Synopsis

Clinical Report Synopsis for Protocol 331-07-203

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Product: OPC-34712

Study Title: A Phase 2, 6-Week, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Oral OPC-34712 Once Daily and Aripiprazole Once Daily for Treatment of Hospitalized Adult Patients with Acute Schizophrenia

Investigator(s) and Study Center(s): Multicenter (74 Centers; Multinational)

Publications: None.

Studied Period:

Date of first signed informed consent: 21 Jul 2009

Date of last study observation: 16 Sep 2010

Clinical Phase: 2

Objective: The objective of the study was to establish the optimal dose of OPC-34712 for the treatment of acute schizophrenia based on efficacy, safety, and tolerability during a 6-week treatment period.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled study designed to assess the tolerability, safety, and efficacy of OPC-34712 (0.25 to 6 mg) for the treatment of adult subjects hospitalized with an acute relapse of schizophrenia. Aripiprazole (10 to 20 mg) was included as a positive control to confirm the assay sensitivity of the study.

Subjects were to remain hospitalized through Week 3, and if stable, thereafter could continue as outpatients through Week 6. Non-responders (defined as subjects with Clinical Global Impression–Improvement [CGI–I] score >4) could withdraw and switch to open-label OPC-37412 at Week 4 or Week 5. Efficacy and safety data were to be collected through Week 6. Pharmacokinetics (PK) blood draws were to occur postdose within prespecified time intervals on Day 1 and Week 3.

After a Screening period of up to 14 days, individual participation for subjects who completed the study was to range from 6 to 12 weeks, consisting of a 6-week double-blind treatment period, and a 30-day follow-up, if applicable. Subjects (including those in the non-responder arm) had the option to enter an open-label rollover study after completion of treatment. Only subjects who did not enter the open-label study were

followed up via telephone contact or clinic visit 30 (+ 2) days after the last dose of study medication.

Number of Subjects: A total of 450 subjects were planned to be enrolled in the trial: 459 subjects were actually enrolled as shown in the table below. A total of 268/459 (58.4%) subjects completed double-blind treatment and 126/459 (27.5%) subjects discontinued the trial during double-blind treatment. Reasons for discontinuation included subject withdrew consent (61/459 subjects, 13.3%), AEs (31/459 subjects, 6.8%), lack of efficacy (30/459 subjects, 6.5%), protocol deviations (2/459 subjects, 0.4%), and lost to follow-up (2/459 subjects, 0.4%). A total of 454/459 (98.9%) subjects were analyzed for efficacy and 459 (100.0%) subjects for were analyzed for safety.

Non-responders were permitted to receive open-label OPC-34712 beginning at Week 4 of the trial. Sixty-five (of 459) (14.2%) subjects transitioned to open-label OPC-34712 and were included in non responder open-label arm of the trial. Of these, 59/65 (90.8%) subjects completed the trial.

Treatment Group	Planned N		Actual N
OPC-34712, 0.25 mg once daily (QD)	45		42
OPC-34712, 1 mg QD starting dose ± 0.5 mg (Low-dose)	90		89
OPC-34712, 2.5 mg QD starting dose ± 0.5 mg (Mid-dose)	90		90
OPC-34712, 5 mg QD starting dose ± 1 mg (High-dose)	90		93
Placebo	90		95
Aripiprazole, 15 mg QD starting dose ± 5 mg	45		50
Open-label OPC-34712, 2.5 mg starting dose ± 0.5 mg (Non-responders)	Not applicable		65

Diagnosis and Main Criteria for Inclusion: The study population included male and female subjects between 18 and 65 years of age, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) diagnosis of schizophrenia who had been recently hospitalized (ie, <14 days prior to Screening) or who would benefit from hospitalization for an acute relapse. The diagnosis of schizophrenia was confirmed by the Mini International Neuropsychiatric Interview (MINI) for Psychotic Disorders with a Positive and Negative Syndrome Scale (PANSS) Total Score ≥80 AND a Clinical Global Impression–Severity of Illness scale (CGI–S) score ≥4.

Test Product and Reference Products, Doses, Mode of Administration, Lot No(s): Study drug was provided in blister cards containing OPC-34712 0.25-mg, 1-mg, and 5-mg tablets; aripiprazole 10-mg and 15-mg tablets; and corresponding matching placebo tablets for OPC-34712 (round and brick red) and aripiprazole (round and white) packaged using a double-dummy design. Dose groups are listed above (under Number of Subjects). Each subject received an oral, 6-tablet, daily single dose (the minimum number of active tablets required to achieve the prescribed dose and placebo, ie, four brick red and two white tablets) for six weeks. OPC-34712 tablets and matching placebo as well as

aripiprazole and its matching placebo were manufactured by Otsuka Pharmaceutical Co. (OPC), Ltd. (Japan). Open-label OPC-34712 for the non-responder group came from the same lots as for randomized subject groups. Lots are listed below.

