Synopsis

Clinical Report Synopsis for Protocol 331-08-210

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

Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712)

Protocol Title: A Phase 2, Multicenter, Open-label Study to Assess the Safety and Tolerability of Oral OPC-34712 as Monotherapy in Adult Patients with Schizophrenia

Coordinating Investigator and Trial Sites: [redacted], MD; 73 trial sites in the following 12 countries: Bulgaria, Croatia, India, South Korea, Philippines, Romania, Russian Federation, Serbia, Slovakia, Taiwan, Ukraine, and the United States

Publications: None to date.

Trial Period:

Date of first signed informed consent: 09 Sep 2009

Date of last trial observation: 15 Sep 2011

Clinical Phase/Trial Type: Phase 2/therapeutic use

Objectives:

Primary: To assess the long-term safety and tolerability of oral brexpiprazole as monotherapy in adult patients with schizophrenia.

Secondary: To assess the long-term efficacy of oral brexpiprazole as monotherapy in adult patients with schizophrenia.

Methodology: This was a multicenter, 52-week, open-label trial designed to assess the long-term safety, tolerability, and efficacy of oral brexpiprazole (1 to 6 mg) as monotherapy in adult patients with schizophrenia. Initially, the protocol was approved as a 6-week trial and was extended to be a 52-week trial with Amendment 2. Subjects who completed the Week 6 visit of the original protocol (dated 08 May 2009) or Amendment 1 (dated 16 Jul 2009) before institutional review board approval of Amendment 2 (52-week trial) were not permitted to re-enroll in the trial under Amendment 2.

Enrollment into the trial was drawn from eligible subjects who completed participation in Protocol 331-07-203 and who, in the investigator's judgment, could potentially benefit from treatment with oral brexpiprazole for schizophrenia. The trial was conducted on an outpatient basis. Hospitalization for psychosocial reasons (eg, homelessness or need for shelter that was unrelated to the subject's underlying psychiatric condition) was considered outpatient status for the purpose of enrollment. Subjects remaining in the

hospital at the Week 6 visit of Protocol 331-07-203 (for other than psychosocial reasons) were permitted to enroll in this trial at that visit if they were to be discharged from the hospital before the Week 1 visit of this trial.

The trial consisted of a screening visit, a treatment phase, and safety follow up.

Screening/Baseline: Subjects were to be screened for eligibility at the last visit (ie, Week 6) of Protocol 331-07-203. Subjects were to sign a separate informed consent form for participation in Protocol 331-08-210 before any procedures specific to the open-label trial were performed. The assessments from the Week 6 visit of Protocol 331-07-203 were to serve as the baseline measures for Protocol 331-08-210. The subject's medical history was to be updated if necessary.

Subjects who had provided informed consent for Amendment 1 of Protocol 331-08-210 (dated 16 Jul 2009) and had received at least one dose of open-label brexpiprazole under Amendment 1 were to provide informed consent for Amendment 2 at or before the Week 6 visit in order to be considered for long-term treatment in Amendment 2.

Treatment Phase: Eligible subjects were to begin open-label brexpiprazole treatment at a starting dose of 2 mg daily. The first dose of open-label brexpiprazole was to be given 1 day after the Week 6 visit of Protocol 331-07-203, so that treatment continued without interruption. Dose adjustments to brexpiprazole (increases and/or decreases) were permitted at scheduled and unscheduled visits to optimize therapeutic benefit; however, the dose had to remain in the range of 1 to 6 mg daily. Trial visits were to occur at Day 4 and at the end of Weeks 1, 2, 4, and 6 for the 6-week enrollers and at Day 4 and at the end of Weeks 1, 2, 4, 6, 8, 14, 20, 26, 32, 38, 44, and 52 for the 52-week enrollers. The duration of the Treatment Phase was to be 52 weeks for those enrolled under Amendment 2.

Follow-up: Subjects were to be followed up for safety via telephone contact or clinic visit 30 (+/- 2) days after the last dose of open-label trial medication.

