Statistical Review and Evaluation

NDA#: 20-639

FEB 3 1997

Applicant: Zeneca Pharmaceuticals

Name of Drug: Seroquel (quetiapine)

Documents Reviewed: Vols 1.357 (ISE), 1.301, 1.302,1.303, 1.304, 1.306, 1.310

Medical Officer: Andrew Mosholder, M.D., HFD-120

Background

The sponsor has submitted three (3) six-week adequate, randomized, placebo-controlled trials in support of Seroquel's efficacy and safety in patients with **acute exacerbations of schizophrenia**. A fourth trial, **0012** compared 450mg tid, 450mg bid, and 50mg bid. **Trial 0001/0008** enrolled patients in the US and Europe. **Trial 0006** enrolled patients in the US, **Trial 0013** enrolled patients in the US and Canada, and **Trial 0012** enrolled patients from Europe, Israel, and Canada.

All tables and figures were supplied by the sponsor

Study 0001/0008

This 6-week study randomized a total of 286 patients among 37 centers in the US (59%) and Europe (41%): N=96 High dose, N=94 Low dose, N=96 Placebo. This is more than 50% greater then the number 'evaluable' patients called for in the protocol (165). The sponsor explained that over-recruitment was due to a "burst of enrollment across most of the centers just before completion of the study". In a supplementary document dated December 20, 1996 submitted at the Division's request, the sponsor explained that a surplus of patients in non-eastern European centers were enrolled to make up for possible non-evaluability of patients in eastern Europe where the sponsor had had less experience running clinical trials. A total of 4 patients had no post-baseline data, so that **282 patients comprise the efficacy ITT population.**

The endpoints of interest are BPRS total , key BPRS, CGI Severity and the negative PANSS (only in Europe) and the SANS (done only in the US). **The protocol states that ANCOVA with baseline as the covariate would be used for all analyses.** However, there is no plan for multiple comparisons among treatment arms.

Table 1 displays the baseline conditions and demographics of the treatment groups

Completion rates were 50% for High dose, 43% for Low dose, and 41% for Placebo. 'Treatment failure' accounted for between 40%-50% of the dropouts. See **Table 2.**

Tables 3a and 3b display the visit-wise results of the **total BPRS for the LOCF and observed cases analyses, respectively**. It is not surprising that the high dose is statistically significant but the low dose is not, since the trial was planned (power= 90%) to find a 9 point difference between the high dose and placebo arms for the BPRS. See **Figure 1** for the influence of dropouts. **These figures display the average scores of disjoint dropout cohorts over time for each clinical endpoint, together with the averages of completers and the resulting LOCF.**

Tables 4a and 4b display the results of the **CGI Severity** for LOCF and observed cases, respectively. See **Figure 2** for the influence of dropouts.

Tables 5a and 5b display the results of the **key positive symptom BPRS cluster** for the LOCF and observed cases, respectively. See **Figure 3** for the influence of dropouts.

Tables 6a and 6b display the results of the **Negative PANSS** for LOCF and observed cases, respectively. Note than the PANSS was administered only in Europe. Small sample sizes are likely responsible for the non-significant trend in favor of the high dose.

Tables 7a and 7b display the results of the **SANS summary score** for the LOCF and observed cases, respectively. Note than the SANS was administered only in the US. See **Figure 4** for the influence of dropouts.

Study 0006

This Phase II trial consisted of one flexible dosing arm of Seroquel (75 mg/day - 750 mg/day) and a placebo arm. The protocol called for 50 patients per arm in order to have 90% power to detect an 8 point difference in change from baseline BPRS between the Seroquel arm and placebo.

Table 8 displays the baseline conditions and demographics of the treatment groups.

A total of 109 patients were randomized (Seroquel N=54, Placebo N=55) among 11 centers in the US. However, 3 patients had no post-baseline data leaving 53/group available for analysis. For the 106 patients analyzed, the completion rates were 53% for Seroquel and 42% for placebo. See **Table 9**

Tables 10a and 10b display the visit-wise results of the **total BPRS for the LOCF and observed cases analyses, respectively**. The borderline statistical result for the LOCF is likely due to the less than anticipated treatment difference at 6 weeks (-8.1 vs -2.1). Note that there was no difference at all for the completers. Thus, **Figure 5** indicates that the entire treatment difference in the LOCF analysis is due to dropouts in the first 4 weeks of the trial.

Tables 11a and 11b display the results of the **CGI Severity** for LOCF and observed cases, respectively. The LOCF produced statistical significance while the completers did not. See **Figure 6** for the influence of dropouts.

Tables 12a and 12b display the results of the **key positive symptom BPRS cluster** for the LOCF and observed cases, respectively. This endpoint shows a similar profile of a nearly significant LOCF analysis and a null completers analysis. See **Figure 7** for the influence of dropouts.

Tables 13a and 13b display the results of the **SANS summary score** for the LOCF and observed cases, respectively. Note than the SANS was administered only in the US. Again, close to statistical significance emerged in the LOCF analysis; however, the placebo group had a favorable trend in the completers analysis. See **Figure 8** for the influence of dropouts.

Trial 0013

This Phase III trial randomized a total of 361 patients among 26 in the US and Canada to 5 fixed doses of Seroquel (75 mg N=53, 150 mg N=48, 300 mg N=52, 600 mg N=51, 750 mg N=54) or 12 mg haloperidol (N=52) or placebo (N=51). The target sample size of 50/arm resulted from simulations of various dose-response models using a power of 90%. This size was also deemed adequate (power=80%) for what the sponsor calls "comparisons of interest", (i.e. active treatment vs placebo). **Dunnett's correction was used for these comparisons to placebo. P-values in tables are corrected for multiple comparisons.**

Table 14 displays the baseline conditions and demographics of the treatment groups.

Withdrawal rates ranged from 50%-70% with the highest in the placebo, 75 mg and haloperidol groups. See **Table 15.**

Tables 16a and 16b display the visit-wise results of the **total BPRS for the LOCF and observed cases analyses, respectively**. All but the 75 mg/day dose of Seroquel were statistically significantly different from placebo for the LOCF analysis, whereas none were significant in the completers analysis. See **Figure 9** for the influence of dropouts.

Tables 17a and 17b display the results of the **CGI Severity** for LOCF and observed cases, respectively. The LOCF produced statistical significance while the completers did not. See **Figure 10** for the influence of dropouts.

Tables 18a and 18b display the results of the **key positive symptom BPRS cluster** for the LOCF and observed cases, respectively. This endpoint shows a similar profile of a nearly significant LOCF analysis and a null completers analysis. See **Figure 11** for the influence of dropouts.

Tables 19a and 19b display the results of the **SANS summary score** for the LOCF and observed cases, respectively. Note than the SANS was administered only in the US. Again, close to statistical significance emerged in the LOCF analysis; however, the placebo group had a favorable trend in the completers analysis. See **Figure 12** for the influence of dropouts.

Trial 0012

The intent of this trial was to show whether either dosing regimen of 450mg/day (tid vs bid) was better than the low dose (50mg/day), and whether the the higher dose regimens differed from each other. The trial was planned so that 170 patients/arm would provide 90% power to detect a 6 point difference in change from baseline of the total BPRS bteween any two pairs of treatment arms. A total of 618 patients were randomized with 596 contributing at leat one post-baseline observation on the BPRS.

Table 20 displays the baseline conditions and demographics of the treatment groups.

Approximately 50% of all patients completed the 6 week trial. There was no relationship between dose and frequency of dropout due to lack of efficacy. See **Table 21.**

Tables 22a and 22b display the visit-wise results of the **total BPRS for the LOCF and observed cases analyses, respectively**. There was no plan for multiple comparisons in the protocol. However, the p=.005 for the bid dosage is sufficient for statistical significance. Also, the p=.05 for the tid dosage would be just significant using Fisher's LSD. The confidence interval for the difference between the bid and tid dosages at 450mg rule out a 5-6 point average difference for the total BPRS. See **Figure 13** for the influence of dropouts.

Tables 23a and 23b display the results of the **change from baseline for CGI Severity** for LOCF and observed cases, respectively, using CMH with country as strata. The sponsor grouped the actual changes from baseline into -3 or less, -2, -1, 0 1 or greater. This was done because the **planned** analysis of covariance using the actual scores violated some assumptions of the analysis. Those violations, however, are not reason to group cjhange scores if the analysis is changed to a categorical one. A check on the statistically significant result for the bid regimen is a simple Wilcoxon test performed by the sponsor which yielded a p-value of .0046. See **Figure 14** for the influence of dropouts.

Tables 24a and 24b display the results of the **key positive symptom BPRS cluster** for the LOCF and observed cases, respectively. The bid regimen is significant for both the LOCF and observed cases analyses. See **Figure 15** for the influence of dropouts.

Tables 25a and 25b display the results of the **SANS summary score** for the LOCF and observed cases, respectively. The bid dosage is significant for the LOCF analysis. See **Figure 16** for the influence of dropouts.

Demographic Influences on Treatment Differences

The sponsor pooled data over the 3 placebo-controlled studies (all Seroquel patients vs all placebo patients) in order to examine whether treatment differences varied between demographic categories with respect to total BPRS and CGI Severity. There was no clear evidence of interaction between treatment and race or gender for either variable. However, for the total BPRS, there is some suggestion of interaction with age as dichtomized by the sponsor: above and below 40 years. Ages at entrance to the trials were similar in all 3 studies. See **Table 26**. Using a simple t-test, the average difference between those younger than 40 and those at least 40 is 8.8-2.3=6.5 with a standard error of 2.67 resulting in a z-value of 2.43 (p=.007 one-sided). The placebo response in the older group tended to be higher than that in the younger group, and the changes from baseline in the active groups were somewhat less in the older group than those in the younger group.

Discussion

Trials 0008 and 0013 clearly demonstrate statistically significantly differences between Seroquel and placebo. Both trials were able to demonstrate treatment differences of at least 4 total BPRS points in completers at six weeks. The reasons for the null results for completers in **trial 0006** are unclear. The median doses of the Seroquel completers at the end of the trials were similar in both **trials 0006 and 0008**, another dose-escalation trial (450 mg and 500 mg, respectively). The major difference was in the performance of the placebo groups. The placebo group in **trial 0006** decreased from baseline an average of 13.9 points while the placebo average in **trial 0008** was 9.7, making it more difficult to show a difference in **trial 0006**.

As a check on **trial 0008**, this reviewer analysed only the first 165 randomized patients and found the treatment difference to be comparable to that using all patients.

In a submission dated September 24, 1996, the sponsor reanalyzed the data without Dr. **Borison's** center. Omitting Dr. Borison's center had no substantial effect on the results.

David Hoberman, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot JTS 1-29-97.

