Otsuka Pharmaceutical
Development & Commercialization, Inc.

Aripiprazole (OPC-14597)
SYNOPSIS CLINICAL STUDY REPORT

A Multicenter, Open-label Study to Assess Hospitalization Rates in Adult Subjects With Schizophrenia Treated Prospectively for 6 Months With Aripiprazole IM Depot Compared With 6-month Retrospective Treatment With Oral Antipsychotics in a Naturalistic Community Setting in Europe, Canada, and Asia
"ARRIVE"

CONFIDENTIAL – PROPRIETARY INFORMATION
THIS DOCUMENT CONTAINS INFORMATION THAT IS CONFIDENTIAL AND PROPRIETARY TO H. LUNDBECK A/S (LUNDBECK) AND OTSUKA AMERICA PHARMACEUTICAL, INC. (OAPI)
Protocol No. 31-11-284

Indication:	Schizophrenia
Clinical Development Phase:	3b
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
Sponsor Contact:	[redacted], MD Director, Global Clinical Development Phone [redacted] Fax [redacted]
Principal Investigator:	Multicenter (38 activated sites; 11 of those sites with subjects on trial); Multinational in Europe, Canada, and Asia
Study Initiation Date:	30 Jan 2012
Study Completion Date:	11 Oct 2012
Report Issued:	21 Feb 2013

Statement of Compliance with Good Clinical Practices
This trial was conducted in compliance with Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no study procedures were performed on study candidates until written consent had been obtained from them. The informed consent form, protocol, and amendments for this study were submitted to and approved by the institutional review board (IRB) or ethics committee (EC) at each respective study center.

List of Abbreviations and Definition of Terms

AE	Adverse event
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
ECG	Electrocardiogram
ICF	Informed consent form
IM	Intramuscular
NA	Not applicable
PANSS	Positive and Negative Syndrome Scale
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event

1 Synopsis

Clinical Report Synopsis for Protocol 31-11-284

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

Name of Product: Aripiprazole (OPC-14597)

Study Title: A Multicenter, Open-label Study to Assess Hospitalization Rates in Adult Subjects With Schizophrenia Treated Prospectively for 6 Months With Aripiprazole IM Depot Compared With 6-month Retrospective Treatment With Oral Antipsychotics in a Naturalistic Community Setting in Europe, Canada, and Asia

Investigators and Study Centers: Multicenter (38 activated sites; 11 of those sites with subjects on trial); Multinational in Europe, Canada, and Asia

Publications: None to date

Studied Period:

Date of first signed informed consent: 30 Jan 2012

Date of last study observation: 11 Oct 2012

Clinical Phase: 3b

Objectives: The primary objective was to compare inpatient psychiatric hospitalization rates (proportion of subjects with ≥ 1 inpatient psychiatric hospitalization[s]) between Months 4 to 6 (Weeks -12 to -24) of the retrospective period while the subject was receiving oral standard of care antipsychotic treatment(s) with those of Months 4 to 6 (Weeks 12 to 24) of the prospective period after the switch to aripiprazole IM depot in adult subjects with schizophrenia.

The secondary objective was to further evaluate long-term safety and tolerability of aripiprazole IM depot in adult subjects with schizophrenia.

Methodology: This was a multicenter, open-label trial consisting of a screening phase and 3 treatment phases: a Tolerability Assessment Phase (if applicable), an Open-label Aripiprazole IM Depot Treatment Phase, and an Open-label Aripiprazole IM Depot Treatment Extension Phase (if eligible). This was to be a 6-month retrospective followed by 6-month prospective trial to assess the inpatient psychiatric hospitalization rates of subjects receiving oral standard of care (6 month retrospective hospitalization[s]) and that of subjects receiving once monthly aripiprazole IM depot injections prospectively for 6 months (6 months prospective hospitalization[s]). Inpatient psychiatric hospitalization

rates in the last 3 months of oral standard of care were to be compared with those in the last 3 months of aripiprazole IM depot treatment. This trial was terminated early by the sponsor. The reason for study closure is not related to safety because no signals or items of concern have been identified.

