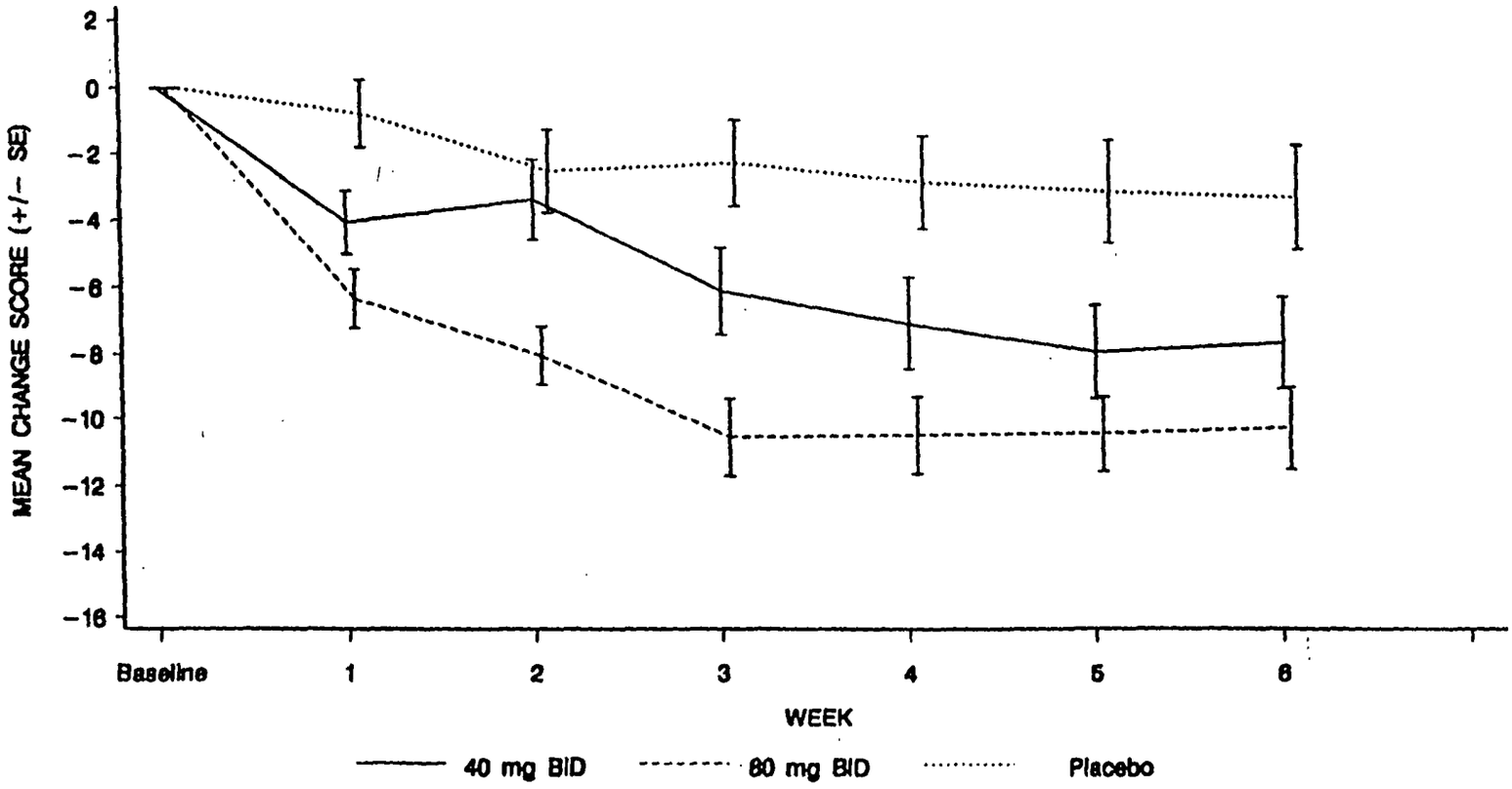
Figure 3.5
BPRSd Total Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, Observed Cases
Ziprasidone Protocol 114



Source Data: Table 5.1.7 Date of Data Extraction: 29MAR96. Date of Table Generation: 05APR96.

Figure 1.45

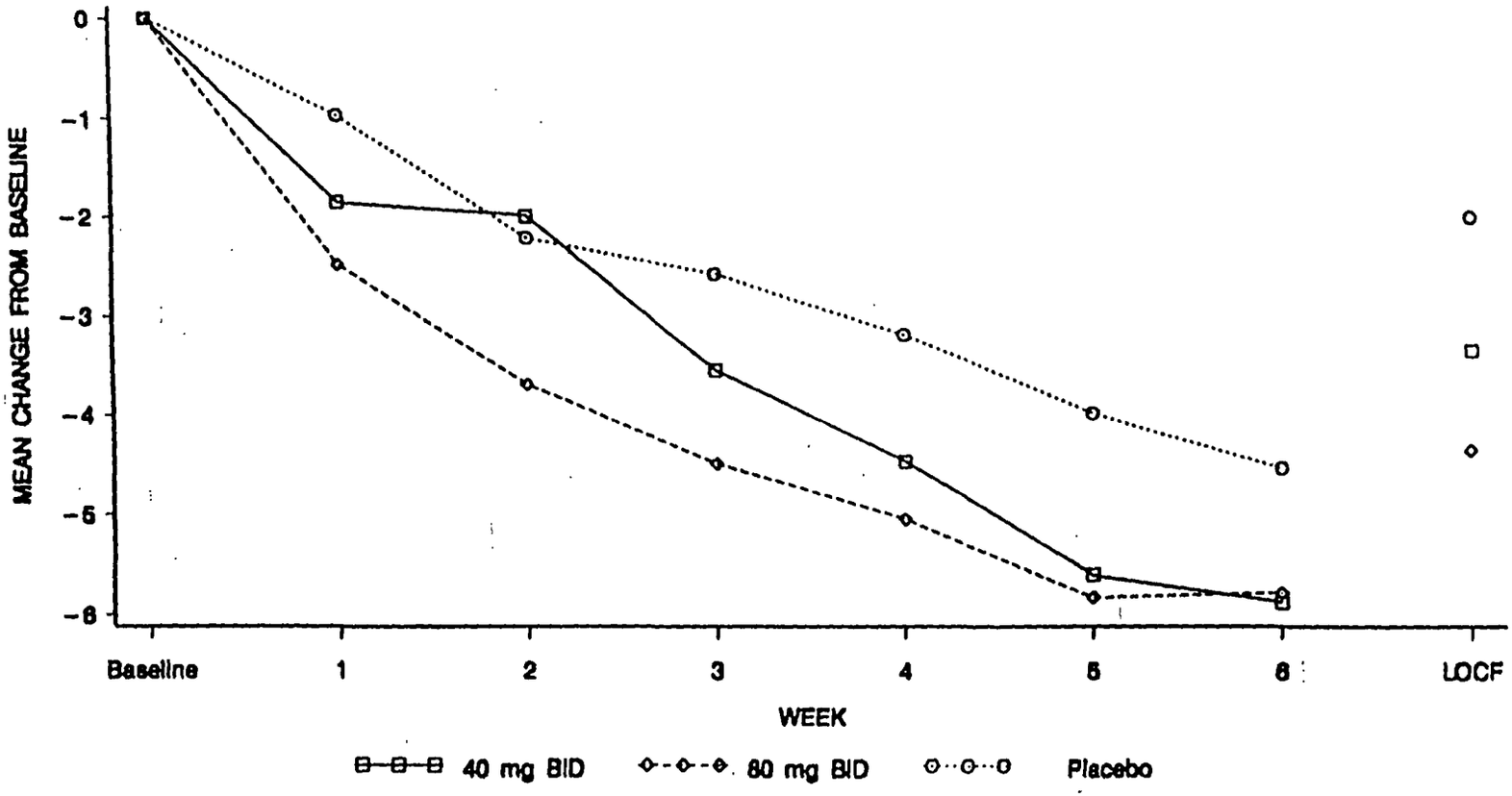
Figure 3.6
BPRSd Total Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 114



Source Data: Appendix III Table 4.10 Date of Data Extraction: 29MAR96. Date of Table Generation: 05APR96.

Figure 1.3S

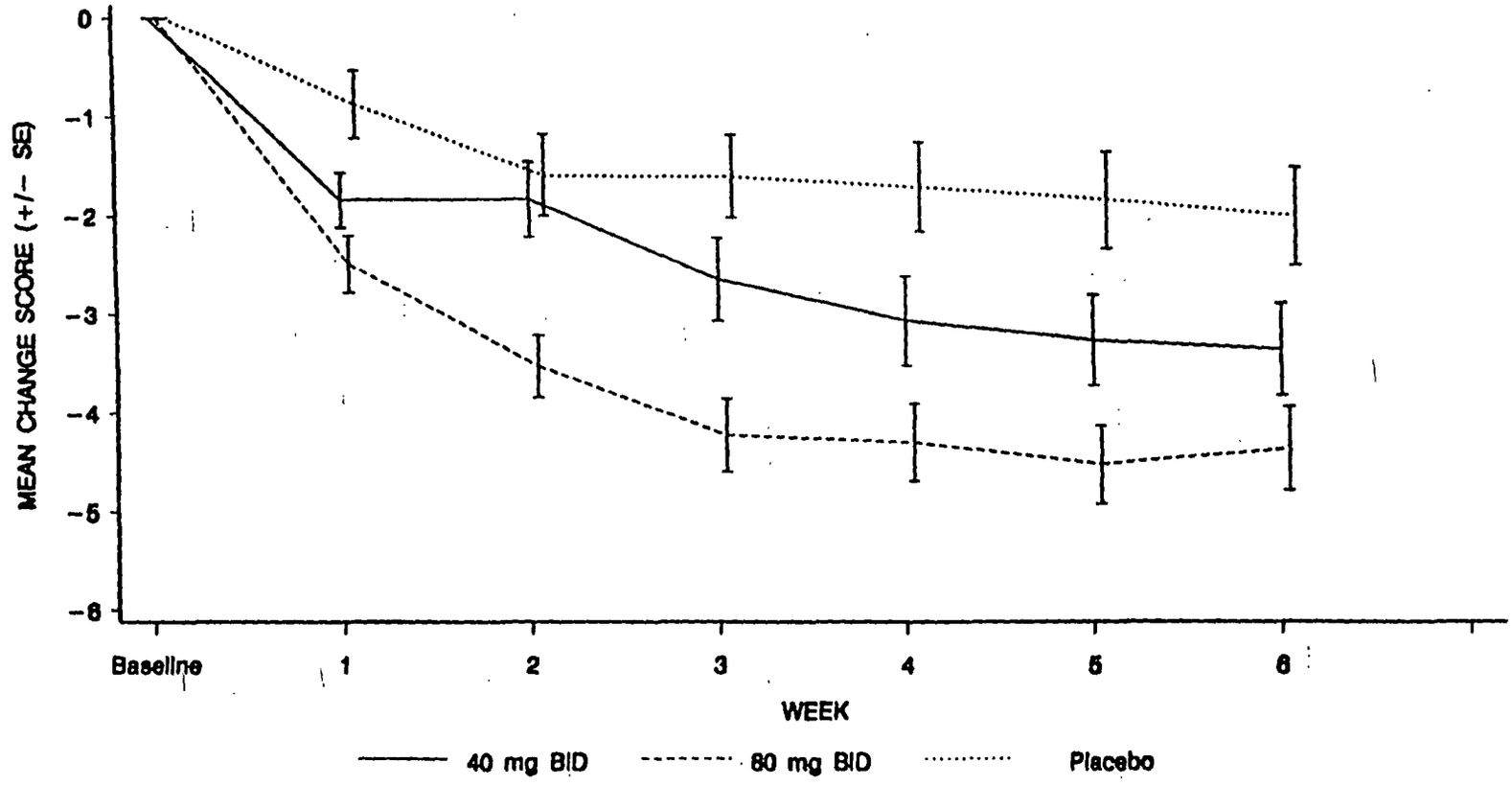
Figure 3.7
BPRSd Core Items Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, Observed Cases
Ziprasidone Protocol 114



Source Data: Table 5.1.10 Date of Data Extraction: 29MAR96. Date of Table Generation: 05APR96.