Summary of Study Medication Lot Numbers		
Product	**Strength**	**Lot Number**
OPC-34712 Placebo Tablets	0 mg	08K94P005A 09B79P005
OPC-34712 Tablets	0.25 mg	09B94A0025
	1 mg	09B79A001A
	5 mg	09B79A005
Aripiprazole Placebo Tablets	0 mg	08L80P000B 09D75P000A 09D75P000B
Aripiprazole Tablets	10 mg	09D75A010
	15 mg	08L80A015B

Criteria for Evaluation:

Primary Outcome Variable, Efficacy:
Change from baseline to Week 6/Early Termination (ET) in PANSS Total Score using the last observation carried forward (LOCF) dataset.

Key Secondary Outcome Variables, Efficacy:
Change from baseline to Week 6/ET for the following variables:

- PANSS Positive Subscale Score
- PANSS Negative Subscale Score
- Personal and Social Performance scale (PSP) score
- CGI–S score

Other Secondary Outcome Variables, Efficacy:

- Mean CGI–I score at Week 6/ET
- Response rate (defined as reduction of ≥30% from baseline in PANSS Total Score or CGI–I score of 1 [very much improved] or 2 [much improved]) at Week 6/ET
- Discontinuation rate for lack of efficacy or receipt of open-label OPC-34712 during the study

Other Secondary Outcome Variables, Safety:

- Frequency, severity, seriousness, discontinuation, and relationship to treatment for adverse events (AEs)
- Review of physical examination findings
- Mean change from baseline and the incidence of clinically significant changes for routine clinical laboratory tests (hematology, serum chemistry including prolactin, and urinalysis)
- Mean change from baseline in coagulation parameters including prothrombin time (PT), activated partial thromboplastin time (aPTT), International Normalized

Ratio (INR); glycosylated hemoglobin (HbA1c); cortisol and adrenocorticotropic hormone (ACTH); and thyroid-stimulating hormone (TSH)

- Mean change from baseline and the incidence of clinically significant changes for 12-lead electrocardiograms (ECGs), vital signs, and body weight
- Mean change from baseline for waist circumference and body mass index (BMI)
- Mean change from baseline for Extrapyramidal Symptoms (EPS) scales (Simpson-Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale [BARS])
- Columbia-Suicide Severity Rating Scale (C-SSRS) summary of suicidal behavior

Other Secondary Outcome Variables:

- Morisky Medication Adherence Scale, 4-item (MMAS-4)
- CogState computerized cognitive test battery

Pharmacokinetics:

- Blood samples were collected to assess plasma concentrations of OPC-34712 and its metabolites.

Pharmacogenomics:

- A blood sample was collected for pharmacogenomic evaluation (part of an optional stand-alone protocol amendment) of genetic variants (genotypes) of cytochrome P450 (CYP) 2D6 and CYP2C19.

Statistical Methods: The primary statistical comparisons of interest were the low-dose, mid-dose, and high-dose OPC-34712 arms (referred to as "flexible dose groups") vs placebo. The statistical analysis was performed by fitting an analysis of covariance (ANCOVA) model to the change from baseline data for the PANSS Total Score at the Week 6 visit (LOCF). The model included baseline PANSS Total Score as a covariate and treatment and study center as main effects. A mixed model repeated measures (MMRM) analysis based on observed cases (OC) data was performed as a sensitivity analysis for the primary endpoint. The comparison of the 0.25-mg/day dose of OPC-34712 vs placebo for change from baseline to Week 6/ET in PANSS Total Score was considered as a secondary analysis. Comparison of the aripiprazole treatment group vs placebo was considered as assay sensitivity of the trial.

