

significantly greater improvement compared with the placebo group at Week 6, analysis of this key secondary measure was performed for all three treatment groups versus the placebo group. The results of the analysis of the change in the PANSS-derived BPRS Core Score for the LOCF data set at Week 6 are shown in Table 4.1.3.5. The analysis showed significantly greater improvement for all three aripiprazole treatment groups compared with the placebo group. The analysis of the change Scores for the LOCF data set for aripiprazole 10 mg showed significantly greater improvement compared with the placebo group from Week 2 through Week 6. Aripiprazole 15 mg was statistically significantly different from placebo at Week 5 and 6. Aripiprazole 20 mg showed significantly greater improvement compared with placebo from Week 2 through Week 6.

The results of the analysis of the mean change from baseline for the OC data set is shown in Table 4.1.3.6. The aripiprazole 10-mg group showed significantly greater improvement compared with the placebo group at Weeks 2, 3 and 6. Aripiprazole 15 mg did not show significantly greater improvement compared with the placebo group at any week. Aripiprazole 20 mg was statistically significantly different from placebo at Week 3. As expected, Week 4 sample sizes decreased substantially and mean change from baseline PANSS-derived BPRS Core Score improved for all treatment groups when the option to move to open-label aripiprazole could be exercised.

Table 4.1.3.5. Mean Change from Baseline in PANSS-Derived BPRS Core Score, LOCF Data Set, Efficacy Sample for Study CN138-001

	PANSS-Derived BPRS Core Score				Pairwise Comparisons P-values		
	Placebo	Aripiprazole	Aripiprazole	Aripiprazole	Ari10 vs	Ari15 vs	Ari20 vs
	N = 107	10 mg N = 103	15 mg N = 103	20 mg N = 97	Placebo	Placebo	Placebo
Baseline	16.92	16.99	16.76	16.68	0.857	0.680	0.530
Day 4	-1.09	-1.11	-1.11	-1.46	0.948	0.951	0.258
Week 1	-1.48	-2.22	-1.98	-2.30	0.077	0.236	0.055
Week 2	-1.51	-3.21	-2.39	-2.84	<0.001	0.069	0.007
Week 3	-1.47	-3.45	-2.26	-3.21	<0.001	0.144	0.002
Week 4	-1.57	-3.59	-2.59	-3.16	<0.001	0.073	0.006
Week 5	-1.40	-3.77	-2.67	-3.31	<0.001	0.034	0.002
Week 6	-1.37	-3.91	-2.88	-3.56	<0.001	0.014	<0.001

Table 4.1.3.6 Mean Change from Baseline in PANSS-Derived BPRS Core Score, OC Data Set, Efficacy Sample for Study CN138-001

	PANSS-Derived BPRS Core Score				Pairwise Comparisons P-values		
	Placebo	Aripiprazole	Aripiprazole	Aripiprazole	Ari10 vs	Ari15 vs	Ari20 vs
	(N)	10 mg (N)	15 mg (N)	20 mg (N)	Placebo	Placebo	Placebo
Baseline	16.78 (107)	16.87 (103)	16.78 (103)	16.69 (97)	0.825	0.998	0.851
Day 4	-1.03 (100)	-1.09 (97)	-1.10 (100)	-1.40 (94)	0.857	0.847	0.264
Week 1	-1.46 (100)	-2.28 (89)	-1.81 (95)	-1.99 (87)	0.067	0.424	0.242
Week 2	-1.94 (88)	-3.45 (86)	-2.30 (89)	-2.72 (81)	0.005	0.502	0.155
Week 3	-2.23 (82)	-4.04 (78)	-2.49 (82)	-3.62 (68)	0.003	0.662	0.030
Week 4	-4.58 (42)	-5.55 (51)	-5.29 (41)	-4.61 (49)	0.195	0.365	0.967
Week 5	-5.89 (31)	-6.65 (45)	-5.60 (37)	-5.70 (40)	0.342	0.731	0.814
Week 6	-5.78 (30)	-7.53 (42)	-7.18 (34)	-6.40 (39)	0.040	0.113	0.478

The mean change from baseline to Week 6 in the PANSS Negative Sub-Scale Score was the second of two key secondary efficacy measures. Since the first key secondary measure showed significantly greater improvement compared with placebo for all the aripiprazole treatment groups, analysis of this key secondary measure was performed for all treatment groups at Week 6 versus placebo. The results of the analysis of the change in the PANSS Negative Sub-Scale Score for the LOCF data set at Week 6 is shown in Table 4.1.3.7. The analysis showed that all aripiprazole treatments had significantly greater improvement compared with the placebo group. The analysis of the change Scores for the LOCF data set for aripiprazole 10 mg was statistically significantly different from placebo from Week 1 through Week 6. Aripiprazole 15 mg was significantly different from placebo from Week 2 through Week 6. Aripiprazole 20 mg was statistically significantly different from placebo from Day 4 through Week 6.

The results of the analysis of the mean change from baseline for the OC data set is shown in Table 4.1.3.8. The aripiprazole 10-mg treatment group showed significantly greater improvement at Weeks 1 through 3, while aripiprazole 15 mg was not statistically significantly different from placebo at any week. Aripiprazole 20 mg showed significantly greater improvement compared with the placebo group at Day 4 through Week 3.

Table 4.1.3.7 Mean Change from Baseline in PANSS Negative Sub-Scale Total Score, LOCF Data Set, Efficacy Sample for Study CN138-001

	PANSS Negative Scale Total Score				Pairwise Comparisons P-values		
	Placebo	Aripiprazole	Aripiprazole	Aripiprazole	Ari10 vs	Ari15 vs	Ari20 vs
	N = 107	10 mg N = 103	15 mg N = 103	20 mg N = 97	Placebo	Placebo	Placebo
Baseline	23.16	23.83	23.54	23.59	0.424	0.647	0.611
Day 4	0.10	-0.67	-0.58	-1.26	0.098	0.141	0.004
Week 1	-0.31	-1.65	-1.42	-1.93	0.022	0.059	0.007
Week 2	0.03	-2.41	-1.65	-2.50	0.001	0.022	0.001
Week 3	0.13	-2.80	-1.74	-2.72	<0.001	0.018	<0.001
Week 4	-0.05	-2.94	-2.32	-2.76	0.001	0.008	0.002
Week 5	0.12	-3.31	-2.22	-3.22	<0.001	0.006	<0.001
Week 6	0.08	-3.52	-2.65	-3.33	<0.001	0.002	<0.001

Table 4.1.3.8 Mean Change from Baseline in the PANSS Negative Subscale Total Score, OC Data Set, Efficacy Sample for Study CN138-001

	PANSS Negative Scale Total Score				Pairwise Comparisons P-values		
	Placebo	Aripiprazole	Aripiprazole	Aripiprazole	Ari10 vs	Ari15 vs	Ari20 vs
	(N)	10 mg (N)	15 mg (N)	20 mg (N)	Placebo	Placebo	Placebo
Baseline	22.65 (107)	23.39 (103)	23.37 (103)	23.31 (97)	0.455	0.467	0.511
Day 4	0.12 (100)	-0.68 (97)	-0.64 (100)	-1.27 (94)	0.094	0.110	0.004
Week 1	-0.27 (100)	-1.67 (89)	-1.26 (95)	-1.89 (87)	0.022	0.101	0.009
Week 2	-0.50 (88)	-2.84 (86)	-1.60 (89)	-2.57 (81)	0.004	0.170	0.012
Week 3	-1.13 (82)	-3.58 (78)	-2.06 (82)	-3.53 (68)	0.006	0.287	0.010
Week 4	-3.99 (42)	-5.29 (51)	-4.91 (41)	-5.02 (49)	0.247	0.437	0.362
Week 5	-5.32 (31)	-6.09 (45)	-4.83 (37)	-6.53 (40)	0.486	0.663	0.278
Week 6	-5.21 (30)	-7.37 (42)	-7.28 (34)	-6.89 (39)	0.075	0.102	0.170

## Secondary Analyses

Additional secondary outcome measures were the PANSS Positive Sub-Scale Score, CGI Improvement Score Responder rates, CGI Severity Score, MADRS, and discontinuation rates. The results for the additional secondary outcome measures are shown in Table 4.1.3.9.

(Note: In the sponsor's original protocol, the secondary efficacy measures were only specified as the mean change from randomization to Week 6 (not all time points) in CGI Severity score, CGI global improvement score, PANSS-Positive Sub-Scale Total Score, PANSS-Negative Sub-Scale Total Score, and the percentage of responders. So this review only reports the results for the change from randomization to Week 6 for the above mentioned additional secondary outcome measures.)

As we can observe from the table, all the aripiprazole treatment groups showed significantly greater improvement compared to placebo in the change PANSS Positive Sub-Scale Score from randomization to Week 6 for the LOCF data set. The analysis of the mean change from baseline for the OC data indicates aripiprazole 10 mg had significantly greater improvement compared with the placebo group at Week 6, while aripiprazole 15 mg and 20 mg were not statistically significantly different from placebo at Week 6.

The analysis of the mean CGI Improvement Scores for the LOCF data set showed that all aripiprazole groups had significantly greater improvement compared with the placebo group at Week 6. However, none of the aripiprazole groups showed statistical significance in the analysis of the mean score for the OC data.

Response rates were analyzed by evaluating all responders, CGI (Improvement) responders, and PANSS responders. Responders are defined as patients who meet either of the following criteria:

- A rating of very much improved (1) or much improved (2) on the CGI Improvement Score, or
- At least a 30% decrease from baseline in the PANSS Total Score.

For the analysis of percentage of responders in the LOCF data, aripiprazole 10 mg and 20 mg showed significantly greater improvement compared with the placebo group at Weeks 6, while aripiprazole 15 mg was not. None of aripiprazole groups showed statistically significantly different from the placebo at Week 6 for the OC data.

For the analysis of the percentage of CGI (Improvement) responders, results analyzed on the LOCF data set showed that only Aripiprazole 20 mg group had significantly greater improvement compared with the placebo group at Week 6. No treatment groups were statistically significantly different from placebo for the OC data set.

For the analysis of the percentage of PANSS responders in the LOCF data, all aripiprazole groups showed significantly greater improvement compared with the placebo group at Weeks 6. In the analysis of the OC data set, none of treatment groups had statistically significant difference from the placebo.

For the analysis of mean change from baseline in the CGI severity of illness score, all aripiprazole groups showed statistically significantly different from the placebo at Week 6 in the LOCF data. However, none of aripiprazole groups did in the analyses for the OC data.

Since the administration of the MADRS was added to the study several months after study initiation per Amendment 2, a substantial number of patients were not administered the MADRS at either baseline or follow-up or both. The sponsor mentioned that although there was a trend toward significance for the aripiprazole 15-mg group in the LOCF data set at Week 6, no statistical conclusions may be drawn due to the small sample size.

One hundred forty-four patients discontinued the study due to lack of efficacy. This includes patients who discontinued from the trial due to lack of efficacy as well as patients who continued in the study on open-label treatment. Patients not responding at the end of Week 3, as evidenced by a CGI Improvement Score  $\geq 4$ , were discontinued from blinded therapy and given open-label aripiprazole. The sponsor mentioned that a lower percentage of patients discontinued due to lack of efficacy in all aripiprazole treatment groups compared with placebo. This lower rate of discontinuation was statistically significant for the aripiprazole 10-mg and aripiprazole 20-mg groups.

Table 4.1.3.9 The Summary of Results for the Secondary Analyses for Study CN138-001 For the LOCF Data Set:

Endpoints	N	Baseline	Change from Baseline to Endpoint (i.e., week 6)	Treatment Difference vs. Placebo	95% CI for Difference	P-Value
<i>PANSS Positive Sub-Scale Total Score</i>						
Aripiprazole 10 mg	103	24.53	-4.98	-3.88	(-5.69, -2.08)	<0.001
Aripiprazole 15 mg	103	24.38	-3.81	-2.71	(-4.52, -0.90)	0.003
Aripiprazole 20 mg	97	24.20	-4.51	-3.41	(-5.25, -1.56)	<0.001
Placebo	107	24.47	-1.10			

Endpoints	Mean at Week 6	P-Value (vs. Placebo)
<i>CGI Improvement Score</i>		
Aripiprazole 10 mg (N=103)	3.33	0.004
Aripiprazole 15 mg (N=103)	3.42	0.006
Aripiprazole 20 mg (N=97)	3.31	0.006
Placebo (N=107)	4.00	

Endpoints	Number (Percent) at Week 6	P-Value (vs. Placebo)
<i>Percentage of Responders</i>		
Aripiprazole 10 mg (N=103)	42 (41)	0.038
Aripiprazole 15 mg (N=103)	36 (35)	0.165
Aripiprazole 20 mg (N=97)	44 (45)	0.005
Placebo (N=107)	28 (26)	

Endpoints	Number (Percent) at Week 6	P-Value (vs. Placebo)
<i>Percentage of CGI Responders</i>		
Aripiprazole 10 mg (N=103)	35 (34)	0.134
Aripiprazole 15 mg (N=103)	32 (31)	0.219
Aripiprazole 20 mg (N=97)	41 (42)	0.005
Placebo (N=107)	25 (23)	

Endpoints	Number (Percent) at Week 6	P-Value (vs. Placebo)
<i>Percentage of PANSS Responders</i>		
Aripiprazole 10 mg (N=103)	31 (30)	0.002
Aripiprazole 15 mg (N=103)	26 (25)	0.028
Aripiprazole 20 mg (N=97)	25 (26)	0.025
Placebo (N=107)	14 (13)	

Endpoints	N	Baseline	Change from Baseline to Endpoint (i.e., week 6)	Treatment Difference vs. Placebo	95% CI for Difference	P-Value
<i>CGI Severity of Illness Score</i>						
Aripiprazole 10 mg	103	4.79	-0.65	-0.47	(-0.77, -0.18)	0.002
Aripiprazole 15 mg	103	4.79	-0.51	-0.33	(-0.63, -0.04)	0.028
Aripiprazole 20 mg	96	4.68	-0.64	-0.46	(-0.76, -0.16)	0.003
Placebo	107	4.64	-0.18			

*For the OC Data Set:*

Endpoints	Baseline & (N)	Change from Baseline to Endpoint & (N)	Treatment Difference vs. Placebo	95% CI for Difference	P-Value
<i>PANSS Positive Sub-Scale Score</i>					
Aripiprazole 10 mg	24.47 (103)	-10.22 (42)	-2.47	(-4.75, -0.19)	0.034
Aripiprazole 15 mg	24.54 (103)	-9.87 (34)	-2.13	(-4.52, 0.26)	0.081
Aripiprazole 20 mg	24.28 (97)	-8.51 (39)	-0.77	(-3.09, 1.55)	0.513
Placebo	24.34 (107)	-7.74 (30)			