Figure 1.45

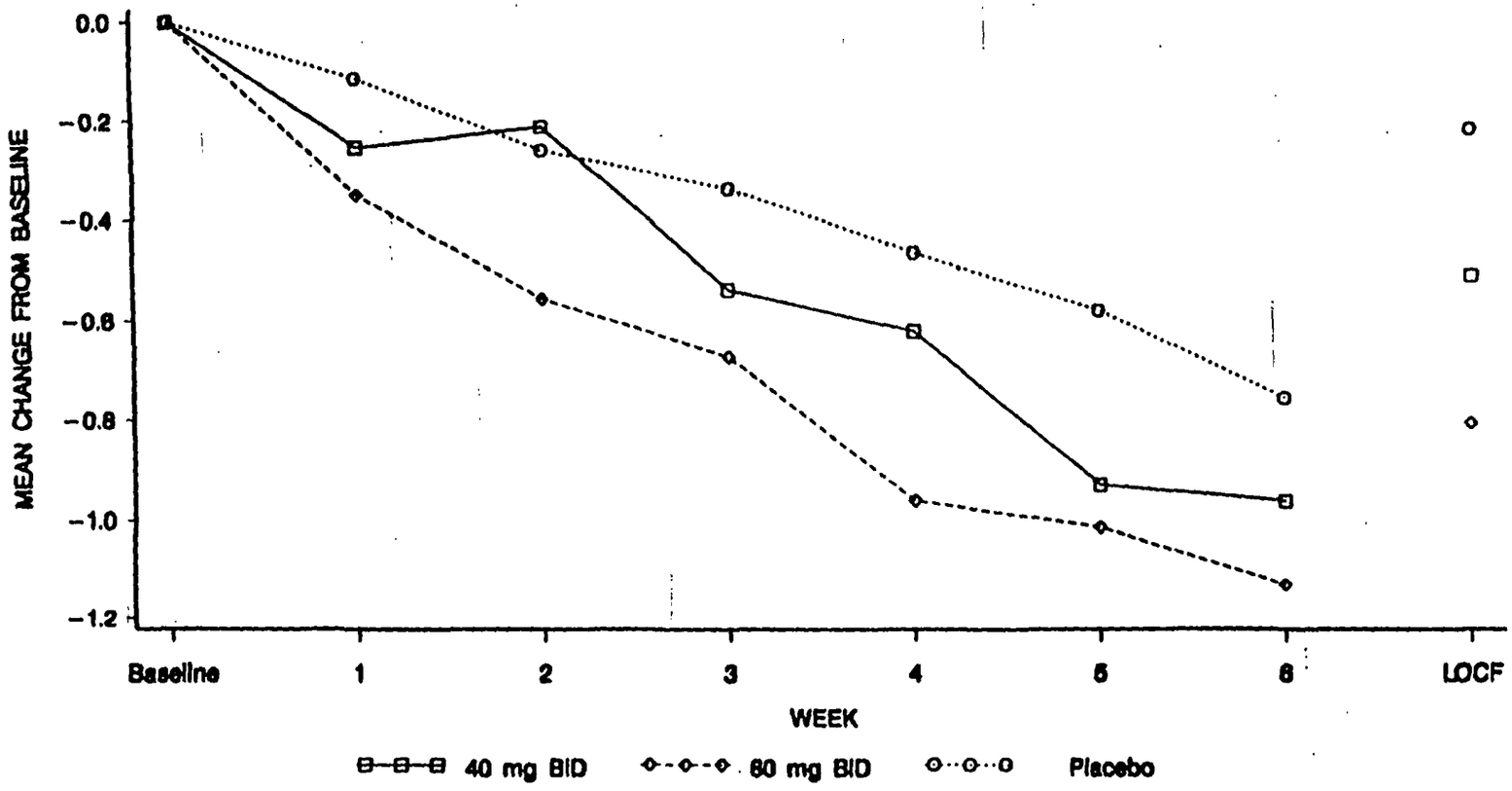
Figure 3.8
BPRSd Core Items Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 114



Source Data: Appendix III Table 5.10 Date of Data Extraction: 29MAR96. Date of Table Generation: 05APR96.

Figure 1.3.5

Figure 3.9
CGI Severity Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, Observed Cases
Ziprasidone Protocol 114

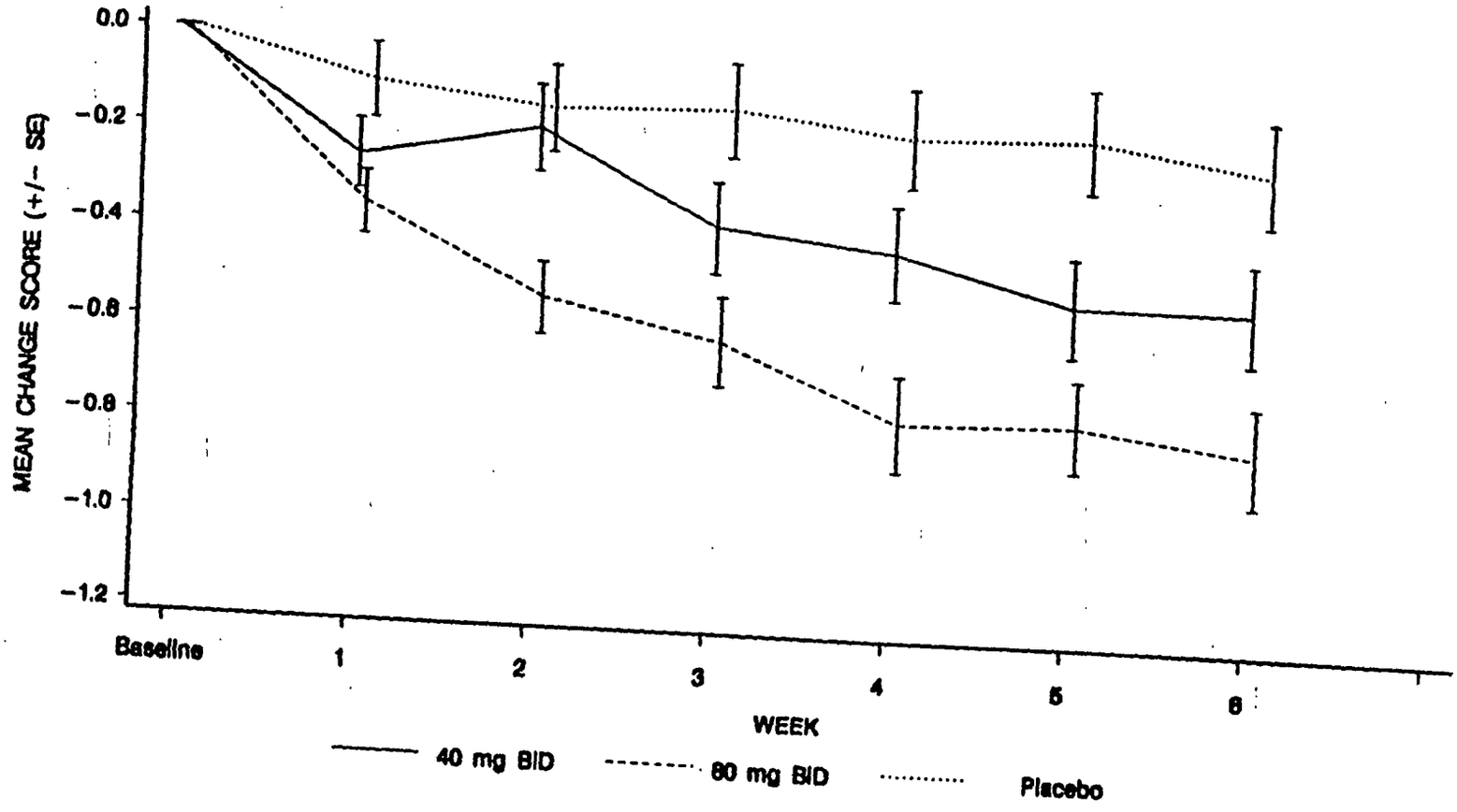


Source Data: Table 5.1.13 Date of Data Extraction: 29MAR96. Date of Table Generation: 05APR96.

Figure 3.10

Figure 1.45

CGI Severity Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 114



Source Data: Appendix III Table 6.10 Date of Data Extraction: 29MAR96. Date of Table Generation: 05APR96.

Table 1.35

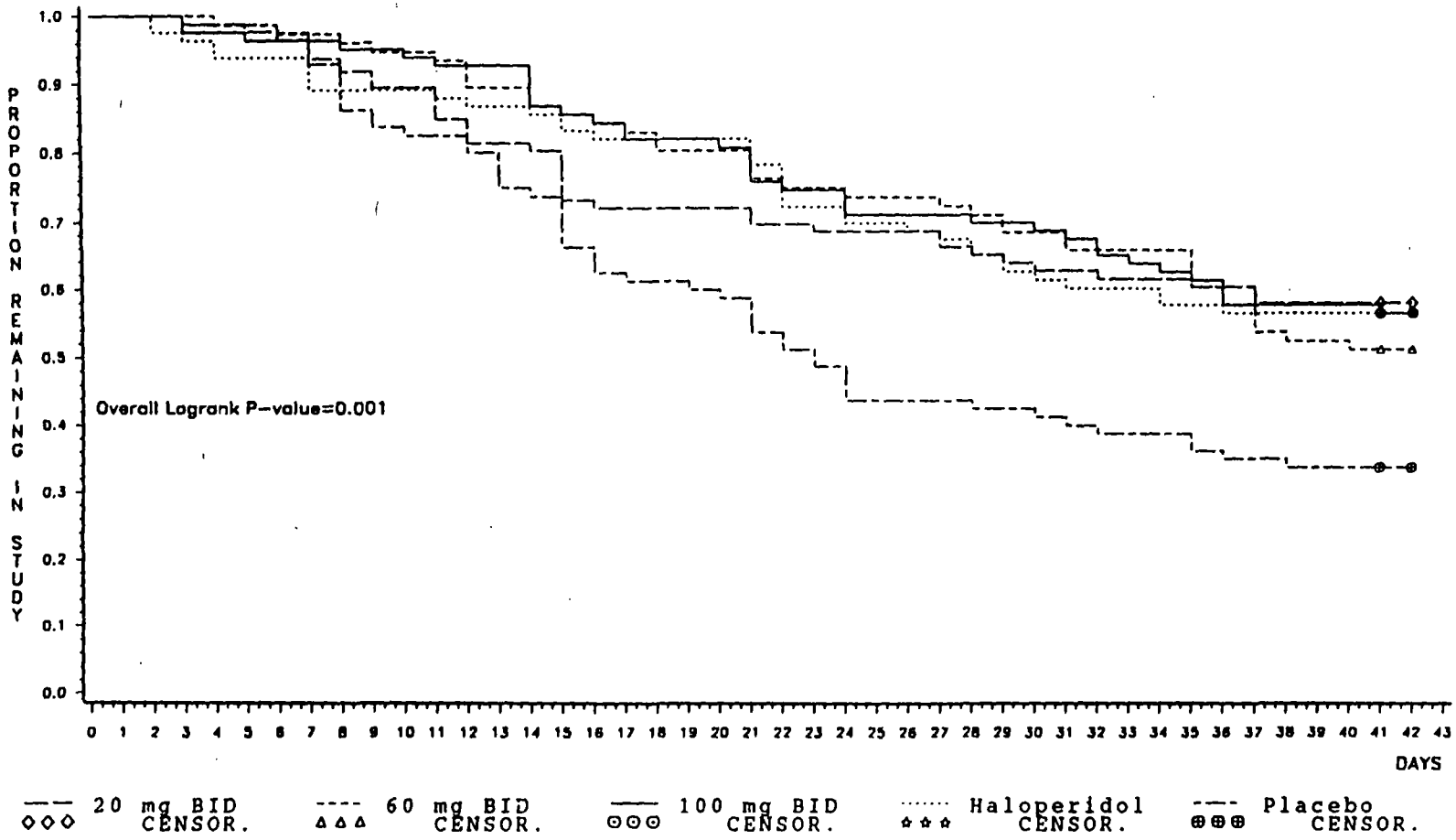
Longitudinal Analyses of Treatment Effects for Primary Efficacy Variables - All Subjects, Observed Cases
Ziprasidone Protocol 114