Dr. Chi Chi 2/3/97

cc:
NDA#20-~~667~~ 639
HFD-120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Dr. Mosholder
HFD-120/Mr. Purvis
HFD-120/Mr. Hardeman
HFD-344/Dr. Lisook
HFD-710/Dr. Chi
HFD-710Dr. Sahlroot
HFD-710/Dr. Hoberman
HFD-710/chron

Psychiatric history and baseline characteristics* (continued)

TABLE 1	SEROQUEL High dose (n = 96)	SEROQUEL Low dose (n = 94)	Placebo (n = 96)
Psychiatric efficacy measures, mean (sd)			
BPRS total score+	41 (10)	39 (10)	38 (10)
CGI Severity of Illness score	5.1 (0.7)	5.1 (0.8)	4.9 (0.7)
SANS summary score**	15.8 (3.6)	15.8 (3.9)	14.5 (3.6)
PANSS(N) score##	27.5 (9.4)	25.5 (8.7)	24.4 (6.6)
Neurologic assessments, n (%)			
Simpson total score			
0	39 (41)	42 (47)	36 (38)
1	15 (16)	13 (15)	13 (14)
2	10 (11)	8 (9)	9 (10)
3 or greater	30 (32)	26 (29)	36 (38)
Barnes Akathisia Global Clinical Assessment of Akathisia			
Absent	56 (60)	53 (57)	55 (59)
Questionable	25 (27)	27 (29)	24 (26)
Mild or Worse	13 (14)	13 (14)	15 (16)
AIMS total score++			
0	52 (55)	45 (49)	39 (41)
1	10 (11)	2 (2)	11 (12)
2	3 (3)	4 (4)	6 (6)
3 or greater	29 (31)	41 (45)	38 (40)

*n is variable since not all data were available for every patient
#all diagnoses assume acute exacerbation of the condition and a chronic or subchronic course
**collected at centres in the US only
##collected at centres in Europe only
+ p = 0.05 high-dose SEROQUEL vs placebo
++ p = 0.03 high-dose SEROQUEL vs low-dose SEROQUEL
sd = standard deviation

Summary of sex, age, weight and race

Characteristic	SEROQUEL High dose (n = 96)	SEROQUEL Low dose (n = 94)	Placebo (n = 96)
Sex, n (%)			
Male	66 (69)	73 (78)	64 (67)
Female	30 (31)	21 (22)	32 (33)
Age (yr), mean (sd)	36 (9)	37 (9)	38 (10)
Weight (kg), mean (sd)			
Male	76 (12)	78 (15)	77 (13)
Female	71 (18)	74 (20)	73 (19)
Race, n (%)			
White (Caucasian)	66 (69)	63 (67)	73 (76)
Non-white	30 (31)	31 (33)	23 (24)

TABLE 2

Disposition of randomized patients - Trial 0008

Disposition	Quetiapine		Placebo
	High dose n (%)	Low dose n (%)	n (%)
Total number randomized	96 (100)	94 (100)	96 (100)
Total number completed	48 (50)*	40 (43)***	39 (41)**
Total number withdrawn	48 (50)	54 (57)	57 (59)
Adverse clinical or lab experience	7 (15)	7 (13)	3 (5)
Intercurrent medical event	1 (2)	1 (2)	0
Protocol violation	1 (2)	1 (2)	0
Treatment failure	25 (52)	34 (63)	42 (74)
Subject withdrew consent	10 (21)	4 (7)	8 (14)
Other	4 (8)	7 (13)	4 (7)

* Patient US-014/01404 withdrew from the trial at Day 38. Efficacy data obtained at this time were included with Day 42 data for the high-dose group (n=49 at Day 42); however, this patient was not considered to have completed the trial.

** Patient US-001/00119 withdrew from the trial at Day 39 and Patient US-014/01409 withdrew from the trial at Day 37. Efficacy data obtained at last visit for these patients were included with Day 42 data for the placebo group (n=41 at Day 42); however, these patients were not considered to have completed the trial.

*** Patient UK-021/00001 withdrew from the trial at Day 37. Efficacy data obtained at this time were included with Day 42 data for the low-dose group (n=39 at Day 42); however, this patient was not considered to have completed the trial. In addition, Patients US-011/01108 and UK-008/00008 were considered by the investigator to have completed the trial but had no Day 42 efficacy data.

TABLE 3a

BPRS total score - least-squares mean change from baseline (LOCF) - Trial 0008

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine high dose	94	41.04	94	-2.41	94	-4.55	94	-6.32	94	-7.58	94	-7.84	94	-8.74
Quetiapine low dose	92	38.89	92	-1.00	92	-2.00	92	-3.27	92	-4.28	92	-4.00	92	-4.16
Placebo	94	38.35	93	-0.46	94	0.11	94	-0.68	94	-0.45	94	-0.21	94	-0.96
II. 2-sided p-values for pairwise comparisons														
Quetiapine high dose vs Placebo				0.1675		0.0108		0.0059		0.0007		0.0003		0.0006
Quetiapine low dose vs Placebo				0.7019		0.2450		0.2030		0.0658		0.0718		0.1515
Quetiapine high dose vs low dose				0.3175		0.1628		0.1357		0.1139		0.0699		0.0413

TABLE 3b

BPRS total score - least-squares mean change from baseline (OC) - Trial 0008

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine high dose	94	41.04	94	-2.23	80	-6.97	70	-12.90	61	-12.10	52	-13.56	49	-15.12
Quetiapine low dose	92	38.89	92	-0.22	85	-3.13	69	-9.00	55	-9.50	46	-10.15	39	-11.39
Placebo	94	38.35	93	-0.02	81	-2.14	60	-9.58	50	-7.93	44	-7.60	41	-9.65
II. 2-sided p-values for pairwise comparisons														
Quetiapine high dose vs Placebo				0.1243		0.0136		0.0807		0.0450		0.0102		0.0297
Quetiapine low dose vs Placebo				0.8889		0.5965		0.7510		0.4472		0.2659		0.5001
Quetiapine high dose vs low dose				0.1598		0.0429		0.0301		0.1899		0.1361		0.1454

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TABLE 4a

TABLE 3.39 CGI Severity of Illness score - least-squares mean change from baseline (LOCF) - Trial 0008

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine high dose	95	5.07	95	-0.08	95	-0.26	95	-0.40	95	-0.47	95	-0.55	95	-0.61
Quetiapine low dose	92	5.05	92	-0.05	92	-0.16	92	-0.19	92	-0.23	92	-0.32	92	-0.30
Placebo	94	4.94	94	0.01	94	0.00	94	-0.04	94	-0.03	94	-0.01	94	-0.08
II. 2-sided p-values for pairwise comparisons														
Quetiapine high dose vs Placebo				0.4074		0.0766		0.0184		0.0071		0.0012		0.0030
Quetiapine low dose vs Placebo				0.5791		0.2630		0.3445		0.2230		0.0625		0.2282
Quetiapine high dose vs low dose				0.7880		0.5194		0.1584		0.1403		0.1690		0.0768

TABLE 4b

CGI Severity of Illness score - least-squares mean change from baseline (OC) - Trial 0008

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine high dose	95	5.07	95	-0.05	80	-0.54	70	-0.97	61	-0.87	52	-0.93	49	-1.05
Quetiapine low dose	92	5.05	92	0.00	84	-0.39	69	-0.62	56	-0.51	46	-0.66	39	-0.65
Placebo	94	4.94	94	0.04	81	-0.29	60	-0.73	50	-0.63	45	-0.49	41	-0.60
II. 2-sided p-values for pairwise comparisons														
Quetiapine high dose vs Placebo				0.3989		0.1007		0.1315		0.2071		0.0290		0.0408
Quetiapine low dose vs Placebo				0.6927		0.5212		0.4925		0.5252		0.3934		0.8518
Quetiapine high dose vs low dose				0.6552		0.2976		0.0234		0.0525		0.2027		0.0786

Table 5a

BPRS positive symptom cluster score - least-squares mean change from baseline (LOCF) - Trial 0008

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Treatment groups														
Quetiapine high dose	94	3.61	94	-0.35	94	-0.52	94	-0.72	94	-0.81	94	-0.86	94	-0.90
Quetiapine low dose	92	3.63	92	-0.32	92	-0.48	92	-0.58	92	-0.65	92	-0.60	92	-0.61
Placebo	94	3.52	94	-0.29	94	-0.36	94	-0.39	94	-0.37	94	-0.35	94	-0.37
2-sided p-values for pairwise comparisons														
Quetiapine high dose vs Placebo			0.6205		0.2582		0.0486		0.0103		0.0035		0.0030	
Quetiapine low dose vs Placebo			0.7614		0.3912		0.2539		0.0993		0.1549		0.1728	
Quetiapine high dose vs low dose			0.8502		0.7891		0.4090		0.3611		0.1335		0.1080	

Table 5b

BPRS positive symptom cluster score - least-squares mean change from baseline (OC) - Trial 0008

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Treatment groups														
Quetiapine high dose	94	3.61	94	-0.29	80	-0.62	70	-1.02	61	-1.06	52	-1.13	49	-1.22
etiapine low dose	92	3.63	92	-0.24	85	-0.48	69	-0.80	55	-0.87	46	-0.84	39	-0.96
ebo	94	3.52	94	-0.23	81	-0.41	60	-0.87	50	-0.78	44	-0.66	41	-0.70
2-sided p-values for pairwise comparisons														
Quetiapine high dose vs Placebo			0.5904		0.2036		0.4073		0.1603		0.0384		0.0302	
Quetiapine low dose vs Placebo			0.9118		0.6656		0.7211		0.6277		0.4335		0.3067	
Quetiapine high dose vs low dose			0.6694		0.3831		0.2170		0.3459		0.2027		0.2847	

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TABLE 6a

PANSS Negative Scale score - least-squares mean change from baseline (LOCF) - Trial 0008

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Treatment groups														
Quetiapine high dose	38	27.47	38	-1.21	38	-2.25	38	-2.97	38	-3.68	38	-3.93	38	-4.39
Quetiapine low dose	38	25.50	38	-0.01	38	-0.91	38	-1.53	38	-2.32	38	-2.39	38	-2.86
Placebo	37	24.43	37	0.02	37	0.36	37	-0.96	37	-1.33	37	-1.54	37	-1.88
2-sided p-values for pairwise comparisons														
Quetiapine high dose vs Placebo				0.2313		0.0369		0.1322		0.0966		0.1013		0.1047
Quetiapine low dose vs Placebo				0.9797		0.2998		0.6632		0.4736		0.5538		0.5186
Quetiapine high dose vs low dose				0.2358		0.2738		0.2742		0.3299		0.2826		0.3149

PANSS Negative Scale data were collected at European sites only.

TABLE 6b

PANSS Negative Scale score - least-squares mean change from baseline (OC) - Trial 0008

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Treatment groups														
Quetiapine high dose	38	27.47	38	-4.02	29	-4.88	26	-5.63	22	-5.49	17	-4.06	16	-4.38
Quetiapine low dose	38	25.50	38	-2.77	38	-2.89	31	-5.02	28	-5.20	25	-2.12	22	-2.57
Placebo	37	24.43	37	-2.15	32	-1.72	22	-5.13	19	-4.78	17	-1.94	15	-2.48
2-sided p-values for pairwise comparisons														
Quetiapine high dose vs Placebo				0.0641		0.0272		0.6484		0.6300		0.1550		0.2671
Quetiapine low dose vs Placebo				0.5350		0.3648		0.9153		0.7575		0.8930		0.9561
Quetiapine high dose vs low dose				0.2035		0.1343		0.5354		0.8256		0.1556		0.2478

PANSS Negative Scale data were collected at European sites only.

TABLE 7a

SANS summary score - least-squares mean change from baseline (LOCF) - Trial 0008

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	Treatment week													
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine high dose	55	15.76	54	-0.23	55	-0.67	55	-1.00	55	-1.41	55	-1.53	55	-1.65
Quetiapine low dose	51	15.82	50	0.07	51	0.20	51	0.14	51	-0.11	51	0.27	51	0.27
Placebo	56	14.50	55	-0.17	56	-0.31	56	0.03	56	0.05	56	-0.09	56	-0.14
II. 2-sided p-values for pairwise comparisons														
Quetiapine high dose vs Placebo				0.8957		0.5210		0.0737		0.0198		0.0220		0.0210
Quetiapine low dose vs Placebo				0.6543		0.3750		0.8605		0.7982		0.5766		0.5381
Quetiapine high dose vs low dose				0.5618		0.1283		0.0528		0.0407		0.0051		0.0041

SANS data were collected at US sites only.