Endpoints	Mean at Week 6 (N)	P-Value (vs. Placebo)
<i>CGI Improvement Score</i>		
Aripiprazole 10 mg	1.90 (42)	0.336
Aripiprazole 15 mg	1.85 (34)	0.247
Aripiprazole 20 mg	2.10 (39)	0.909
Placebo	2.13 (30)	

Endpoints	Number Responding/N at Week 6 (%)	P-Value (vs. Placebo)
<i>Percentage of Responders</i>		
Aripiprazole 10 mg	35/42 (83)	0.484
Aripiprazole 15 mg	29/34 (85)	0.381
Aripiprazole 20 mg	33/39 (85)	0.406
Placebo	23/30 (77)	

Endpoints	Number Responding/N at Week 6 (%)	P-Value (vs. Placebo)
<i>Percentage of CGI Responders</i>		
Aripiprazole 10 mg	32/42 (76)	0.560
Aripiprazole 15 mg	28/34 (82)	0.248
Aripiprazole 20 mg	32/39 (82)	0.243
Placebo		

Endpoints	Number Responding/N at Week 6 (%)	P-Value (vs. Placebo)
<i>Percentage of PANSS Responders</i>		
Aripiprazole 10 mg	25/42 (60)	0.178
Aripiprazole 15 mg	20/34 (59)	0.220
Aripiprazole 20 mg	20/39 (51)	0.515
Placebo	13/30 (43)	

Endpoints	Baseline & (N)	Change from Baseline to Endpoint & (N)	Treatment Difference vs. Placebo	95% CI for Difference	P-Value
<i>CGI Severity of Illness Score</i>					
Aripiprazole 10 mg	4.80 (103)	-1.60 (42)	-0.18	(-0.62, 0.27)	0.435
Aripiprazole 15 mg	4.83 (103)	-1.47 (34)	-0.05	(-0.52, 0.41)	0.820
Aripiprazole 20 mg	4.72 (96)	-1.40 (39)	0.02	(-0.43, 0.47)	0.924
Placebo	4.64 (107)	-1.42 (30)			

Endpoints	Number (Percent)	P-Value (vs. Placebo)
<i>Rate of Discontinuation</i>		
Aripiprazole 10 mg (N=103)	28 (27)	0.005
Aripiprazole 15 mg (N=103)	36 (35)	0.140
Aripiprazole 20 mg (N=97)	31 (32)	0.026
Placebo (N=107)	49 (46)	

### Subgroup Analysis

Subgroup analyses were performed by gender on the PANSS Total Score and is shown in Table 11 of the Appendix. The sponsor did not make any comment about the results of this analysis.

#### **4.1.3.5 The Sponsor's Overall Efficacy Conclusions**

All three fixed doses of aripiprazole were shown to be effective in the treatment of patients with schizophrenia in acute relapse based on the predefined primary and key secondary endpoints of the PANSS Total Score, PANSS-derived BPRS Core Score, and PANSS Negative Sub-Scale Score.

## 4.2 Phase II Studies

### 4.2.1 Study 31-93-202

#### 4.2.1.1 Disposition of Patients

A total of 103 patients were randomized into this study: 34 patients in the OPC-14597 group, 34 in the haloperidol group, and 35 patients in the placebo group. A total of 53 patients completed the study: 21 patients in the OPC-14597 group, 20 patients in the haloperidol group, and 12 patients in the placebo group.

#### 4.2.1.2 Demographics and Patient Characteristics

Baseline demographics were determined at the screening visit and included sex, age, weight and race. Of the 103 patients randomized, there were more males (n=91) than females (n=12). There was also a slightly higher number of Caucasians than Blacks, Hispanics or Other, with the majority of the patients being Caucasian (n=54) or Black (n=44). Distribution was generally equivalent across all treatment groups for race. Mean ages and weights by sex were also equivalent across treatment groups with the exception of mean weight for the female haloperidol group. Table 4.2.1.1 presents a summary of patient demographics across all treatment groups.

Table 4.2.1.1 Demographic Characteristics- All Randomized Patients for Study 31-93-202

		OPC-14597		Haloperidol		Placebo	
		Male	Female	Male	Female	Male	Female
Age (years)	N	32	2	30	4	29	6
	Mean	32.4	42.5	38.6	38.8	36.9	42.5
	Min	18	37	21	26	21	31
	Max	57	48	65	46	52	59
Weight (kg)	N	32	2	30	4	29	6
	Mean	84.1	67.4	81	86.6	82.1	65.8
	Min	52.2	57.7	59.5	55.8	50.8	50.4
	Max	158.9	77.2	129.8	116.7	118.5	97.6
Race	Caucasian	18	1	15	2	15	3
	Black	13	1	13	2	12	3
	Hispanic	0	0	1	0	1	0
	Other	1	0	1	0	1	0

#### 4.2.1.3 The Sponsor's Efficacy Results

##### Primary Efficacy Variables

The primary efficacy variables were 1) change from baseline to last visit in BPRS-total score and 2) a response indicator variable defined by a reduction of at least one point from baseline to last visit in CGI-severity score.

Table 4.2.1.2 shows the sponsor's analysis results for the mean change from baseline in BPRS-total score-for each treatment week with p-values for each treatment group and also Table 4.2.1.3 shows the treatment effects (subtracting placebo effect) of OPC-14597 and haloperidol at the last visit. As it was shown in the table, in the OPC-14597 group, improvement in BPRS-total score appeared prominently after Week 2, with a mean decrease of 8.5 points in total score from baseline to Week 3, which continued throughout the remaining treatment period, with a mean decrease of 10.3 points in total score at Week 4. The analyses of last visit results (LOCF), which included data from patients who discontinued the study, also showed an improvement in the BPRS-total score, with a mean decrease of 7.2 points in total score from baseline. In addition, as shown in the table, the superiority of OPC-14597 over placebo with regard to change from baseline to last visit for BPRS-total score was demonstrated with an estimated treatment difference of 6.25 points (p=0.0142). In addition, the superiority of OPC-14597 over placebo with regard to change from baseline to last visit for BPRS-total score was demonstrated with an estimated treatment difference of 6.25 points.

Table 4.2.1.2 BPRS-Total Score- Mean Change from Baseline and p-Values by Week- Observed Cases for Study 31-93-202

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Last Visit (LOCF)	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
OPC-14597	33	53.0	32	-1.6	28	-2.3	22	-8.5	21	-10.3	33	-7.2
Haloperidol	33	50.3	33	-6.5	30	-6.9	22	-7.4	20	-9.0	33	-8.1
Placebo	35	50.0	35	-3.1	28	-3.6	20	-5.1	14	-9.9	35	-2.1

2 Sided p-values for Pair-Wise Comparison						
OPC-14597 vs. Placebo	0.1732	0.2370	0.5160	0.1718	0.8863	0.0142
Haloperidol vs. Placebo	0.8939	0.0791	0.1607	0.1891	0.4687	0.0083

Table 4.2.1.3 Treatment Effect Based on the Last Visit Efficacy Analysis BPRS-Total Score for Study 31-93-202

	Estimated Treatment Effect	p-Value	Lower 95% Confidence Limit	Upper 95% Confidence Limit
OPC-14597 vs. Placebo	-6.25	0.0142	-11.21	-1.29
Haloperidol vs. Placebo	-6.41	0.0083	-11.21	-1.70

To evaluate responder rates based on CGI-severity score, as shown in Table 4.2.1.4, both OPC-14597 and haloperidol showed a statistically significant (p=0.035 and p=0.003, respectively) responder rates with 42.4% of the OPC-14597 patients responding to treatment and 54.5% of the haloperidol patients responding to treatment. The placebo patient group had 20% of the response rate.

Table 4.2.1.4 Responder Rates Based on at Least One Point Improvement from Baseline at Last Visit in CGI-Severity Score

Treatment Group	CGI-Severity Score			Treatment Comparison	p-Value
	n	No. of Responders	% of Responders		
OPC-14597	33	14	42.4	OPC-14597 vs. Placebo	0.035
Haloperidol	33	18	54.5	Haloperidol vs. Placebo	0.003
Placebo	35	7	20.0		

Secondary Efficacy Variables

PANSS-total score was based on the severity rating for positive and negative symptoms of schizophrenia and general psychopathology, with a lower score indicating less severe symptoms and a reduction in score over time indicating improvement. As shown in Table 4.2.1.5, improvement in PANSS-total score appeared prominently at Week 3, with a mean decrease of 14.0 points from baseline, and which continued further with a mean decrease of 16.4 points from baseline, and which continued further with a mean decrease of 16.4 points at Week 4. The LOCF analyses, which included data from patients who discontinued the study, also showed an improvement in PANSS-total score, with a mean decrease of 11.1 points from baseline. In addition, as shown in Table 4.2.1.6, the superiority of OPC-14597 over placebo with regard to change from baseline to last visit for PANSS-total score was demonstrated with an estimated treatment difference of 12.01 points (p=0.0080).

Table 4.2.1.5 PANSS-Total Score- Mean Change from Baseline and p-Values By Week - Observed Cases for Study 31-93-202

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Last Visit (LOCF)	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
OPC-14597	33	91.8	32	-3.1	29	-5.1	22	-14.0	22	-16.4	33	-11.1
Haloperidol	33	89.0	33	-10.8	30	-14.4	22	-14.0	20	-17.1	33	-15.8
Placebo	35	86.5	35	-1.9	27	-4.3	20	-7.0	13	-15.2	35	-1.1

2 Sided p-values for Pair-Wise Comparison

OPC-14597 vs. Placebo	0.1742	0.9157	0.9967	0.0879	0.6763	0.0080
Haloperidol vs. Placebo	0.4782	0.0137	0.0252	0.0499	0.2574	0.0004

Table 4.2.1.6 Treatment Effect Based on the Last Visit Efficacy Analysis-PANSS Total Score for Study 31-93-202

	Estimated Treatment Effect	p-Value	Lower 95% Confidence Limit	Upper 95% Confidence Limit
OPC-14597 vs. Placebo	-12.01	0.008	-20.79	-3.24
Haloperidol vs. Placebo	-15.62	0.0004	-24.02	-7.22

PANSS-negative sub-scale score was based on the severity rating for negative symptoms of schizophrenia included in the PANSS-total score, with a lower score indicating less severe symptoms and a reduction in score over time indicating improvement. As shown in Table 4.2.1.7, improvement in PANSS negative sub-scale score appeared prominently at Week 3 with a mean decrease of 4.4 points at the Week 4 visit for the OPC-14597 group. In the weekly analysis, OPC-14597 demonstrated a clear trend of improving the negative symptoms of the disease as measured by the PANSS-negative score. The mean change from baseline under the LOCF analysis was a decrease of 2.8 points. As shown in Table 4.2.1.8, OPC-14597 showed a trend towards superiority over placebo with regard to change from baseline to last visit for PANSS-negative sub-scale score with an estimated treatment effect of 2.71 points (p=0.0642).

Table 4.2.1.7 PANSS-Negative Sub-Scale Score-Mean Change from Baseline and p-Value by Week-Observed Cases for Study 31-93-202

Treatment Group	Baseline		Week 1		Week 2		Week 3		Week 4		Last Visit (LOCF)	
	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
OPC-14597	33	23.6	32	-1.3	29	-1.7	22	-4.3	22	-4.4	33	-2.8
Haloperidol	33	22.3	33	-2.0	30	-2.9	22	-3.0	20	-3.3	33	-3.4
Placebo	35	22.2	35	0.3	27	-0.9	20	-1.9	13	-5.2	35	-0.9

2 Sided p-values for Pair-Wise Comparison						
OPC-14597 vs. Placebo	0.3712	0.2675	0.7373	0.0949	0.7438	0.0642
OPC-14597 vs. Haloperidol	0.8519	0.0370	0.1262	0.2408	0.8343	0.0258

Table 4.2.1.8 Treatment Effect Based on the Last Visit Efficacy Analysis-PANSS Negative Sub-Scale Score for Study 31-93-202

	Estimated Treatment Effect	p-Value	Lower 95% Confidence Limit	Upper 95% Confidence Limit
OPC-14597 vs. Placebo	-2.71	0.0642	-5.58	0.16
Haloperidol vs. Placebo	-3.11	0.0258	-5.84	-0.39

#### 4.2.1.4 The Sponsor's Overall Efficacy Conclusions

- OPC-14597 showed statistically significant superiority over placebo in reducing the signs and symptoms of schizophrenia in all illness severity scores as measured by BPRS-total, BPRS-core, CGI-severity, CGI-improvement, and PANSS-total, with efficacy being seen prominently after 2 weeks of treatment and continuing throughout the remainder of the study. This may be attributed to dose escalation in the first two weeks to reach maximum dose.
- OPC-14597 was superior to placebo and comparable to haloperidol with regard to responder rates based on at least one point reduction in the CGI-severity score from baseline to last visit, a 30% reduction in BPRS-total score from baseline to last visit, or

a score of one or two in the CGI-improvement score at last visit in schizophrenic patients.

- Although not-statistically significant, OPC-14597 demonstrated a clear trend of improving negative symptoms of schizophrenia based on PANSS-negative score.
- Patients in the haloperidol group showed improvement in psychosis, confirming that the patient population of this study was responsive to active treatment.

#### 4.2.2 Study 31-94-202

##### 4.2.2.1 Disposition of Patients

A total of 176/307 (57.3%) patients completed the study: 37/59 (62.7%) patients in the OPC-2 mg group, 35/60 (58.3%) patients in the OPC-10mg group, 41/61 (67.2%) patients in the OPC-30 mg group, 34/63(54%) patients in the haloperidol group, and 29/64 (45.3%) patients in the placebo group. Patients in the OPC-14597 group, particularly patients in the OPC-30mg group, completed the study at a higher rate (58.3-67.2%) compared to patients in the haloperidol group (54%) and the placebo group (45.3%).

##### 4.2.2.2 Demographics and Patient Characteristics

Table 4.2.2.1 shows the patients' demographic characteristics. Treatment groups were generally comparable for demographic characteristics. Patients were primarily male (247/307, 80.5%) with about one fifth of the patients female (60/307, 19.5%). Mean age ranged from 37.2 to 40.1 years (range: 18-65 years) in males and from 38.8 to 43.2 years (range: 19-63) in females across treatment groups. About half of the patients were Caucasian (159/307, 51.8%) with the rest being black (115/307, 37.5%), Hispanic (24/307, 7.8%), Asian (3/307, 1.0%) and other (6/307, 2.0%). Mean weight ranged from 79.7 to 86.4 kg in males and 68.8-79.1 in females across treatment groups.