The key secondary efficacy endpoints were change from baseline to Week 6/ET in the following four endpoints: PANSS Positive and Negative Subscale Scores, PSP score, and CGI–S score, and were tested sequentially in the order listed for each comparison of OPC-34712 treatment group vs placebo using the LOCF dataset as the primary dataset. The analysis of these key secondary efficacy endpoints was identical to the analysis of the primary endpoint (PANSS Total Score). Comparisons between one of the low-dose, mid-dose, and high-dose OPC-34712 treatment groups vs placebo in the key secondary endpoints was only conducted when the corresponding comparison in the primary

endpoint was significant at an alpha level of 0.0167, and used the alpha level of 0.0167 in the sequential tests. Comparison between the 0.25-mg/day dose of OPC-34712 vs placebo in these key secondary efficacy endpoints also was conducted only if the corresponding comparison in the primary endpoint was significant at an alpha level of 0.0167, and also used the alpha level of 0.0167 in these sequential tests.

The OC dataset at Week 6 was also used for the analysis of the primary and secondary change from baseline endpoints (eg, PANSS [total, positive, and negative], PSP, CGI–S) and mean CGI–I score to corroborate the analyses based on the LOCF dataset. In addition, by-visit analyses were conducted for the primary and secondary efficacy change from baseline endpoints and mean CGI–I score to provide information regarding the onset of the treatment effect.

Similar to the analysis of the primary efficacy endpoint, comparisons of the aripiprazole treatment group vs placebo were also made for all secondary efficacy endpoints using the same analyses specified above to provide sensitivity analyses on these endpoints, so that no alpha was spent on this comparison.

Pharmacokinetic and Pharmacogenomic Methods:
Plasma concentrations of OPC-34712 and its metabolites at baseline and Week 3 were summarized descriptively. No inferential statistical comparisons were planned or performed. Results of CYP2D6 and CYP2C19 metabolizer genotype and phenotype were provided.

RESULTS

Efficacy Results:
The mean change from baseline to Week 6 (LOCF) in PANSS Total Score and PANSS subscale scores is summarized in the table below. During double-blind treatment, the numeric improvement (ie, decrease) in PANSS Total Score was greater for the low- (1.0 ± 0.5 mg/day), mid- (2.5 ± 0.5 mg/day), and high-dose (5.0 ± 1.0 mg/day) OPC-34712 groups compared to the placebo group; however, due to the magnitude of the change observed in the placebo group (ie, −13.77 points), the treatment difference between OPC-34712 and placebo was not statistically significant for any of these OPC-34712 doses. Treatment with the fixed 0.25-mg/day dose of OPC-34712 resulted in a smaller decrease in PANSS Total Score than that observed for placebo (−9.76 points versus −13.77 points, respectively). The aripiprazole group, included to confirm assay sensitivity, also did not show significant differentiation from placebo for the primary endpoint. Results for the PANSS subscale scores were similar to the results for PANSS Total Score. Subgroup analyses did not show any consistent influence of gender, age, or race on the primary efficacy results.

Change from Baseline to Week 6 (LOCF) in PANSS Total and Subscale Scores						
Efficacy Variable	**OPC-34712 0.25 mg (N = 41)**	**OPC-34712 1.0 ± 0.5 mg (N = 88)**	**OPC-34712 2.5 ± 0.5 mg (N = 90)**	**OPC-34712 5.0 ± 1.0 mg (N = 92)**	**Aripiprazole 15 ± 5 mg (N = 50)**	**Placebo (N = 93)**
PANSS Total Score						
Baseline mean (SD)	97.07 (8.54)	96.33 (9.93)	98.59 (10.50)	97.76 (10.99)	97.12 (10.68)	97.62 (9.91)
LSM change at Week 6	−9.76	−18.47	−15.22	−17.64	−18.02	−13.77
Treatment diff[a] (95% CI)	4.62 (−2.89, 12.12)	−4.70 (−10.2, 0.82)	−1.44 (−6.96, 4.07)	−3.86 (−9.32, 1.59)	−3.64 (−10.7, 3.38)	- -
p-value[b]	0.2263	0.0949	0.6066	0.1646	0.3074	-
PANSS Positive Subscale Score						
Baseline mean (SD)	25.36 (3.39)	25.03 (3.73)	25.44 (3.79)	25.48 (3.78)	25.86 (3.73)	25.68 (3.63)
LSM change at Week 6	−3.21	−5.86	−4.59	−5.70	−6.61	−4.46
Treatment diff[a] (95% CI)	1.61 (−0.75, 3.97)	−1.41 (−3.24, 0.42)	−0.13 (−1.96, 1.69)	−1.24 (−3.05, 0.56)	−1.79 (−4.00, 0.42)	- -
p-value[b]	0.1807	0.1313	0.8879	0.1764	0.1111	-
PANSS Negative Subscale Score						
Baseline mean (SD)	24.02 (4.46)	24.52 (4.11)	25.84 (4.62)	25.14 (4.99)	23.92 (4.20)	24.96 (4.53)
LSM change at Week 6	−2.03	−3.73	−3.47	−3.85	−3.18	−3.12
Treatment diff[a] (95% CI)	1.00 (−0.86, 2.86)	−0.61 (−1.94, 0.72)	−0.35 (−1.69, 0.99)	−0.73 (−2.05, 0.59)	−0.15 (−1.90, 1.59)	- -
p-value[b]	0.2896	0.3701	0.6074	0.2777	0.8611	-

