Synopsis

Clinical Report Synopsis for Protocol 31-08-263

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

Name of Product: Aripiprazole (OPC-14597)

Study Title: A Multicenter, Randomized, Double-blind Study to Evaluate the Efficacy, Safety and Tolerability of an Oral Aripiprazole/Escitalopram Combination Therapy in Patients With Major Depressive Disorder

Investigator(s) and Study Center(s): Multicenter (29 centers; multinational with subjects enrolled at sites in Canada, France, India, Malaysia, Poland, South Africa, and United States)

Publications: None to date.

Studied Period:

Date of first signed informed consent: 04 Oct 2010

Date of last study observation: 01 Sep 2011

Clinical Phase: 3

Primary: To compare the efficacy of an oral aripiprazole/escitalopram combination therapy (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) with aripiprazole monotherapy (3 mg, 6 mg, 12 mg) and escitalopram monotherapy (10 mg, 20 mg) in patients with major depressive disorder (MDD) who demonstrated an incomplete response to a prospective 8-week trial of escitalopram monotherapy.

Secondary: To evaluate the safety and tolerability of an oral aripiprazole/escitalopram combination therapy in patients with MDD who demonstrated an incomplete response to a prospective 8-week trial of escitalopram monotherapy.

Methodology: This was a multicenter, randomized, double-blind trial designed to assess the efficacy, safety, and tolerability of an oral aripiprazole/escitalopram combination therapy in subjects with MDD who demonstrated an incomplete response to a prospective trial of escitalopram and reported a treatment history for the current MDD episode of an inadequate response to at least one and no more than 3 adequate trials of an approved antidepressant other than escitalopram. An inadequate response was defined as less than a 50% reduction in depressive symptom severity as assessed by the subject's self-report on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ) and evaluated by the investigator as part of the subject's medical

and psychiatric history. An adequate trial was defined as an antidepressant treatment for at least 6 weeks duration (or at least 3 weeks for combination treatments) at an approved dose as specified in the ATRQ.

The trial was organized as follows:

Phase A (Screening Phase): The Screening Phase ranged from a minimum of 7 days to a maximum of 42 days, consisting of a Screening and Baseline Visit to assess trial eligibility criteria and to wash out prohibited concomitant pharmacotherapy. Screening evaluations included the Mini International Neuropsychiatric Interview (MINI) to confirm the subject's diagnosis of MDD, the ATRQ to measure responsiveness to prior antidepressant therapy during the current depressive episode, the 17-item Hamilton Depression Rating Scale (HAM-D17) to assess symptom severity, the Clinical Global Impression - Severity of Illness scale (CGI-S) to evaluate overall clinical severity, and the Columbia-Suicide Severity Rating Scale (C-SSRS) to assess suicidality. Safety screening assessments included a full physical examination, clinical laboratory tests, an electrocardiogram (ECG), vital signs, and a medical history review. An interactive voice response system (IVRS) or interactive web response system (IWRS) was used to obtain the subject identifier for each subject with a signed informed consent form.

Phase B (Single-blind Prospective Treatment Phase): Subjects who met entrance criteria at the end of the Screening Phase (ie, Baseline Visit) who were diagnosed with either a single or recurrent episode of MDD and were assessed on the HAM-D17 with a total score of ≥ 18 were enrolled into the 8-week Prospective Treatment Phase (Phase B), in which all subjects were assigned single-blind escitalopram monotherapy (10 or 20 mg/day). Subjects enrolled in the Prospective Treatment Phase attended trial visits at the end of Weeks 1, 2, 3, 4, 6, and 8. If a subject discontinued the trial prematurely during the Prospective Treatment Phase, every effort was made to complete the Week 8 evaluations.