Table 4.2.2.1 Demographic Characteristics- All Randomized Patients for Study 31-94-202

Demographic Characteristics		OPC-14597 mg/day				Haloperidol mg/day		Placebo			
		2 mg		10 mg		30 mg		10 mg			
		M	F	M	F	M	F	M	F		
Age (years)	N	47	12	49	11	46	15	52	11	53	11
	Mean	40.1	38.8	37.2	40.6	38.8	38.9	38.0	43.2	37.5	40.5
	Min	22	19	18	23	18	24	19	25	19	28
	Max	65	51	64	56	61	57	60	63	57	55
Weight (kg)	N	47	12	49	11	46	15	52	11	53	10
	Mean	83.3	77.1	82.9	68.8	79.7	78.6	82.9	79.1	86.4	75.2
	Min	53.1	50.8	54	40.9	54.5	55.4	55.8	62.2	53.6	50.4
	Max	137.1	133.5	129.4	96.7	143	103.5	141.2	101.2	168.0	101.2
Race	Caucasian	22	11	20	6	19	11	28	9	28	5
	Black	19	1	19	5	23	3	19	2	20	4
	Hispanic	5	0	7	0	2	0	4	0	5	1
	Asian	0	0	1	0	1	1	0	0	0	0
	Other	1	0	2	0	1	0	1	0	0	1

### 4.2.2.3 The Sponsor's Efficacy Results

#### Primary Efficacy Variable (after excluding Center 003)

The principal investigator at Center 003, Richard L. Borison, M.D., had his employment terminated by the Augusta Veterans Affairs medical Center on June 7, 1996 due to allegations of research misconduct, so the analysis results for this study should be based on the data after excluding the center 003.

Table 4.2.2.2 shows the study results for the primary efficacy variables after excluding Center 003. As it was shown in the table, superiority of the OPC-30 mg group versus placebo ( $p < 0.05$ ) was demonstrated at last visit for the primary efficacy variable CGI-improvement after excluding Center 003. This treatment difference was also statistically significant after correction for multiple comparison by Dunnett's method at the two-tailed 0.05 level. The superiority of OPC-30mg over placebo with regard to change from baseline to last visit for BPRS-core score was not demonstrated after excluding Center 003. Significant differences were noted in the comparison of haloperidol versus placebo at last visit for BPRS-Core and trends towards significance for CGI-improvement ( $p = 0.0811$ ) after excluding Center 003.

Table 4.2.2.2 Treatment Effects (Last Visit Analysis) of Primary Efficacy Variables Excluding Center 003

Variable	Treatment Comparison	Estimated Treatment Effect	Value of t statistic	P-value	Lower 95% CL	Upper 95% CL
BPRS-core	OPC-14597: 2mg vs. Placebo	-0.31	-0.38	0.7034	-1.94	1.31
	OPC-14597: 10 mg vs. Placebo	-0.11	-0.13	0.8939	-1.75	1.53
	OPC-14597: 30 mg vs. Placebo	-1.29	-1.58	0.1165	-2.89	0.32
	Haloperidol: 10 mg vs. Placebo	-1.61	-1.97	0.0495	-3.22	-0
CGI-Improvement	OPC-14597: 2mg vs. Placebo	-0.15	-0.55	0.5860	-0.69	0.39
	OPC-14597: 10 mg vs. Placebo	-0.33	-1.21	0.2260	-0.87	0.21
	OPC-14597: 30 mg vs. Placebo	-0.75	-2.80	0.0055	-1.29	-0.22
	Haloperidol: 10 mg vs. Placebo	-0.47	-1.75	0.0811	-1.00	0.06

#### Secondary Efficacy Variables (after excluding Center 003)

Treatment effects for the secondary efficacy variables based on the last visit efficacy analysis excluding Center 003 are summarized in Table 4.2.2.3.

Superiority of the OPC-30mg group versus placebo ( $p < 0.05$ ) was demonstrated at last visit for secondary efficacy variables BPRS-total, and PANSS-total. A trend towards superiority of OPC-30 mg versus placebo was noted for PANSS-negative ( $p = 0.0817$ ). Trends toward significance were also noted in the comparison of haloperidol versus placebo for PANSS-total ( $p = 0.0733$ ) after excluding Center 003.

**Table 4.2.2.3 Treatment Effects (Last Visit Analysis) of Secondary Efficacy Variables Excluding Center 003**

Variable	Treatment Comparison	Estimated Treatment Effect	P-value	Lower 95% CL	Upper 95% CL
BPRS-total	OPC-14597: 2mg vs. Placebo	-3.09	0.1703	-7.52	1.34
	OPC-14597: 10 mg vs. Placebo	-3.12	0.1675	-7.56	1.32
	OPC-14597: 30 mg vs. Placebo	-6.32	0.0048	-10.69	-1.94
	Haloperidol: 10 mg vs. Placebo	-3.27	0.1415	-7.64	1.10
PANSS-total	OPC-14597: 2mg vs. Placebo	-4.89	0.1849	-12.13	2.35
	OPC-14597: 10 mg vs. Placebo	-5.52	0.1357	-12.78	1.74
	OPC-14597: 30 mg vs. Placebo	-10.66	0.0037	-17.82	-3.50
	Haloperidol: 10 mg vs. Placebo	-6.53	0.0733	-13.67	0.62
PANSS-negative	OPC-14597: 2mg vs. Placebo	-0.70	0.4947	-2.70	1.31
	OPC-14597: 10 mg vs. Placebo	-1.13	0.2680	-3.14	0.88
	OPC-14597: 30 mg vs. Placebo	-1.76	0.0817	-3.74	0.22
	Haloperidol: 10 mg vs. Placebo	-0.43	0.6663	-2.41	1.55

#### 4.2.2.4 The Sponsor's Overall Efficacy Conclusions

- In general, all three dose groups of OPC-14597 (2, 10 or 30 mg/day) were superior to placebo in the treatment of psychosis. Among the three OPC-14597 doses, 30 mg can be distinguished from the other two doses with respect to efficacy
- While no definitive conclusions can be drawn, the results with the 30 mg dose of OPC-14597 are suggestive of an early onset (Week 1) of treatment effect.
- Of all the treatment groups, only the OPC-14597 30 mg dose was found to show significant improvement in the negative symptoms of psychosis.
- OPC-14597 was found to be most effective at a dose of 30 mg/day, in a 4-week duration, for the treatment of schizophrenic patients.
- The patients of the haloperidol group showed improvement in psychosis, which confirmed that the patient population of this study was responsive to an active treatment

(Note: The sponsor did not mention but it is clearly that they made the above conclusions based on the whole data. Since the data from Center #3 were invalid, these conclusions were not accurate.)

### 4.3 Long-Term Studies : Studies 31-98-217 and 31-98-304-01

#### 4.3.1 Disposition of Patients

A total of 1452 patients signed the informed consent form; 158 of these patients filed screening and did not enter the placebo washout phase. The remaining 1294 patients underwent placebo washout and were randomized to receive double-blind treatment; 433 to the haloperidol group and 861 to the aripiprazole group. The completion rate was significantly higher for patients on aripiprazole (43%) compared with those on haloperidol (30%). This difference was primarily due to the lower rate of discontinuation for adverse events other than worsening schizophrenia. The disposition of all enrolled patients is

presented in Table 12 of the appendix. The time to discontinuation due to all reasons for the Randomized Sample is presented by treatment group in Figure 4 of the appendix.

#### 4.3.2 Data Sets

The distribution of patients within each of the patient samples is presented by treatment group for all randomized patients in Table 4.3.1.

Table 4.3.1 Number of Patients in Samples for Studies 31-98-217 and 31-98-304-01

Sample	Haloperidol	Aripiprazole	Total
Randomized	433	861	1294
Safety	431	859	1290
Efficacy	430	853	1283

Four of the 1294 randomized patients (two from the haloperidol group and two from the aripiprazole group) were excluded from the Safety Sample because they did not receive study medication according to the dosing record.

#### 4.3.3 Demography and Patient Characteristics

Demographic characteristics are presented by treatment group in Table 4.3.2 for patients in the Randomized Sample. According to the table, the treatment groups were comparable with respect to age, gender, race and weight.

Table 4.3.2 Demographic Characteristics for the Randomized Sample for Studies 31- 98-217 and 31-98-304-01

Variable		Haloperidol N = 433	Aripiprazole N = 861	Total N = 1294
Age (years)	Mean	36.8	37.3	37.1
	Median	36	36	36
	Min-Max	18 - 63	18 - 65	18 - 65
	S.E.	0.5	0.4	0.3
Gender N (%)	Men	247 (57)	511 (59)	758 (59)
	Women	186 (43)	350 (41)	536 (41)
Race N (%)	White	378 (87)	733 (85)	1111 (86)
	Black	41 (10)	99 (11)	140 (11)
	Hispanic	3 (1)	7 (1)	10 (1)
	Asian/Pacific Islander	2 (1)	4 (1)	6 (1)
	Other	9 (2)	18 (2)	27 (2)
Weight (kg)	Mean	73.1	74.5	74.0
	Median	71	72	72
	Min-Max	38 - 153	36 - 143	36 - 153
	S.E.	0.8	0.6	0.5
	Missing	0	3	3

#### 4.3.4 The Sponsor's Efficacy Results

Table 4.3.3 shows the summary results of the primary and supportive efficacy endpoints and Table 4.3.4 shows the summary results of the secondary efficacy endpoints.

Table 4.3.3 Summary of Primary and Supportive Endpoint Efficacy Results for the Randomized Sample for Studies 31-98-217 and 31-98-304-01

Variable	Haloperidol	Aripiprazole	P-value
Number Randomized Patients	433	861	
Number of Patients in Efficacy Sample	430	853	
Number (%) Responders	298 (69%)	610 (72%)	0.362
Time to Failure to Maintain Response in Responders	Relative Risk (95% CI)		
Treatment (Aripiprazole: Haloperidol)	0.881 (0.645 - 1.204)		0.427
Proportion of Patients Maintaining Response [% (S.D.)]			
Week 8	93% (1.5%)	92% (1.1%)	
Week 26	81% (2.6%)	84% (1.6%)	
Week 52	73% (3.1%)	77% (1.8%)	
Time to Failure in All Patients	Relative Risk (95% CI)		
Treatment (Aripiprazole: Haloperidol)	0.858 (0.721 - 1.021)		0.084
Proportion of Patients not yet Failed [% (S.D.)]			
Week 8	69% (2.3%)	71% (1.6%)	
Week 26	56% (2.6%)	60% (1.7%)	
Week 52	49% (2.7%)	54% (1.8%)	
Proportion of Patients On-treatment and Still in Response [N%]			
Week 8	192 (44%)	449 (52%)	0.005
Week 26	145 (33%)	380 (44%)	<0.001
Week 52	117 (27%)	343 (40%)	<0.001

Table 4.3.4 Summary of Rating Scale Secondary Efficacy Results for the Efficacy Sample by the LOCF for Studies 31-98-217 and 31-98-304-01

Variable	Haloperidol N=430	Aripiprazole N=853
<b>PANSS Total Score</b>		
Mean Baseline	94.7	95.1
Change at Week 8	-20.9	-21.8
95% CI for treatment effect		(-3.41, 1.85)
P-value		0.560
Change at Week 26	-20.7	-22.2
95% CI for treatment effect		(-4.27, 1.48)
P-value		0.341
<b>PANSS Negative Sub-Scale Score</b>		
Mean Baseline	24.7	24.7
Change at Week 8	-4.2	-4.7
95% CI for treatment effect		(-1.15, 0.14)
P-value		0.126
Change at Week 26	-4.4	-5.1
95% CI for treatment effect		(-1.52, -0.08)
P-value		0.029
<b>MADRS Total Score</b>		
Mean Baseline	12.8	12.5
Mean at Week 8	-2.6	-3.4
95% CI for treatment effect		(-1.74, -0.11)
P-value		0.027
Change at Week 26	-2.0	-2.9
95% CI for treatment effect		(-1.95, -0.15)
P-value		0.022

#### **4.3.4.1 Primary Efficacy Endpoint**

Time to failure to maintain response was analyzed only for the responders. Definitions of “response” and “failure to maintain response” can be found in Section 3.3.3. of this review. Worsening schizophrenia was defined by the modified COSTART dictionary terms “psychosis” and “schizophrenic reaction”.

Of the 853 patients in the Efficacy Sample that were randomized to aripiprazole, 610 (72%) met the criteria to be classified as responders. Of the 430 patients in the Efficacy Sample that were randomized to haloperidol, 298 (69%) were considered responders.

Out of these responders, the proportion of patients who did not experience failure by Weeks 8, 26, and 52 is summarized in Table 4.3.3. The relative risk for failure for the aripiprazole arm was 88% (95% CI: 65% - 120 %) of that for the haloperidol arm ( $p=0.4271$ ). It indicated that the risk of failing to maintain response in the aripiprazole group was 12% lower than that of haloperidol.

#### **4.3.4.2 Supportive and Efficacy Endpoints**

A numerically greater percentage of randomized patients in the aripiprazole group (54%) had not failed by Week 52 when compared with the haloperidol group (49%). In the analysis of time to failure for all randomized patients, the estimated relative risk (aripiprazole: haloperidol) was 0.858 (95% CI: 0.721, 1.021) indicating that the patients in the aripiprazole group had a 14% lower risk of failure compared to the haloperidol group. This result had a trend towards statistical significance ( $p=0.084$ ).

A significantly greater percentage of patients randomized to aripiprazole compared to patients randomized to haloperidol who remained on treatment and were in response. This was evaluated at three time points, Week 8 ( $p=0.005$ ), Week 26 ( $p<0.001$ ) and Week 52 ( $p<0.001$ ).

#### **4.3.4.3 Secondary Efficacy Endpoints**

Aripiprazole was statistically superior to haloperidol as determined by the time to discontinuation due to either lack of response to study drug or adverse event ( $p<0.0010$ ). The risk ratio for this event was 0.692 (95% CI: 0.573 – 0.837) indicating that the risk of discontinuation due to either lack of response to study drug or adverse event was 31% lower for the aripiprazole treated patients relative to the patients treated with haloperidol.

For other secondary time-to-event variables: time to first response (all randomized patients), time to discontinuation due to lack of response to study drug (all randomized patients), and time from first response to failure to maintain response (responders only), no statistically significant differences were observed between the two treatment groups.

Aripiprazole showed significant improvement over haloperidol in the treatment of negative and depressive symptoms. The improvement in treatment of negative symptoms

was demonstrated by significant differences in the comparison of mean change from baseline in the PANSS Negative Sub-Scale Score at Weeks 26 ( $p=0.029$ ) and 52 ( $p=0.011$ ) based on the LOCF data set. The improvement in treatment of depressive symptoms was demonstrated by statistical differences in the comparison of mean change from baseline in MADRS Total Score at Weeks 8 ( $p=0.027$ ), 26 ( $p=0.022$ ), and 52 ( $p=0.031$ ) (LOCF data set).

