**SYNOPSIS**

**Clinical Study Report CN138087**

**TITLE OF STUDY:** A Prospective, Multicenter, Open-label Study of Aripiprazole in the Management of Patients with Schizophrenia or Schizoaffective Disorder in General Psychiatric Practices (Broad Effectiveness Trial with Aripiprazole - BETA)

**INVESTIGATORS AND STUDY CENTERS:** Patients were enrolled at 292 sites in the Main Study; 27 sites also participated in the Substudy.

**PUBLICATIONS:** None

**STUDY PERIOD:** Date first patient enrolled: 06-May-2002  
Date last patient completed: 31-Jan-2003

**CLINICAL PHASE:** IIIB

**OBJECTIVES:**

**Main Study:**

The primary objective of this study was to evaluate the effectiveness of 8 weeks of treatment with aripiprazole in a large number of patients with schizophrenia or schizoaffective disorder who were treated in a general psychiatric practice setting. The overall effectiveness of aripiprazole was evaluated by the Clinical Global Impression-Improvement Rating Scale (CGI-Improvement Scale). The primary research hypothesis was that aripiprazole would prove effective in the treatment of these patients, as evidenced by the upper bound of the 95% confidence interval (CI) for the mean CGI-Improvement Score being less than 4 (which corresponds to no change) at the end of the 8-week Treatment Phase.

Secondary objectives included evaluation of: dosing patterns and use of concomitant medications; patients' and caregivers' medication preferences using the Preference of Medicine (POM) assessment; investigators' impressions of treatment effects using the Investigator’s Assessment Questionnaire, and the safety and tolerability of aripiprazole in the same population.

**Substudy:**

A Substudy was conducted in a subset of patients from the Main Study to evaluate the effectiveness of aripiprazole on dimensions of patient outcomes not captured in the Main Study including: sexual function (using the Patient Self-Evaluation of Sexual Function Scale), tobacco use (using the Fagerstrom Test for Nicotine Dependence [FTND]), daytime somnolence (using the Excessive Daytime Sleepiness [EDS] Scale from the Sleep-Awake Activity Inventory [SWAI]), and Dysmetabolic Syndrome.

**METHODOLOGY:**

**Main Study:** This was a multicenter, open-label, randomized (aripiprazole or standard of care treatment), prospective study of aripiprazole use in patients with schizophrenia or schizoaffective disorder for whom an alteration in medication was clinically reasonable or initiation of antipsychotic treatment was required.

The study was conducted in the general psychiatric practice setting. Following a 1- to 14-day Screening Phase, qualified patients were randomized in a 4:1 ratio to receive either open-label aripiprazole or standard of care for 8 weeks. The recommended starting dose for aripiprazole was 15 mg per day; however doses could range from 10 - 30 mg per day. Patients receiving standard of care were administered a single new antipsychotic medication based on the investigator’s judgment, and were dosed according to the package...
All patients who completed the 8-week Treatment Phase before aripiprazole was commercially available were eligible to continue their assigned treatment in an Extension Phase lasting a maximum of 24 weeks or until aripiprazole was commercially available (whichever was sooner).

Substudy: A subset of randomized patients at selected study centers who signed an addendum to the Informed Consent Form describing the Substudy, were eligible to participate in the Substudy. The same eligibility criteria, treatment groups, medication assignments, and visit schedule used in the Main Study were used in the Substudy.

This study report presents results from the 8-week Treatment Phase of the Main Study and the Substudy. Results from the Extension Phase will be presented in an addendum to this report upon completion of the analyses.

NUMBER OF PATIENTS:

Main Study: A total of 1649 patients enrolled in the study and 1599 were randomized: 825 (52%) were men and 774 (48%) were women. Randomized patients were between the ages of 18 and 76 years of age. One thousand two hundred and ninety-five (1295) were randomized to the aripiprazole group and 304 were randomized to the standard of care group. There were 1520 patients in the Safety Sample, 1483 patients in the Effectiveness Sample, and 1469 in the POM Sample. A total of 1015 (64%) patients completed the 8-week open-label Treatment Phase: 842 (65%) patients in the aripiprazole group and 173 (57%) patients in the standard of care group.

Substudy: A total of 139 patients from the Main Study participated in the Substudy: 117 from the aripiprazole group and 22 from the standard of care group. There were 139 patients in the Substudy Randomized Sample, 136 in the Substudy Safety Sample, and 133 in the Substudy Effectiveness Sample.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: The diagnosis and main criteria for inclusion were the same for the Main Study and Substudy. Patients with a diagnosis of schizophrenia or schizoaffective disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), for whom an alteration in medication was clinically reasonable or initiation of antipsychotic treatment was required, were included in the study. This included patients who had symptoms that were not optimally controlled, patients experiencing tolerability problems, and patients with a recent diagnosis of schizophrenia or schizoaffective disorder with no prior or recent antipsychotic treatment.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Aripiprazole 10-mg tablet, one or two per day, administered orally, batch number 2B57248 or aripiprazole 15-mg tablet one or two per day, administered orally, batch number 2B5270. One 10-mg tablet and one 15-mg tablet could be orally administered once per day for a 25-mg dose.