TABLE 7b

SANS summary score - least-squares mean change from baseline (OC) - Trial 0008

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	Treatment week													
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine high dose	55	15.76	54	-0.20	47	-1.01	44	-1.62	39	-2.37	35	-2.77	33	-3.52
Quetiapine low dose	51	15.82	50	0.20	46	-0.09	36	-0.82	27	-1.42	30	-0.62	18	-0.94
Placebo	56	14.50	55	-0.18	47	-0.42	35	-0.52	31	-0.36	37	-0.50	26	-0.93
II. 2-sided p-values for pairwise comparisons														
Quetiapine high dose vs Placebo				0.9741		0.3383		0.1011		0.0114		0.0079		0.0082
Quetiapine low dose vs Placebo				0.4926		0.5934		0.6723		0.2100		0.8981		0.9981
Quetiapine high dose vs low dose				0.4679		0.1309		0.2192		0.2390		0.0220		0.0180

SANS data were collected at US sites only.

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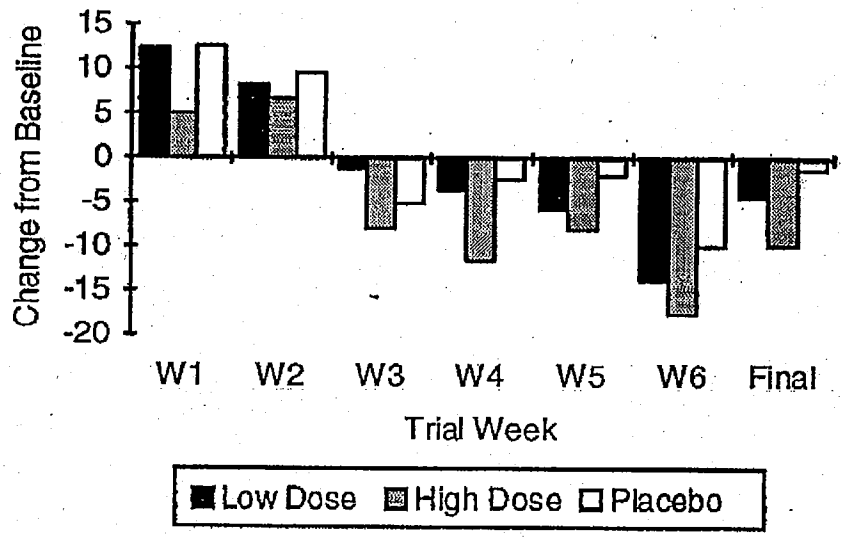
FIGURE 1

BPRS total score – mean change from baseline for patients withdrawing by trial week – Trial 0008



CGI Severity of Illness score – mean change from baseline for patients withdrawing by trial week – Trial 0008

FIGURE 2

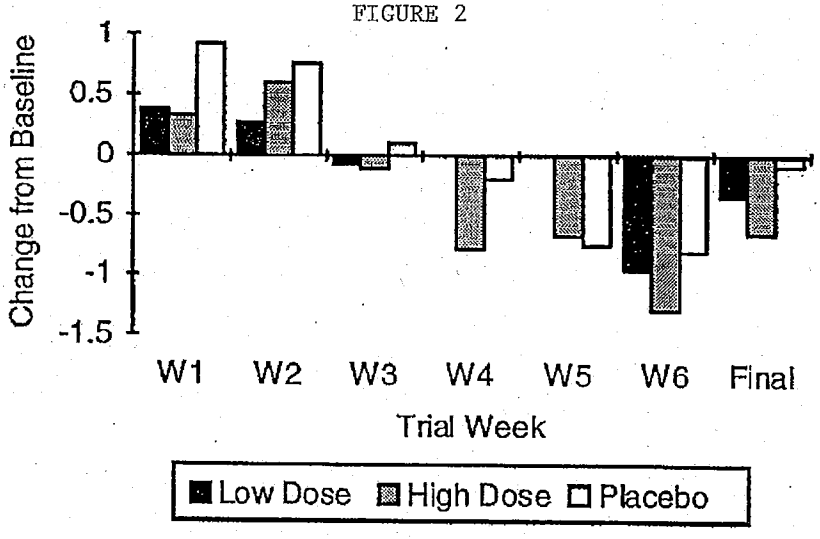


Figure 3

BPRS positive symptom cluster score – mean change from baseline for patients withdrawing by trial week – Trial 0008

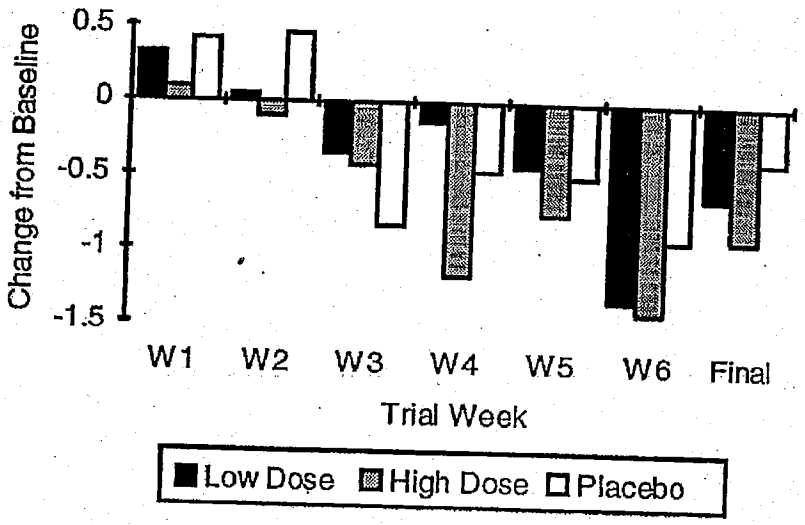


FIGURE 4

SANS summary score – mean change from baseline for patients withdrawing by trial week – Trial 0008

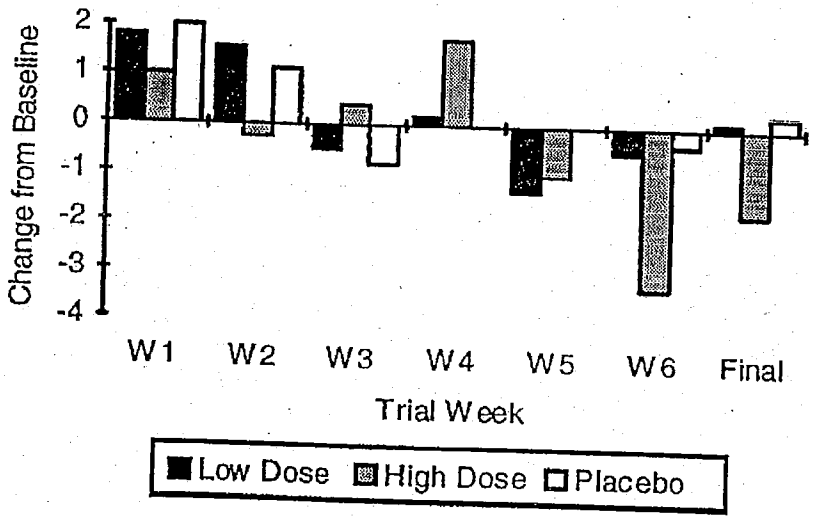


TABLE 8

Psychiatric history and baseline characteristics

	SEROQUEL (n = 54)	Placebo (n = 55)
Diagnosis* (n (%))		
Chronic undifferentiated	27 (50)	25 (45)
Chronic paranoid	19 (35)	20 (36)
Other	8 (15)	10 (18)
Age at first treatment (mean (sd))	22 (6)	22 (5)
No. of hospitalisations# (n (%))		
≤8	26(58)	16 (36)
>8	19 (42)	29 (64)
Unknown	9	10
Psychiatric efficacy measures or variables (mean (sd))		
BPRS total score	56 (8)	54 (7)
CGI Severity of Illness score#	5.0 (0.9)	4.6 (0.8)
SANS summary score	14 (3)	14 (4)
Neurologic assessments (n(%))		
Simpson total score		
10	14 (26)	16 (32)
11	11 (21)	4 (8)
12	10 (19)	6 (12)
13+	18 (34)	24 (48)
AIMS total score		
0	22 (42)	26 (50)
1	4 (8)	3 (6)
2	4 (8)	2 (4)
3+	23 (43)	21 (40)

*all diagnoses assume acute exacerbation of schizophrenia

#p = 0.03

Summary of sex, age, weight and race

	SEROQUEL (n = 54)	Placebo (n = 55)
Age - yr (mean (sd))	36 (9)	37 (8)
Sex (n(%))		
Males	48 (89)	50 (91)
Females	6 (11)	5 (9)
Race (n(%))		
White (Caucasian)	32 (59)	34 (62)
Non-white	22 (41)	21 (38)
Weight - kg (mean (sd))		
Males	77 (18)	80 (15)
Females	77 (20)	87 (14)

TABLE 9

Disposition of randomized patients - Trial 0006

Disposition	Quetiapine n (%)	Placebo n (%)
Total number randomized	54 (100)	55 (100)
Total number completed	28 (52)	22* (40)
Total number withdrawn	26 (48)	33 (60)
Adverse clinical or lab experience	2 (8)	2 (6)
Protocol violation	1 (4)	0
Treatment failure	16 (62)	27 (82)
Subject withdrew consent	5 (19)	3 (9)
Other	2 (8)	1 (3)

* Patient 004/00406 withdrew from the trial at Trial Day 40. Efficacy data obtained at this time were included with Trial Day 42 data for the placebo group (n=23 at Day 42). However, this patient was not considered to have completed the trial.

TABLE 10a

BPRS total score - least-squares mean change from baseline (LOCF) - Trial 0006

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine	53	55.79	53	-3.18	53	-5.55	53	-7.00	53	-8.44	53	-8.66	53	-8.08
Placebo	53	54.09	53	-0.73	53	-0.47	53	-2.03	53	-1.78	53	-1.25	53	-2.13
II. 2-sided p-values for pairwise comparisons														
Quetiapine vs. Placebo				0.2023		0.0508		0.0888		0.0224		0.0186		0.0694

TABLE 10b

BPRS total score - least-squares mean change from baseline (OC) - Trial 0006

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine	53	55.79	53	-3.51	46	-7.35	41	-11.80	35	-13.11	32	-14.64	28	-13.64
Placebo	53	54.09	53	-0.83	47	-2.61	39	-9.43	30	-11.91	27	-13.17	23	-13.85
II. 2-sided p-values for pairwise comparisons														
Quetiapine vs. Placebo				0.1648		0.0656		0.3572		0.6045		0.6296		0.9510

Appears This Way
On Original

TABLE 11a

CGI Severity of Illness score - least-squares mean change from baseline (LOCF) - Trial 0006

	Baseline		Treatment week											
			Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine	53	4.96	53	0.03	53	-0.07	53	-0.30	53	-0.28	53	-0.30	53	-0.22
Placebo	53	4.64	53	0.15	53	0.29	53	0.24	53	0.28	53	0.28	53	0.23
II. 2-sided p-values for pairwise comparisons														
Quetiapine vs. Placebo				0.4776		0.0770		0.0192		0.0122		0.0191		0.0693

TABLE 11b

CGI Severity of Illness score - least-squares mean change from baseline (OC) - Trial 0006

	Baseline		Treatment week											
			Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine	53	4.96	53	-0.01	46	-0.32	41	-0.72	35	-0.74	32	-0.86	28	-0.65
ebo	53	4.64	53	0.13	47	0.04	39	-0.24	30	-0.58	27	-0.67	23	-0.72
2-sided p-values for pairwise comparisons														
Quetiapine vs. Placebo				0.4003		0.0592		0.0269		0.4367		0.4981		0.8410

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On Original

TABLE 12a

BPRS positive symptom cluster score - least-squares mean change from baseline (LOCF) - Trial 0006

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine	53	4.32	53	-0.34	53	-0.65	53	-0.73	53	-0.96	53	-0.99	53	-0.89
Placebo	53	4.03	53	-0.13	53	-0.21	53	-0.30	53	-0.22	53	-0.19	53	-0.33
II. 2-sided p-values for pairwise comparisons														
Quetiapine vs. Placebo				0.2236		0.0470		0.0704		0.0038		0.0030		0.0557