Phase B+ (Single-blind Phase B Responder): Subjects who met criteria for a response at the end of the Prospective Treatment Phase (Week 8 Visit) continued treatment with the single-blind escitalopram monotherapy at the dose (10 or 20 mg/day) taken during the final week of Phase B for an additional 6 weeks, for a total of 14 weeks. Treatment response was defined as ≥ 50% reduction in depressive symptom severity between the Baseline Visit and the Week 8 Visit, as measured by the HAM-D17 Total Score; OR a HAM-D17 Total Score of < 14 at the Week 8 Visit; OR a Clinical Global Impression - Improvement scale (CGI-I) Score of < 3 at the Week 6 or 8 Visits. These subjects attended visits at the end of Weeks 11 and 14 during this extension of treatment with single-blind escitalopram.

Phase C (Double-blind Randomization Phase): Subjects who met criteria for an incomplete response at the end of the Prospective Treatment Phase (Week 8 Visit) entered a 6-week Double-blind Randomization Phase (Phase C). Incomplete response was defined as less than a 50% reduction in depressive symptom severity between the Baseline Visit and the Week 8 Visit, as measured by the HAM-D17 Total Score; AND

a HAM-D17 Total Score of ≥ 14 at the Week 8 Visit; AND a CGI-I Score of ≥ 3 at the Week 6 and 8 Visits.

Subjects with an incomplete response at the end of the Prospective Treatment Phase (Week 8 Visit) were randomized into the 6-week Randomization Phase in a 1:1:1 ratio to receive one of the following double-blind treatment regimens:

- Oral aripiprazole/escitalopram combination therapy (aripiprazole 3, 6, or 12 mg/day in combination with the escitalopram dose taken during the final week of Phase B/Prospective Treatment Phase [either 10 or 20 mg/day]);
- Aripiprazole monotherapy (3, 6, or 12 mg/day); or
- Continued escitalopram monotherapy (either 10 or 20 mg/day, whichever dose was taken during the final week of Phase B/Prospective Treatment Phase).

Treatment assignments were obtained by accessing the IVRS or IWRS. Randomized subjects attended weekly visits during Phase C (ie, Weeks 9, 10, 11, 12, 13, and 14).

If a subject discontinued the trial prematurely either during the Randomization Phase or during continued escitalopram monotherapy in Phase B+, every effort was made to complete the Week 14 Visit evaluations.

Subjects who completed trial visits through the Week 14 Visit, whether or not they were randomized into Phase C or continued with single-blind escitalopram monotherapy in Phase B+ (and who did not meet remission criteria at the end of Phase B+), may have been offered entry into an optional 52-week, open-label rollover trial.

Follow-up: Subjects who did not enter the open-label trial had a safety follow-up via a 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 subjects needed to be screened and 1200 subjects enrolled into Phase B (Single-blind Prospective Treatment Phase) from approximately 70 United States (US) and non-US sites globally in order to randomize 600 subjects into Phase C (Double-blind Randomization Phase). Additional sites may have been included if required.

This trial was terminated early by the sponsor in order to allow support of additional programs in the central nervous system therapeutic area where limited therapies are available and, thus, there exists 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 of the early termination, the number of subjects enrolled was significantly less than the planned sample size.

A total of 221 subjects were screened, 137 subjects were enrolled into Phase B, and 71 subjects completed Phase B. Twenty-six subjects were enrolled into Phase B+ and 19 subjects completed Phase B+. A total of 45 subjects were randomized into Phase C

(16 subjects to the aripiprazole/escitalopram combination therapy group, 14 to the escitalopram group, and 15 to the aripiprazole group) and 32 subjects completed Phase C. A total of 45 subjects were included in the Safety Sample, which comprised the randomized subjects in Phase C who received at least one dose of double-blind trial medication, and the Intent-to-treat Sample, which comprised the randomized subjects in Phase C who received at least one dose of double-blind trial medication and had at least one post-randomization efficacy evaluation in Phase C.