A detailed summary of the trial design is as follows:

Screening Phase
Eligibility was determined during a Screening Phase of 2 to 28 days. The investigator obtained a comprehensive review of past medical history, inclusive of all hospitalizations and medical interventions for the 7 months prior to the date the subject signed the informed consent form (ICF). This 7-month period allowed for the required 4-week outpatient treatment period in addition to the 6 months of retrospective hospitalization and intervention data required. If a subject had been hospitalized for any psychiatric reason during the 4 weeks prior to signing the ICF or at any time during the screening period, then he/she was not eligible to enter the trial. Any antipsychotic(s) other than aripiprazole the subject was receiving were tapered off and discontinued during the screening period prior to the subject receiving the first dose of oral aripiprazole in the Tolerability Assessment Phase or the first aripiprazole IM depot injection in Open-label Aripiprazole IM Depot Treatment Phase, depending on the subject's point of entry into the trial.

Tolerability Assessment Phase (Phase A)
Subjects meeting eligibility criteria during the Screening Phase and who had no history of tolerating oral aripiprazole entered the Tolerability Assessment Phase. During this phase, tolerability to oral aripiprazole and the subject's clinical status were evaluated. Subjects were seen in the clinic on the last day of the Screening Phase and weekly thereafter for a minimum of 1 week and maximum of 4 weeks, until tolerability to oral aripiprazole had been determined, based on the investigator's discretion, or until the subject was terminated from the trial. The recommended initial dose of oral aripiprazole in the Tolerability Assessment Phase was 10 mg/day or 15 mg/day, depending on the subject's symptoms and the investigator's judgment. The investigator was permitted to titrate the dose of oral aripiprazole up to 30 mg/day based on clinical need. Subjects proceeded to the Open-label Aripiprazole IM Depot Treatment Phase after 1 week if they tolerated oral aripiprazole according to the investigator's judgment. If a subject could not tolerate oral aripiprazole, or required inpatient psychiatric hospitalization based on the investigator's clinical judgment, the subject was withdrawn from the trial.

Open-label Aripiprazole IM Depot Treatment Phase (Phase B)
Subjects who successfully completed the Tolerability Assessment Phase or subjects that were currently receiving oral aripiprazole monotherapy or were currently taking any antipsychotic other than oral aripiprazole and had a history of tolerating oral aripiprazole entered the Open-label Aripiprazole IM Depot Treatment Phase directly. All subjects entering the Open-label Aripiprazole IM Depot Treatment Phase began treatment with aripiprazole IM depot 400 mg and received concomitant oral aripiprazole for the first 14 days of entering the Open-label Aripiprazole IM Depot Treatment Phase to achieve

therapeutic plasma concentrations of aripiprazole. The oral dose was determined by the investigator using the following criteria:

1) Subjects who were in the Tolerability Assessment Phase were initially dosed at 10 mg/day, if they were on a previous dose of 10 to 20 mg/day. They received an initial dose of 15 mg/day if they had a previous dose of > 20 to 30 mg/day.
2) Subjects who were on oral aripiprazole at trial entry were initially dosed at 10 mg/day, if they were on a previous dose of 10 to 20 mg/day. They received an initial dose of 15 mg per day if they had a previous dose of > 20 to 30 mg/day.
3) For subjects treated with antipsychotics other than oral aripiprazole prior to trial entry, who had a history of tolerating oral aripiprazole, the recommended oral aripiprazole starting dose was 10 mg/day.

Although these initial doses were recommended, the investigator had the option to titrate the oral aripiprazole dose for efficacy to a maximum of 20 mg/day or decrease the dose for tolerability to a minimum of 10 mg/day at any time during the first 14 days of Open-label Aripiprazole IM Depot Treatment Phase, if necessary. Rescue therapy with oral aripiprazole was permitted as described in the protocol.

Aripiprazole IM depot 400 mg was the starting IM depot dose for all subjects. However, investigators had the option to decrease the dose of aripiprazole IM depot to 300 mg if needed for tolerability or to increase the dose to 400 mg subsequently to address efficacy as needed. Dose-adjustments between aripiprazole IM depot 400 mg and 300 mg were permitted as often as necessary to maintain symptomatic stability with acceptable tolerability. Aripiprazole IM depot (400 or 300 mg) was administered by IM injection into the gluteal muscle monthly (28 ± 2 days) in the clinic for a total of 6 injections.