Number of Subjects:
Planned: Approximately 300 subjects
Enrolled: 244 subjects entered the trial (including 179 subjects who had received prior brexpiprazole, 41 who had received prior placebo, and 24 who had received prior aripiprazole), and of these, 216 subjects were part of the original protocol specified 6-week enrollers and 28 were part of the Amendment 2 permitted 52-week enrollers.
Treated: 242 subjects received at least 1 dose of investigational medicinal product (IMP).
Analyzed: Data from 242 subjects who received at least 1 dose of IMP were analyzed for safety, and 240 who were enrolled and had baseline and post-baseline observations on PANSS total score were analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion:
Eligible male and female subjects who completed Protocol 331-07-203 and who, in the investigator's judgment, could have potentially benefited from treatment with oral brexpiprazole for schizophrenia. This included subjects who completed Week 6 on double-blind treatment as well as those who initiated open-label brexpiprazole in the non-

responder open-label arm of Protocol 331-07-203 and remained on treatment through Week 6.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, Batch or Lot No(s): Brexpiprazole was provided to the investigator by the sponsor (or contractor) and consisted of brexpiprazole 1-mg tablets (lot number 09B79A001A) and 5-mg tablets (lot number 09B79A005) manufactured by Otsuka Pharmaceutical Co, Ltd. (Japan). The starting dose of brexpiprazole was to be 2 mg. The dose was allowed to be increased to 4 mg daily at the Day 4 visit and further increased to 6 mg daily at the Week 1 visit, or at the investigator's discretion after the Week 1 visit to a maximum of 6 mg daily. The dose of brexpiprazole was allowed to be decreased at any time after Screening/Baseline, at scheduled or unscheduled visits. Dose decreases had to occur in 1-mg increments, with the frequency of decreases based upon tolerability. A decrease to 1 mg/day was permitted for subjects who were unable to tolerate the 2-mg starting dose. Those unable to tolerate the 1-mg daily dose of brexpiprazole had to be withdrawn from the trial. Rechallenge with higher doses of brexpiprazole (ie, 2 mg, 4 mg, or 6 mg) was permitted following dose decreases, if clinically warranted based on the investigator's judgment. Subjects had to return to the clinic for unscheduled visits if dose adjustments for brexpiprazole were required between scheduled visits. All doses of brexpiprazole were to be taken orally once daily and were administered without regard to meals. Subjects were to take trial medication at the same time each day.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration, Batch or Lot No(s): Not applicable.

Criteria for Evaluation:

Primary Outcome Variables:

Safety: Frequency and severity of adverse events (AEs).

Secondary Outcome Variables:

Efficacy: Change from baseline in the following parameters:

- Positive and Negative Syndrome Scale (PANSS) total score,
- Clinical Global Impression - Severity of Illness scale (CGI-S) score,
- Personal and Social Performance (PSP) scale total score,
- PANSS positive and negative subscale scores.

Mean score for the Clinical Global Impression - Improvement scale (CGI-I) was assessed to monitor maintenance of effect. 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), and discontinuation rate for lack of efficacy were also examined.

Safety: AEs related to extrapyramidal symptoms (EPS), physical examinations, vital signs, body weight, body mass index (BMI), waist circumference, clinical laboratory tests (hematology, serum chemistry, urinalysis, and pregnancy tests), electrocardiograms

(ECGs), the Abnormal Involuntary Movement Scale (AIMS), the Simpson Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS), and the Columbia-Suicide Severity Rating Scale (C-SSRS). Additionally, the incidence of treatment-emergent metabolic syndrome was summarized.

Other Outcomes:

Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form score, Morisky Medication Adherence Scale, 4-item score, Resource Utilization Form responses, CogState computerized cognitive test battery.