No significant differences were observed between treatments in mean change from Baseline in PANSS Total Score, PANSS Positive Sub-Scale Score, CGI Severity of Illness Score, or in mean CGI Improvement Score.

#### **4.3.5 The Sponsor's Efficacy Conclusions**

The results from analyses of the primary and supportive efficacy measures demonstrate that aripiprazole was able to provide long-term maintenance therapy to patients who were initially in acute relapse that was similar or superior to the long-term maintenance effects of haloperidol.

- The overall estimated risk ratio (0.881) for failure to maintain response in responders favored aripiprazole, however, this improvement was not statistically significant.
- In the analysis of time to failure in all patients, the estimated relative risk of 0.858 favored aripiprazole and exhibited a trend toward statistical significance ( $p=0.084$ ).
- Among all randomized patients, a significantly greater percentage of patients treated with aripiprazole demonstrated response at Weeks 8, 26 and 52.

### **5. Statistical Reviewer's Findings and Comments**

#### **5.1 Pivotal Phase III Studies: Studies 31-97-201, 31-97-202 and CN138-001**

1. Three primary efficacy endpoints were prospectively specified for Studies 31-97-201 and 31-97-202, but the sponsor did not clearly address either in the protocols or study reports what their decision rules were for these studies. It was indeed mentioned in the protocols and study reports that "The treatment comparisons will be tested by following the step-down procedure, i.e., first aripiprazole 30 mg vs. placebo will be tested at two-tailed 0.05 level; if rejected, aripiprazole 15 mg (or 20 mg for Study 31-97-202) vs. placebo will be tested at two-tailed 0.05 level."

Now that the sponsor wished to use  $\alpha=0.05$ , without any adjustment for testing the results for each primary endpoint of Studies 31-97-201 and 31-97-202, in order to protect the overall type I error rate of 0.05, it was judged by the statistical reviewer that winning on all three primary efficacy endpoints is necessary for claiming a positive study.

2. When the three pivotal phase III studies were evaluated, most of values can be reproduced by this reviewer. There was no inconsistent finding between the reviewer and the sponsor.

3. For Study 31-97-201, an internal audit revealed that data generated at Study Centers 007 and 001 could not be validated, so the sponsor performed the sensitivity analysis of the mean change from baseline for the PANSS Total Score by excluding the 19 patients randomized at these centers. They showed the results in the study report and concluded that they were consistent with those of the overall analysis. This reviewer checked their results and further performed the same kind of sensitivity analyses for the other two primary endpoints. The results did not show much difference to affect the conclusions on the overall analyses for either LOCF and OC data sets.
4. According to Tables 4.1.1.5 and 4.1.2.5, the sponsor had statistically significant results shown on all three primary efficacy endpoints for the LOCF data sets for Studies 31-97-201 and 31-97-202. However, this reviewer noticed that for Study 31-97-202 except the comparison between aripiprazole 20 mg and the placebo on the PANSS Positive Sub-Scale Score ( $p=0.045$ ), the sponsor had p-values greater than 0.05 for the OC data analyses. So, the dropout cohort analyses were studied to see if the results for the LOCF or OC data analyses were biased. Notice that dropout cohorts were formed by patients that had their last primary efficacy measurement in the same week interval.

Figures 5.1 to 5.3 showed us the PANSS total score over time for different dropout cohorts from the sponsor. This reviewer confirmed their results. The average changes of PANSS Total Scores from the baseline to each study week in which the patients dropped out the study right after were reported in Tables 5.1 below.

Table 5.1 Average Changes of PANSS Total Score for Dropout Cohort Analyses for Study 31-97-202

Group	Week 1 (n)	Week 2 (n)	Week 3 (n)	Week 4 (n)
Placebo	12.615 (26)	6.287 (21)	-4.1496 (4)	-18.2 (52)
Risperidone 6 mg	-0.873 (11)	-7.302 (16)	8.8141 (7)	-22.7 (61)
Aripiprazole 20 mg	5.265 (20)	-8.308 (9)	2.3 (8)	-23.4 (61)
Aripiprazole 30 mg	5.907 (16)	6.4 (7)	-2.24 (5)	-20.1 (68)

Carefully observing Table 5.1 and Figures 5.1, this reviewer noticed that the average change of PANSS Total Score for the placebo group patients at Week 1 was much bigger than the rest of treatment groups. It tells us that these patients had worse results. Moreover, most of dropout patients in the study were happening in the early two weeks. The placebo group had more dropout patients than the other treatment groups.

With almost 25% of patients dropping out after the first week' evaluation, the bad values carried from the dropout patients in the placebo group at Week 1 could make a difference at the LOCF analyses, especially, in the situation that the placebo patients had improvement as the study continued. On the other hand, with more poorly performed patients dropping out from the placebo group than the other treatment groups, the OC analyses may be biased against the treatment groups.

To investigate the influence of these 26 placebo group patients who dropped out before the second week of the study, this reviewer calculated the unadjusted mean of changes from baseline to Week 1 for the rest of placebo group patients. It was found to

be -7.13. Comparing this value with the OC results (see Table 5.3) after Week 1 (i.e., -9.0 at Week 2, -15.5 at Week 3 and -18.2 at Week 4), the fact that the patients in the placebo group also had improvement as the study continued was confirmed. Moreover, this value of mean change was much closer to the OC values for aripiprazole 20mg and 30mg groups at Week 1. Similarly, this reviewer also calculated the unadjusted mean of changes by Excluding the 47 patients who dropped out before Week 3. The calculated value -14.732 was also much closer to the OC values for aripiprazole 20mg and 30mg groups at Week 2. This tells us that these dropout patients did have worse responses than the average. Therefore, this reviewer suspected that the results from the LOCF analyses and OC analyses for the PANSS total score were both biased.

The other two primary endpoints: changes on the PANSS Positive Sub-Scales and changes on CGI Severity of Illness Score had similar problems. Table 5.4 and 5.5 show the unadjusted means of changes from baseline to each study week for the OC data Sets and Table 5.6 and 5.7 the average changes of scores for dropout cohort analyses.

Table 5.3 Unadjusted Mean Change from Baseline in PANSS Total Score for OC Data Set in Efficacy Sample for Study 31-97-202

Variable	Week	PANSS Total Score							
		Placebo		Risperidone 6 mg		Aripiprazole 20 mg		Aripiprazole 30 mg	
		N	Mean	N	Mean	N	Mean	N	Mean
Mean Baseline		103	95.0	95	93.6	98	94.0	96	92.3
Mean Change From Baseline	1	102	-2.2	95	-8.0	96	-8.8	95	-8.8
	2	77	-9.0	84	-14.1	77	-15.9	79	-13.5
	3	56	-15.5	68	-18.4	68	-18.9	73	-18.6
	4	52	-18.2	61	-22.7	61	-23.4	68	-20.1

Table 5.4 Unadjusted Mean Change from Baseline in PANSS Positive Sub-Scale Score for OC Data Set in Efficacy Sample for Study 31-97-202

Variable	Week	PANSS Positive Sub-Scale Score							
		Placebo		Risperidone 6 mg		Aripiprazole 20 mg		Aripiprazole 30 mg	
		N	Mean	N	Mean	N	Mean	N	Mean
Mean Baseline		103	24.5	95	23.9	98	24.8	96	24.0
Mean Change From Baseline	1	102	-0.843	95	-3.074	96	-2.656	95	-2.484
	2	77	-2.506	84	-4.917	77	-5.299	79	-3.797
	3	56	-4.661	68	-5.765	68	-6.338	73	-4.959
	4	52	-5.346	61	-7.148	61	-7.623	68	-5.662

Table 5.5 Unadjusted Mean Change from Baseline in CGI Severity of Illness Score for OC Data Set in Efficacy Sample for Study 31-97-202

Variable	Week	CGI Severity of Illness Score							
		Placebo		Risperidone 6 mg		Aripiprazole 20 mg		Aripiprazole 30 mg	
		N	Mean	N	Mean	N	Mean	N	Mean
Mean Baseline		103	4.8	95	4.8	98	4.8	96	4.7
Mean Change From Baseline	1	102	-0.157	95	-0.379	96	-0.281	95	-0.284
	2	77	-0.247	84	-0.702	77	-0.649	79	-0.570
	3	56	-0.589	68	-0.838	68	-0.812	73	-0.726
	4	52	-0.712	61	-1.082	61	-0.951	68	-0.853

Figure 5.1 PANSS Total Scores over Time for Different Dropout Cohorts: Placebo vs. Risperidone for Study 31-97-202

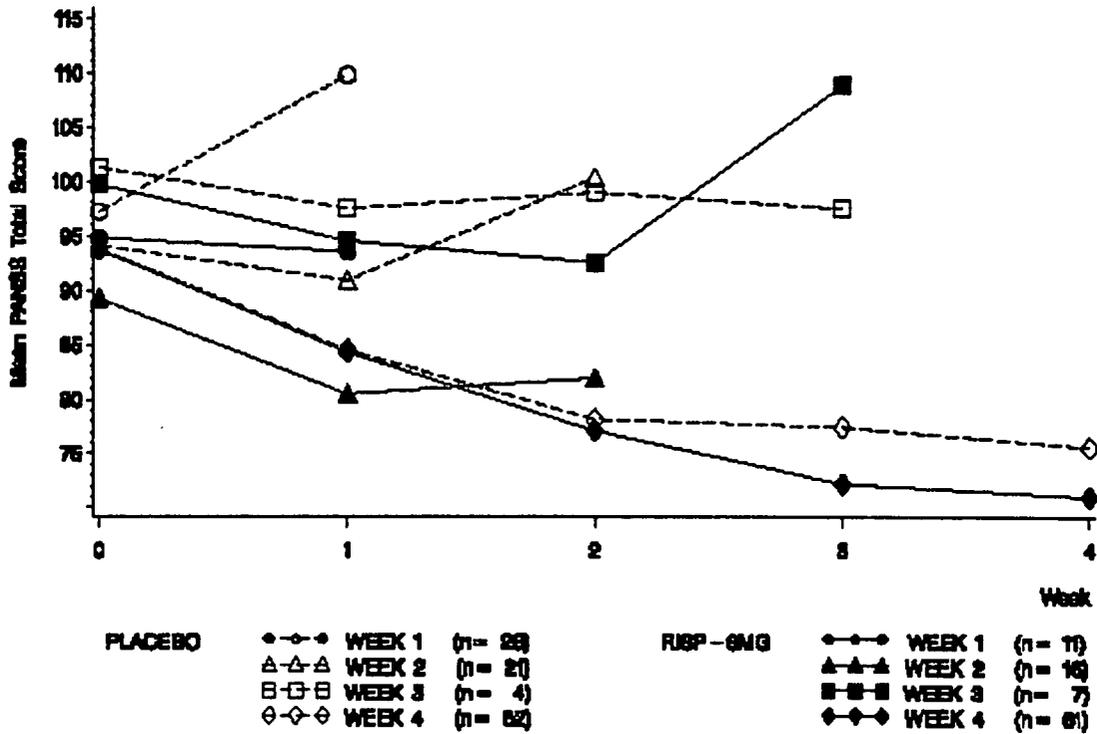


Figure 5.2 PANSS Total Scores over Time for Different Dropout Cohorts: Placebo vs. Aripiprazole 20 mg for Study 31-97-202

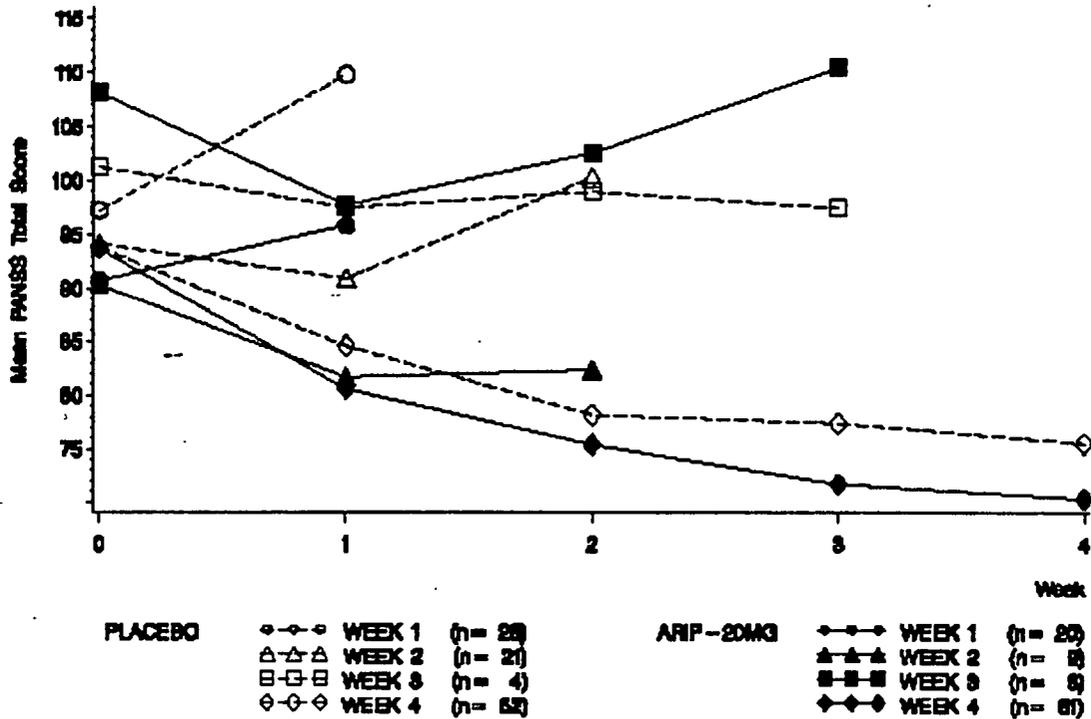


Figure 5.3 PANSS Total Scores over Time for Different Dropout Cohorts: Placebo vs. Aripiprazole 30 mg for Study 31-97-202