During the Open-label Aripiprazole IM Depot Treatment Phase, subjects were assessed at baseline (Day 0) and Weeks 1, 2, 4, 8, 12, 16, 20, and 24. At each visit and at any unscheduled visits, the subject's clinical status was evaluated. All hospitalizations and interventions (psychiatric and nonpsychiatric), in addition to all other assessments outlined in the protocol, were recorded in the source documentation.

<u>Open-label Aripiprazole IM Depot Treatment Extension Phase (Phase C)</u>
Subjects who completed the Open-label Aripiprazole IM Depot Treatment Phase and whom the investigator believed would receive benefit from continued treatment with aripiprazole IM depot, were eligible to enter the Open-label Aripiprazole IM Depot Treatment Extension Phase. In this phase subjects were to be allowed to continue treatment with aripiprazole IM depot until 31 Dec 2014 or until aripiprazole IM depot was commercially available in the respective country whichever occurred sooner. Subjects were to continue to receive an aripiprazole IM depot (400 or 300 mg) injection monthly (every 28 days but not less than 26 days) in the Open-label Aripiprazole IM Depot Treatment Extension Phase. Subjects were to be permitted to have repeated decreases to 300 mg for tolerability and increase back to 400 mg as necessary to maintain symptomatic stability with acceptable tolerability based on the investigator’s judgment.

Subjects who had not yet completed the Open-label Aripiprazole IM Depot Treatment Phase at the time aripiprazole IM depot became commercially available, in the respective country, would not have had the option to enter the Open-label Aripiprazole IM Depot Treatment Extension Phase. Rescue therapy with oral aripiprazole was permitted and assessments were to be conducted as described in the protocol.

Subjects who completed or withdrew from the trial (unless they had withdrawn their consent for participation in the trial) were to receive a telephone call for safety follow-up at 30 ± 3 days after the last trial visit.

The duration of this trial from first subject enrolled to last subject completed was originally estimated to be up to 37 months, including an estimated 1.5-year enrollment period. The total length of participation in the trial (from a minimum of 7 months and 2 days to a maximum of 9 months) for an individual subject depended on the screening duration (2 to 28 days), Tolerability Assessment Phase duration (0 to 1 month), Open-label Aripiprazole IM Depot Treatment Phase duration (6 months) and a 30-day follow-up. All subjects who completed the Open-label Aripiprazole IM Depot Treatment Phase had the option to enter the Open-label Aripiprazole IM Depot Treatment Extension Phase. The Open-label Aripiprazole IM Depot Treatment Extension Phase of the trial was to continue until 31 Dec 2014 or until aripiprazole IM depot was commercially available in the respective country whichever occurs sooner. Due to the early termination of the trial, sites placed subjects on appropriate therapy per the investigator's judgment before discontinuing IM depot; Canadian subjects were offered enrollment into Trial 31-11-283.

Number of Subjects: Approximately 700 subjects were to be screened at approximately 125 sites in Europe, Canada, and Asia to enroll an estimated sample size of 500 subjects to be able to detect a difference of 15% or higher between pre-switch and post-switch hospitalization rates. After 250 subjects completed the Open-label Aripiprazole IM Depot Treatment Phase, an interim analysis was to be conducted. This trial was terminated early by the sponsor. The reason for study closure is not related to safety because no signals or items of concern have been identified. As a result of the early termination of the trial, the number of subjects enrolled was significantly less than the projected sample size. A total of 33 subjects were screened for the trial, and 30 subjects were treated. Three subjects completed the trial.. The most frequent reason for subject discontinuation from the trial was that the sponsor discontinued the trial (CT-2). Of the 30 subjects enrolled in the trial, 19 subjects entered Phase A, and 19 subjects entered Phase B. Phase B consisted of the 8 subjects from Phase A and 11 entered Phase B directly from Screening. Three subjects completed Phase B and entered Phase C (CT-1.1).