TABLE 12b

BPRS positive symptom cluster score - least-squares mean change from baseline (OC) - Trial 0006

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine	53	4.32	53	-0.37	46	-0.76	41	-1.12	35	-1.33	32	-1.34	28	-1.10
Placebo	53	4.03	53	-0.15	47	-0.33	39	-0.88	30	-0.90	27	-0.98	23	-1.15
II. 2-sided p-values for pairwise comparisons														
Quetiapine vs. Placebo				0.2115		0.0547		0.2968		0.1183		0.2328		0.8892

Appears This Way
On Original

TABLE 13a

TABLE 3.29 SANS summary score - least-squares mean change from baseline (LOCF) - Trial 0006

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine	51	14.06	49	-0.05	51	-0.13	51	-0.57	51	-0.87	51	-1.05	51	-1.04
Placebo	51	13.96	50	0.57	51	0.92	51	0.85	51	0.70	51	0.62	51	0.56
II. 2-sided p-values for pairwise comparisons														
Quetiapine vs. Placebo				0.2449		0.1153		0.0437		0.0240		0.0299		0.0519

TABLE 13b

SANS summary score - least-squares mean change from baseline (OC) - Trial 0006

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine	51	14.06	49	-0.04	45	-0.15	38	-0.85	27	-0.75	31	-1.11	28	-0.88
Placebo	51	13.96	50	0.62	44	0.49	34	-0.65	24	-1.40	26	-1.35	23	-1.40
II. 2-sided p-values for pairwise comparisons														
Quetiapine vs. Placebo				0.2084		0.3766		0.8116		0.5172		0.8189		0.6783

Appears This Way
On Original

FIGURE 5

BPRS total score – mean change from baseline for patients withdrawing by trial week – Trial 0006

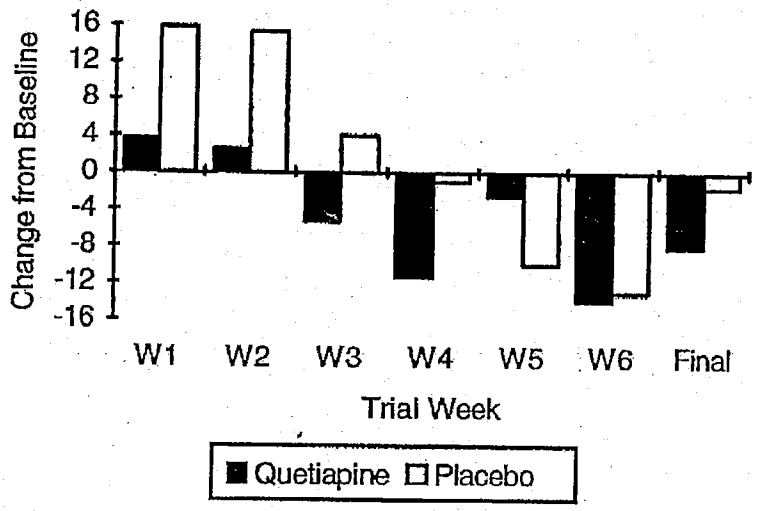


FIGURE 6

CGI Severity of Illness score – mean change from baseline for patients withdrawing by trial week – Trial 0006

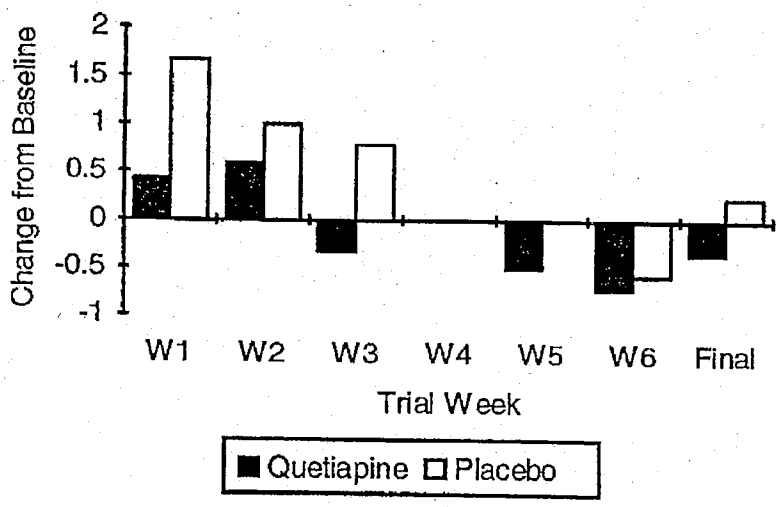


FIGURE 7

BPRS positive symptom cluster score – mean change from baseline for patients withdrawing by trial week – Trial 0006

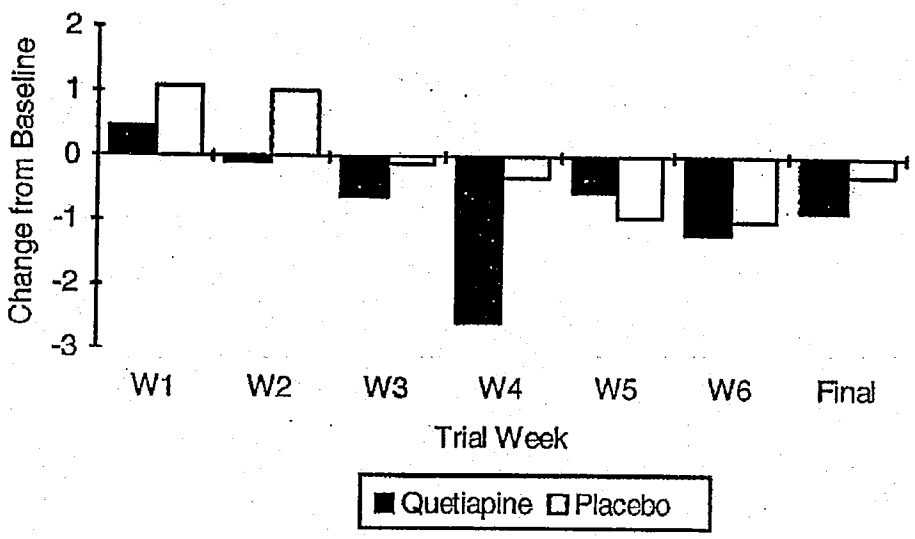


FIGURE 8

SANS summary score – mean change from baseline for patients withdrawing by trial week – Trial 0006

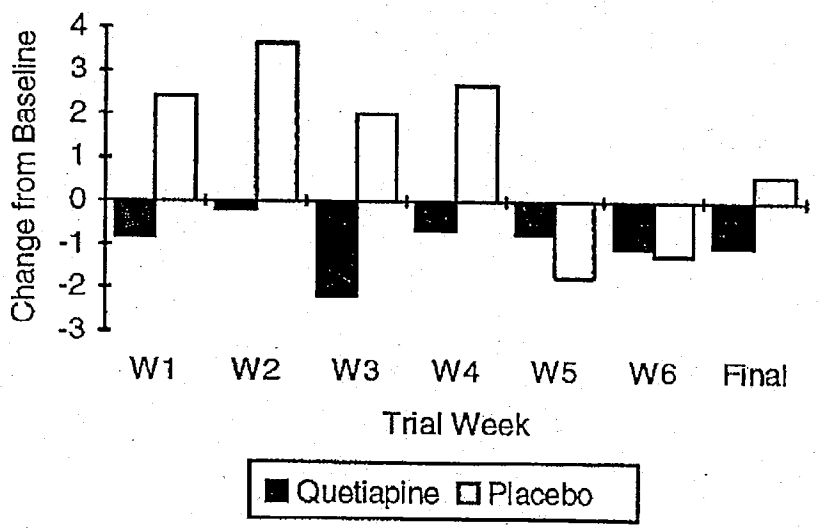


TABLE 14

Baseline efficacy and neurologic assessments*

Assessment	Treatment group: SEROQUEL 75 mg (n = 52)	SEROQUEL 150 mg (n = 48)	SEROQUEL 300 mg (n = 51)	SEROQUEL 600 mg (n = 51)	SEROQUEL 750 mg (n = 54)	Haloperidol (n = 50)	Placebo (n = 51)
Psychiatric efficacy variables, mean (sd)							
BPRS total score	46 (11)	47 (10)	45 (11)	44 (11)	46 (11)	44 (9)	45 (9)
CGI Severity of Illness score	4.9 (0.9)	5.0 (0.9)	5.1 (0.9)	4.9 (0.8)	5.0 (0.8)	5.0 (0.8)	4.9 (0.8)
SANS summary score	15 (4)	15 (3)	14 (3)	14 (4)	16 (4)	15 (4)	14 (4)
Neurologic assessments, n (%)							
Simpson Scale total score							
10	22 (44)	16 (35)	20 (41)	17 (35)	14 (29)	17 (35)	19 (38)
11	6 (12)	7 (15)	4 (8)	8 (16)	6 (12)	9 (18)	5 (10)
12	5 (10)	7 (15)	4 (8)	4 (8)	4 (8)	6 (12)	5 (10)
13+	17 (34)	16 (35)	21 (43)	20 (41)	25 (51)	17 (35)	21 (42)
AIMS total score							
0	30 (58)	20 (42)	27 (53)	26 (51)	25 (49)	23 (46)	28 (55)
1	4 (8)	6 (13)	5 (10)	2 (4)	2 (4)	2 (4)	4 (8)
2	2 (4)	3 (6)	3 (6)	2 (4)	4 (8)	5 (10)	5 (10)
3+	16 (31)	19 (40)	16 (31)	21 (41)	20 (39)	20 (40)	14 (28)

*n is variable since not all data were available for every patient.

Summary of sex, age, weight, and race

Characteristic	Treatment group: SEROQUEL 75 mg (n = 53)	SEROQUEL 150 mg (n = 48)	SEROQUEL 300 mg (n = 52)	SEROQUEL 600 mg (n = 51)	SEROQUEL 750 mg (n = 54)	Haloperidol (n = 52)	Placebo (n = 51)
Sex, n (%)							
Men	39 (74)	39 (81)	37 (71)	38 (75)	38 (70)	42 (81)	41 (80)
Women	14 (26)	9 (19)	15 (29)	13 (25)	16 (30)	10 (19)	10 (20)
Age (y), mean (sd)	37 (10)	38 (9)	38 (9)	39 (8)	35 (10)	37 (10)	36 (8)
Weight (kg), mean (sd)							
Men	79 (16)	80 (18)	86 (18)	83 (17)	80 (14)	82 (16)	83 (16)
Women	75 (21)	71 (20)	68 (10)	75 (22)	75 (16)	74 (25)	68 (15)
Race, n (%)							
White	36 (68)	36 (75)	36 (69)	36 (71)	38 (70)	37 (71)	35 (69)
Non-white	17 (32)	12 (25)	16 (31)	15 (30)	16 (30)	15 (29)	16 (32)

TABLE 15

Disposition of randomized patients - Trial 0013

Disposition	Quetiapine 75 mg n (%)	Quetiapine 150 mg n (%)	Quetiapine 300 mg n (%)	Quetiapine 600 mg n (%)	Quetiapine 750 mg n (%)	Placebo n (%)	Haloperidol n (%)
Total number randomized	53 (100)	48 (100)	52 (100)	51 (100)	54 (100)	51 (100)	52 (100)
Total number completed	17 (32)	21 (44)	24 (46)	27 (53)	26 (48)	16 (31)	18 (35)
Total number withdrawn	36 (68)	27 (56)	28 (54)	24 (47)	28 (52)	35 (69)	34 (65)
Lack of efficacy	27 (75)	23 (85)	22 (79)	16 (67)	19 (68)	30 (86)	17 (50)
Refused to continue/ lost to follow-up	8 (22)	4 (15)	5 (18)	7 (29)	6 (21)	3 (9)	13 (38)
Adverse experience/ intercurrent illness	0	0	0	0	1 (4)	2 (6)	4 (12)
Protocol noncompliance	1 (3)	0	1 (4)	1 (4)	2 (7)	0	0

