Synopsis

Clinical Report Synopsis for Protocol 31-08-257

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

Name of Product: Aripiprazole (OPC-14597)

Study Title: A Multicenter, 52-week, Open-label Study to Assess the Safety and Tolerability of an Oral Aripiprazole/Escitalopram Combination Therapy in Patients with Major Depressive Disorder

Investigators and Study Centers: Multicenter (67 centers; Multinational [Australia, Estonia, India, Mexico, South Korea, and United States (US)])

Publications: None to date

Studied Period:

Date of first signed informed consent: 18 Nov 2010

Date of last study observation: 15 Sep 2011

Clinical Phase: 3

Objective: To assess the 52-week safety and tolerability of an oral aripiprazole/escitalopram combination therapy in the treatment of patients with Major Depressive Disorder (MDD).

Methodology: This was a multicenter, 52-week, open-label trial designed to assess the safety and tolerability of an oral aripiprazole/escitalopram combination therapy in outpatients with MDD. Enrollment into the trial was from eligible subjects who completed participation in Protocol 31-08-255, 31-08-256, or 31-08-263 ("rollover" subjects).

The trial was organized as follows:

Screening Phase: Rollover subjects were assessed for trial eligibility at the Week 14 Visit of Protocol 31-08-255, 31-08-256, or 31-08-263. The assessments from the Week 14 Visit (± 2 days) served as the baseline measurements for the current protocol. The only additional Baseline assessment required for rollover subjects other than the review of entrance criteria and obtaining informed consent was the completion of the Resource Utilization Form.

Treatment Phase: Eligible rollover subjects began open-label aripiprazole/escitalopram combination treatment 1 day after the Week 14 Visit. Dose adjustments to both

aripiprazole and escitalopram were permitted to optimize therapeutic benefit. While dose adjustments were allowed, escitalopram doses were not to be altered the same week that doses of aripiprazole were changed. Additionally, it was recommended that no adjustments be made to escitalopram during the first 6 weeks of the Treatment Phase while the daily dose of aripiprazole was being titrated and initially established. Trial visits occurred at the end of Weeks 1, 2, 4, 6, 8, 14, 20, 26, 32, 38, 44, and 52. The duration of the Treatment Phase was to be 52 weeks. If a subject discontinued the trial prematurely during the Treatment Phase, every effort was made to complete the Week 52 evaluations.

Follow-up: Subjects who completed the trial were to have a safety follow-up via telephone contact or clinic visit approximately 30 (± 3) days after the last dose of trial medication. This contact also applied to subjects withdrawn prematurely from the trial.

Number of Subjects: It was anticipated that approximately 1500 rollover subjects would be enrolled from approximately 210 US and ex-US sites. This trial was terminated early due to a decision by the sponsor to allow the support of additional programs in the central nervous system therapeutic area where limited therapies are available and thus, there exists a heightened unmet medical need. The closure of the aripiprazole/escitalopram combination therapy program is unrelated to any safety issues, and no signals or items of concern have been identified. As a result, the number of subjects enrolled was significantly less than the proposed sample size. A total of 173 subjects were enrolled into the trial, and 170 subjects were included in the Safety Sample.

Diagnosis and Main Criteria for Inclusion: Male and female outpatients 18 to 66 years of age, inclusive, at the time of informed consent. Subjects who participated in Protocol 31-08-255, 31-08-256, or 31-08-263 and who, in the opinion of the investigator, could potentially benefit from administration of oral aripiprazole/escitalopram combination therapy were enrolled. Eligible subjects included those who completed participation in the Randomization Phase (Phase C, Week 14 Visit) or met criteria for a response at the end of the Prospective Treatment Phase (Phase B, Week 8 Visit) and at the end of Phase B+ (Week 14 Visit) did not meet criteria for remission (defined as a Montgomery-Asberg Depression Rating Scale Total Score of ≤ 10).

Test Product, Dose, Mode of Administration, Batch, or Lot No(s):
Aripiprazole/escitalopram combination therapy for open-label treatment consisted of aripiprazole and escitalopram tablets supplied as one capsule throughout the trial in child-resistant blister packaging for 7 (+ 3) days. The same therapeutic doses were used in this trial as the doses in Protocol 31-08-255 (3 mg/10 mg, 3 mg/20 mg, 6 mg/10 mg, 6 mg/20 mg, 12 mg/10 mg, or 12 mg/20 mg).