Table 1-1 Subject Disposition				
Number of Subjects	**Phase A N (%)**	**Phase B N (%)**	**Phase C N (%)**	**Total Enrolled N (%)**
Screened				33
Screen Failure				3
Entered	19 (100.0)	19 (100.0)	3 (100.0)	30 (100.0)
Treated	19 (100.0)	19 (100.0)	3 (100.0)	30 (100.0)
Completed	NA	3 (15.8)	0	NA
Discontinued	11 (57.9)	16 (84.2)	3 (100.0)	30 (100.0)
Entered Next Phase	8 (42.1)	3 (15.8)	NA	NA
Analyzed for Safety	19 (100.0)	19 (100.0)	3 (100.0)	NA
Analyzed for Efficacy	NA	19 (100.0)	3 (100.0)	NA

NA = not applicable.
Source: CT-1.1.

In the Safety Sample, there were twice as many males as females (20 and 10, respectively) and all were white, non-Hispanic or Latino (CT-3.1).

Diagnosis and Main Criteria for Inclusion: Male and female subjects, aged 18 to 65 years, inclusive, with a diagnosis of schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria and a history of the illness for at least 1 year (12 months) prior to screening, who had at least one inpatient psychiatric hospitalization within the 2 years (24 months) prior to screening but had been managed on an outpatient basis during the 4 weeks prior to signing the ICF and during the screening period, who had been prescribed oral antipsychotic treatment in the last 7 months prior to screening (with at least 7 months retrospective data by records or a reliable source, pertaining to all hospitalizations and interventions) and showed a response to the treatment (other than clozapine) according to the investigator's opinion, and who would have required a change in treatment for any reason (eg, lack of efficacy, poor compliance, or side effects) and would have potentially benefited from extended treatment with a long-acting injectable formulation.

Test Product, Dose, Mode of Administration, Batch or Lot No(s): The investigational products were aripiprazole IM depot 400 mg supplied as lyophilized vials and aripiprazole oral tablets. Both doses of aripiprazole IM depot used in this trial (400 mg and 300 mg) were obtained from the 400 mg lyophilized vials. Aripiprazole IM depot was to be administered every month (28 days ± 2 days during the Open-label Aripiprazole IM Depot Treatment Phase and 28 [-2/+10] days during the Open-label Aripiprazole IM Depot Treatment Extension Phase). All doses of aripiprazole IM depot were injected into the gluteal muscle, and care was taken to avoid inadvertent injection into a blood vessel.

Oral aripiprazole tablets were supplied as round, white tablets containing 5 mg, 10 mg or 15 mg of aripiprazole packaged in child-resistant blister cards to assess tolerability during

the Tolerability Assessment Phase (if needed), during the Open-label Aripiprazole IM Depot Treatment Phase for the first 14 days as concomitant treatment with the first 400 mg aripiprazole IM depot injection, and for administration as rescue therapy at daily doses recommended in the protocol or adjusted by the investigator.

The lot numbers of trial medication were as follows:

Aripiprazole 5mg tablets	lot 08L890A005
Aripiprazole 10mg tablets	lot 08L80A010A
Aripiprazole 15mg tablets	lot 08L80A015A
Aripiprazole 400mg vials	lot 09J98A400, 09K93A400, and 11C81A400

Criteria for Evaluation: The criteria for evaluation listed below were to be analyzed per protocol. For this synoptic clinical study report, data presented were limited to trial discontinuations due to adverse events (AEs), serious adverse events (SAEs), laboratory data, electrocardiogram (ECG), and deaths based on data collected. This trial was discontinued early by the sponsor. The reason for study closure is not related to safety because no signals or items of concern have been identified.