BPRS total score - least-squares mean change from baseline (LOCF) - Trial 0013

TABLE 16a

		Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
		n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups															
Quetiapine	75 mg	52	45.71	52	-3.62	52	-3.56	52	-2.13	52	-1.91	52	-2.38	52	-2.24
	150 mg	48	47.15	48	-3.83	48	-6.58	48	-6.77	48	-7.99	48	-8.66	48	-8.67
	300 mg	51	45.29	51	-4.11	51	-7.07	51	-8.67	51	-9.64	51	-9.04	51	-8.59
	600 mg	51	43.45	51	-3.94	51	-5.79	51	-6.72	51	-7.31	51	-6.92	51	-7.68
	750 mg	53	45.72	53	-3.27	53	-4.65	53	-7.22	53	-7.55	53	-6.08	53	-6.33
Placebo		51	45.31	51	-2.23	51	0.02	51	1.05	51	1.17	51	1.76	51	1.71
Haloperidol 12 mg		50	44.00	50	-4.60	50	-8.60	50	-8.52	50	-7.53	50	-8.32	50	-7.58
II. P-values for pairwise comparisons from Dunnett's test															
Qtp 75 mg vs Placebo					0.9301		0.4162		0.6119		0.6620		0.4103		0.5041
Qtp 150 mg vs Placebo					0.8909		0.0294		0.0143		0.0038		0.0010		0.0021
Qtp 300 mg vs Placebo					0.8039		0.0143		0.0010		0.0003		0.0005		0.0019
Qtp 600 mg vs Placebo					0.8562		0.0632		0.0132		0.0074		0.0076		0.0057
Qtp 750 mg vs Placebo					0.9783		0.1800		0.0065		0.0050		0.0180		0.0224
Hpl 12 mg vs Placebo					0.2360		0.0004		0.0003		0.0014		0.0003		0.0016
Qtp 300 mg* vs Hpl 12 mg					0.9994		0.9534		1.0000		0.8952		0.9991		0.9967
III. 95% Confidence Interval: Diff (LCL, UCL)															
Qtp 300 mg* vs Hpl 12 mg					0.49 (-4.5, +5.5)		1.53 (-4.5, +7.6)		-0.15 (-6.7, +6.4)		-2.11 (-8.9, +4.7)		-0.72 (-7.7, +6.2)		-1.01 (-8.3,+6.3)

*Best quetiapine dose overall.
Diff=difference between treatments (Quetiapine 300 mg - Haloperidol 12 mg), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit.
Qtp=Quetiapine, Hpl=Haloperidol.

TABLE 16b

BPRS total score - least-squares mean change from baseline (OC) - Trial 0013

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine 75 mg	52	45.71	52	-3.62	46	-5.01	25	-10.16	22	-10.58	17	-14.87	16	-14.24
150 mg	48	47.15	48	-3.83	46	-7.09	37	-9.22	25	-14.79	23	-16.46	21	-16.75
300 mg	51	45.29	51	-4.11	49	-7.37	40	-11.26	32	-16.90	29	-16.01	24	-17.64
600 mg	51	43.45	51	-3.94	42	-7.32	35	-9.92	30	-14.94	29	-13.84	27	-16.53
750 mg	53	45.72	53	-3.27	48	-4.63	36	-11.15	31	-13.72	30	-11.14	29	-12.72
Placebo	51	45.31	51	-2.23	46	-0.91	30	-2.03	26	-3.86	21	-3.75	17	-7.06
Haloperidol 12 mg	50	44.00	50	-4.60	45	-9.43	35	-11.75	24	-15.56	19	-17.74	18	-17.11
II. P-values for pairwise comparisons from Dunnett's test														
Qtp 75 mg vs Placebo				0.9301		0.3441		0.0448		0.1765		0.0250		0.3804
Qtp 150 mg vs Placebo				0.8909		0.0608		0.0531		0.0048		0.0034		0.1056
Qtp 300 mg vs Placebo				0.8039		0.0412		0.0058		0.0002		0.0028		0.0556
Qtp 600 mg vs Placebo				0.8562		0.0558		0.0306		0.0025		0.0194		0.0913
Qtp 750 mg vs Placebo				0.9783		0.4270		0.0083		0.0081		0.1284		0.4788
Hpl 12 mg vs Placebo				0.2360		0.0010		0.0014		0.0009		0.0007		0.0364
Qtp 300 mg* vs Hpl 12 mg				0.9994		0.8752		0.9999		0.9907		0.9827		1.0000
III. 95% Confidence Interval: Diff (LCL, UCL)														
Qtp 300 mg* vs Hpl 12 mg				0.49 (-4.5, +5.5)		2.07 (-4.2, +8.4)		0.50 (-6.4, +7.4)		-1.34 (-9.3, +6.6)		1.72 (-7.4, +10.8)		-0.53 (-11.1, +10.1

*Best quetiapine dose overall.
Diff=difference between treatments (Quetiapine 300 mg - Haloperidol 12 mg),
LCL=lower 95% confidence limit, UCL=upper 95% confidence limit.
Qtp=Quetiapine, Hpl=Haloperidol.

CGI Severity of Illness score - least-squares mean change from baseline (LOCF) - Trial 0013

TABLE 17a

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	Treatment week													
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine 75 mg	52	4.90	52	-0.20	52	-0.28	52	-0.18	52	-0.05	52	-0.13	52	-0.15
150 mg	48	5.00	48	-0.11	48	-0.18	48	-0.31	48	-0.32	48	-0.45	48	-0.49
300 mg	51	5.08	51	-0.28	51	-0.48	51	-0.64	51	-0.69	51	-0.73	51	-0.69
600 mg	51	4.88	51	-0.03	51	-0.33	51	-0.45	51	-0.52	51	-0.46	51	-0.46
750 mg	54	5.00	54	-0.17	54	-0.29	54	-0.49	54	-0.60	54	-0.54	54	-0.46
Placebo	51	4.92	51	-0.07	51	0.10	51	0.23	51	0.22	51	0.25	51	0.25
Haloperidol 12 mg	50	5.02	50	-0.36	50	-0.62	50	-0.64	50	-0.62	50	-0.71	50	-0.69
II. P-values for pairwise comparisons from Dunnett's test														
Qtp 75 mg vs Placebo				0.8494		0.1271		0.1348		0.5034		0.2321		0.2215
Qtp 150 mg vs Placebo				0.9991		0.3803		0.0304		0.03311		0.0045		0.0039
Qtp 300 mg vs Placebo				0.4219		0.0056		0.0001		<0.0001		<0.0001		0.0001
Qtp 600 mg vs Placebo				0.9987		0.0625		0.0030		0.0013		0.0030		0.0049
Qtp 750 mg vs Placebo				0.9205		0.1039		0.0011		0.0002		0.0007		0.0042
Hpl 12 mg vs Placebo				0.0468		0.0001		0.0001		0.0001		0.0001		0.0001
Qtp 300 mg* vs Hpl 12 mg				0.9805		0.8894		1.0000		0.9957		1.0000		1.0000
III. 95% Confidence Interval: Diff (LCL, UCL)														
Qtp 300 mg* vs Hpl 12 mg				0.07 (-0.3, +0.4)		0.14 (-0.3, +0.6)		0 (-0.5, +0.5)		-0.07 (-0.6, +0.4)		-0.02 (-0.6, +0.5)		0 (-0.6, +0.6)

*Best quetiapine dose overall.
Diff=difference between treatments (Quetiapine 300 mg - Haloperidol 12 mg),
LCL=lower 95% confidence limit, UCL=upper 95% confidence limit.
Qtp=Quetiapine, Hpl=Haloperidol.

TABLE 17b

CGI Severity of Illness score - least-squares mean change from baseline (OC) - Trial 0013

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	Treatment week													
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine 75 mg	52	4.90	52	-0.20	47	-0.37	25	-0.79	22	-0.62	17	-1.03	16	-1.03
150 mg	48	5.00	48	-0.11	46	-0.23	37	-0.51	25	-0.74	23	-0.95	21	-1.10
300 mg	51	5.08	51	-0.28	48	-0.49	41	-0.70	32	-1.02	29	-1.06	24	-1.21
600 mg	51	4.88	51	-0.03	42	-0.49	35	-0.79	30	-1.16	29	-1.14	27	-1.19
750 mg	54	5.00	54	-0.17	48	-0.35	36	-0.67	31	-0.93	30	-0.78	29	-0.75
Placebo	51	4.92	51	-0.07	46	0.04	30	-0.04	26	-0.21	22	-0.13	17	-0.34
Haloperidol 12 mg	50	5.02	50	-0.36	45	-0.67	36	-0.82	24	-1.07	20	-1.35	18	-1.35
II. P-values for pairwise comparisons from Dunnett's test														
Qtp 75 mg vs Placebo				0.8494		0.1052		0.0173		0.4179		0.0143		0.1957
Qtp 150 mg vs Placebo				0.9991		0.4403		0.1642		0.1705		0.0159		0.0990
Qtp 300 mg vs Placebo				0.4219		0.0173		0.0166		0.0060		0.0024		0.0357
Qtp 600 mg vs Placebo				0.9987		0.0219		0.0075		0.0011		0.0009		0.0381
Qtp 750 mg vs Placebo				0.9205		0.1341		0.0332		0.0203		0.0559		0.5341
Hpl 12 mg vs Placebo				0.0468		0.0002		0.0015		0.0026		0.0001		0.0066
Qtp 300 mg* vs Hpl 12 mg				0.9805		0.7658		0.9808		0.9998		0.7048		0.9896
III. 95% Confidence Interval: Diff (LCL, UCL)														
Qtp 300 mg* vs Hpl 12 mg				0.07 (-0.3, +0.4)		0.18 (-0.3, +0.6)		0.11 (-0.4, +0.7)		0.05 (-0.6, +0.7)		0.29 (-0.4, +1.0)		0.14 (-0.7, +1.0)

*Best quetiapine dose overall.
Diff=difference between treatments (Quetiapine 300 mg - Haloperidol 12 mg), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit.
Qtp=Quetiapine, Hpl=Haloperidol.

TABLE 18a

BPRS positive symptom cluster score - least-squares mean change from baseline (LOCF) - Trial 0013

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	Treatment week													
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine 75 mg	52	3.84	52	-0.35	52	-0.46	52	-0.29	52	-0.29	52	-0.34	52	-0.38
150 mg	48	3.95	48	-0.27	48	-0.52	48	-0.57	48	-0.68	48	-0.70	48	-0.74
300 mg	51	3.77	51	-0.31	51	-0.71	51	-0.84	51	-0.93	51	-0.81	51	-0.87
600 mg	51	3.54	51	-0.38	51	-0.54	51	-0.77	51	-0.76	51	-0.70	51	-0.73
750 mg	53	3.63	53	-0.32	53	-0.47	53	-0.72	53	-0.68	53	-0.60	53	-0.58
Placebo	51	3.74	51	-0.24	51	-0.20	51	-0.07	51	-0.05	51	-0.02	51	0.05
Haloperidol 12 mg	50	3.63	50	-0.39	50	-0.74	50	-0.81	50	-0.72	50	-0.80	50	-0.74
II. 2-sided p-values for pairwise comparisons														
Qtp 75 mg vs Placebo				0.9521		0.5886		0.8062		0.7417		0.5157		0.2446
Qtp 150 mg vs Placebo				0.9998		0.4064		0.1164		0.0318		0.0216		0.0061
Qtp 300 mg vs Placebo				0.9913		0.0553		0.0035		0.0007		0.0040		0.0007
Qtp 600 mg vs Placebo				0.8678		0.3353		0.0095		0.0100		0.0177		0.0064
Qtp 750 mg vs Placebo				0.9896		0.5170		0.0178		0.0264		0.0564		0.0379
Hpl 12 mg vs Placebo				0.3875		0.0091		0.0013		0.0045		0.0011		0.0013
Qtp 300 mg* vs Hpl 12 mg				0.9901		0.9999		1.0000		0.8072		1.0000		0.9741
III. 95% Confidence Interval: Diff (LCL, UCL)														
Qtp 300 mg* vs Hpl 12 mg				0.07 (-0.3, +0.5)		0.03 (-0.5, +0.6)		-0.03 (-0.6, +0.5)		-0.22 (-0.8, +0.4)		-0.01 (-0.6, +0.6)		-0.13 (-0.7, +0.5)

*Best quetiapine dose overall.
Diff=difference between treatments (Quetiapine 300 mg - Haloperidol 12 mg), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit.
Qtp=Quetiapine, Hpl=Haloperidol.