Diagnosis and Main Criteria for Inclusion: The trial population included male and female outpatients between the ages of 18 and 65 years of age, inclusive, with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* diagnosis of a single or recurrent, nonpsychotic episode of MDD, confirmed by the MINI. The current episode was at least 8 weeks in duration. Additionally, subjects must have reported a treatment history for the current episode of an inadequate response to at least one and no more than 3 adequate trials of an approved antidepressant other than escitalopram.

Test Product, Dose, Mode of Administration, Batch or Lot No(s): Trial medication was provided to the investigator(s) by the sponsor (or designee) and consisted of aripiprazole and or escitalopram tablets supplied as one blinded capsule (ie, one over-encapsulated tablet) throughout the trial in a child-resistant blister package. When accessed by the site, the IVRS or IWRS assigned a specific blister card to be dispensed to a subject.

Blinded over-encapsulated capsules for Phase B and B+ contained only escitalopram tablets (10 or 20 mg). Subjects took one capsule daily in Phase B and B+. For Phase C, double-blind trial medication was supplied as capsules containing either aripiprazole/escitalopram combination therapy (3/10, 3/20, 6/10, 6/20, 12/10, or 12/20 mg), aripiprazole monotherapy (3, 6, or 12 mg), or escitalopram monotherapy (10 or 20 mg). All subjects randomized into Phase C took one capsule of double-blind trial medication daily.

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 monotherapy:
  - 3-mg capsule (lot 27241.28)
  - 6-mg capsule (lot 27241.30)
  - 12-mg capsule (lot 27241.32/30120.8)
- Escitalopram monotherapy:
  - 10-mg capsule (lots 27241.22 and 27241.24)
  - 20-mg capsule (lots 27241.26/30120.3, 27241.27, and 27241.35)

- 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)

The initial dose of escitalopram during Phase B was 10 mg/day with an increase to 20 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 20 mg/day until the Week 2 or 3 Visits. In addition, the daily dose may have been reduced to 10 mg/day if significant tolerability issues arose on the 20-mg/day dose. Subjects who experienced tolerability issues with the initial 10-mg/day dose did not need to be challenged with the 20-mg/day dose. However, no dose decreases were allowed after the Week 4 Visit and no dose increases were allowed after the Week 3 Visit. The intention of this dosing paradigm was to have subjects treated at a maximum tolerated dose (MTD) during the Prospective Treatment Phase to optimize an efficacious response to escitalopram monotherapy. Subjects not able to tolerate 10 mg/day of escitalopram were discontinued from the trial. Subjects who met criteria for a response at the end of the Prospective Treatment Phase were not randomized but continued treatment with single-blinded escitalopram monotherapy for an additional 6 weeks (ie, Phase B+) at the established MTD taken during the final week of Phase B (either 10 or 20 mg/day). No dose adjustments were allowed for escitalopram monotherapy during Phase B+.

Subjects randomized to oral aripiprazole/escitalopram combination therapy began dosing with 6 mg/day of aripiprazole in combination with the MTD of escitalopram taken during the final week of Phase B (either 10 or 20 mg/day). No dose adjustments were allowed for escitalopram during Phase C. Subjects were titrated to the aripiprazole target dose of 12 mg/day at the Week 9 Visit if the initial 6-mg/day dose was tolerated. 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 10, 11, or 12 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 must have been established by the Week 12 Visit. No dose increases were allowed for aripiprazole after the Week 12 Visit; however, doses may have been decreased at any visit, based upon tolerability. All dose increases were made based upon tolerability and were made no more frequently than at weekly intervals to achieve the maximum tolerated aripiprazole daily dose by no later than the Week 12 Visit.

Subjects randomized to aripiprazole monotherapy began dosing with 6 mg of aripiprazole per day and followed the same dosing guidelines and regimen as indicated for aripiprazole as part of the oral aripiprazole/escitalopram combination therapy.