Aripiprazole was manufactured by Bristol-Myers Squibb. Escitalopram was manufactured by Forest Laboratories. The over-encapsulation was performed by Boston Analytical.

The lot numbers of trial medication were as follows:

- Aripiprazole/escitalopram combination therapy:
  - 3/10-mg capsule (lot 27241.23/30120.9)
  - 3/20-mg capsule (lot 27241.29/30120.12)
  - 6/10-mg capsule (lot 27241.25/30120.10)
  - 6/20-mg capsule (lot 27241.31)
  - 12/10-mg capsule (lot 27241.33/30120.11)
  - 12/20-mg capsule (lots 27241.34 and 33327.19)

During the Treatment Phase, rollover subjects took their first dose of aripiprazole/escitalopram combination therapy 1 day after the Week 14 Visit from Protocol 31-08-255, 31-08-256, or 31-08-263. The initial daily dose of escitalopram for rollover subjects was either 10 mg or 20 mg (ie, the final prescribed daily dosage being taken during Week 8 [the final week of Phase B] of Protocol 31-08-255, 31-08-256, or 31-08-263).

Rollover subjects began aripiprazole dosing at 6 mg/day. If 6 mg/day was well tolerated, the dose was increased to the target dose of 12 mg/day at the Week 1 Visit. For those subjects who experienced tolerability issues, the titration schedule may have been slowed so that the daily dose was not increased to 12 mg/day until the Week 2, 3, or 4 Visits. In addition, the daily dose may have been reduced to 3 mg/day if significant tolerability issues arose on the initial 6 mg/day dose. However, a maximum tolerated aripiprazole daily dose of 3, 6, or 12 mg was established by the Week 4 Visit. The intention of this guidance was to ensure that the doses achieved in this 52-week trial adequately assessed the safety of the doses that were achieved in the acute efficacy trials (ie, Protocol 31-08-255, 31-08-256, or 31-08-263). However, this recommended titration schedule as well as all dose adjustments were ultimately made based upon the clinical judgment of the investigator as it related to tolerability and therapeutic response.

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

Criteria for Evaluation:

Primary Outcome Variables:
The primary evaluation of safety included frequency and severity of adverse events (AEs), including serious AEs (SAEs), and discontinuations due to AEs.

Other Outcome Variables:
Efficacy: Evaluation of efficacy included the mean Clinical Global Impression Severity of Illness Scale (CGI-S) Score and the mean Patient Global Impression of Severity Scale (PGI-S) Score at baseline and each time point.

Safety: In addition to AEs, safety variables examined in this trial included physical examinations, vital signs, body weight, body mass index (BMI), clinical laboratory tests,

electrocardiograms (ECGs), the Abnormal Involuntary Movement Scale (AIMS), the Simpson Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS), the Columbia-Suicide Severity Rating Scale (C-SSRS), and the Massachusetts General Hospital Sexual Functioning Inventory (MGH SFI).

Outcome: Outcome data included the Sheehan Disability Scale (SDS), the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF), and the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ). Responses to the Resource Utilization Form were summarized appropriately to explore the impact of treatment on health care resources.

Statistical Methods: Descriptive statistics were provided for both safety and efficacy data. Safety tabulations include the frequency of AEs, SAEs including deaths, as well as clinically significant changes in clinical laboratory tests, vital signs, ECGs, body weight, waist circumference, and BMI. For summaries of efficacy (CGI-S and PGI-S) and safety (AIMS, SAS, BARS, and MGH SFI) rating scales, the mean score at entry into the trial was provided as well as the mean scores at each time point. The observed cases data set was used for summaries at baseline and each time point. The incidence of suicidality, suicidal behavior, and suicidal ideation was calculated based on the potential suicide events recorded on the C-SSRS. Descriptive statistics are provided for time on aripiprazole/escitalopram combination therapy.

Pharmacokinetic/pharmacodynamic Methods: Not applicable.