TABLE 18b

BPRS positive symptom cluster score - least-squares mean change from baseline (OC) - Trial 0013

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	Treatment week													
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine 75 mg	52	3.84	52	-0.35	46	-0.55	25	-0.95	22	-1.02	17	-1.48	16	-1.52
150 mg	48	3.95	48	-0.27	46	-0.55	37	-0.75	25	-1.03	23	-1.06	21	-1.08
300 mg	51	3.77	51	-0.31	49	-0.71	40	-1.00	32	-1.45	29	-1.22	24	-1.61
600 mg	51	3.54	51	-0.38	42	-0.62	35	-1.11	30	-1.43	29	-1.30	27	-1.39
750 mg	53	3.63	53	-0.32	48	-0.46	36	-1.01	31	-1.07	30	-0.96	29	-0.99
Placebo	51	3.74	51	-0.24	46	-0.27	30	-0.37	26	-0.52	21	-0.60	17	-0.68
Haloperidol 12 mg	50	3.63	50	-0.39	45	-0.76	35	-1.03	24	-1.12	19	-1.43	18	-1.42
II. 2-sided p-values for pairwise comparisons														
Qtp 75 mg vs Placebo				0.9521		0.5933		0.2114		0.4232		0.0994		0.1651
Qtp 150 mg vs Placebo				0.9998		0.5995		0.5016		0.3772		0.5758		0.7331
Qtp 300 mg vs Placebo				0.9913		0.1626		0.0850		0.0121		0.2416		0.0647
Qtp 600 mg vs Placebo				0.8678		0.3986		0.0393		0.0160		0.1560		0.2012
Qtp 750 mg vs Placebo				0.9896		0.8587		0.0885		0.2584		0.7296		0.8452
Hpl 12 mg vs Placebo				0.3875		0.0292		0.0237		0.0809		0.0385		0.0859
Qtp 300 mg* vs Hpl 12 mg				0.9901		0.9994		1.0000		0.7303		0.9605		0.9791
III. 95% Confidence Interval: Diff (LCL, UCL)														
Qtp 300 mg* vs Hpl 12 mg				0.07 (-0.3, +0.5)		0.05 (-0.5, +0.6)		0.03 (-0.6, +0.7)		-0.32 (-1.1, +0.5)		0.21 (-0.7, +1.1)		-0.19 (-1.2, +0.8)

*Best quetiapine dose overall.
Diff=difference between treatments (Quetiapine 300 mg - Haloperidol 12 mg), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit.
Qtp=Quetiapine, Hpl=Haloperidol.

SANS summary score - least-squares mean change from baseline (LOCF) - Trial 0013

TABLE 19a

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine 75 mg	46	14.59	45	-0.10	46	-0.45	46	-0.17	46	-0.32	46	-0.40	46	-0.62
150 mg	45	14.73	44	-0.27	45	-0.50	45	-0.72	45	-0.42	45	-0.85	45	-0.78
300 mg	49	14.24	49	-0.46	49	-1.53	49	-1.92	49	-1.67	49	-1.47	49	-1.56
600 mg	49	14.35	48	-0.11	48	-0.46	49	-1.06	49	-1.23	49	-0.88	49	-0.98
750 mg	48	15.46	47	-0.18	47	-0.41	47	-0.82	47	-0.84	48	-0.57	48	-0.50
Placebo	50	13.88	50	0.82	50	0.68	50	0.88	50	0.80	50	1.12	50	0.76
Haloperidol 12 mg	50	14.72	47	-0.84	50	-1.77	50	-1.79	50	-1.60	50	-1.75	50	-1.83
II. P-values for pairwise comparisons from Dunnett's test														
Qtp 75 mg vs Placebo				0.3107		0.2707		0.3627		0.3604		0.1155		0.2068
Qtp 150 mg vs Placebo				0.1702		0.2405		0.0667		0.2855		0.0230		0.1371
Qtp 300 mg vs Placebo				0.0667		0.0024		0.0001		0.0018		0.0009		0.0059
Qtp 600 mg vs Placebo				0.2798		0.2589		0.0131		0.0147		0.0168		0.0618
Qtp 750 mg vs Placebo				0.2253		0.3054		0.0407		0.0754		0.0599		0.2771
Hpl 12 mg vs Placebo				0.0020		0.0001		0.0001		0.0006		0.0001		0.0003
Qtp 300 mg* vs Hpl 12 mg				0.9301		0.9952		0.9998		1.0000		0.9932		0.9950
III. 95% Confidence Interval: Diff (LCL, UCL)														
Qtp 300 mg* vs Hpl 12 mg				0.38 (-1.0, +1.7)		0.24 (-1.4, +1.8)		-0.13 (-1.8, +1.5)		-0.07 (-1.8, +1.7)		0.28 (-1.5, +2.0)		0.27 (-1.5, +2.1)

*Best quetiapine dose overall.
Diff=difference between treatments (Quetiapine 300 mg - Haloperidol 12 mg), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit.
Qtp=Quetiapine, Hpl=Haloperidol

TABLE 19b

SANS summary score - least-squares mean change from baseline (OC) - Trial 0013

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine 75 mg	46	14.6	45	-0.10	41	-0.77	21	-1.52	16	-2.08	14	-2.10	13	-3.22
150 mg	45	14.7	44	-0.27	41	-0.74	35	-1.28	25	-1.01	23	-2.15	21	-2.02
300 mg	49	14.2	49	-0.46	47	-1.53	38	-2.39	32	-2.38	29	-2.30	24	-3.14
600 mg	49	14.2	48	-0.11	40	-0.89	34	-1.64	29	-2.80	28	-2.05	27	-2.67
750 mg	48	15.5	47	-0.18	46	-0.45	34	-1.47	28	-1.09	29	-0.82	27	-0.85
Placebo	50	13.9	50	0.82	42	0.38	27	0.68	23	0.54	19	1.29	16	-0.61
Haloperidol 12 mg	50	14.7	50	-0.84	45	-1.98	34	-2.55	23	-2.37	19	-3.27	16	-3.46
II. P-values for pairwise comparisons from Dunnett's test														
Qtp 75 mg vs Placebo				0.3107		0.3162		0.0445		0.0518		0.0058		0.0672
Qtp 150 mg vs Placebo				0.1702		0.3345		0.0414		0.3081		0.0011		0.4248
Qtp 300 mg vs Placebo				0.0667		0.0186		0.0003		0.0047		0.0003		0.0317
Qtp 600 mg vs Placebo				0.2798		0.2323		0.0114		0.0012		0.0009		0.0956
Qtp 750 mg vs Placebo				0.2253		0.5970		0.0217		0.2407		0.0630		0.9989
Hpl 12 mg vs Placebo				0.0020		0.0007		0.0001		0.0047		0.0001		0.0100
Qtp 300 mg* vs Hpl 12 mg				0.9301		0.9422		0.9995		1.0000		0.6690		0.9964
III. 95% Confidence Interval: Diff (LCL, UCL)														
300 mg* vs Hpl 12 mg				0.38 (-1.0, +1.7)		0.44 (-1.2, +2.1)		0.16 (-1.6, +1.9)		-0.01 (-2.2, +2.2)		0.97 (-1.2, +3.2)		0.31 (-2.1, +2.7)

*Best quetiapine dose overall.
Diff=difference between treatments (Quetiapine 300 mg - Haloperidol 12 mg), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit.
Qtp=Quetiapine, Hpl=Haloperidol.

FIGURE 9

BPRS total score – mean change from baseline for patients withdrawing by trial week – Trial 0013

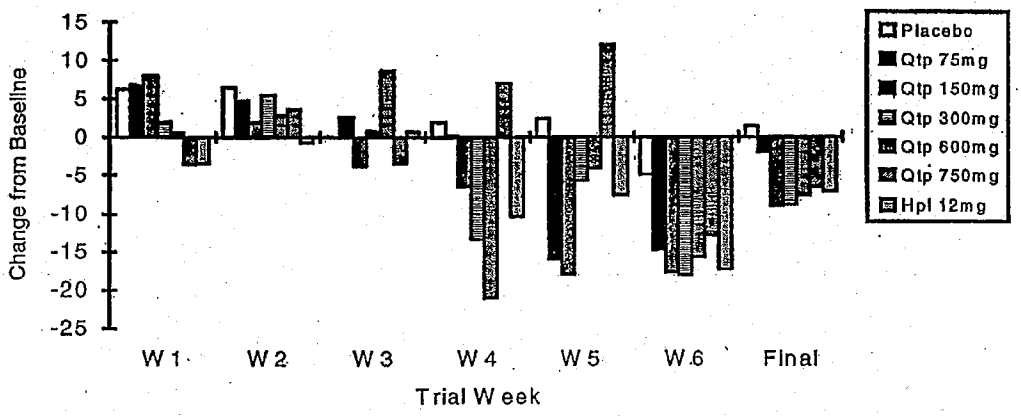
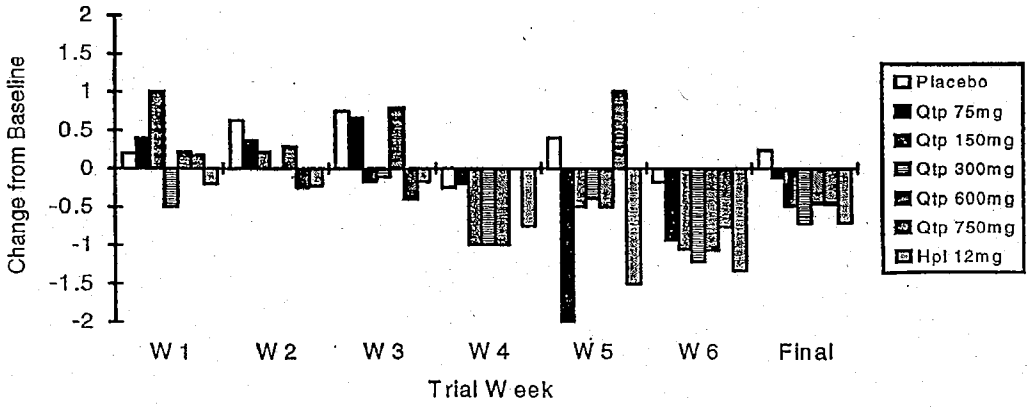


FIGURE 10

CGI Severity of Illness score – mean change from baseline for patients withdrawing by trial week – Trial 0013



FIFURE 11

BPRS positive symptom cluster score – mean change from baseline for patients withdrawing by trial week – Trial 0013