Subjects randomized to escitalopram monotherapy began dosing with the MTD of escitalopram taken during the final week of Phase B (either 10 or 20 mg/day) and remained on this dose throughout Phase C. No dose adjustments were allowed for escitalopram monotherapy during Phase C. This escitalopram monotherapy dosing guideline and regimen were the same as indicated for escitalopram as part of the oral aripiprazole/escitalopram combination therapy.

All doses of trial medication were taken orally once daily, without regard to meals.

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

Criteria for Evaluation:

Primary Outcome Variable:

The primary outcome endpoint for determination of efficacy was the mean change from the end of Phase B (Week 8 Visit) to the end of Phase C (Week 14 Visit) in the Montgomery-Asberg Depression Rating Scale (MADRS) Total Score using the last observation carried forward (LOCF) dataset.

Key Secondary Outcome Variables:

The key secondary efficacy endpoints included:

- Mean CGI-I Score at the end of Phase C (Week 14 Visit, LOCF);
- Mean change from the end of Phase B (Week 8 Visit) to the end of Phase C (Week 14 Visit, LOCF) in the Sheehan Disability Scale (SDS) Mean Score (note: this was a change to the protocol-specified analyses [protocol amendment 2] which provided for mean change in SDS Total Score).

Other Outcome Variables included:

1) MADRS Response;
2) MADRS Remission;
3) CGI-I Response;
4) Time to achieve partial MADRS response;
5) Time to achieve MADRS response;
6) Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) Total Score;
7) HAM-D17 Anxiety Subscale Score;
8) Patient Global Impression of Improvement (PGI-I) Response;
9) Patient Global Impression of Severity (PGI-S) Score;
10) CGI-S Score;
11) Overall General Subscore (sum of first 14 items) of the Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF);
12) Hamilton Anxiety Rating Scale (HAM-A) Total Score;
13) Mean PGI-I Score;

14) MADRS individual item scores;
15) SDS individual item scores;
16) Satisfaction with Medication Score (item 15) of the Q-LES-Q-SF;
17) Overall Life Satisfaction Score (item 16) of the Q-LES-Q-SF;
18) MADRS Total Score;
19) MADRS Response relative to baseline.

Safety: Standard safety variables analyzed included adverse events, physical examinations, vital signs, body weight, body mass index (BMI), clinical laboratory tests, and ECGs. In addition to the analyses of standard safety variables, other safety variables including Abnormal Involuntary Movement Scale (AIMS), Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), C-SSRS, and Massachusetts General Hospital Sexual Functioning Inventory (MGH SFI) were also evaluated.

Pharmacokinetics (PK): Plasma concentrations of aripiprazole and escitalopram were collected at the end of Weeks 12 and 14 for randomized subjects. Escitalopram, aripiprazole, and dehydro-aripiprazole plasma concentrations were to be summarized by treatment and dose. The primary objective of the collection of the PK samples was to determine the exposure to the treatments during the trial and also to perform any additional PK/pharmacodynamic modeling if data permitted.

Statistical Methods:
The statistical analysis of the primary endpoint was performed by fitting an analysis of covariance (ANCOVA) model to the change from the end of Phase B (Week 8 Visit) for the MADRS Total Score at the Week 14 Visit (LOCF). The model included the MADRS Total Score at the end of Phase B as a covariate and treatment as the main effect.

The difference of the treatment effect between the combination therapy and each of the monotherapies was compared through a t-statistic based on the difference between least squares means derived from the ANCOVA model utilizing the computing software SAS®, version 9.2. The means, standard errors, and 95% confidence intervals for the treatment differences and p-values for every trial week in Phase C (LOCF) are presented.

The primary statistical analysis based on the ANCOVA model was performed repeatedly on the observed case (OC) dataset.

For the secondary outcome variables, the comparison of the treatment effect between the combination therapy and each of the monotherapies was performed. The CGI-I Score was analyzed by the Cochran-Mantel-Haenszel (Row Mean Scores) test at a 2-sided significance level of 0.05. The SDS Mean Score was analyzed similarly as the primary efficacy endpoint at a 2-sided significance level of 0.05. Additionally, the same analyses were performed on the OC dataset.