Efficacy Results:
At the end of the trial, the mean (standard deviation [SD]) changes from baseline in the CGI-S and PGI-S Scores were −0.6 (1.0) and −0.4 (1.3), respectively.

Outcome Results:
No meaningful changes from baseline were observed at any time point in the SDS Mean Score, Q-LES-Q-SF Overall General Subscore, or the CPFQ Total Score.

Safety Results:
The majority of subjects received at least 29 days of trial medication. Overall, 113 of 170 subjects (66.5%) had a total of 259 treatment-emergent AEs (TEAEs). The most common TEAEs (incidence ≥ 5% of subjects) were akathisia, nausea, somnolence, headache, dizziness and fatigue. The majority of TEAEs were reported as mild or moderate in severity. Five subjects (2.9%) had severe TEAEs (1 subject had gastrointestinal necrosis, obstructive inguinal hernia, small intestinal obstruction, obstructive umbilical hernia, and pseudomembranous colitis; and 1 subject each experienced one of the following: anxiety, bruxism, hematoma, and musculoskeletal pain).

A total of 5 subjects (2.9%) had serious TEAEs during the trial (1 subject had gastrointestinal necrosis, obstructive inguinal hernia, small intestinal obstruction, obstructive umbilical hernia, and pseudomembranous colitis; 1 subject had a bile duct

stone, acute cholecystitis, cholelithiasis, and pancreatitis; 1 subject had anxiety and insomnia; and 1 subject each had hyperglycemia and increased ALT).

Overall, 20 of 170 subjects (11.8%) experienced AEs that led to discontinuation of the trial medication. No deaths were reported during the trial. One subject reported a pregnancy during the trial.

A total of 18 of 170 subjects (10.6%) had extrapyramidal symptoms (EPS)-related TEAEs. The most frequently reported EPS-related TEAE was akathisia (8.8%).

Overall, 84 of 170 subjects (49.4%) had potentially drug-related TEAEs. The most common potentially drug-related TEAEs (incidence ≥ 5% of subjects) were akathisia, nausea, somnolence, and dizziness.

No meaningful changes from baseline were observed in any laboratory parameters during the trial.

The most common potentially clinically significant laboratory test abnormalities reported during the trial were elevated total fasting cholesterol, elevated fasting triglycerides, elevated fasting low-density lipoprotein (LDL) cholesterol calculation, and elevated fasting glucose.

No meaningful changes from baseline were observed at any time point in the SAS, BARS, AIMS, or MGH SFI. No subject reported 'yes' to question 4 (active suicidal ideation with some intent to act, without specific plan) or question 5 (active suicidal ideation with specific plan and intent) on the C-SSRS. No subject had suicidal behavior during the trial (actual or attempted).

Conclusions:

- At the end of the trial, the mean (SD) changes from baseline in the CGI-S and PGI-S Scores were −0.6 (1.0) and −0.4 (1.3), respectively.
- No meaningful changes from baseline were observed at any time point in the SDS Mean Score, Q-LES-Q-SF Overall General Subscore, or the CPFQ Total Score.
- The majority of subjects received at least 29 days of trial medication.
- Overall, 113 of 170 subjects (66.5%) had a total of 259 TEAEs. The most common TEAEs (incidence ≥ 5% of subjects) were akathisia, nausea, somnolence, headache, dizziness, and fatigue. The majority of TEAEs were reported as mild or moderate in severity. Five subjects (2.9%) had severe TEAEs.
- A total of 5 subjects (2.9%) had serious TEAEs during the trial (1 subject had gastrointestinal necrosis, obstructive inguinal hernia, small intestinal obstruction, obstructive umbilical hernia, and pseudomembranous colitis; 1 subject had a bile duct stone, acute cholecystitis, cholelithiasis, and pancreatitis; 1 subject had anxiety and insomnia; and 1 subject each experienced hyperglycemia and increased ALT).

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- A total of 18 of 170 subjects (10.6%) reported EPS-related TEAEs. The most frequently reported EPS-related TEAE was akathisia (8.8%).
- Overall, 84 of 170 subjects (49.4%) reported potentially drug-related TEAEs. The most common potentially drug-related TEAEs (incidence ≥ 5% of subjects) were akathisia, nausea, somnolence, and dizziness.
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