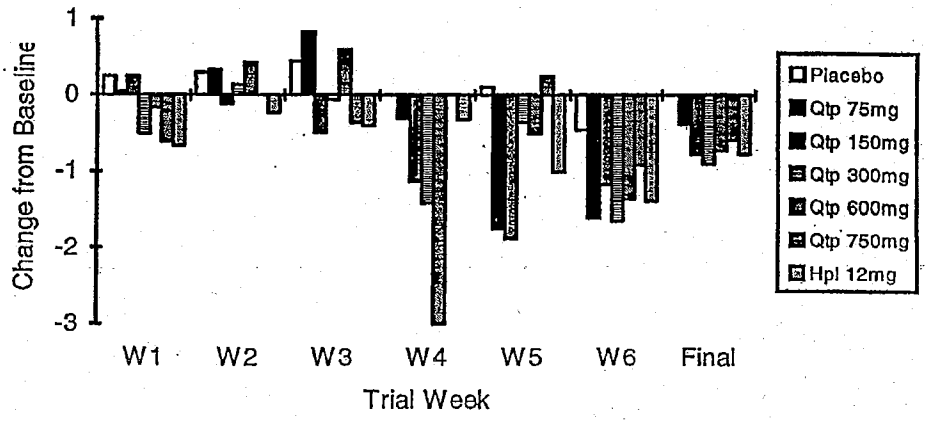


FIGURE 12

SANS summary score – mean change from baseline for patients withdrawing by trial week – Trial 0013

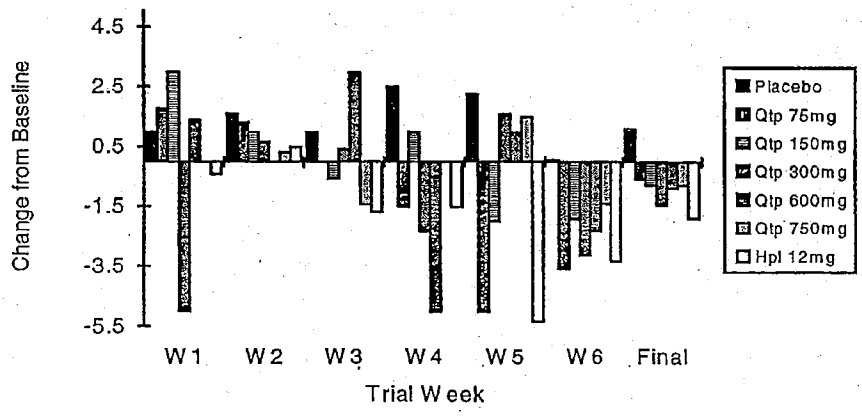


TABLE 20

Summary of baseline characteristics - Trial 0012

	Quetiapine total daily dose & regimen		
	150 mg TID (n = 209)	225 mg BID (n = 200)	25 mg BID (n = 209)
Age (yr)			
n	209	200	209
mean	34	37	36
SD	9	11	11
min	20	18	19
max	64	64	65
Gender (n, %)			
men	128 (61)	135 (68)	146 (70)
women	81 (39)	65 (33)	63 (30)
Weight (kg)			
n	209	199	208
mean	75	74	74
SD	17	17	14
min	43	44	47
max	140	169	130
Race (n, %)			
Caucasian	195 (93)	191 (96)	201 (96)
Afro-Caribbean	6 (3)	3 (2)	3 (1)
Hispanic	2 (1)	1 (1)	0
Oriental	3 (1)	0	0
Asian	2 (1)	2 (1)	2 (1)
Mixed/Undefined	0	1 (1)	3 (1)
Other	1 (1)	2 (1)	0
Diagnosis (n,%)			
Schizophrenia*			
Catatonic	7 (3)	5 (3)	5 (2)
Disorganized	31 (15)	27 (14)	40 (19)
Paranoid	134 (64)	136 (68)	134 (64)
Undifferentiated	37 (18)	32 (16)	30 (14)
Age at first treatment			
n	207	199	209
mean	24	26	26
SD	7	9	8
min	10	7	12
max	50	60	58
Number of hospitalizations (n, %)			
0	23 (11)	10 (5)	26 (12)
1-5	100 (48)	107 (54)	103 (49)
6-10	41 (20)	49 (25)	38 (18)
11-15	16 (8)	14 (7)	24 (11)
16-20	9 (4)	6 (3)	7 (3)
>20	19 (9)	10 (5)	10 (5)
Unknown	1 (0)	4 (2)	1 (0)

TABLE 20 (cont)

Antipsychotic medication response (n, %)			
Fully responsive	18 (9)	21 (11)	22 (11)
Partially responsive	97 (46)	103 (52)	95 (45)
Poorly responsive	75 (36)	61 (31)	66 (32)
Non-responsive	15 (7)	8 (4)	13 (6)
First episode	1 (0)	3 (2)	6 (3)
Unknown	3 (1)	4 (2)	7 (3)
Baseline BPRS total score# (mean, SD)	42.7 (10.4)	42.1 (10.7)	41.7 (10.0)
Baseline CGI Severity of Illness score (n, %)			
Moderate	54 (26)	51 (26)	62 (31)
Marked	87 (42)	92 (47)	85 (43)
Severe	58 (28)	44 (23)	45 (23)
Most severe	6 (3)	8 (4)	6 (3)

TABLE 21

Disposition of randomized patients - Trial 0012

Disposition	Quetiapine total daily dose & regimen		
	150 mg TID n (%)	225 mg BID n (%)	25 mg BID n (%)
Total number randomized	209 (100)	200 (100)	209 (100)
Total number completed	112 (54)	102 (51)	90 (43)
Total number withdrawn	97 (46)	98 (49)	119 (57)
Lack of efficacy	64 (66)	60 (61)	80 (67)
Refused to continue/ lost to follow-up	20 (21)	19 (19)	26 (22)
Adverse event/ intercurrent illness	7 (7)	12 (12)	7 (6)
Protocol noncompliance	6 (6)	7 (7)	6 (5)

TABLE 22a

BPRS total score - least-squares mean change from baseline (LOCF) - Trial 0012

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment Groups														
Quetiapine 225 mg BID	195	42.14	195	-3.74	195	-6.08	195	-7.79	195	-8.66	195	-9.49	195	-9.98
150 mg TID	204	42.74	203	-2.00	204	-4.36	204	-6.43	204	-7.09	204	-8.49	204	-8.59
25 mg BID	197	41.68	197	-1.99	197	-3.18	197	-4.68	197	-4.75	197	-5.54	197	-5.41
II. 2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID				0.0811		0.0239		0.0307		0.0100		0.0140		0.0055
150 mg TID vs 25 mg BID				0.9926		0.3545		0.2184		0.1199		0.0636		0.0503
225 mg BID vs 150 mg TID				0.0804		0.1745		0.3395		0.2938		0.5274		0.3943
III. 95% confidence interval: Diff (LCL, UCL)														
225mg BID vs 150mg TID				-1.74 (-3.68, +0.21)		-1.73 (-4.22, +0.77)		-1.36 (-4.16, +1.43)		-1.58 (-4.52, +1.37)		-1.00 (-4.12, +2.11)		-1.39 (-4.58, +1.81)

Diff=difference between treatments (225 mg BID - 150 mg TID), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit

TABLE 22b

BPRS total score - least-squares mean change from baseline (OC) - Trial 0012

	Baseline		Treatment week: Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment Groups														
Quetiapine 225 mg BID	195	42.14	195	-4.10	180	-8.12	141	-13.15	121	-16.66	108	-19.33	103	-21.15
150 mg TID	204	42.74	203	-2.38	177	-6.57	145	-12.24	133	-14.67	122	-18.36	114	-19.62
25 mg BID	197	41.68	197	-2.33	174	-5.63	134	-10.51	117	-13.29	100	-16.52	94	-17.21
II. 2-sided p-values for pairwise comparisons														
225mg BID vs 25mg BID				0.0776		0.0487		0.0766		0.0323		0.0977		0.0273
150 mg TID vs 25 mg BID				0.9612		0.4561		0.2433		0.3672		0.2650		0.1682
225mg BID vs 150mg TID				0.0836		0.2181		0.5302		0.1908		0.5507		0.3667
III. 95% confidence interval: Diff (LCL, UCL)														
225mg BID vs 150mg TID				-1.72 (-3.67, +0.23)		-1.55 (-4.02, +0.92)		-0.91 (-3.77, +1.94)		-1.99 (-4.96, +0.99)		-0.96 (-4.13, +2.20)		-1.53 (-4.86, +1.80)

Diff=difference between treatments (225 mg BID - 150 mg TID), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit.

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TABLE 23a

CGI Severity of Illness score - grouped change from baseline (LOCF) - Trial 0012 (continued)

	Treatment week					
	Baseline n (%)	Week 1 n (%)	Week 2 n (%)	Week 3 n (%)	Week 4 n (%)	Week 5 n (%)	Week 6 n (%)
2-sided p-values for pairwise comparisons							
25mg BID vs. 25 mg BID		0.6130	0.1230	0.0790	0.0160	0.0070	0.0290
150 mg TID vs. 25 mg BID		0.2330	0.4140	0.1530	0.1800	0.3310	0.3440
25 mg BID vs 150 mg TID		0.2260	0.4490	0.6520	0.0920	0.2140	0.4450

moderate=4, marked=5, severe=6, and most severe=7.

TABLE 23b

CGI Severity of Illness score - grouped change from baseline (OC) - Trial 0012 (continued)

	Treatment week						
	Baseline n (%)	Week 1 n (%)	Week 2 n (%)	Week 3 n (%)	Week 4 n (%)	Week 5 n (%)	Week 6 n (%)
2-sided p-values for pairwise comparisons							
25mg BID vs. 25mg BID		0.5960	0.1480	0.1560	0.0230	0.0170	0.1110
150mg TID vs. 25mg BID		0.2230	0.5430	0.2110	0.0920	0.1530	0.2860
25mgBID vs 150mgTID		0.2280	0.5590	0.8790	0.1070	0.4300	0.8370

moderate=4, marked=5, severe=6, and most severe=7.

TABLE 24a

BPRS positive symptom cluster score - least-squares mean change from baseline (LOCF) - Trial 0012

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment groups														
Quetiapine 225 mg BID	195	3.55	195	-0.37	195	-0.63	195	-0.79	195	-0.86	195	-0.92	195	-0.96
150 mg TID	204	3.52	203	-0.23	204	-0.47	204	-0.65	204	-0.68	204	-0.81	204	-0.86
25 mg BID	197	3.47	197	-0.25	197	-0.41	197	-0.53	197	-0.52	197	-0.61	197	-0.62
II. 2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID				0.1445		0.0286		0.0194		0.0054		0.0157		0.0090
150 mg TID vs 25 mg BID				0.7700		0.5862		0.2711		0.1708		0.1063		0.0649
225 mg BID vs 150 mg TID				0.0780		0.0951		0.2054		0.1468		0.4066		0.4239
III. 95% confidence interval: Diff (LCL, UCL)														
225 mg BID vs 150 mg TID				-0.15 (-0.31, +0.02)		-0.17 (-0.37, +0.03)		-0.14 (-0.37, +0.08)		-0.17 (-0.41, +0.06)		-0.10 (-0.35, +0.14)		-0.10 (-0.36, +0.15)

Diff=difference between treatments (225 mg BID - 150 mg TID), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit

TABLE 24b

BPRS positive symptom cluster score - least-squares mean change from baseline (OC) - Trial 0012

	Treatment week													
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
I. Treatment Groups														
Quetiapine 225 mg BID	195	3.55	195	-0.40	180	-0.78	141	-1.16	121	-1.43	108	-1.64	103	-1.79
150 mg TID	204	3.52	203	-0.25	177	-0.62	145	-1.07	133	-1.23	122	-1.55	114	-1.70
25 mg BID	197	3.47	197	-0.27	174	-0.58	134	-0.93	117	-1.13	100	-1.42	94	-1.49
II. 2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID				0.1419		0.0532		0.0750		0.0339		0.1237		0.0476
150 mg TID vs 25 mg BID				0.7932		0.7068		0.2737		0.4622		0.3529		0.1722
225 mg BID vs 150 mg TID				0.0815		0.1176		0.4765		0.1460		0.5070		0.4994
III. 95% confidence interval: Diff (LCL, UCL)														
225 mg BID vs 150 mg TID				-0.14 (-0.31, +0.02)		-0.16 (-0.36, +0.04)		-0.09 (-0.33, +0.15)		-0.19 (-0.45, +0.07)		-0.09 (-0.36, +0.18)		-0.10 (-0.39, +0.19)