Variable	Treatment Comparison	Method*	Treatment Effect	P-Value	95% Confidence Limit Lower	Upper
PANSS Total	40mg bid vs placebo	Wu-Bailey(1)	-1.6869	0.0162	-3.0620	-0.3117
		UWLS(2)	-3.5954	0.0011	-5.7471	-1.4437
		Random(3)	-1.4205	0.0350	-2.7410	-0.0999
	80mg bid vs placebo	Wu-Bailey(1)	-2.4167	0.0005	-3.7694	-1.0639
		UWLS(2)	-5.1072	0.0000	-7.1762	-3.1982
		Random(3)	-1.5448	0.0184	-2.8286	-0.2609
PANSS Negative	40mg bid vs placebo	Wu-Bailey(1)	-0.3897	0.0375	-0.7568	-0.0225
		UWLS(2)	-1.0036	0.0020	-1.6406	-0.3666
		Random(3)	-0.3283	0.0650	-0.6769	0.0204
	80mg bid vs placebo	Wu-Bailey(1)	-0.5335	0.0039	-0.8957	-0.1714
		UWLS(2)	-1.2464	0.0000	-1.8312	-0.6616
		Random(3)	-0.2723	0.1145	-0.6104	0.0659
BPRSd Total	40mg bid vs placebo	Wu-Bailey(1)	-1.0012	0.0127	-1.7890	-0.2134
		UWLS(2)	-2.1795	0.0010	-3.4803	-0.8788
		Random(3)	-0.8849	0.0235	-1.6506	-0.1191
	80mg bid vs placebo	Wu-Bailey(1)	-1.2933	0.0011	-2.0679	-0.5187
		UWLS(2)	-3.1508	0.0000	-4.3504	-1.9512
		Random(3)	-0.7988	0.0353	-1.5424	-0.0552
BPRSd Core	40mg bid vs placebo	Wu-Bailey(1)	-0.3035	0.0175	-0.5537	-0.0532
		UWLS(2)	-0.5813	0.0084	-1.0133	-0.1493
		Random(3)	-0.2768	0.0290	-0.5254	-0.0283
	80mg bid vs placebo	Wu-Bailey(1)	-0.4485	0.0004	-0.6945	-0.2026
		UWLS(2)	-0.8215	0.0001	-1.2192	-0.4238
		Random(3)	-0.3408	0.0056	-0.5821	-0.0996
CGI Severity	40mg bid vs placebo	Wu-Bailey(1)	-0.0757	0.0148	-0.1366	-0.0148
		UWLS(2)	-0.1226	0.0160	-0.2224	-0.0229
		Random(3)	-0.0651	0.0293	-0.1237	-0.0065
	80mg bid vs placebo	Wu-Bailey(1)	-0.1252	0.0000	-0.1851	-0.0653
		UWLS(2)	-0.1822	0.0001	-0.2742	-0.0902
		Random(3)	-0.0954	0.0010	-0.1523	-0.0385

* 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: 29MAR96. Date of Table Generation: 25SEP96.

Figure 2.1S

Figure 1
Kaplan–Meier Curves for Time–to–Discontinuation for All Reasons by Treatment Group
All Subjects
Ziprasidone Protocol 115



Source Data: Appendix III Table 28 Date of Data Extraction: 22OCT96 Date of Figure Generation: 23OCT96

PAGE 173

Table 2.2S

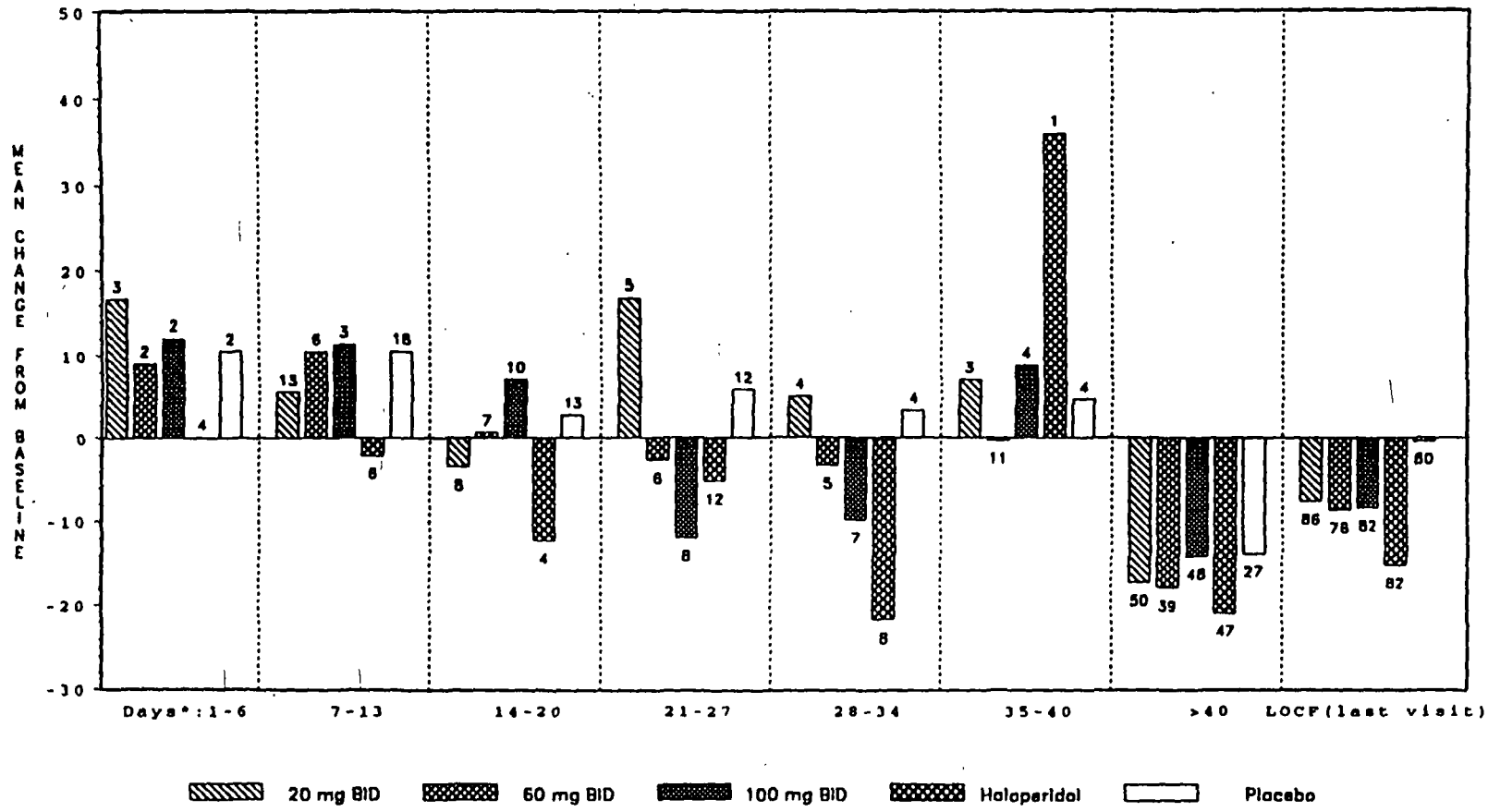
Table 5.1.16
Treatment Effects at Last Observation for Primary Efficacy Variables - All Subjects
Ziprasidone Protocol 115

Variable	Treatment Comparison	Estimated Treatment Effect*	P-Value**	Lower 95% Confidence Limit**	Upper 95% Confidence Limit**
PANSS Total	Dose-Response^	-5.18	0.023	-9.64	-0.71
	20 mg BID vs Pbo	-6.77	0.031	-12.93	-0.62
	60 mg BID vs Pbo	-8.23	0.011	-14.59	-1.87
	100 mg BID vs Pbo	-8.01	0.012	-14.28	-1.74
	Zipras. vs Pbo	-7.67	0.003	-12.79	-2.55
	Haloperidol vs Pbo	-13.84	0.000	-20.08	-7.61
PANSS Negative	Dose-Response^	-1.46	0.030	-2.77	-0.15
	20 mg BID vs Pbo	-1.44	0.121	-3.26	0.38
	60 mg BID vs Pbo	-1.75	0.069	-3.63	0.14
	100 mg BID vs Pbo	-2.20	0.020	-4.05	-0.35
	Zipras. vs Pbo	-1.80	0.020	-3.31	-0.28
	Haloperidol vs Pbo	-2.53	0.008	-4.38	-0.68
BPRSd Total	Dose-Response^	-2.75	0.038	-5.34	-0.15
	20 mg BID vs Pbo	-3.59	0.049	-7.16	-0.01
	60 mg BID vs Pbo	-4.39	0.020	-8.09	-0.69
	100 mg BID vs Pbo	-4.24	0.023	-7.88	-0.60
	Zipras. vs Pbo	-4.07	0.008	-7.05	-1.09
	Haloperidol vs Pbo	-7.21	0.000	-10.84	-3.59
BPRSd Core	Dose-Response^	-1.06	0.025	-1.99	-0.13
	20 mg BID vs Pbo	-1.40	0.034	-2.68	-0.11
	60 mg BID vs Pbo	-1.35	0.046	-2.68	-0.02
	100 mg BID vs Pbo	-1.74	0.009	-3.04	-0.43
	Zipras. vs Pbo	-1.49	0.006	-2.56	-0.42
	Haloperidol vs Pbo	-3.16	0.000	-4.46	-1.86
CGI Severity	Dose-Response^	-0.26	0.016	-0.48	-0.05
	20 mg BID vs Pbo	-0.33	0.030	-0.63	-0.03
	60 mg BID vs Pbo	-0.33	0.035	-0.64	-0.02
	100 mg BID vs Pbo	-0.43	0.006	-0.73	-0.13
	Zipras. vs Pbo	-0.36	0.004	-0.61	-0.12
	Haloperidol vs Pbo	-0.75	0.000	-1.05	-0.44

*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 17.1.2, 18.1.2, 19.1.2, 20.1.2 and 21.1.2)
^Dose-response relationship between ziprasidone groups and placebo was examined by means of linear contrast with coefficients derived from a linear response using orthogonal polynomials.
Source Data: Appendix V Tables 15,16. Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