The endpoints of CPFQ Total Score, HAM-D17 Anxiety Subscale Score, PGI-S Score, CGI-S Score, Q-LES-Q-SF Overall General Subscore, Satisfaction with Medication

Score (item 15) of the Q-LES-Q-SF, Overall Life Satisfaction Score (item 16) of the Q-LES-Q-SF, HAM-A Total Score, MADRS Total Score, MADRS individual item scores, and SDS individual item scores were analyzed similarly as the primary efficacy endpoint at a 2-sided significance level of 0.05, where the covariate was the baseline (the end of Phase A) assessment for the analysis of MADRS Total Score and the end of Phase B assessment for the other endpoints.

The PGI-I Score was analyzed by the Cochran-Mantel-Haenszel (Row Mean Scores) test at a 2-sided significance level of 0.05.

Response and remission rates in MADRS and response rate of PGI-I and CGI-I were evaluated by the Cochran-Mantel-Haenszel General Association Test in an LOCF analysis.

Time to achieve partial MADRS response and time to achieve MADRS response from the end of Phase B were estimated by the Kaplan-Meier method and the treatment differences were compared by log-rank tests.

Additionally, the same analyses were performed on the OC dataset. The analyses for PGI-I Score and change from baseline in MADRS Total Score, CPFQ Total Score, CGI-S Score, Q-LES-Q-SF Overall General Subscore, HAM-A Total Score, MADRS individual item scores, SDS individual item scores, HAM-D17 Anxiety Subscale Score, and PGI-S Score were performed by trial week. The baseline was defined as the end of Phase A assessment for the analysis of MADRS Total Score and the end of Phase B assessment for the other endpoints.

Safety measurements collected in Phase C of the trial were summarized. Safety measurements collected in Phase B and B+ are listed but were not summarized.

Pharmacokinetic/pharmacodynamic Methods: Due to the early termination of the trial, none of the PK samples were analyzed. No further analysis is planned.

Efficacy Results: Because the trial was terminated early, the analyses performed were not statistically powered to detect statistically significant differences between treatment groups. The LS mean (SE) change in MADRS Total Score at the end of Phase C (Week 14 Visit) indicated greater numeric improvement in the aripiprazole/escitalopram combination therapy group (−9.0 [2.1]) compared to either the escitalopram (−3.6 [2.2]) or aripiprazole (−3.8 [2.1]) monotherapy groups. No clinically meaningful differences in the secondary or other efficacy analyses were observed between the aripiprazole/escitalopram combination therapy and either the escitalopram or aripiprazole monotherapy treatment groups.

Pharmacokinetic/pharmacodynamic Results: Due to the early termination of the trial, none of the PK samples were analyzed and at the direction of the sponsor, the samples were destroyed. Thus, no data are reported, and no further analysis is planned.

Safety Results: In Phase C, 36 of 45 subjects (80.0%) experienced a total of 92 treatment-emergent adverse events (TEAEs). Similar numbers of subjects reported at least 1 TEAE in the aripiprazole/escitalopram combination therapy group (12 of 16 subjects; 75.0%), the escitalopram group (11 of 14 subjects; 78.6%), and the aripiprazole group (13 of 15 subjects; 86.7%). The most common TEAEs (incidence ≥ 5% of subjects overall) reported during treatment with double-blind trial medication were restlessness (13.3%); somnolence and dry mouth (each 11.1%); nausea, fatigue, akathisia, dizziness, headache, and insomnia (each 8.9%); asthenia, upper respiratory tract infection, lethargy, and tremor (each 6.7%). Of these most common TEAEs, restlessness was reported by a higher percentage of subjects in the aripiprazole group (4 of 15 subjects, 26.7%) than in the aripiprazole/escitalopram combination therapy group (2 of 16 subjects, 12.5%) or the escitalopram group (0 subjects) and upper respiratory tract infection was the most frequently reported TEAE in the aripiprazole/escitalopram combination therapy group (3 of 16 subjects, 18.8%); no subjects in either of the two monotherapy groups experienced this latter TEAE.