Diff=difference between treatments (225 mg BID - 150 mg TID), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit

TABLE 25a

SANS Summary score - least-squares mean change from baseline (LOCF) - Trial 0012

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Treatment Groups														
Olanzapine 225 mg BID	189	14.38	188	-0.52	189	-0.80	189	-1.15	189	-1.36	189	-1.53	189	-1.68
150 mg TID	197	14.69	194	-0.14	197	-0.76	197	-1.05	197	-1.32	197	-1.30	197	-1.37
25 mg BID	190	14.38	188	-0.10	190	-0.39	190	-0.81	190	-0.74	190	-0.81	190	-0.85
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID				0.0553		0.1382		0.2647		0.0698		0.0415		0.0216
150 mg TID vs 25 mg BID				0.8712		0.1764		0.4413		0.0829		0.1563		0.1425
225 mg BID vs 150 mg TID				0.0768		0.8854		0.7220		0.9237		0.5212		0.3929
95% confidence interval: Diff (LCL, UCL)														
225 mg BID vs 150 mg TID				-0.38 (-0.81, +0.04)		-0.04 (-0.58, +0.50)		-0.11 (-0.71, +0.49)		-0.03 (-0.69, +0.62)		-0.22 (-0.91, +0.46)		-0.30 (-1.00, +0.40)

Diff=difference between treatments (225 mg BID - 150 mg TID), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit

TABLE 25b

SANS summary score - least-squares mean change from baseline (OC) - Trial 0012

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean
Treatment Groups														
Olanzapine 225 mg BID	189	14.38	188	-0.59	176	-1.11	139	-1.89	119	-2.53	106	-3.02	100	-3.56
150 mg TID	197	14.69	194	-0.21	171	-1.19	138	-2.29	127	-3.01	117	-3.34	110	-3.73
25 mg BID	190	14.38	188	-0.16	166	-0.75	130	-1.76	116	-1.83	97	-2.66	93	-2.75
2-sided p-values for pairwise comparisons														
225 mg BID vs 25 mg BID				0.0524		0.2034		0.6984		0.0724		0.3929		0.0591
150 mg TID vs 25 mg BID				0.8347		0.1276		0.1125		0.0023		0.0962		0.0212
225 mg BID vs 150 mg TID				0.0807		0.7900		0.2195		0.2089		0.4121		0.6886
95% confidence interval: Diff (LCL, UCL)														
225 mg BID vs 150 mg TID				-0.38 (-0.81, +0.05)		0.08 (-0.48, +0.63)		0.40 (-0.24, +1.05)		0.48 (-0.27, +1.22)		0.33 (-0.46, +1.11)		0.17 (-0.65, +0.98)

Diff=difference between treatments (225 mg BID - 150 mg TID), LCL=lower 95% confidence limit, UCL=upper 95% confidence limit

FIGURE 13

BPRS total score – mean change from baseline for patients withdrawing by trial week – Trial 0012

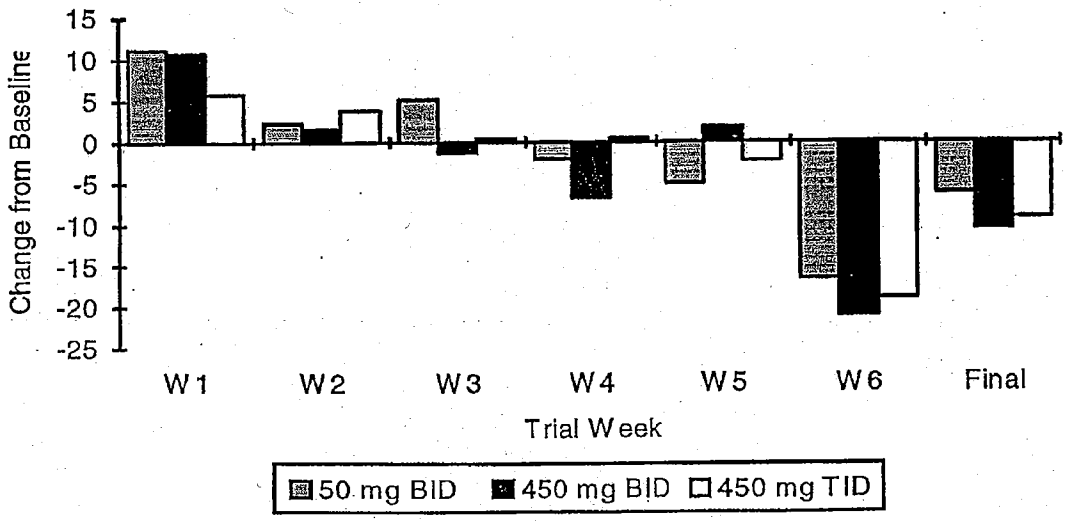

FIGURE 14

CGI Severity of Illness score – mean change from baseline for patients withdrawing by trial week – Trial 0012

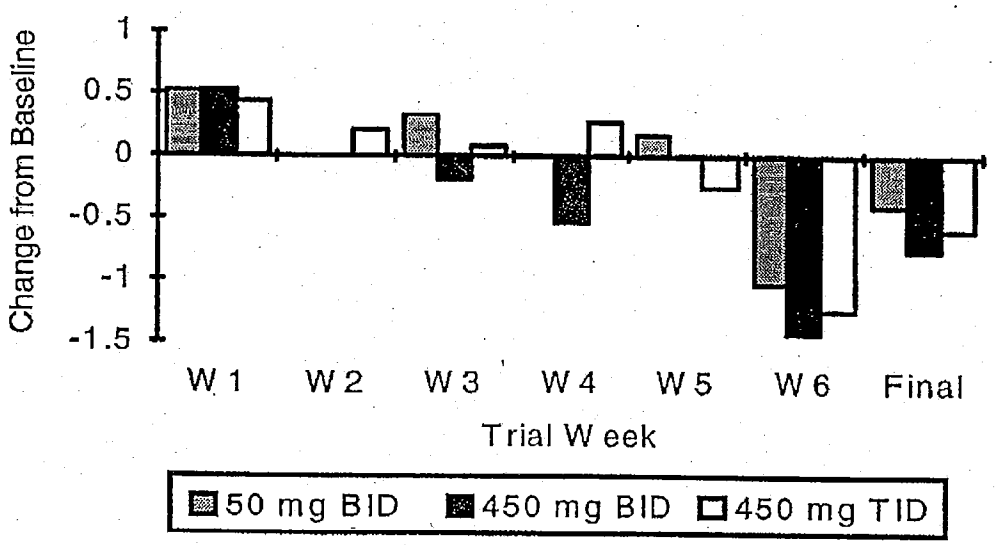

FIGURE 15

BPRS positive symptom cluster score – mean change from baseline for patients withdrawing by trial week – Trial 0012

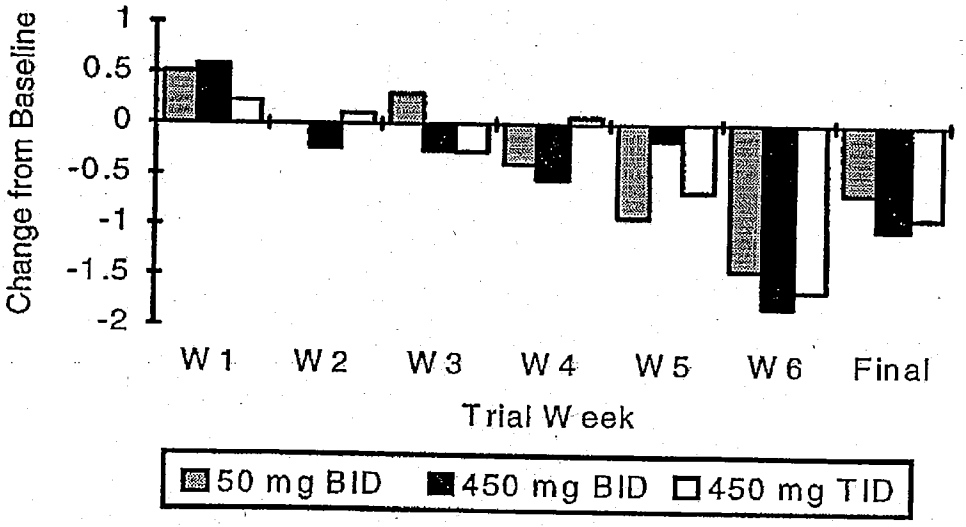

FIGURE 16

SANS summary score – mean change from baseline for patients withdrawing by trial week – Trial 0012

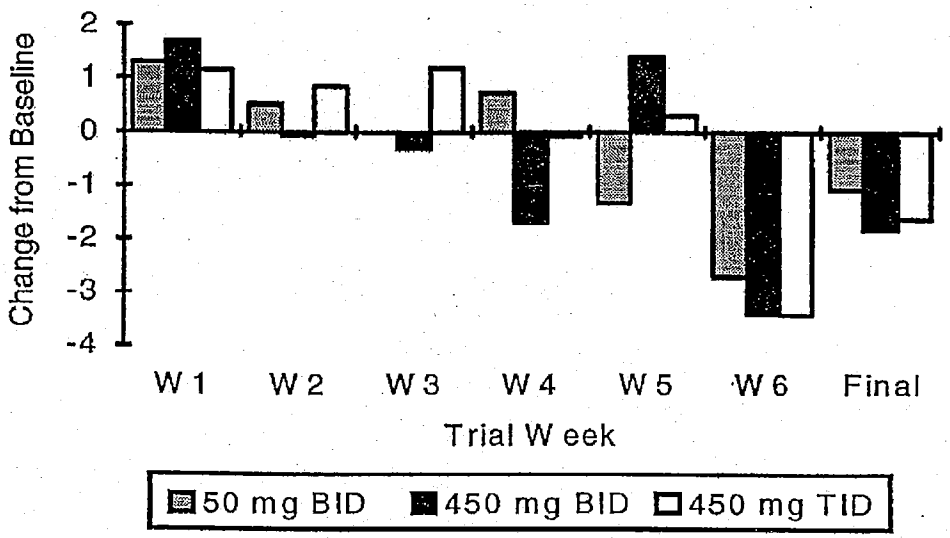

TABLE 26

BPRS total score and CGI Severity of Illness score in relation to age

	<40 years				40 to 64 years			
	Quetiapine		Placebo		Quetiapine		Placebo	
	n	mcb±SD	n	mcb±SD	n	mcb±SD	n	mcb±SD
I. BPRS total score								
Trial 13	148	-8.0±15.6	33	0.8±11.1	107	-4.8±15.3	18	2.6±12.5
Trial 6	36	-8.7±15.5	35	1.9±16.5	17	-6.9±17.3	18	-8.6±15.9
Trial 8	122	-7.1±15.0	54	0.9±16.2	64	-7.3±14.8	40	-4.0±17.7
Total	306	-7.7±15.3	122	1.1±15.0	188	-5.8±15.3	76	-3.5±16.5
II. CGI Severity of Illness score								
Trial 13	149	-0.4±1.2	33	0.3±1.0	107	-0.4±0.9	18	0.1±0.9
Trial 6	36	-0.4±1.2	35	0.5±1.5	17	-0.3±1.3	18	-0.2±1.7
Trial 8	122	-0.5±1.2	54	0.0±1.2	65	-0.5±1.2	40	-0.2±1.4
Total	307	-0.4±1.2	122	0.2±1.2	189	-0.5±1.1	76	-0.1±1.2

mcb=mean change from baseline.
SD=standard deviation.