Primary Efficacy Endpoint: The primary endpoint of this trial was to be the comparison of inpatient psychiatric hospitalization rates (proportion of subjects with ≥ 1 inpatient psychiatric hospitalization[s]) between Months 4 to 6 (Weeks -12 to -24) of the retrospective period while the subject was receiving oral standard of care antipsychotic treatment(s) with those of Months 4 to 6 (Weeks 12 to 24) of the prospective period after the switch to aripiprazole IM depot. The comparison was to be the proportion of pre-switch (to aripiprazole IM depot) inpatient psychiatric hospitalization to the proportion of post-switch inpatient hospitalization. Hospitalization data of the last 3 months of the retrospective and prospective treatment periods were to be compared. The retrospective treatment period refers to the treatment period with oral standard of care prior to the 4-week outpatient treatment period before screening.

Other Endpoints: The last 3 months of the retrospective and prospective (Open-label Aripiprazole IM Depot Treatment Phase) treatment periods were to be compared for the following endpoints:

- Number of inpatient psychiatric hospitalizations per subject
- Cumulative duration of inpatient psychiatric hospitalizations
- Mean duration of inpatient psychiatric hospitalizations
- Number and mean duration of all other (non-inpatient) psychiatric treatment visits including, but not limited to, partial hospitalizations, intensive outpatient programs, assertive community treatment programs, emergency room visits, hospitalizations for psychosocial reasons, etc
- Number of inpatient nonpsychiatric hospitalizations per subject
- Cumulative duration of inpatient nonpsychiatric hospitalizations
- Mean duration of inpatient nonpsychiatric hospitalizations

- Number and mean duration of all other (outpatient or non-inpatient) nonpsychiatric treatment visits including, but not limited to, emergency room visits

In addition, the following endpoints were to be assessed in the Open-label Aripiprazole IM Depot Treatment Phase:

- Mean change from baseline (Day 0) to Week 24 in Positive and Negative Syndrome Scale (PANSS) total score
- Mean change from baseline (Day 0) to Week 24 in PANSS positive and negative subscale scores
- Mean change from baseline (Day 0) to Week 24 in Clinical Global Impression of Severity (CGI-S) score
- Mean Clinical Global Impression of Improvement (CGI-I) score at Week 24
- Discontinuation rate due to all causes
- Time to discontinuation due to all causes
- Proportion of responders (ie, defined as ≥ 30% decrease from baseline in PANSS total score or a score of 1 [very much improved] or 2 [much improved] on the CGI-I scale)
- Mean change from baseline (Day 0) to Week 24 in Quality of Life Scale score
- Mean change from baseline (Day 0) to Week 24 in Subjective Well-being under Neuroleptic Treatment - short version score
- Mean change from baseline (Day 0) to Week 24 in Drug Attitude Inventory total score
- Mean change from baseline (Day 0) to Week 24 in Impact of Weight on Quality of Life Lite total score
- Mean change from baseline (Day 0) to Week 24 in Investigator's Assessment Questionnaire total score

Efficacy and Other Results:
Due to the low number of enrolled subjects and the sponsor's early termination of the study, the primary efficacy and other endpoints were not evaluated.

Safety Results: Adverse events were examined by frequency, severity, seriousness, and discontinuation (all-cause and due to AEs). The Columbia-Suicide Severity Rating Scale was to be completed at baseline and all subsequent visits to assess the risk of suicide events and to classify reported suicide events.

The incidence of clinically significant changes was calculated for vital signs and routine laboratory tests. Mean change from baseline and incidence of clinically significant changes were calculated for ECG parameters, prolactin concentrations, lipid/metabolic profile (fasting glucose, fasting total cholesterol, fasting high density lipoprotein , fasting low density lipoprotein , fasting triglycerides), and body weight. A central ECG service was utilized to review all ECGs to standardize interpretations for the safety analysis.

Extrapyramidal symptoms were evaluated by calculating the mean change from baseline in Simpson-Angus Scale, Abnormal Involuntary Movement Scale, and Barnes Akathisia Rating Scale scores when applicable. Injection site pain was evaluated by mean Visual Analogue Scale scores as reported by the subject after each injection and at each trial visit. The investigator ratings of localized pain, redness, swelling, and induration at the injection site were also tabulated for post-injection site evaluations at each visit. By-subject listings of physical examination findings were reviewed as a further assessment of safety.