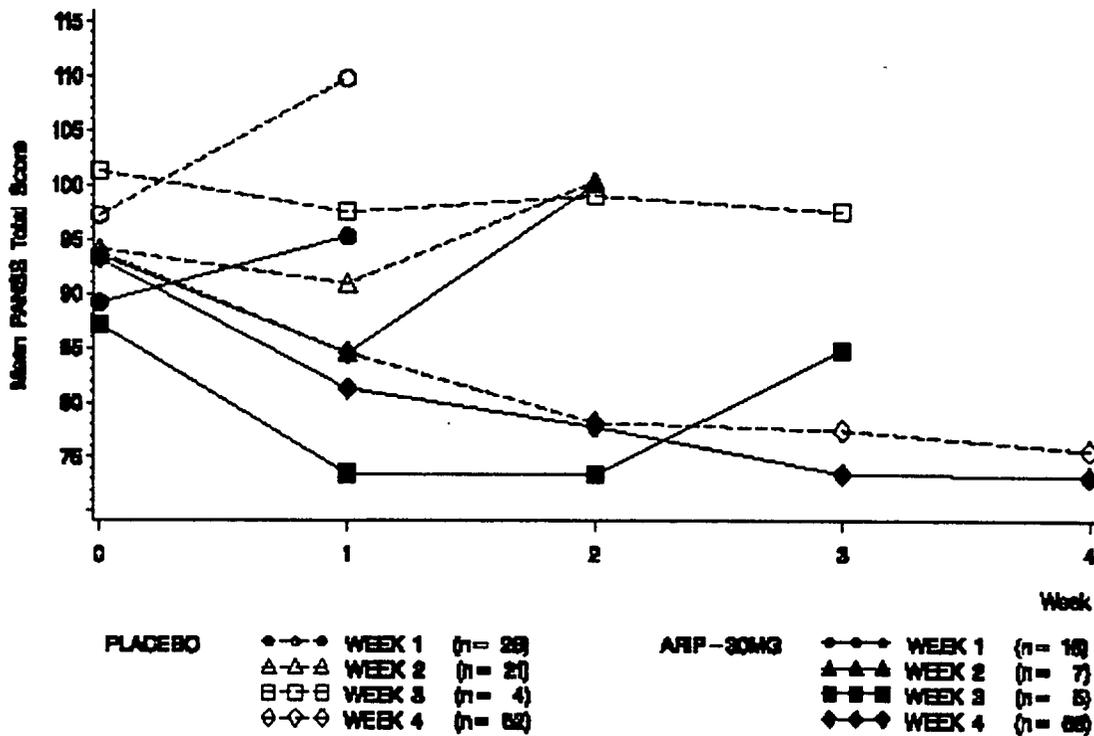


Table 5.6 Average Changes of PANSS Positive Score for Dropout Cohort Analyses for Study 31-97-202

Group	Week 1	Week 2	Week 3	Week 4
Placebo	2.846*	1.334	-0.502	-5.346
Risperidone 6 mg	0.452	-2.81	1.721	-7.148
Aripiprazole 20 mg	2	-5.448	-0.628	-7.623
Aripiprazole 30 mg	1.624	-0.148	1.0102	-5.662

\* The values of OC analyses after excluding the dropout patients at week 1 was -2.025 and the unadjusted average changes for the placebo group were -2.506, -4.661 and -5.346 at Weeks 2, 3 and 4.

Table 5.7 Mean Changes of CGI Severity of Illness Score for Dropout Cohort Analyses for Study 31-97-202

Group	Week 1	Week 2	Week 3	Week 4
Placebo	0.347*	0.284	0.249	-0.712
Risperidone 6 mg	-0.182	-0.439	0.0001	-1.082
Aripiprazole 20 mg	0.4	0.006	0.2513	-0.951
Aripiprazole 30 mg	0.315	0.143	-0.199	-0.853

\*The values of OC analyses after excluding the dropout patients at week 1 was -0.325 and the unadjusted average changes for the placebo group were -0.247, -0.589 and -0.7115 at Weeks 2, 3 and 4.

5. The first two pivotal phase III studies of aripiprazole, i.e., Studies 31-97-201 and 31-97-202 were designed in the treatment of psychosis. So, the sponsor recruited patients with either schizophrenia or schizoaffective disorder. The sponsor, however, only reported the analyses for all patients (both schizophrenia and schizoaffective diagnoses) and patients with schizophrenia alone in each study's report. They were later requested by us (the clinical reviewer and statistical reviewer) to provide the analyses on the three primary efficacy endpoints for the subgroup of patients with schizoaffective diagnosis. We are interested to know if the results shown for this subgroup have similar magnitude of the drug/placebo differences as the schizophrenic sample. Since the sample sizes for this subgroup were small in these studies, it is understood that the test results between the treatment groups and placebo may not be significant.

Table 5.8 and 5.9 show the LOCF data analysis results on the three primary efficacy endpoints for Studies 31-97-201 and 31-97-202, respectively by this reviewer (Note: results were the same as the sponsor's). Comparing the values of treatment effects in Table 5.8 with Table 4.1.1.8 and in Table 5.9 with Table 4.1.2.8. We noticed that for Study 31-97-201, except aripiprazole 30 mg on PANSS Total Scores, other treatment effects in schizoaffective patients were smaller than schizophrenic patients. However, for Study 31-97-202, except aripiprazole 30 mg on PANSS Positive Sub-Scale Score and on CGI Severity of Illness Score, other treatment effects in schizoaffective patients were bigger than patients with schizophrenia. The treatment effects between these two subgroups seemed not much different in both studies.

Although it is not the purpose, it was noticed that the aripiprazole 15 mg had better improvement results than aripiprazole 30 mg for Study 31-97-201. Similarly, the aripiprazole 20 mg had better improvement results than aripiprazole 30 mg for Study 31-97-202. Moreover, it is interesting to know that for Study 31-97-202 none of the comparisons between the aripiprazole groups and placebo showed a p-value less than 0.05 on any primary endpoint, nevertheless, all three comparisons between risperidone 6 mg and placebo were significant.

Table 13 in the Appendix shows the Observed Case analysis results on the three primary efficacy endpoints for the subgroup of patients with schizophrenia alone and schizoaffective disorder for both studies. It was noticed that for Study 31-97-202, the OC analysis results did not show separation between aripiprazole and placebo. As a matter of fact, patients in the placebo group even had more average of improvement than those in the aripiprazole groups. The sponsor's explanation was that this may be due to the very small sample sizes (only 9 patients in the placebo group), the very high placebo response in schizoaffective patients in this study and the high discontinuation rate for the placebo group (only 9 patients in the OC analysis compared to 25 in the LOCF).

Table 5.8 Efficacy Analysis Results for the LOCF Data Set for Patients with Schizoaffective for Study 31-97-201

	N	Change from Baseline to Endpoint (i.e., week 4)	Treatment Effect	P-value (vs. placebo)
<b>PANSS Total</b>				
Haloperidol 10 mg	40	-11.8106	-9.4656	0.1452
Aripiprazole 15 mg	27	-14.1604	-11.8154	0.0972
Aripiprazole 30 mg	29	-12.227	-9.882	0.1569
Placebo	28	-2.345		
<b>PANSS Positive Sub-Scale Score</b>				
Haloperidol 10 mg	40	-4.4990	-3.9198	0.0328
Aripiprazole 15 mg	27	-3.7573	-3.1781	0.1125
Aripiprazole 30 mg	29	-3.4067	-2.8275	0.1554
Placebo	29	-0.5792		
<b>CGI Severity of Illness Score</b>				
Haloperidol 10 mg	40	-0.4076	-0.2636	0.3132
Aripiprazole 15 mg	27	-0.6418	-0.4978	0.0837
Aripiprazole 30 mg	29	-0.4548	-0.3108	0.2709
Placebo	29	-0.1440		

Table 5.9 Efficacy Analysis Results for the LOCF Data Set for Patients with Schizoaffective for Study 31-97-202

	N	Change from Baseline to Endpoint (i.e., week 4)	Treatment Effect	P-value (vs. placebo)
<b>PANSS Total</b>				
Risperidone 6 mg	24	-17.34	-15.901	0.0195
Aripiprazole 20 mg	33	-11.27	-9.831	0.1144
Aripiprazole 30 mg	28	-10.74	-9.301	0.1523
Placebo	25	-1.439		
<b>PANSS Positive Sub-Scale Score</b>				
Risperidone 6 mg	24	-5.495	-4.6898	0.0175
Aripiprazole 20 mg	33	-4.303	-3.4978	0.0546
Aripiprazole 30 mg	28	-2.749	-1.9438	0.3001
Placebo	25	-0.8052		
<b>CGI Severity of Illness Score</b>				
Risperidone 6 mg	24	-0.7881	-0.7657	0.0094
Aripiprazole 20 mg	33	-0.3891	-0.3667	0.1762
Aripiprazole 30 mg	28	-0.3459	-0.3235	0.2479
Placebo	25	-0.0224		

6. The primary efficacy variable of Study CN138-001 was the mean change from baseline to Week 6 but it was noticed that in the study design, patients showing no improvement or a worsening of symptoms (i.e., Clinical Global Impression [CGI] Improvement  $\geq 4$ ) at the end of Week 3, were offered the option of open-label aripiprazole treatment during Weeks 4, 5 and 6. Due to large amount of patients who chose the open-label aripiprazole treatment during Weeks 4 to 6, the results of OC analysis showed insignificant after Week 4 although the results of LOCF analysis showed significant. Since the results of OC analyses were significant from Week 1 to Week 3 by the Hochberg's procedure, this reviewer thinks that the insignificant results of OC analyses should not be a concern.

7. In conclusion, all three pivotal studies were positive. However, as discussed in Comment #4, the biasness of LOCF and OC analysis results for Study 31-97-202 was a concern to this reviewer.

## **5.2 Phase II Studies: Studies 31-93-202 and 31-94-202**

1. Two primary efficacy variables were defined for Study 31-93-202. They were: (1) change from baseline in BPRS total score at last visit and (2) improvement by at least one point over baseline in CGI severity score at last visit. The analysis method specified in the protocol for variable (1) was the Wilcoxon rank-sum test, and for variable (2) was either Fisher exact test or chi-square test. However, the sponsor's statistical analysis method shown in their study reports for these two variables were ANCOVA and Cochran-Mantel-Haenszel test instead, respectively.

They were later requested to re-analyze the data by using the protocol-specified methods for the above two primary efficacy variables. The p-value for variable (1) became 0.17 by the Wilcoxon rank-sum test and p-values for variable (2) by Fisher exact test and chi-square test were 0.066 and 0.045, respectively.

Like pivotal phase III studies 31-97-201 and 31-97-202, they did not pre-specify any method for multiple efficacy endpoints, the significant results shown on both efficacy variables were deemed to be necessary for claiming a positive study. So, it was determined by this reviewer that Study 31-93-202 was a negative study.

2. Since the principal investigator at Center 003, Richard L. Borison, M.D. had his employment terminated by the Augusta Veterans Affairs Medical Center on June 7, 1996 due to allegations of research misconduct, the efficacy analyses for study 31-94-202 should be based on the data without Center 003. According to the data presented in 4.2.2.2 of this review, none of aripiprazole dosage groups showed significant results on the BPRS-Core score, one of two primary efficacy endpoints. Similar to Study 31-93-202, the sponsor did not pre-specify any method for multiple endpoints, so Study 31-94-202 was determined as a negative study.

## **5.3 Long-Term Studies : Studies 31-98-217 and 31-98-304-01**

This was a negative study according to the sponsor's test result of p-value, 0.427 on the primary efficacy endpoint: time to failure to maintain response. Although the sponsor had protocol-specified intention to pool data from both studies for efficacy and safety evaluations, we did not usually accept the results by the combined data analyses. Now that the results showed insignificant, there was no need to further discuss this issue.

#### 5.4 Additional Comment (For Subgroup Analysis)

The sponsor reported a table (Table 5.10) for model-based mean change of PANSS Total Score from baseline at endpoint by gender, age, race and baseline score in the LOCF data set of the combined studies. For three individual pivotal phase III studies, however, they only performed the subgroup analyses for gender on the PANSS Total Score among those four categories. This reviewer performed the subgroup analyses for gender on the PANSS Positive Sub-Scale Score and CGI Severity of Illness Score for Studies 31-97-201 and 31-97-202, and for age and race for all three primary endpoints for Studies 31-97-201 and 31-97-202 as well as for one primary endpoint for Study CN138-001.

The subgroup analyses for gender are shown in Tables 6, 6A, 8, 8A and 11 of the Appendix. The subgroup analyses for age are shown in the following Table 5.11 and Tables 14 and 15 of the Appendix. The subgroup analyses for race are shown in Tables 16-18 of the Appendix. Note that, the ANOVA model used for obtaining the means of change of scores included the baseline value as a covariate. The sponsor's protocols did not mention any subgroup analysis.

According to Table 5.10, the sponsor summarized in the Integrated Summary of Efficacy that "Efficacy was found to be similar for men and women. For the subset of age, because the number of patients  $\geq 65$  years was minimal (1%), data was insufficient for useful evaluation of efficacy in that population. In order to evaluate efficacy in older patients, a subset was evaluated at  $\geq 50$  years. Although aripiprazole patients  $\geq 50$  years did not show a difference relative to placebo due to a high placebo response, the actual PANSS scores at endpoint for aripiprazole patients who were 50 years or older was similar to those for patients  $< 50$  years old. For the subset of race, efficacy was found to be similar for whites and blacks. In this data set, Hispanic patients (N=42) had a high placebo response compared with other races." and "For baseline psychiatric status, patients who were more severely ill (PANSS Total Score  $> 91$ ) showed a greater improvement at endpoint compared with patients who were less ill (PANSS Total Score  $\leq 91$ ); however this result might be expected because more severely ill patients are able to show a greater change. The PANSS Total Score of 91 was the median value observed in the database."

Since the magnitude of mean change of PANSS Total Score at Endpoint for patients who were less than 50 year old in the placebo group was extremely small comparing to other treatment groups. This reviewer performed the subgroup analyses for age ( $< 50$  and  $\geq 50$ ) to observe any difference between these age groups for each pivotal study and showed the results in Table 5.11.

It was interesting to find that for each study the placebo group' magnitude of mean change of PANSS Total Score was greater than one of aripiprazole groups in older patients (age $\geq$ 50). For Study 31-97-201, the placebo group of older patients had bigger magnitude of mean change of PANSS Total Score than the aripiprazole 30mg group of older patients. For Study 31-97-202, the placebo group of older patients had bigger magnitude of mean change of PANSS Total Score than the aripiprazole 20 mg group of older patients. Also, for Study CN138-001, the placebo group of older patients had bigger magnitude of mean change of PANSS Total Score than the aripiprazole 15 mg group. Although there were not many patients greater or equal to 50 year old in the studies, this consistent finding seems to tell us that aripiprazole may not be an effective drug for the older patients suffering from schizophrenia.