CI = confidence interval; LOCF = last observation carried forward; LSM = least squares mean; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

[a] Treatment difference in adjusted mean change for OPC-34712 - placebo or aripiprazole - placebo.

[b] Derived from either ANCOVA-1 (with treatment and trial center as main effects, and baseline value as covariate) for OPC-34712 flexible doses vs placebo, or ANCOVA-2 (with treatment as main effect and baseline value as covariate) for 0.25 mg/day OPC-34712 vs placebo and aripiprazole vs placebo.

The mean PANSS Total Score at the last double-blind visit for the 65 subjects who discontinued double-blind treatment to enter the non-responder open-label arm was 100.65, which represented a mean increase from baseline of 2.55 points. During open-label treatment, the PANSS Total Score decreased (ie, improved) by a mean of −11.68 points relative to the baseline value for these subjects.

Results for the analyses of the secondary efficacy endpoints are summarized in the table below. Consistent with the evaluation of the primary efficacy endpoint, the results for treatment with either OPC-34712 or aripiprazole were not significantly different from placebo for any of the secondary efficacy endpoints. Whereas the low-, mid-, and high-dose OPC-34712 groups and the aripiprazole group demonstrated numeric improvements in PSP, CGI-S, and CGI-I scores that were greater than the placebo group, the minimal numeric improvements in efficacy scale scores for 0.25 mg/day OPC-34712 showed this dose to be ineffective. Response rate was defined as a reduction of ≥ 30% from baseline in PANSS Total Score or a CGI–I score of 1 (very much improved) or 2

(much improved) at Week 6/ET. The response rates for OPC-34712 at Week 6 (LOCF) ranged from 40.5% in the 0.25 mg/day OPC 34712 group to 57.3% in the 1.0 ± 0.5 mg/day OPC-34712 group; however, the 49.5% response rate in the placebo group precluded any statistically significant treatment comparisons. The discontinuation rate for lack of efficacy or receipt of open-label treatment was highest in the 0.25 mg/day OPC-34712 and placebo groups.

Summary of Results at Week 6 (LOCF) for Secondary Efficacy Endpoints						
Efficacy Variable	**OPC-34712 0.25 mg (N = 41)**	**OPC-34712 1.0 ± 0.5 mg (N = 88)**	**OPC-34712 2.5 ± 0.5 mg (N = 90)**	**OPC-34712 5.0 ± 1.0 mg (N = 92)**	**Aripiprazole 15 ± 5 mg (N = 50)**	**Placebo (N = 93)**
PSP Score						
N	39	86	84	90	50	90
Baseline mean (SD)	47.71 (12.05)	45.80 (10.57)	44.79 (12.30)	45.05 (11.56)	46.72 (9.41)	46.11 (10.94)
LSM change at Week 6	5.01	11.40	9.81	11.47	10.62	7.61
Treatment diff[a] (95% CI)	−2.36 (−7.57, 2.85)	3.80 (−0.26, 7.85)	2.20 (−1.92, 6.32)	3.86 (−0.16, 7.89)	3.25 (−1.53, 8.03)	- -
p-value[b]	0.3726	0.0664	0.2944	0.0596	0.1819	-
CGI-S Score						
Baseline mean (SD)	4.81 (0.63)	4.84 (0.64)	4.99 (0.61)	5.02 (0.61)	4.90 (0.71)	5.00 (0.60)
LSM change at Week 6	−0.42	−1.04	−0.81	−1.05	−1.01	−0.77
Treatment diff[a] (95% CI)	0.38 (−0.03, 0.79)	−0.28 (−0.60, 0.05)	−0.04 (−0.37, 0.28)	−0.28 (−0.60, 0.04)	−0.21 (−0.59, 0.18)	- -
p-value[b]	0.0685	0.0989	0.8006	0.0898	0.2851	-
CGI-I Score						
Mean at Week 6 (SD)	3.66 (1.48)	3.08 (1.58)	3.17 (1.45)	3.04 (1.50)	3.04 (1.52)	3.34 (1.54)
Probability[c] (95% CI)	0.46 (0.351, 0.575)	0.57 (0.485, 0.649)	0.53 (0.448, 0.604)	0.55 (0.475, 0.634)	0.57 (0.468, 0.670)	- -
p-value	0.4008	0.1117	0.2739	0.1045	0.1149	-
Response Rate at Week 6						
N	42	89	90	93	50	95
Proportion, n (%)	17 (40.48)	51 (57.30)	42 (46.67)	48 (51.61)	30 (60.00)	47 (49.47)
RR[d] (95% CI)	0.89 (0.57, 1.40)	1.19 (0.95, 1.48)	0.91 (0.66, 1.25)	1.02 (0.78, 1.34)	1.15 (0.85, 1.56)	- -
p-value	0.6200	0.1501	0.5271	0.8670	0.3892	-
Discontinuation Rate for LOE or Receipt of Open-label OPC-34712						
N	42	89	90	93	50	95
Discontinued, n (%)	13 (30.95)	20 (22.47)	16 (17.78)	15 (16.13)	8 (16.00)	23 (24.21)
RR[d] (95% CI)	1.06 (0.59, 1.88)	0.82 (0.49, 1.38)	0.67 (0.36, 1.23)	0.61 (0.33, 1.10)	0.63 (0.30, 1.34)	- -
p-value	0.8540	0.4492	0.1854	0.0946	0.2133	-