No serious TEAEs were reported during Phase C. Adverse events that led to discontinuation from the trial medication during Phase C were reported by 2 subjects in the aripiprazole/escitalopram combination therapy group (TEAEs of nausea and asthenia in 1 subject each). A severe TEAE of dizziness was reported in 1 subject in the escitalopram group.

Mean changes from baseline in clinical laboratory, vital sign, or ECG parameters during Phase C did not show any clinically relevant differences between treatment groups. (A notable increase in mean gamma-glutamyl transferase observed from the end of Phase B to Week 14 (70.75 U/L) in the escitalopram group is likely due to 1 subject.)

The most frequently reported potentially clinically significant laboratory test abnormalities during Phase C (incidence ≥ 10% of subjects overall) were elevated fasting triglycerides, elevated fasting glucose, elevated fasting total cholesterol, and elevated fasting low-density lipoprotein cholesterol. Potentially clinically significant ECG abnormalities included increased QT interval corrected for heart rate by Bazett's formula (QTcB) (2 subjects in the aripiprazole group), ventricular premature beat (1 subject in the aripiprazole group), and supraventricular premature beat and symmetrical T-wave inversion (1 subject each in the aripiprazole/escitalopram combination therapy group).

Extrapyrimidal symptoms (EPS) were evaluated using the following rating scales: SAS, AIMS, and BARS. No meaningful differences were observed between the aripiprazole/escitalopram combination therapy and either the escitalopram or aripiprazole groups in SAS Total Score, AIMS scores, or BARS Global Clinical Assessment Score.

No meaningful differences in MGH SFI scores were noted. No subjects had active suicidal ideation (as defined as an answer of 'yes' on question 4 or 5 on the C-SSRS) or had suicidal behavior during Phase C (actual or attempted).

Conclusions:

- The analysis of LS mean change in MADRS Total Score at the end of Phase C (Week 14 Visit) indicated greater numeric improvement in the aripiprazole/escitalopram combination therapy group compared to either the escitalopram or aripiprazole monotherapy groups. No clinically meaningful differences in the secondary or other efficacy analyses were observed between the aripiprazole/escitalopram combination therapy and either the escitalopram or aripiprazole monotherapy treatment groups.
- The aripiprazole/escitalopram combination therapy was generally well tolerated when administered for 6 weeks to subjects with MDD who demonstrated an incomplete response to a prospective 8-week trial of escitalopram monotherapy.
- A total of 36 of 45 subjects (80.0%) experienced at least 1 TEAE during Phase C. The most common TEAEs (incidence ≥ 5% of subjects overall) reported during treatment with double-blind trial medication were restlessness, somnolence, dry mouth, nausea, fatigue, akathisia, dizziness, headache, insomnia, asthenia, upper respiratory tract infection, lethargy, and tremor (all reported at an incidence < 15% of subjects).
- No serious TEAEs were reported during Phase C. Adverse events that led to discontinuation from the trial medication during Phase C were reported for 2 subjects in the aripiprazole/escitalopram combination therapy group (TEAEs of nausea and asthenia in 1 subject each).
- No meaningful differences were observed during Phase C in clinical laboratory tests, vital sign assessments, ECG parameters, body weight, or BMI between the aripiprazole/escitalopram combination therapy and either the escitalopram or aripiprazole monotherapy groups.
- There were no meaningful differences between the aripiprazole/escitalopram combination therapy and either the escitalopram or aripiprazole monotherapy groups in SAS Total Score, AIMS scores, or BARS Global Clinical Assessment Score. No meaningful differences MGH SFI scores were noted, and no subjects with suicidal ideation or suicidal behavior (actual or attempted) as measured by the C-SSRS.