Table 5.10 PANSS Total Score: Model-Based Mean Change from Baseline at Endpoint by Gender, Age, Race and Baseline Score; LOCF Data Set, Efficacy Sample; Short-Term, Placebo-Controlled Efficacy Studies (31-93-202, 31-94-202, 31-97-202 and CN 138-001)

Subgroup		PANSS Total Score at Endpoint							
		N	Placebo	N	Haloperidol	N	Risperidone	N	Aripiprazole
Gender	Men	301	-2.8	137	-13.4	67	-14.1	661	-12.6
	Women	103	-3.2	49	-14.1	28	-15.3	224	-13.9
Age (years)	< 50	351	-1.8	162	-14.2	87	-14.2	743	-13.3
	$\geq$ 50	53	-9.8	24	-9.4	8	-17.6	142	-10.8
Race	White	204	-2.0	115	-14.4	53	-15.0	492	-12.7
	Black	140	-2.4	51	-11.5	36	-15.8	260	-13.7
	Hispanic	42	-10.9	14	-14.1	4	-1.8	91	-9.0
	Asian	10	14.1	1	-14.0	1	11.4	21	-22.5
Baseline PANSS Total	Above Median (> 91)	196	-5.7	105	-18.1	49	-17.1	433	-17.9
	Below Median ( $\leq$ 91)	208	0.1	81	-9.4	46	-11.4	452	-8.0

Table 5.11 Model Based Mean Change of PANSS Total Score for Age Subgroups of Patients for Pivotal Studies

Study 31-97-201	Age $\geq$ 50			Age <50		
	n	Mean	SE	n	Mean	SE
Aripiprazole 15mg	12	-18.45	6.36	87	-13.91	2.52
Aripiprazole 30mg	14	-8.69	5.79	86	-10.87	2.53
Haloperidol 10mg	11	-15.65	6.53	88	-12.63	2.50
Placebo	11	-14.44	6.52	91	-0.42	2.46

Study 31-97-202	Age $\geq$ 50			Age <50		
	n	Mean	SE	n	Mean	SE
Aripiprazole 20mg	14	-10.11	4.15	84	-14.87	2.44
Aripiprazole 30mg	20	-14	3.42	76	-12.83	2.57
Risperidone 6mg	8	-17.09	5.44	87	-15.16	2.40
Placebo	13	-11.68	4.22	90	-3.54	2.36

CN138-001	Age $\geq$ 50			Age <50		
	n	Mean	SE	N	Mean	SE
Aripiprazole 10mg	22	-15.33	5.58	81	-14.14	2.56
Aripiprazole 15mg	17	-3.88	6.33	86	-12.92	2.49
Aripiprazole 20mg	19	-18.51	5.98	78	-13.08	2.61
Placebo	22	-14.30	5.57	85	2.17	2.50

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Concurrence:

Dr. Jin

Dr. Chi

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HFD-120/Dr. Katz  
HFD-120/Dr. Laughren  
HFD-120/Dr. Dubitsky  
HFD-120/Mr. Hardean  
HFD-700/Dr. Anello  
HFD-710/Dr. Chi  
HFD-710/Dr. Jin  
HFD-710/Dr. Chen

This review consists of 89 pages. MS Word: C:/yfchen/NDA21436/review.doc

## 6. Appendices

Table 1 Disposition of Patients, All Patients (Schizophrenia and Schizoaffective Disorder)

	<u>Number of Patients</u>				
<b>Enrolled</b>	<b>502</b>				
<b>Entered Placebo Washout</b>	<b>460</b>				
<b>Discontinued</b>	<b>46</b>				
Did not qualify for randomization	<b>18</b>				
Adverse event	<b>4</b>				
Lost to follow-up	<b>11</b>				
Patient withdrew consent	<b>13</b>				
	<u>Number (%) of Patients</u>				
	<u>Placebo</u>	<u>Haloperidol</u>		<u>Aripiprazole</u>	
		<u>10 mg</u>	<u>15 mg</u>	<u>30 mg</u>	<u>Total</u>
<b>Randomized Sample</b>	<b>106</b>	<b>104</b>	<b>102</b>	<b>102</b>	<b>414</b>
<b>Completed Study</b>	<b>58 (55)</b>	<b>62 (60)</b>	<b>68 (67)</b>	<b>60 (59)</b>	<b>248 (60)</b>
<b>Discontinued</b>	<b>48 (45)</b>	<b>42 (40)</b>	<b>34 (33)</b>	<b>42 (41)</b>	<b>166 (40)</b>
Adverse event	<b>17 (16)</b>	<b>11 (11)</b>	<b>9 (9)</b>	<b>8 (8)</b>	<b>45 (11)</b>
Lost to follow-up	<b>1 (1)</b>	<b>0</b>	<b>0</b>	<b>1 (1)</b>	<b>2 (&lt;1)</b>
Patient withdrew consent (personal reasons)	<b>12 (11)</b>	<b>20 (19)</b>	<b>15 (15)</b>	<b>10 (10)</b>	<b>57 (14)</b>
Patient met withdrawal criteria <sup>a</sup>	<b>1 (1)</b>	<b>0</b>	<b>1 (1)</b>	<b>1 (1)</b>	<b>3 (1)</b>
Noncompliance	<b>1 (1)</b>	<b>1 (1)</b>	<b>0</b>	<b>1 (1)</b>	<b>3 (1)</b>
Insufficient clinical response	<b>15 (14)</b>	<b>6 (6)</b>	<b>5 (5)</b>	<b>15 (15)</b>	<b>41 (10)</b>
Patient withdrew consent (lack of effect)	<b>1 (1)</b>	<b>4 (4)</b>	<b>4 (4)</b>	<b>6 (6)</b>	<b>15 (4)</b>

<sup>a</sup> Patient 97201-1-3 in the placebo group was withdrawn for administrative reasons. Patient 97201-1-2 in the aripiprazole 15-mg group and Patient 97201-1-1 in the aripiprazole 30-mg group were withdrawn because the study site was closed.

Figure 1: Time to Discontinuation Due to All Reasons, Randomized Sample for Study 31-97-201

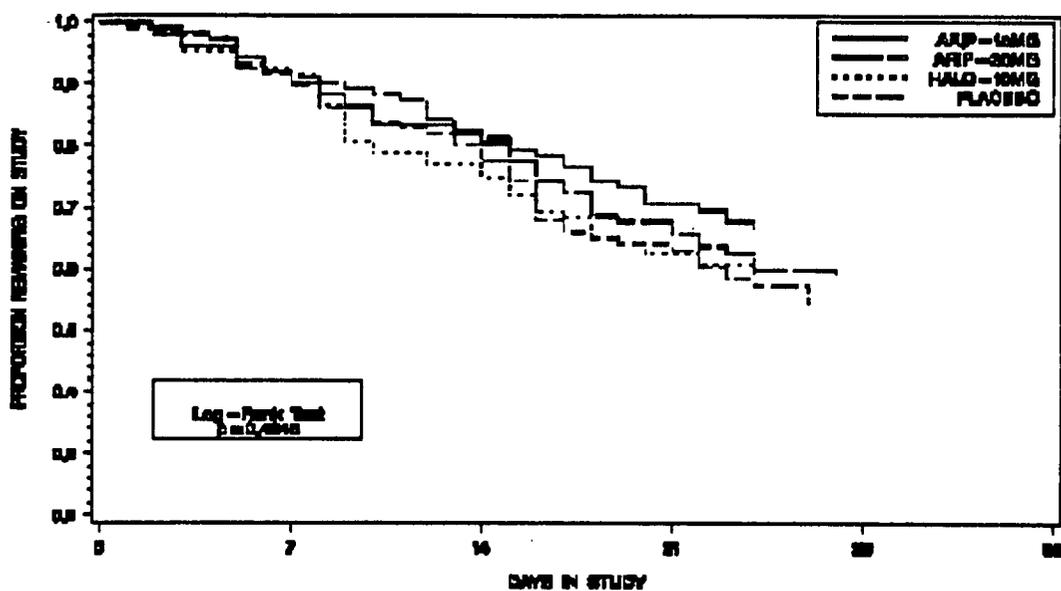


Table 2 Disposition of Patients with Schizophrenia

	Number (%) of Patients					
	Placebo	Haloperidol		Aripiprazole		Total
		10 mg	15 mg	30 mg		
Randomized Sample	75	61	74	72	282	
Completed Study	44 (59)	41 (67)	53 (72)	42 (58)	180 (64)	
Discontinued	31 (41)	20 (33)	21 (28)	30 (42)	102 (36)	
Adverse event	11 (15)	6 (10)	5 (7)	6 (8)	28 (10)	
Lost to follow-up	1 (1)	0	0	1 (1)	2 (1)	
Patient withdrew consent (personal reasons)	6 (8)	9 (15)	10 (14)	9 (13)	34 (12)	
Patient met withdrawal criteria <sup>a</sup>	0	0	1 (1)	0	1 (<1)	
Noncompliance	1 (1)	0	0	0	1 (<1)	
Insufficient clinical response	11 (15)	2 (3)	2 (3)	9 (13)	24 (9)	
Patient withdrew consent (lack of effect)	1 (1)	3 (5)	3 (4)	5 (7)	12 (4)	

<sup>a</sup> Patient 97201-1-2 in the aripiprazole 15-mg group was withdrawn because the study site was closed.

Table 3 Disposition of Patients: All Patients (Schizophrenia and Schizoaffective Disorder)

	Number of Patients				
<b>Enrolled</b>	487				
<b>Entered Placebo washout</b>	448				
<b>Discontinued</b>	44				
Did not qualify for randomization	21				
Patient withdrew consent	12				
Reasons for withdrawal not noted	11				
	Number (%) of Patients				
	Placebo	Risperidone 6 mg	Aripiprazole		Total
			20 mg	30 mg	
<b>Randomized Sample</b>	103	99	101	101	404
<b>Completed Study</b>	52 (50)	62 (63)	61 (60)	67 (66)	242 (60)
<b>Discontinued</b>	51 (50)	37 (37)	40 (40)	34 (34)	162 (40)
Adverse event	17 (17)	8 (8)	11 (11)	8 (8)	44 (11)
Lost to follow-up	0	2 (2)	0	2 (2)	4 (1)
Patient withdrew consent (personal reasons)	11 (11)	12 (12)	18 (18)	9 (9)	50 (12)
Patient met withdrawal criteria <sup>a</sup>	0	0	0	1 (1)	1 (< 1)
Noncompliance	0	1 (1)	1 (1)	2 (2)	4 (1)
Protocol Violation	1 (1)	1 (1)	0	0	2 (< 1)
Insufficient clinical response	17 (17)	8 (8)	9 (9)	8 (8)	42 (10)
Patient withdrew consent (lack of effect)	5 (5)	5 (5)	1 (1)	4 (4)	15 (4)

<sup>a</sup> Patient 97-202-71-22 in the aripiprazole 30-mg group did not receive study medication according to the dosing record.

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Figure 2 Time to Discontinuation Due to All Reasons, Randomized Sample for Study 31-97-202

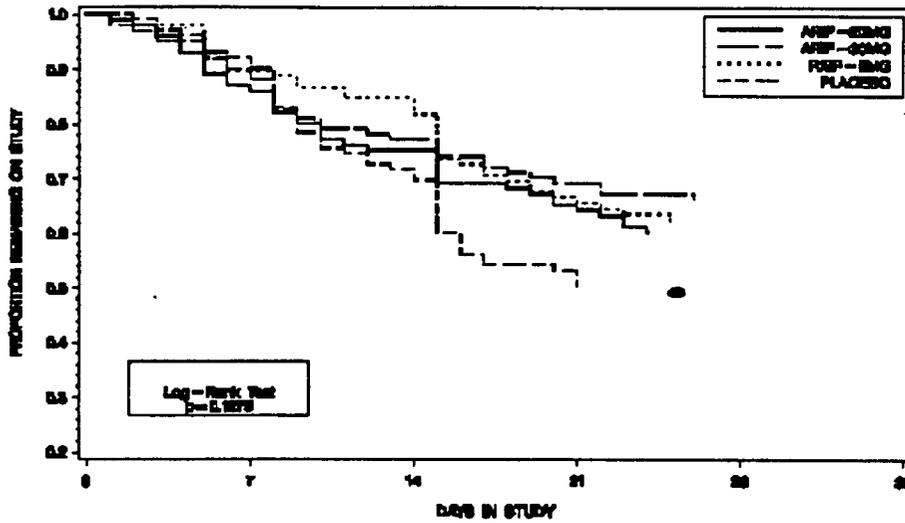


Table 4 Disposition of Patients with Schizophrenia

	Number (%) of Patients				
	Placebo	Risperidone		Aripiprazole	
		6 mg	20 mg	30 mg	Total
<b>Randomized Sample</b>	78	74	66	71	289
<b>Completed Study</b>	43 (55)	47 (64)	42 (64)	51 (72)	183 (63)
<b>Discontinued</b>	35 (45)	27 (36)	24 (36)	20 (28)	106 (37)
Adverse event	10 (13)	5 (7)	6 (9)	5 (7)	26 (9)
Lost to follow-up	0	2 (3)	0	1 (1)	3 (1)
Patient withdrew consent (personal reasons)	9 (12)	9 (12)	13 (20)	5 (7)	36 (12)
Noncompliance	0	1 (1)	0	2 (3)	3 (1)
Protocol Violation	1 (1)	0	0	0	1 (<1)
Insufficient clinical response	11 (14)	6 (8)	5 (8)	5 (7)	27 (9)
Patient withdrew consent (lack of effect)	4 (5)	4 (5)	0	2 (3)	10 (3)

Table 5 The Summary of Model-Based Mean Change from Baseline in PANSS Total Score by Study Center, LOCF Data Set, Efficacy Sample for Study 31-97-201

Center	Visit	PANSS Total Score							
		Placebo		Haloperidol 10 mg		Aripiprazole 15 mg		Aripiprazole 30mg	
		N	Mean	N	Mean	N	Mean	N	Mean
Overall	Baseline	102	100.9	99	99.9	99	98.8	100	99.6
	Endpoint	102	-2.9	99	-13.8	99	-15.5	100	-11.4
023	Endpoint	7	0.6	7	-13.7	7	-19.1	7	-4.0
039	Endpoint	7	-3.1	7	-11.6	6	-16.5	7	-8.8
043	Endpoint	7	2.5	7	-4.8	7	-7.9	7	-5.7
027	Endpoint	6	-4.1	5	-8.8	6	-4.9	6	-0.7
030	Endpoint	6	0.5	6	-8.0	6	-23.6	6	-14.7
036	Endpoint	6	9.9	6	-9.8	6	3.8	6	-10.1
025	Endpoint	5	-17.8	5	-6.0	5	-32.7	5	-18.8
031	Endpoint	4	5.8	3	-3.4	4	-26.2	3	-18.1
007	Endpoint	4	-6.4	4	-7.8	3	-10.4	4	-2.0
028	Endpoint	4	2.9	4	-3.5	4	-7.5	4	-7.1
020	Endpoint	4	-6.6	4	-16.1	3	-28.5	3	8.5
038	Endpoint	3	22.1	3	-15.8	3	-8.1	3	4.8
026	Endpoint	3	0.1	3	-16.9	3	-29.9	3	-11.0
029	Endpoint	3	40.6	3	-18.5	3	5.7	3	-37.0