CGI-I = Clinical Global Impression-Improvement scale, CGI-S = Clinical Global Impression-Severity of Illness scale; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; LOE = lack of efficacy; LSM = least squares mean; PSP = Personal and Social Performance scale; RR = relative risk; SD = standard deviation.

[a]Treatment difference in adjusted mean change for OPC-34712 - placebo or aripiprazole - placebo.

[b]Derived from either ANCOVA-1 (with treatment and trial center as main effects, and baseline value as covariate) for OPC-34712 flexible doses vs placebo, or ANCOVA-2 (with treatment as main effect and baseline value as covariate) for 0.25 mg/day OPC-34712 vs placebo and aripiprazole vs placebo.

[c]Chance to be better than placebo derived from CMH row mean scores differ test controlling for trial center.

[d]Derived using CMH test stratified by trial center.

In the efficacy analyses by trial visit (LOCF), some statistically significant improvements in secondary efficacy endpoints were observed at time points prior to Week 6. Mean change from baseline in PSP score was significantly different from placebo for the

5.0 ± 1.0 mg/day OPC-34712 group at Week 3 of double-blind treatment (p = 0.0369), but the difference did not retain significance at Week 6 (p = 0.0596). Mean CGI-S scores consistently decreased (improved) during the 6-week double-blind treatment period in all groups except for the 0.25 mg/day OPC-34712 group. The 5.0 ± 1.0 mg/day OPC-34712 group was significantly different from placebo at Week 2 (p = 0.0324) and Week 3 (p = 0.0261). Mean CGI-I score was significantly different from placebo at Week 2 in the 2.5 ± 0.5 mg/day OPC-34712 group (p = 0.0351) and the aripiprazole group (p = 0.0488) and approached statistical significance in the 5.0 ± 1.0 mg/day OPC-34712 group (p = 0.0584). Despite these early indications of efficacy, no significant differences from placebo were observed for these parameters after Week 3.

Mean scores on the PSP, CGI-S, and CGI-I all improved during open-label treatment with OPC-34712. Of note, the median CGI-I score for the 65 subjects who entered the non-responder open-label arm decreased from 5 at the end of double-blind treatment to 3 at the end of open-label treatment. The collective efficacy data from this trial suggest an active dose range of 1 to 6 mg/day OPC-34712 for the treatment of schizophrenia.

Pharmacokinetic Results:

OPC-34712 and its metabolite plasma concentrations were comparable with previous data observed in schizophrenic patients (Trial 331-08-205 and Trial 331-08-209).

Safety Results (Double-blind Treatment):

A total of 459 subjects received at least one dose of trial medication during the 6-week double-blind treatment period and were included in the safety analysis set. Of these, 65 subjects received at least one dose of open-label OPC-34712 in the non-responder open-label arm. The average daily dose at the end of double-blind treatment was 0.25, 1.30, 2.74, and 5.45 mg in the 0.25, 1.0 ± 0.5, 2.5 ± 0.5, 5.0 ± 1.0 mg/day OPC-34712 groups, respectively. The average daily dose of OPC-34712 during open-label treatment was 2.79 mg.