Statistical Methods: Data summaries are limited to tabulations of trial discontinuations due to AEs, SAEs, and deaths. Data listings for trial discontinuations due to AEs, SAEs, and deaths are also provided.

Safety Results: A total of 33 subjects were screened and 30 subjects were treated. In Phase B, 10 of 19 subjects (52.6%) experienced at least 1 treatment-emergent adverse event (TEAE) (CT-8.1), and the total number of TEAEs reported was 23 (CT-8.2.1). The most common TEAEs (≥ 10% of subjects) in Phase B were fatigue (2 of 19 subjects [10.5%]) and insomnia (3 of 19 subjects [15.8%]). In Phase C, 1 of 3 subjects (33.3%) experienced one TEAE (CT-8.2.1). The only TEAE in Phase C was diabetes mellitus, which was reported in 1 subject (33.3%) (CT-8.2.2). The majority of TEAEs were reported to be mild or moderate in severity (CT-8.2.3). One subject (Subject [redacted]) in Phase B experienced 2 SAEs (schizophrenia and drug-induced liver injury), both of which were considered severe (CT-8.5.3). The event of drug induced liver injury as called by the investigator was not supported by the lab value (eg, total bilirubin was within normal limits). No other SAEs were reported.

Overall, 6 of 19 subjects in Phase B experienced a potentially drug-related TEAE. The most common potentially drug-related TEAEs (incidence ≥ 10% of subjects) were fatigue (2 of 19 subjects [10.5%]), and insomnia (3 of 19 subjects [10.5%]) (CT-8.3.2).

Overall, only 1 subject in Phase B experienced any AE leading to discontinuation (schizophrenia) (Subject [redacted]). No deaths, Hy's Law cases, or pregnancies were reported during the trial (CT-8.6.3, CT-9.1, CT-10.3).

The most common potentially clinically relevant laboratory test abnormalities reported during the trial were elevated fasting triglycerides (Phase B and C; subject [redacted] was not part of this group), elevated total fasting cholesterol (Phase B), elevated fasting glucose (Phase B and C), elevated fasting low-density lipoprotein cholesterol calculation (Phase B), and elevated creatine phosphokinase (Phase B) (CT-10.2 and CT-13.1.1).

There were no clinically relevant abnormalities in vital signs reported in Phase A, B, or C (CT-11.1). Two subjects experienced potentially clinically relevant ECG abnormalities (CT-12.1). Subject [redacted] experienced an event of supraventricular premature beat in Phase B. The subject had an associated AE of heart palpitations beginning on Day 49,

which was mild and continuing. Subject [redacted] experienced an event of symmetrical T-wave inversion in Phase B. The subject did not have any other associated AEs.

Conclusions:

- Due to the low number of enrolled subjects and the sponsor's early termination of the trial, the primary efficacy and other endpoints outlined in the protocol were not evaluated.
- In Phase B, 10 of 19 subjects (52.6%) experienced at least 1 TEAE. One of three subjects in Phase C (33.3%) experienced one TEAE.
- The most common TEAEs in Phase B (≥ 10% of subjects) were fatigue (10.5%) and insomnia (15.8%). The only TEAE in Phase C was diabetes mellitus, which was reported in 1 subject (33.3%). The majority of TEAEs were reported as mild or moderate in severity.
- One subject in Phase B experienced 2 SAEs (schizophrenia and drug induced liver injury), both of which were considered severe. The event of drug induced liver injury as called by the investigator was not supported by the lab value (eg, total bilirubin was within normal limits).
- No other SAEs were reported.
- Overall, 6 of 19 subjects in Phase B experienced a potentially drug-related TEAE. The most common potentially drug-related TEAEs (≥ 10% of subjects) were fatigue (10.5%), and insomnia (10.5%).
- The most common potentially clinically relevant laboratory test abnormalities reported during the trial were elevated fasting triglycerides, elevated total fasting cholesterol, elevated fasting glucose, elevated fasting low density lipoprotein cholesterol calculation, and elevated creatine phosphokinase.
- There were no clinically relevant abnormalities in vital signs reported. Two subjects experienced potentially clinically relevant ECG abnormalities.