Statistical Methods:

The frequency and severity of AEs were summarized. Descriptive statistics were provided for each secondary efficacy endpoint. Mean changes from baseline and the incidence of clinically significant changes were calculated for vital signs, body weight, routine laboratory tests (including prolactin), and ECG parameters. Mean change from baseline was calculated for coagulation parameters (prothrombin time, activated partial thromboplastin time, and international normalized ratio), glycosylated hemoglobin, cortisol, adrenocorticotropic hormone, thyroid-stimulating hormone, waist circumference, and body mass index (BMI; derived programmatically from body weight and height measurements). Incidence of laboratory test values that met the criteria for drug induced liver injury (DILI) was also calculated. A central ECG service was utilized to review all ECGs in order to standardize interpretations for the safety analysis. Extrapyramidal symptoms (EPS) were evaluated by calculating mean change from baseline in SAS, AIMS, and BARS. The C-SSRS was used to monitor and classify suicidality. By-subject listings of physical examination findings were provided. Change from baseline was evaluated for the Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form score. In addition, summary statistics were provided for the Morisky Medication Adherence Scale, 4-item score. Responses to the Resource Utilization Form were summarized appropriately to explore the impact of treatment on health care resources. Changes in composite score for the CogState computerized cognitive test battery and results for the individual test domains were examined as exploratory endpoints. The safety data were analyzed by the total subject group including 6-week enrollers plus 52-week enrollers (all treated subjects), by 6-week enrollers separately, and by 52-week enrollers separately, with the exception of AEs, for which data from all treated subjects are presented for the first 6 weeks (and there is no 6-week enroller only presentation). All safety data presented for the 52-week enrollers are based on their entire trial participation, including the first 6 weeks of treatment (applies to all safety variables, including AEs).

Descriptive statistics for the secondary efficacy endpoints were summarized at each trial visit using an observed cases (OC) dataset and at the last visit using a last observation carried forward (LOCF) dataset. Efficacy data were analyzed by the total subject group of 6-week enrollers plus 52 week enrollers, by 6-week enrollers separately, and by 52-week enrollers separately. Data presented for the 52-week enrollers are based on their entire trial participation, including the first 6 weeks of treatment.

Efficacy Results:
Efficacy was assessed as a secondary endpoint in this trial. Numeric improvement was seen from baseline to the last visit (all subjects) for each of the efficacy endpoints in the total population. Mean (standard deviation [SD]) changes from baseline to the last visit were as follows: PANSS total score (-5.36 [12.69]); CGI-S score (-0.30 [0.88]); PSP total score (3.76) [10.91]); PANSS positive subscale score (-1.45 [4.26]); and PANSS negative subscale scores (-1.51 [3.32]). The mean CGI-I score at the last visit was 3.07 (1.22). Similar results were observed for subanalyses of the 6-week and 52-week enrollers (mean change from baseline to Week 6 and Week 52, respectively; LOCF) for all endpoints included above.

Overall, the response rate (where responders were defined as having a reduction of ≥ 30% from baseline in PANSS Total Score or CGI-I score of 1 [very much improved] or 2 [much improved] at the last visit) was 35.2% (86/244 subjects), and the discontinuation rate for lack of efficacy was 2.0% (5/244 subjects) in the total population.

Safety Results:
The primary endpoint of this trial was the frequency and severity of AEs. At least 1 treatment-emergent adverse event (TEAE) was reported for 43.0% (104/242) of treated subjects during the first 6 weeks of treatment and 75.0% (21/28) of 52-week enroller subjects during the entire trial. The incidence of TEAEs by prior treatment group was similar in the prior brexpiprazole (78/178 subjects, 43.8%) and prior placebo (19/41 subjects, 46.3%) treatment groups compared with subjects who had previously received aripiprazole (7/23 subjects, 30.4%) in the double-blind lead-in trial (Trial 331-07-203).

The only TEAE to be reported in ≥ 5% of subjects during the first 6 weeks was insomnia, which was reported in 5.0% (12/242) of subjects. For the 52-week enrollers, the most frequently reported TEAEs (ie, those reported in > 10% of subjects) were viral respiratory tract infection and increased weight (4/28 subjects each, 14.3%) and nasopharyngitis and somnolence (3/28 subjects each, 10.7%). EPS-related TEAEs were reported for 9.9% (24/242) of subjects during the first 6 weeks and for 3.6% (1/28) for the 52-week enrollers. Most TEAEs were mild or moderate in intensity.