A total of 321/459 subjects (69.9%) experienced at least one treatment-emergent adverse event (TEAE) during double-blind treatment. Nervous system, psychiatric, and gastrointestinal disorders were the 3 most common system organ classes (SOCs) in which TEAEs were reported, both for the overall trial population and for the combined OPC-34712 groups. Overall, the most frequently reported TEAEs during double-blind treatment (≥ 10% of all subjects) were insomnia (54/459 subjects, 11.8%) and headache (47/459 subjects, 10.2%). A potential dose-response relationship was observed for akathisia, increased blood creatine phosphokinase (CPK), and somnolence in the OPC-34712 treatment groups.

The majority of TEAEs were mild or moderate in intensity. Severe TEAEs were reported during double-blind treatment for 20/314 subjects (6.4%) who received OPC-34712 (2/42 subjects, 4.8% in 0.25 mg/day OPC-34712 group; 4/89 subjects, 4.5% in 1.0 ± 0.5 mg/day OPC-34712 group; 6/90 subjects, 6.7% in 2.5 ± 0.5 mg/day OPC-34712

group; and 8/93 subjects, 8.6% in 5.0 ± 1.0 mg/day OPC-34712 group), 3/95 subjects (3.2%) in the placebo group, and 1/50 subjects (2.0%) in the aripiprazole group. Potentially drug-related TEAEs (ie, TEAEs classified by the investigator as related or possibly related to double-blind trial medication) were reported by 144/314 subjects (45.9%) who received OPC-34712, 40/95 (42.1%) subjects who received placebo, and 21/50 subjects (42.0%) who received aripiprazole. The most common TEAE with a potential relationship to double-blind trial medication was akathisia in the total OPC-34712 group (25/314 subjects, 8.0%), insomnia (8/95 subjects, 8.4%) in the placebo group, and increased weight and restlessness (3/50 subjects each, 6.0%) in the aripiprazole group.

One death was reported during the trial. Subject [redacted], a [redacted]-year old [redacted], completed treatment with 5.0 ± 1.0 mg/day OPC-34712 on Day 42 and died on Day 54, 11 days after having completed the trial (12 days after the last dose of trial medication). The subject complained of chest discomfort and was later found unresponsive. The investigator considered the death to be unlikely related to trial medication.

A total of 17/459 (3.7%) subjects experienced serious TEAEs during double-blind treatment. The most frequently reported serious TEAE was schizophrenia, which was reported as a worsening, exacerbation, or aggravation of schizophrenia (3 subjects who received OPC-34712 and 1 who received placebo) that resulted in hospitalization or prolonged the hospital stay. In addition, 2 subjects who received OPC-34712 experienced an exacerbation of paranoid schizophrenia (preferred term: schizophrenia, paranoid type) that was considered serious. All of these events were either unrelated or unlikely related to administration of trial medication. Four serious TEAEs were considered possibly related to administration of trial medication (rhabdomyolysis and dizziness in 2.5 ± 0.5 mg/day OPC-34712 group and rhabdomyolysis and complex partial seizures in aripiprazole group).

A total of 31/459 subjects (6.8%) discontinued double-blind treatment due to TEAEs (23/314 subjects, 7.3% in the combined OPC-34712 groups; 5/95 subjects, 5.3% in the placebo group; and 3/50 subjects, 6.0% in the aripiprazole group). Among subjects who received low-, mid-, or high-dose OPC-34712, the incidence of TEAEs that resulted in discontinuation increased with increasing dose. In the total population, the most frequent TEAEs (reported by 2 or more subjects overall) that led to discontinuation of double-blind treatment were schizophrenia (10/459 subjects, 2.2%), psychotic disorder (4/459 subjects, 0.9%), agitation (2/459 subjects, 0.4%) and rhabdomyolysis (2/459 subjects, 0.4%). Preferred terms of schizophrenia and psychotic disorder represented a worsening, marked deterioration, or exacerbation of the condition.

Decreased hematocrit (≤ 37% and ≥ 3% point decrease from baseline for males; ≤ 32% and ≥ 3% point decrease from baseline for females) and decreased hemoglobin (≤ 11.5 g/dL for males; ≤ 9.5 g/dL for females) were the most frequently occurring potentially clinically relevant findings for hematology parameters in the OPC-34712 groups; however, there was no apparent dose-response relationship for these abnormalities, and hemoglobin and/or hematocrit values for more than half of these

subjects were abnormally low at baseline. For subjects receiving double-blind OPC-34712, the incidence of decreased hematocrit was 17/310 (5.5%) and for placebo subjects, 4/92 (4.3%). The incidence of decreased hemoglobin in the OPC-34712 groups was 7/310 (2.3%) and 0/92 (0%) for the placebo group.