Figure 2.25

Figure 2.1
PANSS Total Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 115



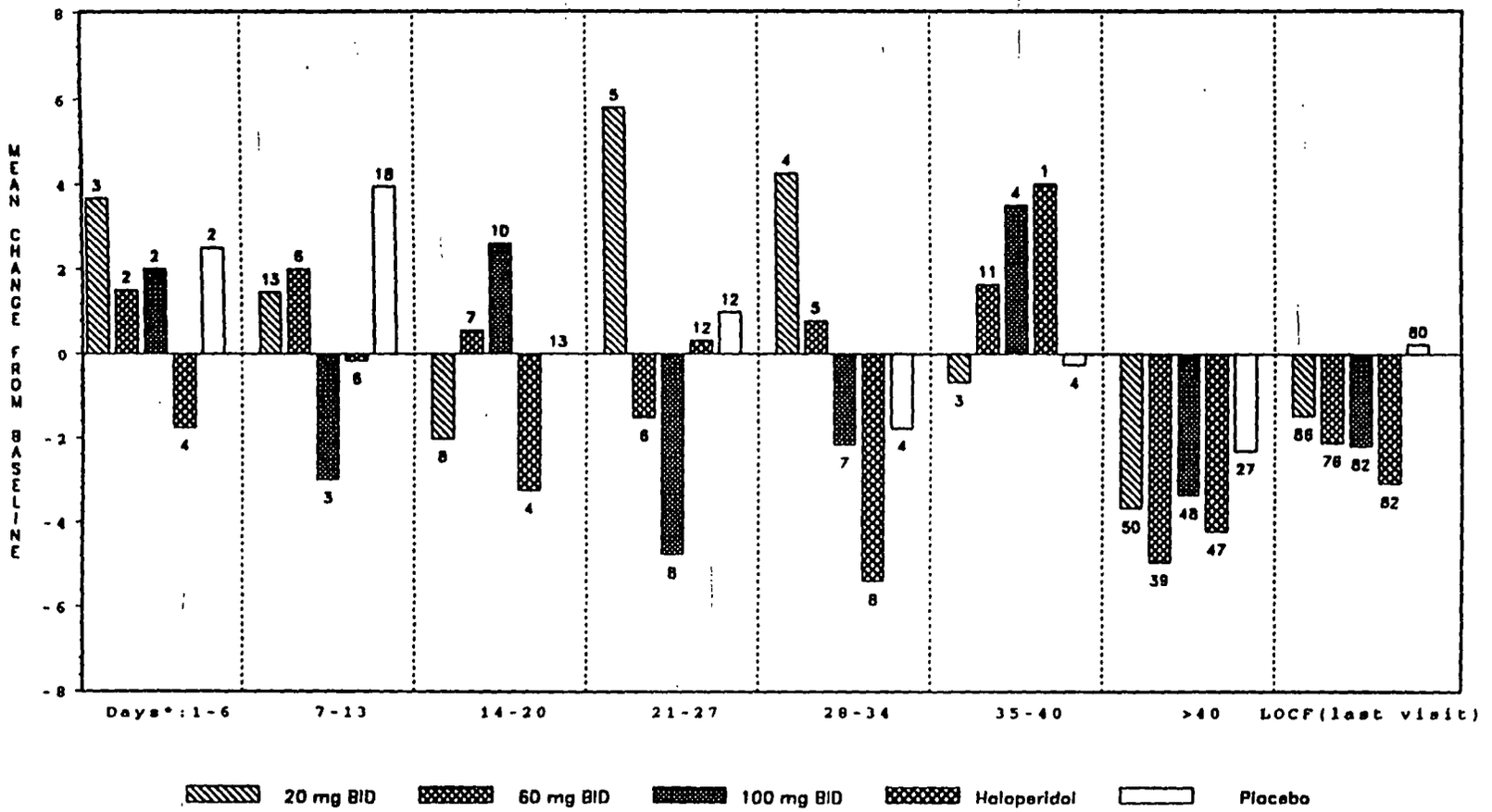
* Duration of Participation (in Days).

Source Data: Appendix III Table 29, Appendix V Table 15 Date of Data Extraction: 22OCT96 Date of Figure Generation: 24OCT96

PAGE 174

Figure 2.2S

Figure 2.2
PANSS Negative Subscale Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 115



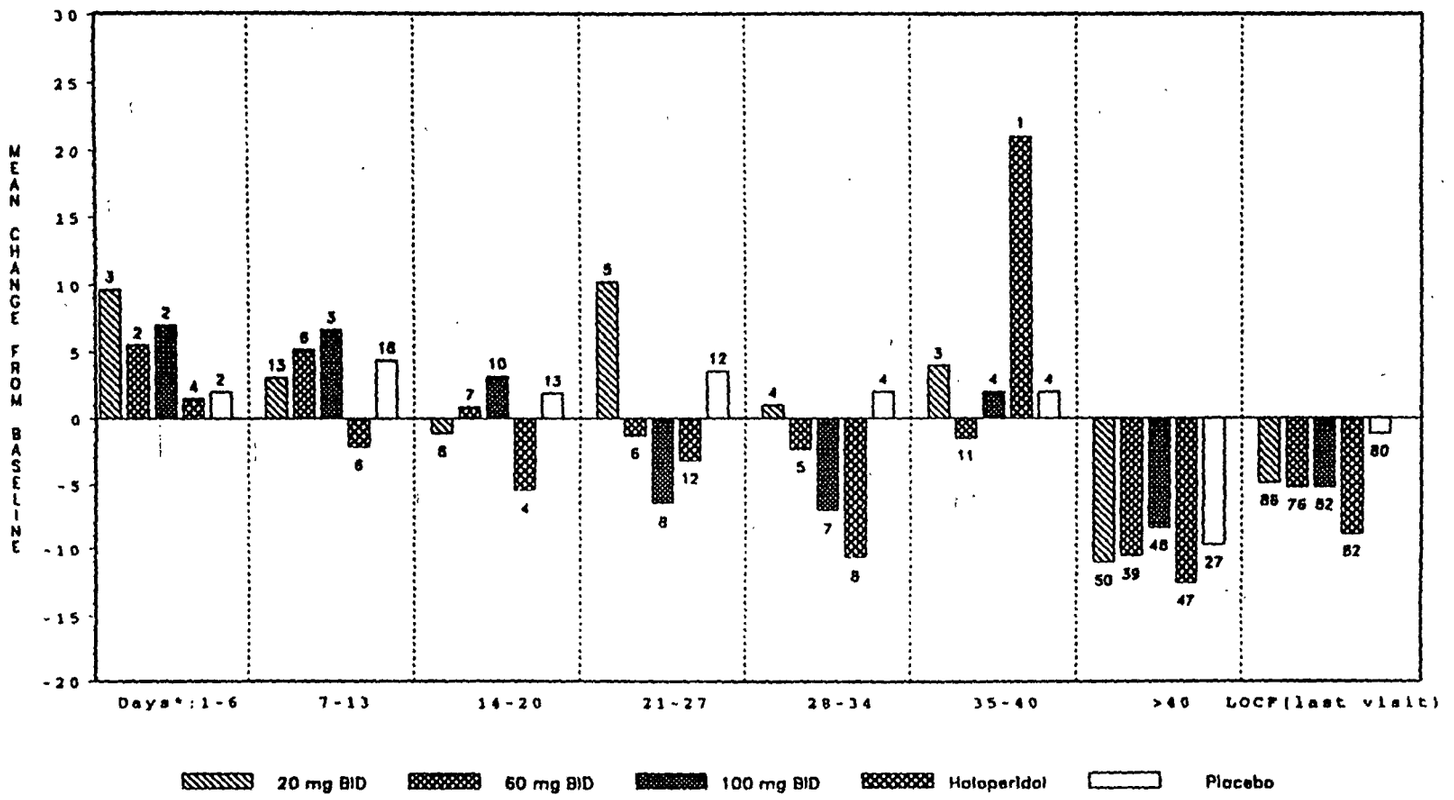
* Duration of Participation (in Days).

Source Data: Appendix III Table 29, Appendix V Table 15 Date of Data Extraction: 22OCT96 Date of Figure Generation: 24OCT96

PAGE 175

Figure 2.25

Figure 2.3
BPRSd Total Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 115



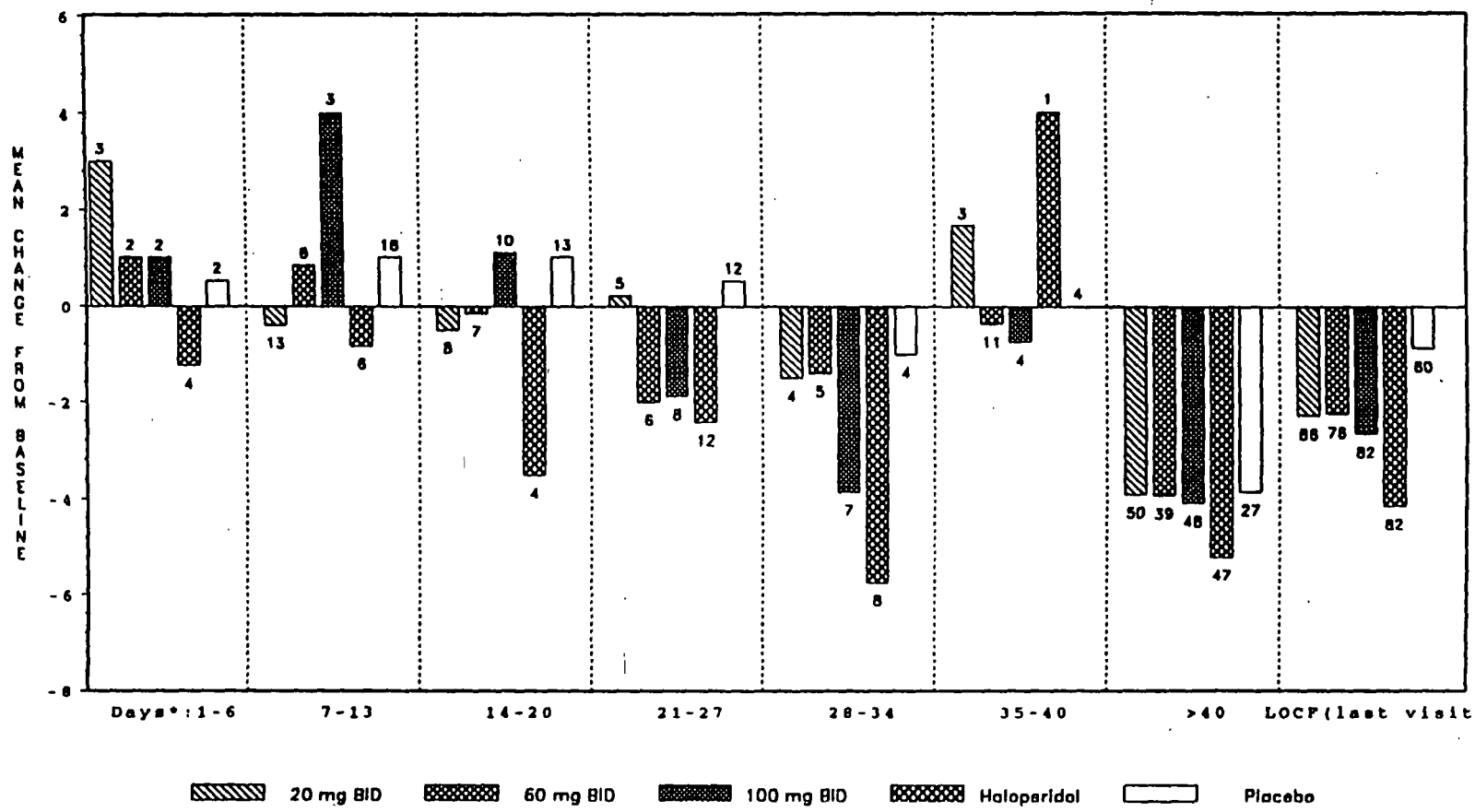
* Duration of Participation (in Days).