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Table 6 Mean Change from Baseline in PANSS Total Score by Gender, LOCF Data Set, Efficacy Sample for Study 31-97-201

Variable	PANSS Total Score							
	Placebo		Haloperidol 10 mg		Aripiprazole 15mg		Aripiprazole 30mg	
	Men N=71	Women N=31	Men N=65	Women N=34	Men N=73	Women N=26	Men N=69	Women N=31
Mean Baseline	100.5	99.4	99.1	100.5	96.1	103.0	98.5	98.7
Endpoint (Week4)	-1.2	-3.7	-12.2	-14.1	-13.5	-17.3	-12.9	-5.4

Table 6A Mean Change from Baseline in PANSS Positive Sub-Scale Score and CGI Severity of Illness Scores by Gender, LOCF Data Set, Efficacy Sample for Study 31-97-201

Variable	PANSS Positive Sub-Scale Score							
	Placebo		Haloperidol 10 mg		Aripiprazole 15mg		Aripiprazole 30mg	
	Men N=71	Women N=31	Men N=65	Women N=34	Men N=73	Women N=26	Men N=69	Women N=31
Mean Baseline	25.27	23.97	24.72	25.94	24.40	25.15	24.36	24.42
Endpoint (Week4)	-0.16	-0.60	-4.01	-4.50	-3.62	-5.04	-4.35	-1.77

Variable	CGI Severity of Illness Score							
	Placebo		Haloperidol 10 mg		Aripiprazole 15mg		Aripiprazole 30mg	
	Men N=71	Women N=31	Men N=65	Women N=34	Men N=73	Women N=26	Men N=69	Women N=31
Mean Baseline	4.94	4.94	4.88	4.79	4.90	4.92	4.84	4.74
Endpoint (Week4)	-0.01	-0.17	-0.47	-0.47	-0.64	-0.61	-0.50	-0.12

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Table 7 The Summary of Model-Based Mean Change from Baseline in PANSS Total Score by Study Center, LOCF Data Set, Efficacy Sample for Study 31-97-202

Center	Visit	PANSS Total Score							
		Placebo		Risperidone 6 mg		Aripiprazole 15 mg		Aripiprazole 30mg	
		N	Mean	N	Mean	N	Mean	N	Mean
Overall	Baseline	103	94.1	95	92.6	98	93.5	96	91.6
	Endpoint	103	-5.0	95	-15.7	98	-14.5	96	-13.9
050	Endpoint	7	-1.1	7	-6.6	7	-19.1	7	-6.3
051	Endpoint	3	-6.8	3	-16.3	3	-18.9	3	-15.3
053	Endpoint	3	-3.7	3	-3.2	3	-29.8	3	0.7
059	Endpoint	7	-26.0	5	-1.3	6	-15.9	5	-18.6
067	Endpoint	6	-0.0	5	-14.6	6	-7.3	6	3.0
069	Endpoint	6	-18.4	5	-7.9	6	-16.4	6	-9.9
071	Endpoint	6	11.5	6	-1.9	6	-3.8	5	-8.7
081	Endpoint	4	5.4	5	-25.8	5	-30.6	4	-25.8
084	Endpoint	7	-12.6	7	-20.8	7	-16.1	7	-23.2
093	Endpoint	5	5.0	5	-37.1	5	-15.1	5	-23.9

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Table 8 Mean Change from Baseline in PANSS Total Score by Gender, LOCF Data Set, Efficacy Sample for Study 31-97-202

Variable	PANSS Total Score							
	Placebo		Risperidone 6mg		Aripiprazole 20mg		Aripiprazole 30mg	
	Men N=73	Women N=30	Men N=67	Women N=28	Men N=71	Women N=27	Men N=63	Women N=31
Mean Baseline	95.5	93.9	94.5	91.3	91.2	101.3	91.9	93.1
Endpoint (Week 4)	-4.6	-5.1	-14.4	-18.6	-13.8	-12.8	-9.8	-20.1

Table 8A Mean Change from Baseline in PANSS Positive Sub-Scale Score and CGI Severity of Illness Scores by Gender, LOCF Data Set, Efficacy Sample for Study 31-97-202

Variable	PANSS Positive Sub-Scale Score							
	Placebo		Risperidone 10 mg		Aripiprazole 15mg		Aripiprazole 30mg	
	Men N=73	Women N=30	Men N=67	Women N=28	Men N=71	Women N=27	Men N=63	Women N=33
Mean Baseline	25.07	23.23	24.22	23.25	24.72	25	24.16	23.64
Endpoint (Week4)	-1.40	-2.45	-4.8	-5.79	-5.02	-4.0	-2.54	-6.10

Variable	CGI Severity of Illness Score							
	Placebo		Risperidone 10 mg		Aripiprazole 15mg		Aripiprazole 30mg	
	Men N=73	Women N=30	Men N=67	Women N=28	Men N=71	Women N=27	Men N=63	Women N=33
Mean Baseline	4.86	4.67	4.96	4.57	4.73	4.96	4.78	4.67
Endpoint (Week4)	-0.18	-0.25	-0.73	-0.77	-0.49	-0.49	-0.43	-0.84

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Table 9 Disposition of Patients in Study CN138-001

Patient Status	Number of Patients (%)				Total
	Placebo	Aripiprazole 10 mg	Aripiprazole 15 mg	Aripiprazole 20 mg	
Enrolled Sample	n/a	n/a	n/a	n/a	508
Baseline failures	n/a	n/a	n/a	n/a	88
<b>Randomized</b>	<b>108</b>	<b>106</b>	<b>106</b>	<b>100</b>	<b>420</b>
<b>Discontinued from double-blind treatment<sup>a</sup></b>	<b>78 (72)</b>	<b>63 (59)</b>	<b>74 (70)</b>	<b>63 (63)</b>	<b>278 (66)</b>
Due to lack of response entered open-label treatment	44 (41)	28 (26)	37 (35)	22 (22)	131 (31)
Adverse event	6 (6)	11 (10)	3 (3)	5 (5)	25 (6)
Lack of efficacy	11 (10)	5 (5)	8 (8)	11 (11)	35 (8)
Patient withdrew consent	13 (12)	18 (17)	24 (23)	18 (18)	73 (17)
Patient unreliability	0	1 (1)	1 (1)	1 (1)	3 (1)
Lost to follow-up	0	0	0	4 (4)	4 (1)
Pregnancy	0	0	0	0	0
Death	0	0	0	0	0
Other known cause	4 (4)	0	1 (1)	2 (2)	7 (2)
<b>Completed double-blind treatment</b>	<b>30 (28)</b>	<b>43 (41)</b>	<b>32 (30)</b>	<b>37 (37)</b>	<b>142 (34)</b>

<sup>a</sup> Patients not responding at the end of Week 3, as indicated by CGI Improvement Score of 4 to 7, were placed on open-label treatment.

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Table 10 Disposition of Patients Who Entered Open-label Treatment for Study CN138001

Patient Status	Number of Patients (%)				Total
	Original Randomized Treatment Group				
	Placebo	Aripiprazole 10 mg	Aripiprazole 15 mg	Aripiprazole 20 mg	
Entered open-label treatment from Week 3 to Week 5	44	28	37	22	131
Discontinued from open-label treatment	22 (50)	10 (36)	18 (49)	9 (41)	59 (45)
Adverse event	5 (11)	2 (7)	4 (11)	1 (5)	12 (9)
Lack of efficacy	13 (30)	8 (29)	10 (27)	6 (27)	37 (28)
Patient withdrew consent	4 (9)	0	3 (8)	2 (9)	9 (7)
Patient unreliability	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Pregnancy	0	0	0	0	0
Death	0	0	0	0	0
Other known cause	0	0	1 (3)	0	1 (1)
Completed open-label treatment	22 (50)	18 (64)	19 (51)	13 (59)	72 (55)

Figure 3: Time to Discontinuation for Any Reason, Randomized Sample for Study CN 138-001

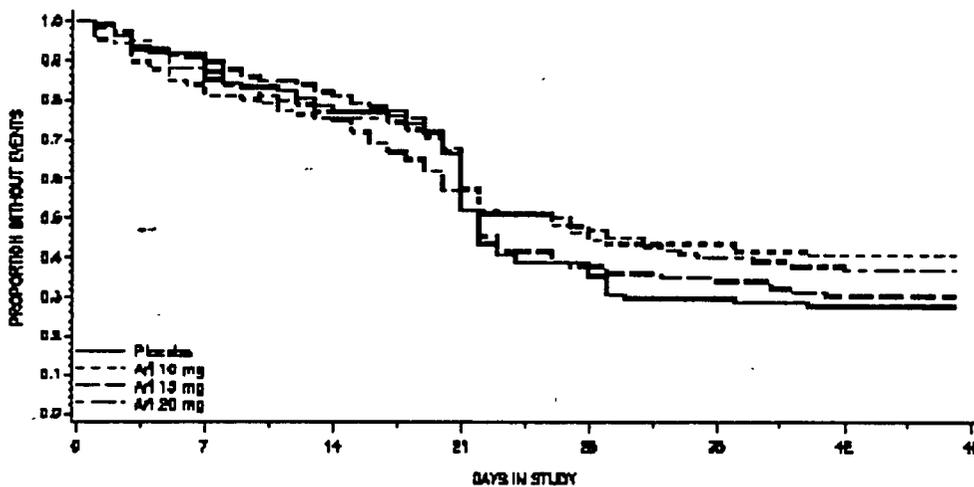


Table 11 Model Based Mean Change from Baseline in PANSS Total Score for Gender in the LOCF Data Set for Study CN138-001

Male	PANSS Total Score			
	Placebo	Aripiprazole 10 mg	Aripiprazole 15 mg	Aripiprazole 20 mg
Phase Variable	N=82	N=80	N=76	N=79
Mean Baseline	92.02	93.44	92.79	97.31
Day 4	-2.28	-4.13	-3.66	-4.74
Week 1	-3.02	-7.51	-7.14	-6.76
Week 2	-1.87	-10.18	-6.66	-9.66
Week 3	-1.40	-12.03	-7.43	-11.89
Week 4	-1.03	-12.82	-9.41	-12.13
Week 5	-0.44	-13.57	-10.26	-13.03
Week 6	-1.05	-14.87	-11.72	-14.31

Female	PANSS Total Score			
	Placebo	Aripiprazole 10 mg	Aripiprazole 15 mg	Aripiprazole 20 mg
Phase Variable	N=25	N=23	N=27	N=18
Mean Baseline	93.64	90.39	94.63	103.89
Day 4	-3.83	-0.99	-7.13	-6.82
Week 1	-0.50	-5.29	-2.76	-11.23
Week 2	-1.03	-9.38	-7.33	-12.26
Week 3	-2.01	-9.38	-9.23	-10.82
Week 4	-1.85	-8.77	-10.51	-10.35
Week 5	-1.55	-10.39	-10.09	-12.89
Week 6	-1.86	-10.99	-10.82	-15.25

Note: The baseline score was used as a covariate in the ANCOVA model.

Figure 4 Time to Discontinuation due to All Reasons in the Randomized Sample for Studies 31-98-217 and 31-98-304-01

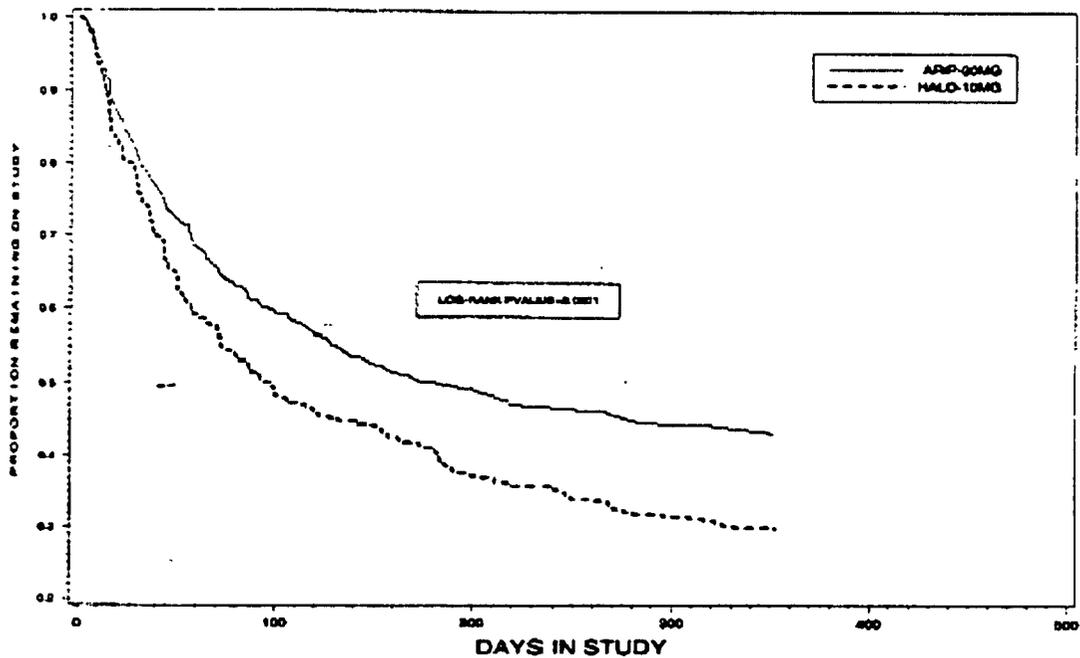


Table 12 Disposition of Patients for Studies 31-98-217 and 31-98-304-01

Patient Status	Number (%) of Patients		
	Haloperidol	Aripiprazole	Total
Enrolled Sample	n/a	n/a	1452
Screening Failures	n/a	n/a	158
Entered Placebo Washout	n/a	n/a	1294
<b>Randomized Sample</b>	<b>433</b>	<b>861</b>	<b>1294</b>
<b>Discontinued From Double-Blind Treatment</b>	<b>305 (70)</b>	<b>494 (57)</b>	<b>799 (62)</b>
Lost to follow-up	10 (2)	24 (3)	34 (3)
Patient withdrew consent (personal reasons)	97 (22)	159 (19)	256 (20)
Insufficient clinical response	38 (9)	63 (7)	101 (8)
Adverse event other than worsening schizophrenia	80 (19)	70 (8)	150 (12)
Adverse event of worsening schizophrenia	58 (13)	143 (17)	201 (16)
Study participation terminated by sponsor	1 (< 1)	2 (< 1)	3 (< 1)
Noncompliance	17 (4)	25 (3)	42 (3)
Protocol violation	3 (1)	8 (1)	11 (1)
Patient met withdrawal criteria	1 (< 1)	0	1 (< 1)
<b>Completed Double-Blind Treatment</b>	<b>128 (30)</b>	<b>367 (43)</b>	<b>495 (38)</b>