Overall, elevated triglycerides (≥ 160 mg/dL for males, ≥ 120 mg/dL for females) were the most frequent serum chemistry values of potential clinical relevance (54/440 subjects, 12.3% overall) and the incidence of this abnormality was similar between the combined OPC-34712 groups (36/301 subjects, 12.0%) and the placebo (11/90 subjects, 12.2%) and aripiprazole (7/49 subjects, 14.3%) groups. Potentially clinically relevant decreases in high density lipoprotein (HDL) cholesterol (ie, ≤ 30 mg/dL) were also observed for a similar percentage of subjects in the combined OPC-34712 group (15/301 subjects, 5.0%), the placebo group (5/90 subjects, 5.6%) and the aripiprazole group (2/49 subjects, 4.1%). Treatment with OPC-34712 demonstrated no apparent dose-response for either of these parameters.

Potentially clinically relevant increases in CPK (≥ 3 × the upper limit of normal [ULN]) occurred for 22/311 subjects (7.1%) in the combined OPC-34712 group, 4/93 subjects (4.3%) in the placebo group, and 3/50 subjects (6.0%) in the aripiprazole group. For this parameter, higher doses of OPC-34712 appeared to be associated with a higher incidence of elevated CPK. A slight dose-response was also observed for the incidence of TEAEs of increased blood CPK.

Throughout the trial, no subjects had values for hepatic laboratory parameters which met the criteria for drug-induced liver injury.

In the aripiprazole group, elevated fasting glucose (≥ 115 mg/dL) was the most common abnormality of potential clinical relevance (8/49 subjects, 16.3% for aripiprazole compared to 25/301 subjects, 8.3% for the combined OPC-34712 groups and 7/90 subjects, 7.8% for placebo).

No clinically relevant changes in ACTH, cortisol, or TSH were observed during the trial.

Mean changes from baseline to the last visit indicated that, on a population basis, prolactin values generally decreased in both males and females in all treatment groups during the trial, including in the placebo group.

Increased standing heart rate (> 120 bpm and ≥ 15 bpm increase from baseline) was the most common vital sign abnormality of potential clinical relevance: 6/311 subjects (1.9%) in the combined OPC-34712 groups, 1/93 subjects (1.1%) in the placebo group, and 1/50 subjects (2.0%) in the aripiprazole group.

At the end of double-blind treatment, potentially clinically relevant weight gain (increase of ≥ 7% in body weight) occurred in a higher percentage of subjects who received low-, mid-, or high-dose OPC-34712 (29/270 subjects, 10.7%) compared to subjects who received either placebo (7/93 subjects, 7.5%) or aripiprazole (2/50 subjects, 4.0%). The

incidence of potentially clinically relevant weight gain appeared to increase as the dose of OPC-34712 increased.

Increased corrected QT interval (QTc) (ie, QTcB and/or QTcF > 450 msec) was the most common potentially clinically relevant change in ECG parameters during double-blind treatment. The incidence of potentially clinically relevant QTc findings during treatment with OPC-34712 was no more than that observed in the placebo group (QTcB > 450 msec in 7/91 subjects [7.7%]) except for the 5.0 ± 1.0 mg/day OPC-34712 group (QTcB > 450 msec in 11/91 subjects [12.1%]). None of the subjects in the trial had a QTc value (by any correction method) > 500 msec; an increase in QTc of ≥ 60 msec from baseline (QTcB, QTcF, and QTcN) occurred in 1 subject in the 5.0 ± 1.0 mg/day OPC-34712 group.

During double-blind treatment, mean SAS Total Score and mean AIMS score decreased in all active treatment groups with the exception of SAS Total Score in the 5.0 ± 1.0 mg/day OPC-34712 group; the treatment difference between this group and placebo was not statistically significant. The change from baseline in BARS Global Score was negative or negligible at the end of double-blind treatment except for the 5.0 ± 1.0 mg/day OPC-34712 group where the mean increase (0.22 points) was significantly different from placebo (0.0 points; treatment difference of 0.22 points, p = 0.0079).