Source Data: Appendix III Table 29, Appendix V Table 15 Date of Data Extraction: 22OCT96 Date of Figure Generation: 24OCT96

PAGE 176

Figure 2.25

Figure 2.4
BPRSd Core Items Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 115



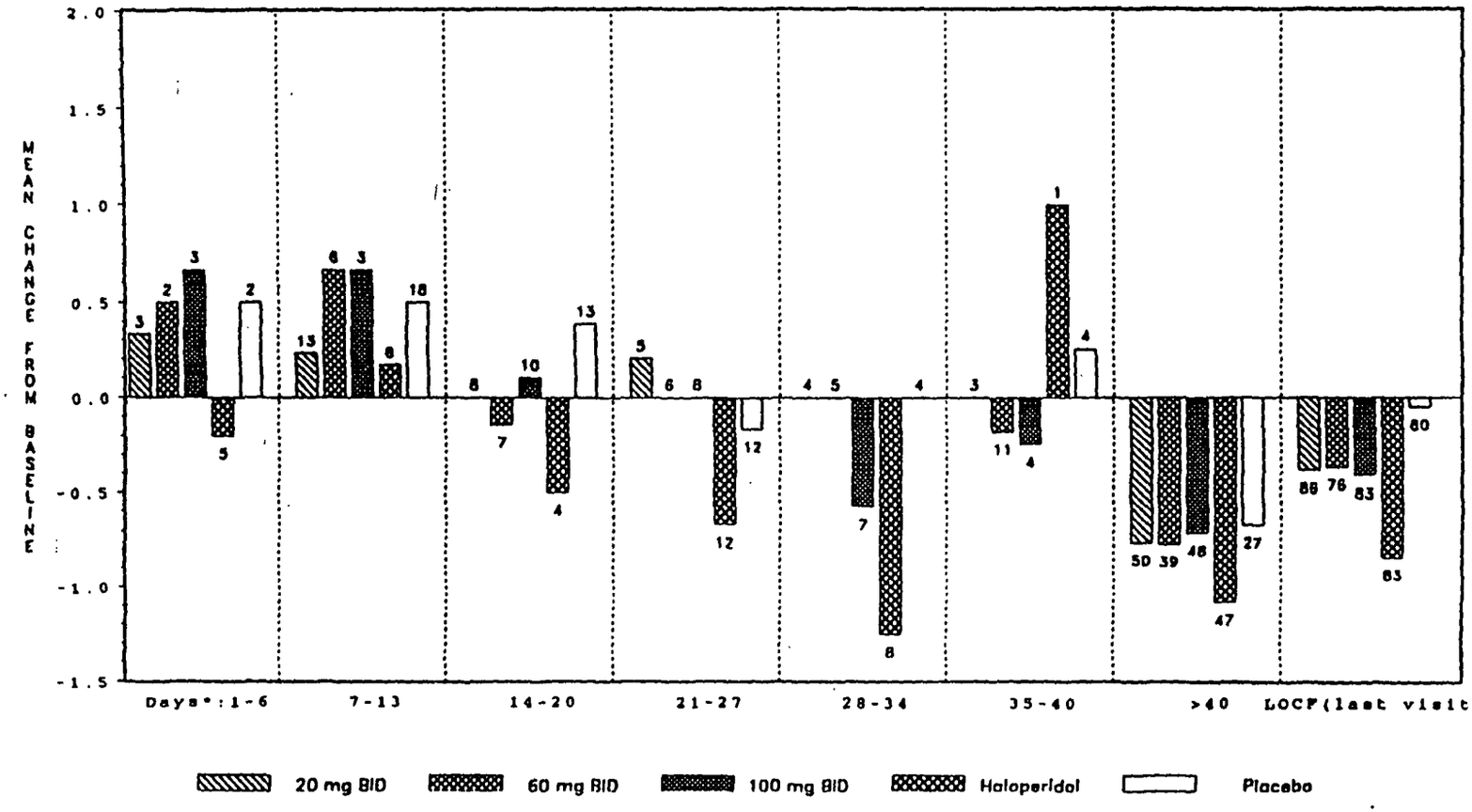
* Duration of Participation (in Days).

Source Data: Appendix III Table 29, Appendix V Table 15 Date of Data Extraction: 22OCT96 Date of Figure Generation: 24OCT96

PAGE 177

Figure 2.25

Figure 2.5
CGI Severity Score – Mean Change from Baseline by Duration of Study Participation – All Subjects
Ziprasidone Protocol 115

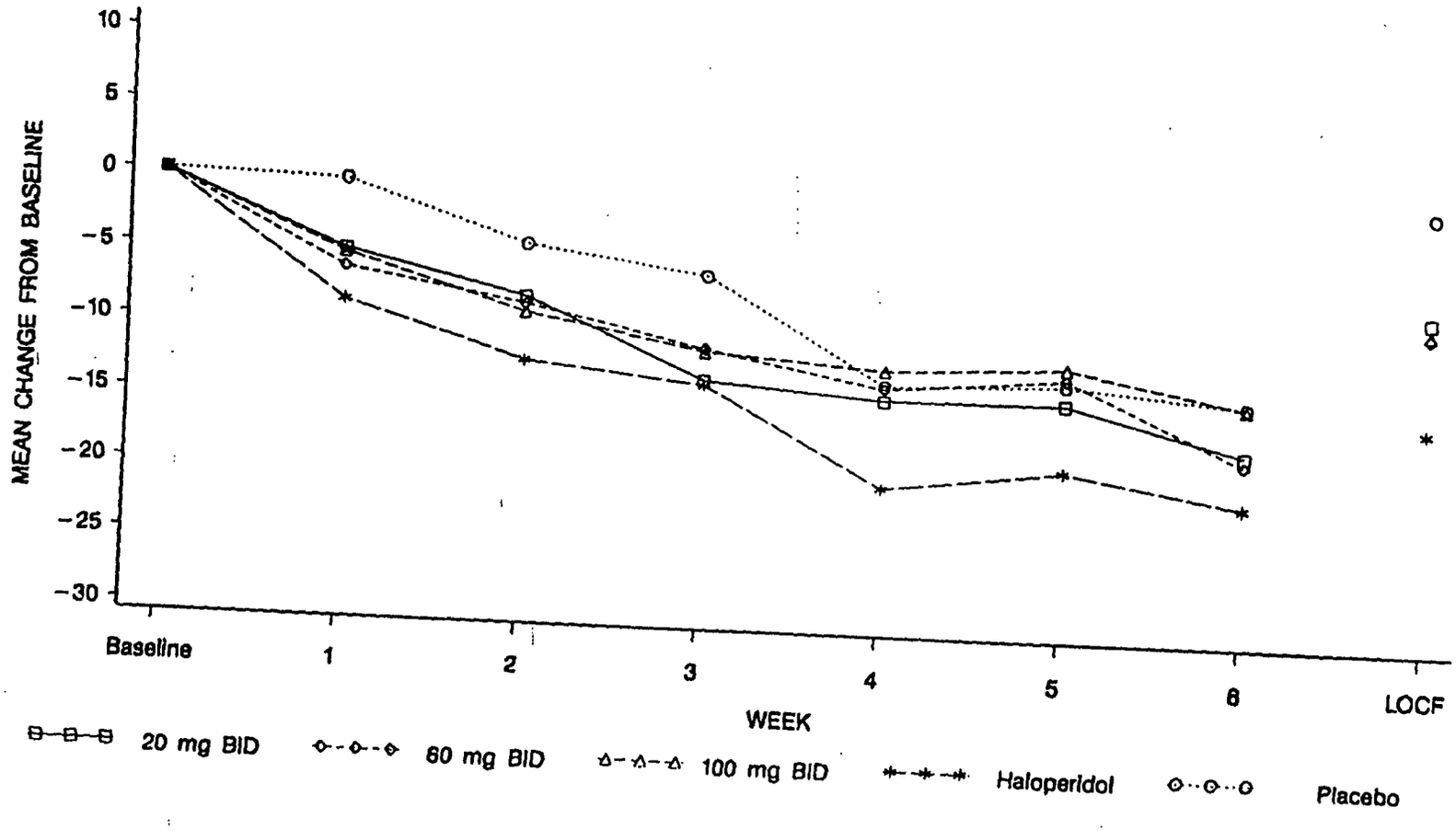


* Duration of Participation (In Days).

Source Data: Appendix III Table 29, Appendix V Table 16 Date of Data Extraction: 22OCT96 Date of Figure Generation: 24OCT96

PAGE 178

Figure 3.1 Figure 2.3.5
PANSS Total Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, Observed Cases
Ziprasidone Protocol 115