Table 13 Subgroup Analysis for the Diagnosis in the OC Data Set for Study 31-97-201 and Study 31-97-202

Study 31-97-201	Schizophrenia Patients alone			Schizoaffective Disorder Patients alone		
	N	Mean	P-Value	N	Mean	P-Value
<b>PANSS Total Score</b>						
Haloperidol 10mg	40	-16.5	0.135	21	-16.22	0.9120
Aripiprazole 15mg	53	-21.3	0.005	15	-33.15	0.0227
Aripiprazole 30mg	42	-17.4	0.086	19	-25.15	0.1965
Placebo	46	-10.0		14	-15.44	
<b>PANSS Positive Sub-Scale Score</b>						
Haloperidol 10mg	40	-4.3	0.104	21	-6.35	0.1248
Aripiprazole 15mg	53	-5.8	0.004	15	-8.40	0.0166
Aripiprazole 30mg	42	-5.9	0.004	19	-7.17	0.0643
Placebo	46	-2.2		14	-3.46	
<b>CGI Severity of Illness Score</b>						
Haloperidol 10mg	40	-0.6	0.122	21	-0.63	0.8589
Aripiprazole 15mg	53	-0.8	0.008	15	-1.29	0.0409
Aripiprazole 30mg	41	-0.6	0.095	19	-0.86	0.3942
Placebo	46	-0.3		14	-0.58	

Study 31-97-202	Schizophrenia Patients alone			Schizoaffective Disorder Patients alone		
	N	Mean	P-Value	N	Mean	P-Value
<b>PANSS Total Score</b>						
Risperidone 6mg	47	-20.6	0.254	14	-30.60	0.6726
Aripiprazole 20mg	42	-23.5	0.069	19	-22.25	0.4146
Aripiprazole 30mg	51	-20.3	0.279	17	-20.11	0.2650
Placebo	43	-16.1		9	-27.65	
<b>PANSS Positive Sub-Scale Score</b>						
Risperidone 6mg	47	-6.6	0.170	14	-9.64	0.3653
Aripiprazole 20mg	42	-7.8	0.023	19	-6.74	0.7037
Aripiprazole 30mg	51	-6.2	0.291	17	-4.46	0.1598
Placebo	43	-4.9		9	-7.57	
<b>CGI Severity of Illness Score</b>						
Risperidone 6mg	47	-1.0	0.072	14	-1.31	0.4519
Aripiprazole 20mg	42	-1.0	0.141	19	-0.92	0.7199
Aripiprazole 30mg	51	-1.0	0.123	17	-0.64	0.2348
Placebo	43	-0.7		9	-1.04	

Table 14 Model Based Mean Change of PANSS Positive Sub-scale Score for Age Subgroups of Patients for Pivotal Studies

Study 31-97-201	Age ≥50			Age <50		
	N	Mean	SE	n	Mean	SE
Aripiprazole 15mg	12	-5.69	1.72	87	-3.77	0.74
Aripiprazole 30mg	14	-3.05	1.58	86	-3.63	0.74
Haloperidol 10mg	11	-3.84	1.78	88	-4.23	0.73
Placebo	11	-3.44	1.78	92	0.09	0.72
Study 31-97-202	Age ≥50			Age <50		
	N	Mean	SE	n	Mean	SE
Aripiprazole 20mg	14	-3.33	1.49	84	-5.07	0.72
Aripiprazole 30mg	20	-4.44	1.23	76	-3.55	0.76
Risperidone 6mg	8	-5.41	1.99	87	-5.02	0.71
Placebo	13	-5.02	1.52	90	-1.22	0.70

Table 15 Model Based Mean Change of CGI Severity of Illness Score for Age Subgroups of Patients for Pivotal Studies

Study 31-97-201	Age ≥50			Age <50		
	N	Mean	SE	n	Mean	SE
Aripiprazole 15mg	12	-1.08	0.29	87	-0.56	0.1
Aripiprazole 30mg	14	-0.29	0.26	86	-0.39	0.1
Haloperidol 10mg	11	-0.50	0.31	88	-0.48	0.1
Placebo	11	-0.33	0.30	92	-0.02	0.1
Study 31-97-202	Age ≥50			Age <50		
	n	Mean	SE	n	Mean	SE
Aripiprazole 20mg	14	-0.45	0.23	84	-0.50	0.11
Aripiprazole 30mg	20	-0.67	0.19	76	-0.54	0.12
Risperidone 6mg	8	-0.38	0.30	87	-0.77	0.11
Placebo	13	-0.56	0.23	90	-0.15	0.11

Table 16 Model Based Mean Change from Baseline in All Three Primary Endpoints for Race Subgroup Analysis for Study 31-97-201

	PANSS Total Score			
	Placebo	Haloperidol 10 mg	Aripiprazole 15 mg	Aripiprazole 30 mg
<b>White</b>				
Baseline Mean & (N)	98.2 (50)	99.6 (64)	98.7 (58)	97.1 (58)
Endpoint (Week 4)	-0.59	-14.12	-13.42	-9.66
<b>Black</b>				
Baseline Mean & (N)	102.85 (34)	96.14 (22)	98.5 (26)	100.88 (25)
Endpoint (Week 4)	-3.59	-11.52	-19.69	-15.05
<b>Hispanic</b>				
Baseline Mean & (N)	103 (14)	103.11 (9)	92.67 (12)	99.25 (12)
Endpoint (Week 4)	-8.4	-5.57	-9.96	1.03
<b>Asian</b>				
Baseline Mean & (N)	84.67 (3)	106 (1)	97 (3)	109.67 (3)
Endpoint (Week 4)	23.17	-15.10	-14.48	-41.65
	PANSS Positive Sub-Scales			
	Placebo	Haloperidol 10 mg	Aripiprazole 15 mg	Aripiprazole 30 mg
<b>White</b>				
Baseline Mean & (N)	24.27 (51)	25.66 (64)	24.97 (58)	24.4 (58)
Endpoint (Week 4)	0.08	-4.71	-3.39	-3.63
<b>Black</b>				
Baseline Mean & (N)	25.85 (34)	23.91 (22)	23.81 (26)	24.44 (25)
Endpoint (Week 4)	-0.28	-3.61	-4.53	-4.54
<b>Hispanic</b>				
Baseline Mean & (N)	25.21 (14)	24.44 (9)	23.92 (12)	24 (12)
Endpoint (Week 4)	-2.77	-0.99	-4.54	0.51
<b>Asian</b>				
Baseline Mean & (N)	21.33 (3)	19 (1)	27 (3)	25.67 (3)
Endpoint (Week 4)	5.99	-10.71	-7.22	-11.86
	CGI Severity of Illness			
	Placebo	Haloperidol 10 mg	Aripiprazole 15 mg	Aripiprazole 30 mg
<b>White</b>				
Baseline Mean & (N)	4.96 (51)	4.89 (64)	4.97 (58)	4.83 (58)
Endpoint (Week 4)	-0.08	-0.57	-0.63	-0.43
<b>Black</b>				
Baseline Mean & (N)	5 (34)	4.73 (22)	4.89 (26)	4.76 (25)
Endpoint (Week 4)	-0.002	-0.51	-0.64	-0.4
<b>Hispanic</b>				
Baseline Mean & (N)	4.93 (14)	4.78 (9)	4.67 (12)	4.92 (12)
Endpoint (Week 4)	-0.23	0.19	-0.59	0.13
<b>Asian</b>				
Baseline Mean & (N)	4 (3)	5 (1)	5 (3)	5 (3)
Endpoint (Week 4)	0.67	0	-1	-1.33

**Table 17 Mean Change from Baseline in All Three Primary Endpoints for Race Subgroup Analysis for Study 31-97-202**

	PANSS Total Score			
	Placebo	Risperidone 10 mg	Aripiprazole 15 mg	Aripiprazole 30 mg
<b>White</b>				
Baseline Mean & (N)	96.30 (57)	96.06 (53)	94.05 (58)	90.93 (58)
Endpoint (Week 4)	-4.59	-16.18	-13.92	-12.33
<b>Black</b>				
Baseline Mean & (N)	93.83 (35)	88.94 (36)	90.64 (30)	92.83 (29)
Endpoint (Week 4)	-5.83	-17.49	-15.47	-12.11
<b>Hispanic</b>				
Baseline Mean & (N)	94.5 (4)	90.5 (4)	102.17 (6)	106.67 (3)
Endpoint (Week 4)	-2.68	5.36	-1.77	-13.70
<b>Asian</b>				
Baseline Mean & (N)	87.33 (3)	102 (1)	103.5 (2)	109 (2)
Endpoint (Week 4)	8.60	4.51	-23.37	-40.28
<b>PANSS Positive Sub-Scales</b>				
	Placebo	Risperidone 10 mg	Aripiprazole 15 mg	Aripiprazole 30 mg
<b>White</b>				
Baseline Mean & (N)	24.96 (57)	24.64 (53)	24.47 (58)	22.93 (58)
Endpoint (Week 4)	-1.92	-5.56	-5.07	-3.23
<b>Black</b>				
Baseline Mean & (N)	24.14 (35)	23.06 (36)	25.17 (30)	25.38 (29)
Endpoint (Week 4)	-1.54	-5.47	-4.52	-3.51
<b>Hispanic</b>				
Baseline Mean & (N)	24 (4)	20.5 (4)	29.67 (6)	31 (3)
Endpoint (Week 4)	-1.07	0.74	-1.26	-6.03
<b>Asian</b>				
Baseline Mean & (N)	23 (3)	22 (1)	23 (2)	25 (2)
Endpoint (Week 4)	0.86	0.28	-8.97	-9.97
<b>CGI Severity of Illness</b>				
	Placebo	Risperidone 10 mg	Aripiprazole 15 mg	Aripiprazole 30 mg
<b>White</b>				
Baseline Mean & (N)	4.95 (57)	4.96 (53)	4.86 (58)	4.64 (58)
Endpoint (Week 4)	-0.20	-0.76	-0.55	-0.56
<b>Black</b>				
Baseline Mean & (N)	4.66 (35)	4.67 (36)	4.63 (30)	4.97 (29)
Endpoint (Week 4)	-0.16	-0.85	-0.46	-0.59
<b>Hispanic</b>				
Baseline Mean & (N)	4.25 (4)	4.75 (4)	5.17 (6)	5 (3)
Endpoint (Week 4)	-0.11	0.24	0.23	-0.63
<b>Asian</b>				
Baseline Mean & (N)	4.67 (3)	5 (1)	5 (2)	4.5 (2)
Endpoint (Week 4)	0.32	0.05	-1.45	-1.05

Table 18 Mean Change from Baseline in All Three Primary Endpoints for Race Subgroup Analysis for Study CN138-001

	PANSS Total Score			
	Aripiperidone 10 mg	Aripiperidone 15 mg	Aripiperidone 20 mg	Placebo
<b>White</b>				
Baseline Mean & (N)	92.25 (53)	92.25 (55)	90.29 (52)	94.69 (49)
Endpoint (Week 4)	-12.63	-7.53	-15.18	2.76
<b>Black</b>				
Baseline Mean & (N)	87.44 (27)	85.67 (27)	89.42 (26)	85.78 (36)
Endpoint (Week 4)	-14.31	-14.23	-12.47	2.27
<b>Hispanic</b>				
Baseline Mean & (N)	99.28 (18)	109.31 (16)	112.83 (12)	98.47 (17)
Endpoint (Week 4)	-20.85	-17.45	-12.18	-23.24
<b>Asian</b>				
Baseline Mean & (N)	80 (1)	92.5 (4)	88.67 (3)	92.5 (4)
Endpoint (Week 4)	-8.37	-20.25	0.13	7.50

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# Statistical Review and Evaluation

## Review of Rat Carcinogenicity Studies

**NDA#:** 21-436

**APPLICANT:** Otsuka Pharm

**NAME OF DRUG:** Aripiprazole

**INDICATION:** Schizophrenia

**STUDIES REVIEWED:** Rat Studies: Otsuka Study No. 009489  
and BMS Study No. 99321 in Volumes  
1.75, and 1.80

**PHARMACOLOGY REVIEWER:** Lois Freed, Ph.D. (HFD-120)

**STATISTICAL REVIEWER:** Roswitha Kelly, M.S. (HFD-710)

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George Chi, Ph.D.  
Director, Division of Biometrics 1

**Distribution:**

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This review consists of 8 pages of text and 16 pages of Tables and Figures.  
File Directory: c:\Data\My Documents\aripiprazole\_rats.doc

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## 1.0 Introduction

The sponsor has submitted two rat and two mouse carcinogenicity studies. As there is basically double the information of the usual bioassay, the multiplicity problem inherent in carcinogenicity analyses is increased. This reviewer, however, performed no further adjustment on the usual 0.025 and 0.005 levels of significance in trend for rare and common tumors, as there is no guidance on this issue. High levels of significance and consistency across gender and studies should be considered when interpreting any findings. This reviewer wrote a separate review for each species but presented the main findings from both species in the summary section.

## 2.0 Otsuka Study No. 009489 in Rats

This was a 104-week carcinogenicity study of OPC-31 in SPF Fischer (F344/DuCrj) rats. The test substance was administered in the diet to 50 animals/sex/group at dose levels of 0, 1, 3, and 10 mg/kg/day. Animals were individually housed and water and feed were available ad lib. Additional 8 satellite animals/sex of the treated groups were maintained for 52 weeks for determination of plasma concentrations. From the main study, surviving animals were terminally sacrificed after 104 weeks of dosing. All animals were subjected to complete necropsy and histopathological examination. Mortality was statistically investigated by life table analysis (two-sided). Overall incidence of neoplastic lesions and number of females with mammary gland tumors were tested one-sided by Cochran-Armitage trend test. Time-related occurrence of mammary gland tumors in females was tested one-sided by Peto's onset rate method.

### 2.1 Sponsor's Findings for Study 009489

The sponsor observed no significant differences in mortality between the control and treated groups of either gender. The final mortality rates (number of animals killed in extremis or found dead) were as follows:

Dose Group (mg/kg/day)	Males	Females
0	13/50 (26%)	7/50 (14%)
1	7/50 (14%)	8/50 (16%)
3	8/50 (16%)	13/50 (26%)
10	10/50 (20%)	12/50 (24%)

Mean body weight in the male high dose group was slightly, but significantly, lower (3-8%) than controls throughout the study. Mean body weight in the female high dose was slightly, but significantly, higher (4-8%) than controls for weeks 30-68. However, mean body weight was comparable to that of controls at the other times.

Among the neoplastic findings, only females showed any statistically significant increase, namely for fibroadenoma of the mammary gland ( $p \leq 0.05$  by Cochran-Armitage trend test) as well as by Fisher's exact test when comparing the high dose with the controls).