The incidence of akathisia was 26/314 (8.3%) in subjects receiving OPC-34712 double-blind treatment as compared to 4/95 (4.2%) subjects who received placebo. When present, akathisia was typically mild. The highest incidence of akathisia occurred during the first week of double-blind treatment. Akathisia events (akathisia and psychomotor hyperactivity) and parkinsonian events (extrapyramidal disorder and tremor) were the most frequently reported classes of EPS-related TEAEs. Overall, EPS-related TEAEs were more common among subjects who received 5.0 ±1.0 mg/day OPC-34712 than for any other treatment group.

The results of the C-SSRS were unremarkable.

Other Outcomes Results:

During double-blind treatment (LOCF), the least squares mean (LSM) changes from baseline in Composite Change score at Week 6 for the OPC-34712 flexible dose groups (1.0 ± 0.5, 2.5 ±0.5, and 5.0 ±1.0 mg/day) and placebo, respectively, were 0.20 (p=0.0281), 0.30 (p=0.0026), 0.13, and -0.03. And, corresponding LSM changes from baseline for the OPC-34712 0.25 mg/day group, the aripiprazole group, and the placebo group, respectively, were -0.26, 0.01, and -0.01. In the observed cases analysis, significance was achieved for the 2.5 ±0.5, and 5.0 ±1.0 mg/day OPC-34712 dose groups. CogState uses 0.2 points as the cut-off for clinically relevant.
At Week 6 on double-blind treatment, the change from baseline in MMAS for the OPC-34712 for all treatment groups suggested that overall compliance improved slightly (and similarly across treatment groups).

Overall Conclusions:

- Neither OPC-34712 nor aripiprazole was significantly different from placebo for the primary and secondary efficacy endpoints at Week 6 (LOCF); however, numeric improvements in efficacy scale scores were similar between the OPC-34712 low, mid, and high flexible dose groups and aripiprazole for several endpoints, including the primary endpoint. Numeric improvements in the 0.25 mg fixed dose OPC-34712 group at the end of double-blind treatment were smaller than those observed for placebo, thus, the 0.25 mg/day dose of OPC-34712 is considered ineffective for the treatment of schizophrenia.
- Factors such as gender, age, and race did not appear to have a consistent influence on efficacy outcomes; however, the small sample size in many of the subgroup categories precluded definitive conclusions.
- The collective efficacy data from this trial suggest an active dose range of 1 to 6 mg/day OPC-34712 for the treatment of schizophrenia.
- OPC-34712 and its metabolite plasma concentrations were comparable with previous data observed in schizophrenic patients (Trial 331-08-205 and Trial 331-08-209).
- OPC-34712 was well tolerated at doses up to 5 ± 1.0 mg/day when administered for 6 weeks to subjects with an acute exacerbation of schizophrenia.
- There were no differences in the incidence of TEAEs between subjects assigned to OPC-34712, placebo, or aripiprazole during double-blind treatment (219/314 subjects, 69.7%, for the combined OPC-34712 groups; 67/95 subjects, 70.5%, for the placebo group; and 35/50 subjects, 70.0%, for the aripiprazole group).
- A potential dose-response was observed for frequency of akathisia, increased blood CPK, and somnolence in the OPC-34712 groups. There were no differences in the incidence of serious TEAEs in the OPC-34712 (12/314 subjects, 3.8%) and placebo (3/95 subjects, 3.2%) groups.
- The C-SSRS and AE data showed no suicidal behavior during double-blind or open-label treatment.
- Discontinuation of treatment for TEAEs was highest in the 5.0 ± 1.0 mg/day OPC-34712 group (11/93 subjects, 11.8%). During double-blind treatment, 23/314 (7.3%) subjects who received OPC-34712 and 5/95 (5.3%) subjects who received placebo discontinued treatment due to TEAEs.
- OPC-34712 did not result in any consistent, clinically relevant changes in laboratory values, vital signs (heart rate or blood pressure), or ECG parameters. Statistically significant increases in weight, BMI, and waist circumference were observed in the 2.5 ± 0.5 mg/day and 5.0 ± 1.0 mg/day OPC-34712 groups as compared with placebo.
- OPC-34712 at doses below 5.0 ± 1.0 mg/day exhibited a favorable profile with respect to movement disorders.

- In the observed cases analysis of LSM change from baseline in CogState Composite Change score at Week 6 during double-blind treatment, the OPC-34712 mid and high-dose treatment groups performed significantly better than did placebo.
- MMAS scores were indicative of favorable adherence to taking study medication.