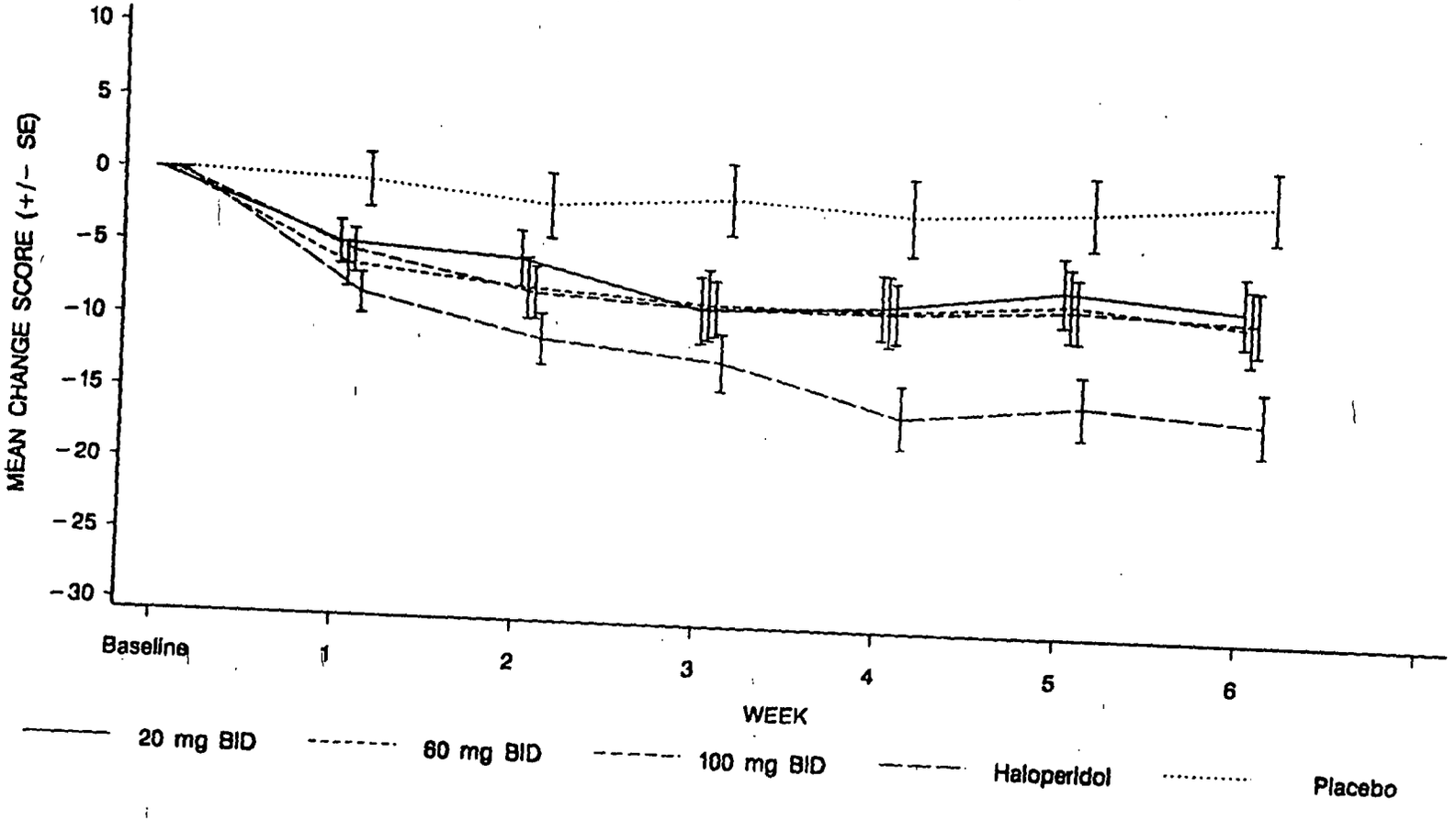


Source Data: Table 5.1.1 Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

PAGE 179

Figure 2.4.5

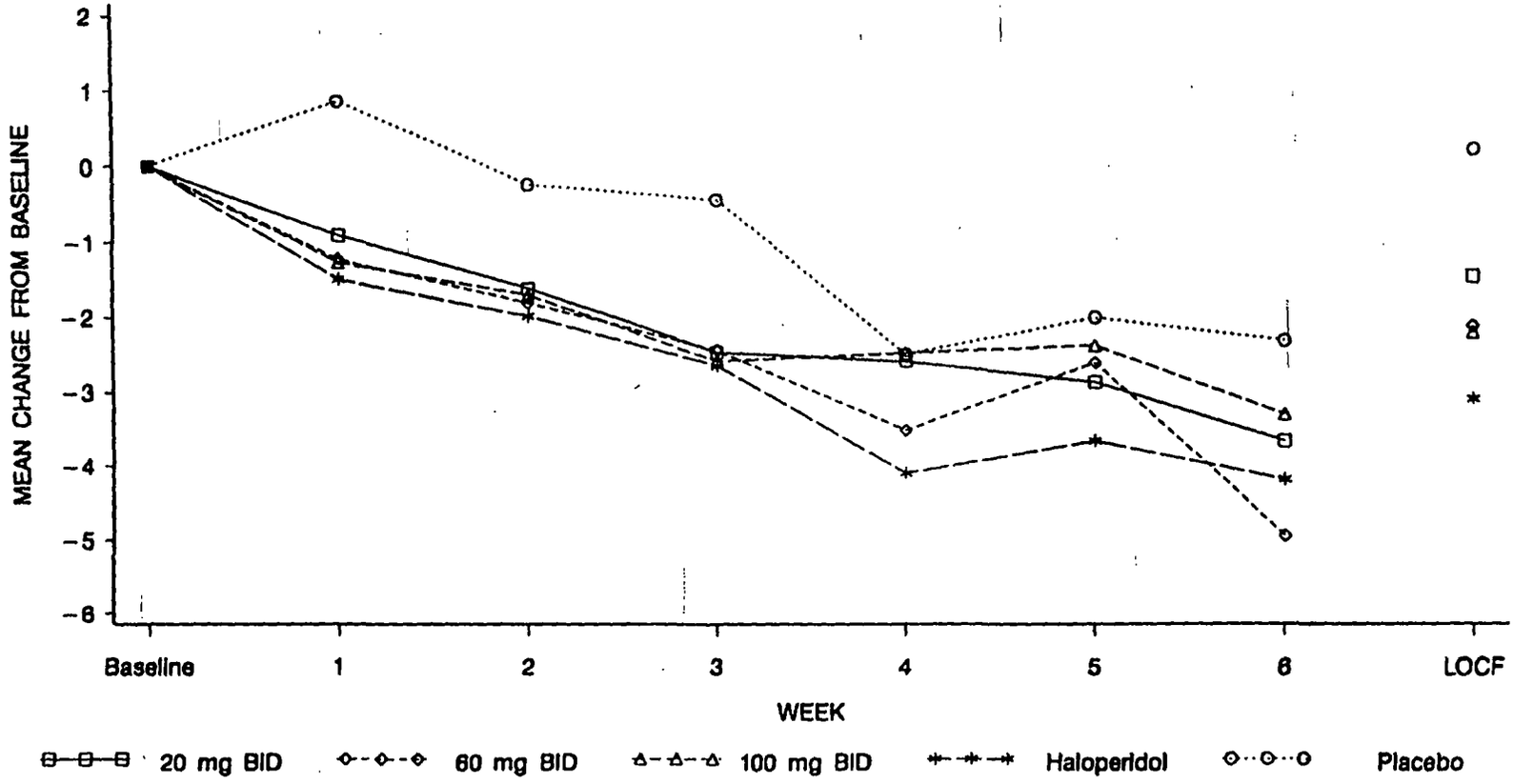
Figure 3.2
PANSS Total Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 115



Source Data: Appendix III Table 2.10 Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

Figure 2.3 S

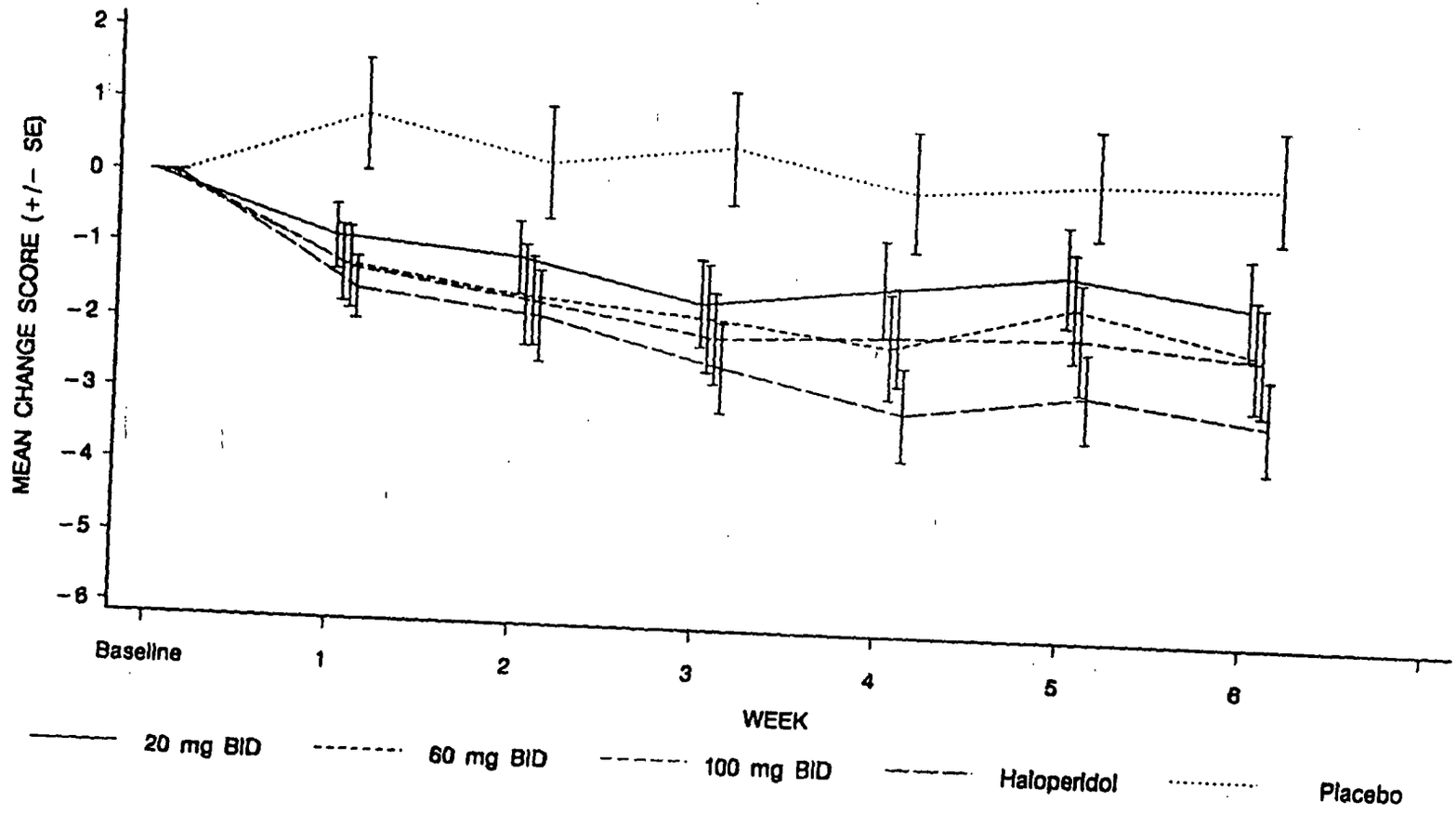
Figure 3.3
PANSS Negative Subscale Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, Observed Cases
Ziprasidone Protocol 115



Source Data: Table 5.1.4 Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

Figure 2.4 S

Figure 3.4
PANSS Negative Subscale Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 115

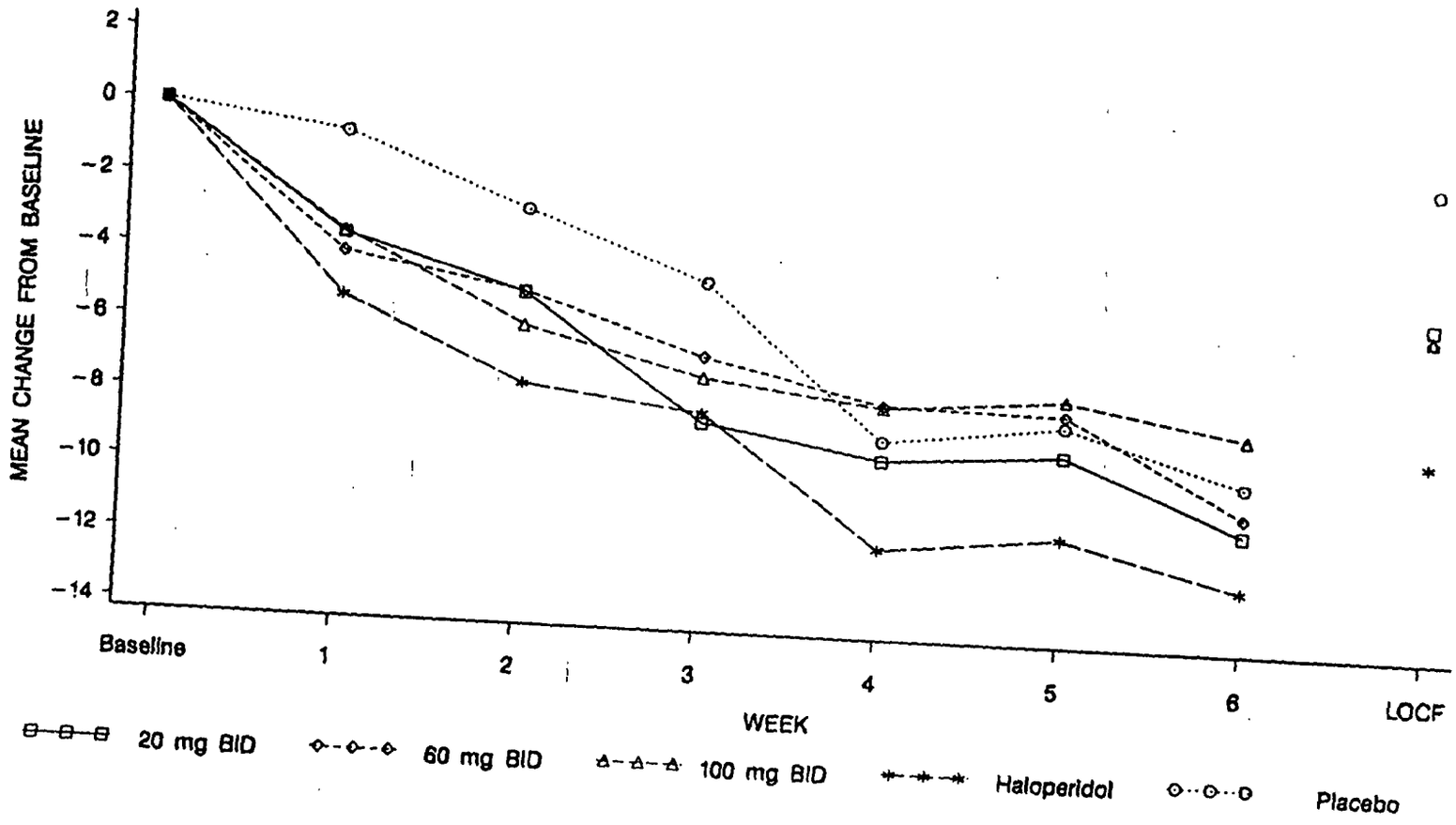


Source Data: Appendix III Table 3.10 Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