Eleven (of 242) subjects experienced a total of 12 serious TEAEs. The most frequently reported serious TEAE was worsening or exacerbation of schizophrenia (preferred term: schizophrenia) reported in 5/242 subjects (2.1%) followed by exacerbation of psychosis (preferred term: psychotic disorder) reported in 4/242 subjects (1.7%). All other serious TEAEs were reported in no more than 1 subject: bronchitis, influenza, and convulsion. All 12 serious TEAEs were reported during the first 6 weeks of treatment with open-label brexpiprazole (1 to 6 mg/day). Three of the 12 events were considered by the investigator to be possibly related to open-label trial medication (1 event each of schizophrenia and psychotic disorder, and the single event of convulsion).

Thirteen (of 242) treated subjects experienced a TEAE that led to discontinuation of the IMP. The most frequently reported TEAE that led to discontinuation was worsening or

exacerbation of schizophrenia (preferred term: schizophrenia) reported in 5/242 subjects (2.1%) followed by exacerbation of psychosis (preferred term: psychotic disorder) reported in 4/242 subjects (1.7%). All other TEAEs that led to discontinuation of IMP were reported in no more than 1 subject each. The majority of the events of schizophrenia (3 of 5) and psychotic disorder (3 of 4) that led to discontinuation of the IMP were considered serious. With exception of one reported event of schizophrenia, all TEAEs that led to discontinuation of IMP occurred during the first 6 weeks of treatment.

Although there were isolated, potentially clinically relevant results for individual subjects in clinical laboratory, vital signs, and/or ECG assessments, there were no clinically relevant mean changes overall for these assessments. Body weight increased slightly during the trial, with a mean (SD) change from baseline to the last visit of 0.6 (2.6) kg, and consistent, small mean (SD) increases from baseline to the last visit in BMI (0.2 [0.9] kg/m^2). Similar incremental increases in mean waist circumference were also observed during the trial.

Conclusions:

- Brexpiprazole (1 to 6 mg/day) was well tolerated when administered for up to 6 weeks or for up to 52 weeks to adult subjects with schizophrenia. During the first 6 weeks of treatment, 43.0% (104/242) of treated subjects reported at least 1 TEAE. During the entire trial, 75.0% (21/28) of subjects enrolled for 52 weeks reported at least 1 TEAE. Most TEAEs were mild or moderate in intensity.
- The only TEAE to be reported in ≥ 5% of subjects during the first 6 weeks of treatment was insomnia (12/242 subjects, 5.0%), and for 52-week enrollers during the entire trial, the most frequently reported TEAEs (ie, those reported in > 10% of subjects) were viral respiratory tract infection and increased weight (4/28 subjects each, 14.3%) and nasopharyngitis and somnolence (3/28 subjects each, 10.7%).
- Schizophrenia and psychotic disorder were the most frequently reported SAEs (5/242 subjects, 2.1% and 4/242 subjects, 1.7%, respectively) and were the TEAEs that most frequently led to discontinuation of the IMP (4/242 subjects each, 1.7%). There were no deaths in this trial.
- Although there were isolated, potentially clinically relevant results for individual subjects in clinical laboratory, vital signs, and/or ECG assessments, there were no clinically relevant mean changes overall for these assessments.
- Brexpiprazole was associated with slight mean increases from baseline in body weight, BMI, and waist circumference.
- The long-term safety and tolerability of brexpiprazole (more than 6 weeks and up to 52 weeks of treatment) appears to be similar to that after short-term exposure (up to 6 weeks); however, this could not be fully characterized in this trial due to the small number of subjects exposed for 52 weeks.
- Assessment of efficacy as a secondary objective showed improvement from baseline, including at the last visit, for each of the efficacy endpoints (eg, PANSS and CGI-I). The response rate (reduction of ≥ 30% from baseline in PANSS total Score or CGI-I score of 1 [very much improved] or 2 [much improved] at the last visit) was

35.2% (86/244 subjects). Discontinuation for lack of efficacy was infrequent (2.0%, 5/244 subjects).