Figure 3.5

Figure 2.3 S

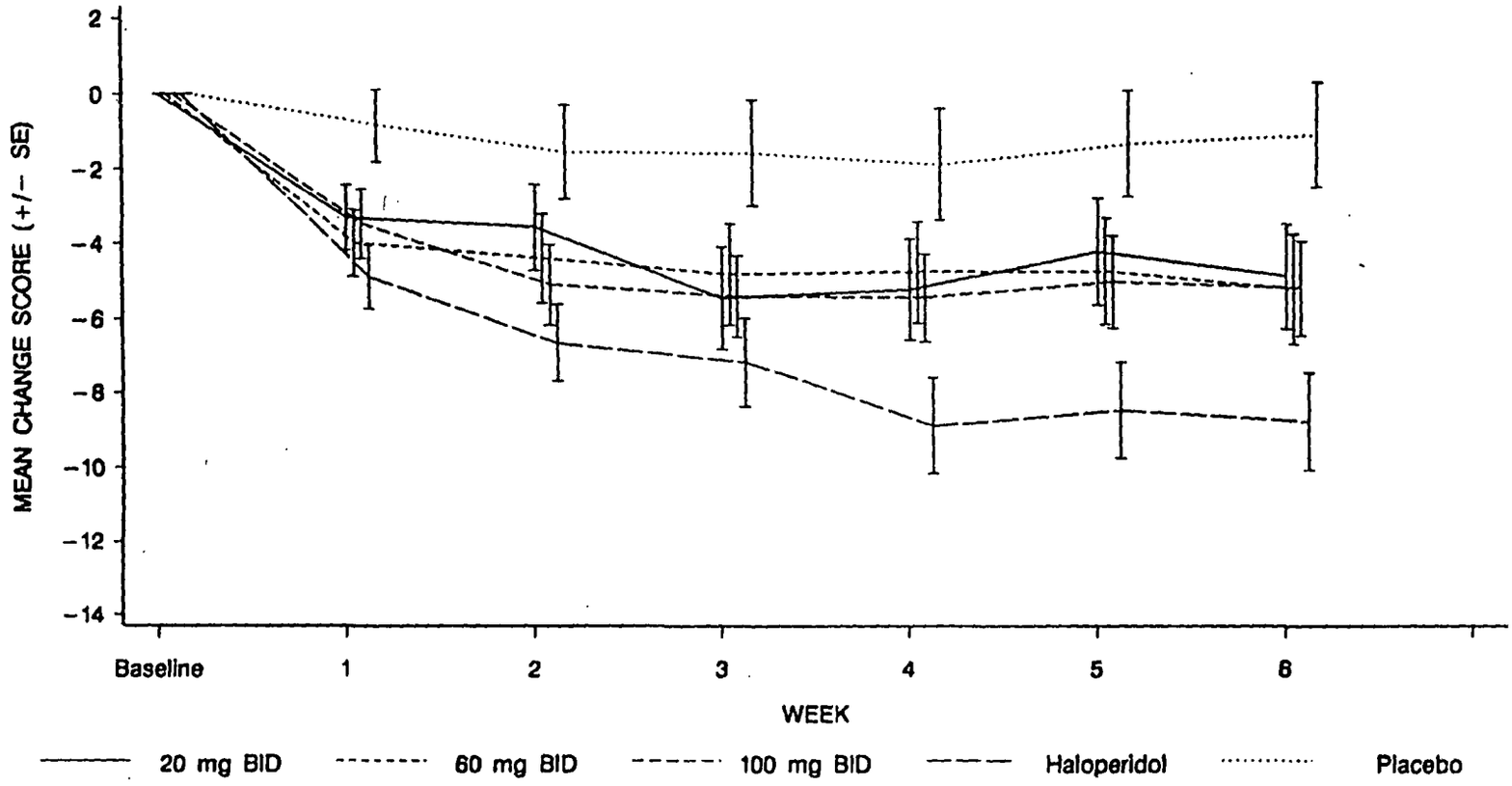
BPRSd Total Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, Observed Cases
Ziprasidone Protocol 115



Source Data: Table 5.1.7 Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

Figure 2.4 S

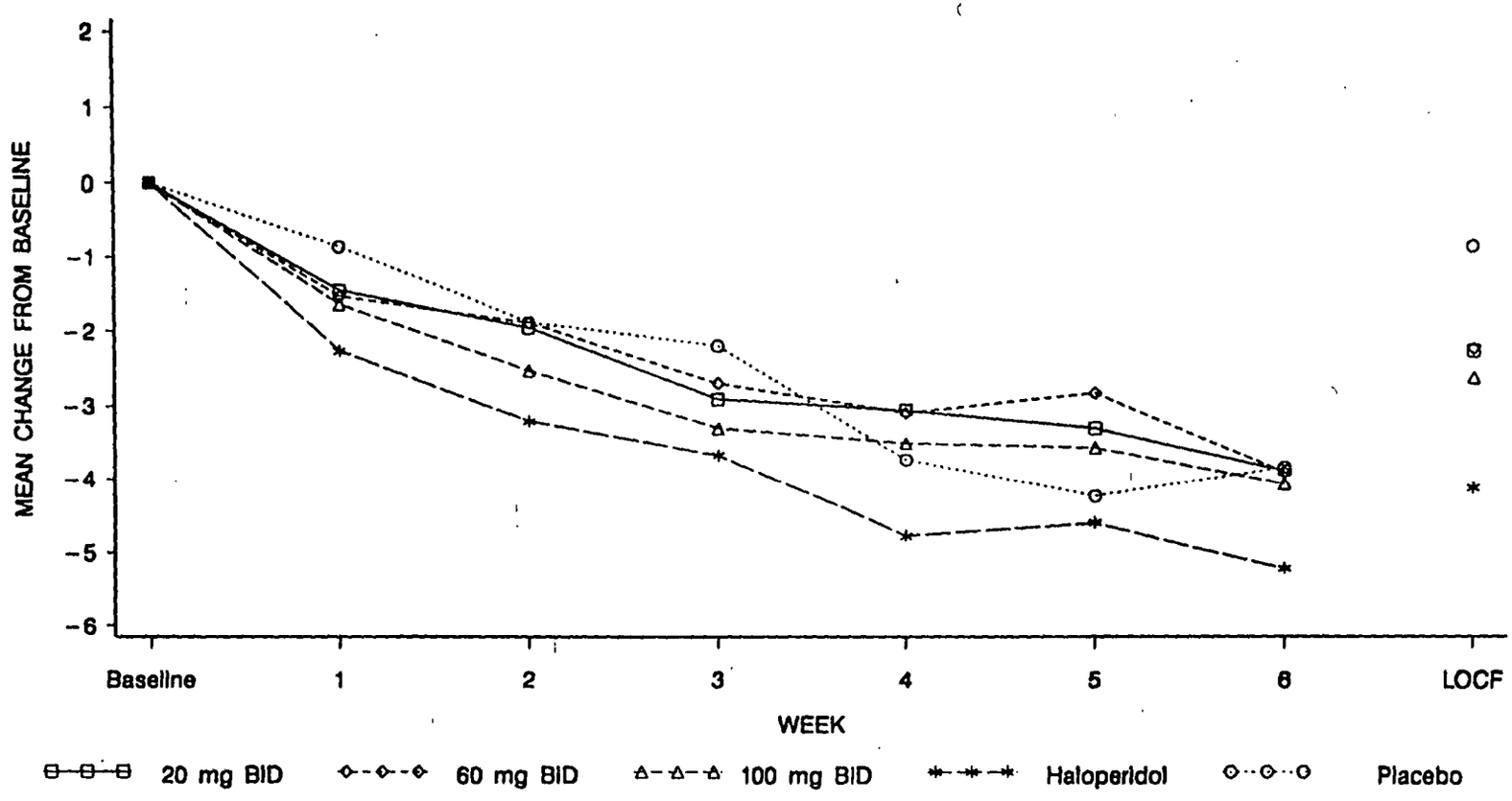
Figure 3.6
BPRSd Total Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 115



Source Data: Appendix III Table 4.10 Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

Figure 2.3 S

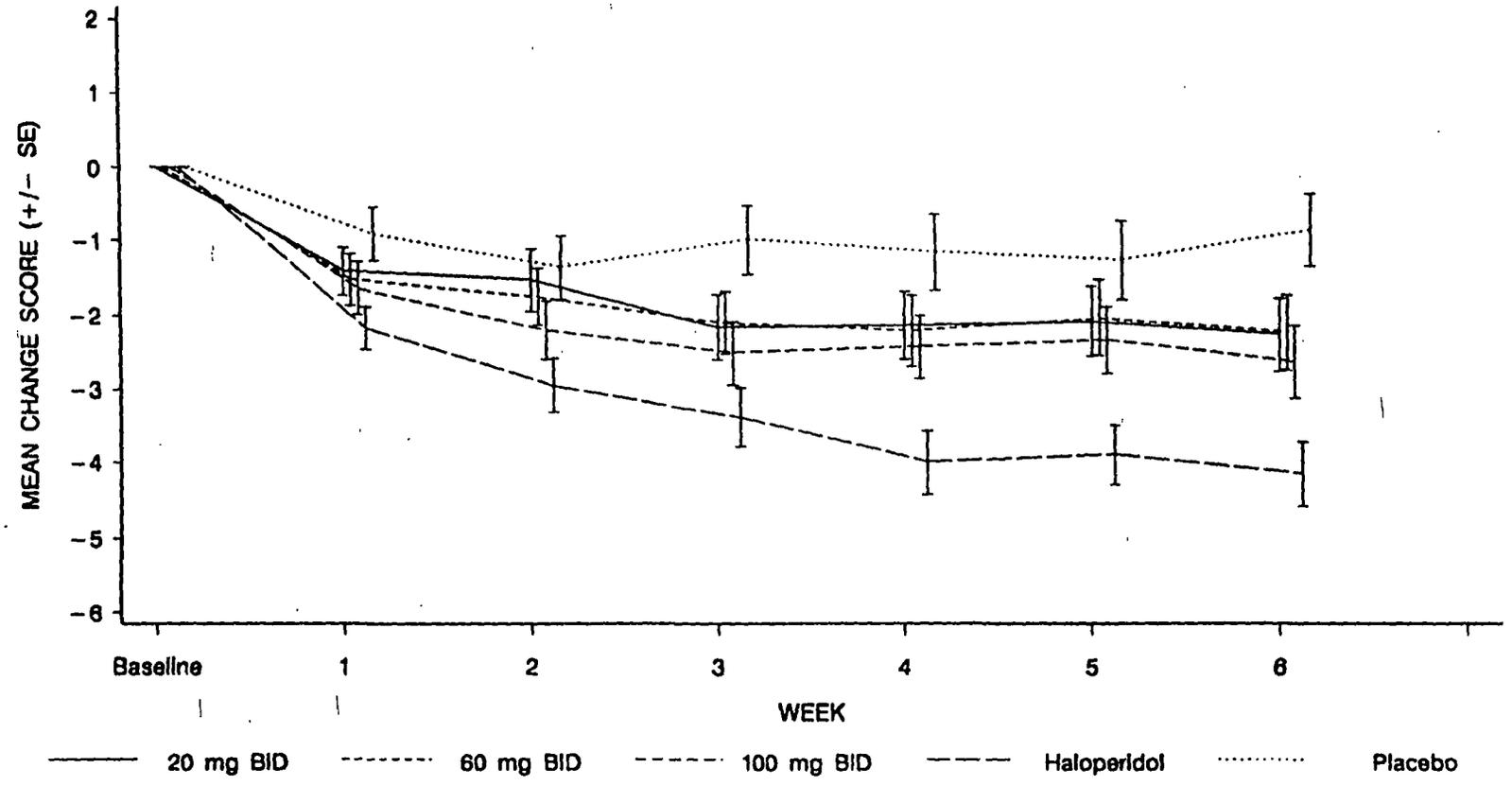
Figure 3.7
BPRSd Core Items Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, Observed Cases
Ziprasidone Protocol 115



Source Data: Table 5.1.10 Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

Figure 2.4 S

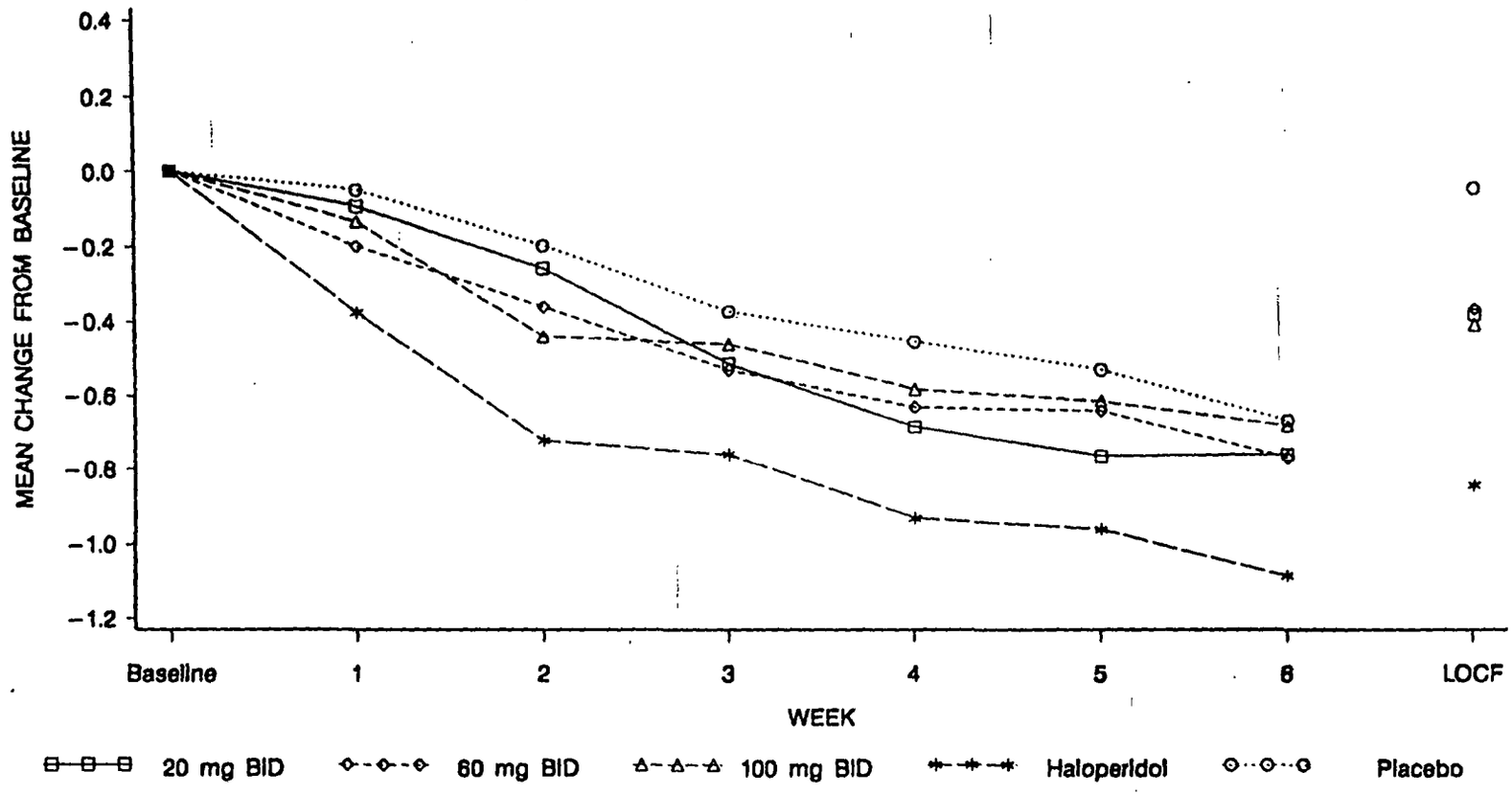
Figure 3.8
BPRSd Core Items Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 115



Source Data: Appendix III Table 5.10 Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

Figure 2.3.5

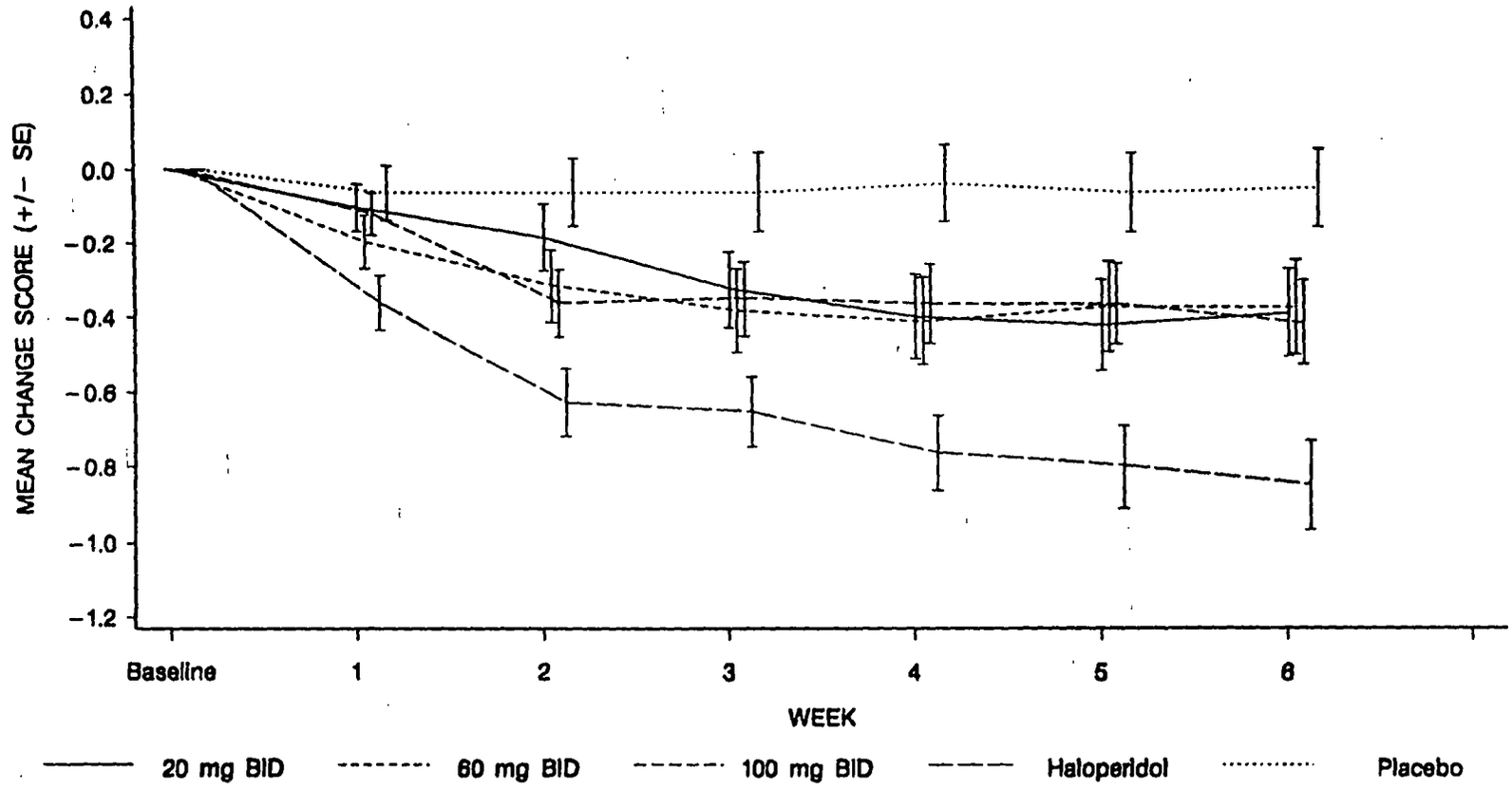
Figure 3.9
CGI Severity Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, Observed Cases
Ziprasidone Protocol 115



Source Data: Table 5.1.13 Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

Figure 2.4 5

Figure 3.10
CGI Severity Score – Mean Change from Baseline by Treatment Group and Week – All Subjects, LOCF
Ziprasidone Protocol 115



Source Data: Appendix III Table 6.10 Date of Data Extraction: 22OCT96. Date of Table Generation: 24OCT96.

Table 2.3 S

Appendix III Table 23
Longitudinal Analyses of Treatment Effects for Primary Efficacy Variables - All Subjects, Observed Cases
Ziprasidone Protocol 115

Variable	Treatment Comparison	Method*	Treatment Effect	P-Value	95% Confidence Limit Lower	Upper
PANSS Total	20 mg BID vs Placebo	Wu-Bailey(1)	-1.7779	0.0221	-3.3004	-0.2553
		UWLS(2)	-2.8610	0.0073	-4.9511	-0.7710
		Random(3)	-1.4506	0.0492	-2.8965	-0.0048
	60 mg BID vs Placebo	Wu-Bailey(1)	-1.9627	0.0132	-3.5157	-0.4097
		UWLS(2)	-3.1565	0.0030	-5.2381	-1.0750
		Random(3)	-1.3200	0.0775	-2.7856	0.1455
	100 mg BID vs Placebo	Wu-Bailey(1)	-2.1875	0.0049	-3.7110	-0.6640
		UWLS(2)	-3.2081	0.0018	-5.2231	-1.1930
		Random(3)	-1.4250	0.0513	-2.8581	0.0080
	Haloperidaol vs Placebo	Wu-Bailey(1)	-3.2232	0.0000	-4.7607	-1.6856
		UWLS(2)	-4.9925	0.0000	-7.0066	-2.9784
		Random(3)	-2.8357	0.0001	-4.2839	-1.3875
PANSS Negative	20 mg BID vs Placebo	Wu-Bailey(1)	-0.3976	0.0865	-0.8523	0.0570
		UWLS(2)	-0.7943	0.0229	-1.4784	-0.1101
		Random(3)	-0.3288	0.1444	-0.7702	0.1127
	60 mg BID vs Placebo	Wu-Bailey(1)	-0.4068	0.0862	-0.8715	0.0579
		UWLS(2)	-0.9443	0.0064	-1.6237	-0.2650
		Random(3)	-0.3480	0.1273	-0.7953	0.0993
	100 mg BID vs Placebo	Wu-Bailey(1)	-0.5386	0.0202	-0.9930	-0.0842
		UWLS(2)	-1.1233	0.0008	-1.7803	-0.4664
		Random(3)	-0.3757	0.0922	-0.8132	0.0617
	Haloperidaol vs Placebo	Wu-Bailey(1)	-0.5655	0.0164	-1.0273	-0.1037
		UWLS(2)	-1.1422	0.0006	-1.7979	-0.4866
		Random(3)	-0.5418	0.0163	-0.9839	-0.0998
BPRSd Total	20 mg BID vs Placebo	Wu-Bailey(1)	-0.9301	0.0310	-1.7752	-0.0850
		UWLS(2)	-1.2418	0.0493	-2.4798	-0.0038
		Random(3)	-0.6762	0.1018	-1.4862	0.1338
	60 mg BID vs Placebo	Wu-Bailey(1)	-1.1018	0.0126	-1.9669	-0.2367
		UWLS(2)	-1.5647	0.0127	-2.7951	-0.3342
		Random(3)	-0.5977	0.1536	-1.4185	0.2232
	100 mg BID vs Placebo	Wu-Bailey(1)	-1.1447	0.0081	-1.9922	-0.2972
		UWLS(2)	-1.5012	0.0134	-2.6916	-0.3109
		Random(3)	-0.6222	0.1287	-1.4249	0.1804
	Haloperidaol vs Placebo	Wu-Bailey(1)	-1.6956	0.0001	-2.5498	-0.8413
		UWLS(2)	-2.5251	0.0000	-3.7136	-1.3367
		Random(3)	-1.3373	0.0012	-2.1483	-0.5262

PAGE 4435