DURATION OF TREATMENT: The duration of treatment was the same for the Main Study and Substudy: 8 weeks of open-label treatment with aripiprazole or standard of care, followed by an optional Extension Phase lasting up to 24 weeks or until aripiprazole was commercially available (whichever was sooner). Patients who completed the 8-Week Treatment Phase after aripiprazole was commercially available were not offered entry into the Extension Phase.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Standard of care treatment (ie, an antipsychotic medication different from the patient’s prestudy antipsychotic medication, if applicable) was administered based on the investigator’s judgment and according to the medication PI. The investigator prescribed and the patient obtained medication through their normal practice (ie, medications for patients randomized to standard of care were not provided by the sponsor).
CRITERIA FOR EVALUATION:

Main Study

Effectiveness: The primary effectiveness measure was the mean CGI-Improvement Score of aripiprazole patients at Week 8. Additional endpoints included: the mean CGI-Improvement Score at all other visits for the aripiprazole group; the mean CGI-Improvement Score at all visits for the standard of care group; the Preference of Medicine Questionnaire (POM) Score at all study visits for both treatment groups; and the Investigator’s Assessment Questionnaire at Week 8 for both treatment groups.

Safety: Data received for safety evaluation consisted of adverse event (AE) reports, vital sign measurements, concomitant medications, and results of clinical laboratory tests. The following variables were examined to further characterize response to aripiprazole: dosing patterns; the number and percentage of patients receiving new CNS concomitant medications; and the number and percentage of patients receiving new anticholinergic medications for EPS.

Substudy

Effectiveness: Effectiveness measures assessed in the Substudy included: the Patient Self-Evaluation of Sexual Function Scale at Weeks 4 and 8; mean change from baseline on the FTND and EDS Total Scores at all visits; and the incidence of Dysmetabolic Syndrome and Metabolic Syndrome during the 8-week Treatment Phase.

Safety: Substudy safety evaluations included measurement of weight and height for determination of BMI.

STATISTICAL METHODS:

Main Study: The primary effectiveness measure was the mean CGI-Improvement Score of aripiprazole patients at Week 8. It was planned for approximately 1400 patients to be randomized to the open-label aripiprazole arm and 350 to the standard of care arm of this study. This sample size was not based on statistical considerations; however, a sample size of 1400 patients ensured a power of more than 99% to exclude “4” (corresponding to no change) from the two-sided 95% CI if the mean score on the CGI-Improvement was 3.7 and the standard deviation (SD) was 1.25 in the aripiprazole arm.

The following samples and data sets were defined: The Randomized Sample included all patients randomized to treatment; the Safety Sample included all patients in the Randomized Sample who took at least one dose of study medication; the Effectiveness Sample included all patients in the Safety Sample who had at least one post-baseline CGI-Improvement evaluation; the POM Sample included all patients in the Safety Sample who had at least one post-baseline POM evaluation; the last observation carried forward (LOCF) data set included data recorded at a given visit or if no observation was recorded at that visit, data carried forward from the previous visit; and the observed cases (OC) data set consisted of the actual observations at each visit. Baseline values were not carried forward or averaged with post-baseline data to impute missing values for the LOCF data set.

The primary effectiveness analysis compared the upper bound of the two-sided 95% CI for the mean CGI-Improvement Score of aripiprazole patients at Week 8 (LOCF data set) to a score of 4 (no change). CGI-Improvement Scores were also summarized by treatment group (including the mean, 95% CI for the mean, standard error [S.E.] of the mean, range and median) for each visit during the 8-week Treatment Phase, and the number and percentage of patients in each CGI-Improvement category at Week 8 was tabulated. All other variables, including the patients’ and caregivers’ POM results and the Investigator’s Assessment Questionnaire results were summarized using descriptive statistics. The Effectiveness Sample was used to summarize the CGI-Improvement results, the POM Sample was used to summarize the POM results, and the Safety Sample was used for tabulation of the Investigator’s Assessment Questionnaire results.
While patients were randomly assigned to treatment group (aripiprazole or standard of care), antipsychotic medications were not randomly assigned for patients receiving standard of care, but were prescribed based on the investigators’ clinical judgement to optimize efficacy and mitigate any pre-existing safety or tolerability issues. In light of this potential bias, and the fact that the standard of care group was comprised of a relatively small number of patients receiving a variety of different antipsychotic medications, direct comparisons were not made between the two treatment groups on any of the effectiveness measures. Safety results for aripiprazole and standard of care patients are presented side by side in the body of this report in order to provide a context for interpreting the safety and tolerability of aripiprazole as used in the general psychiatric practice setting; however, it is inappropriate to draw any conclusions regarding small differences in incidence rates between the two groups in light of the aforementioned considerations.

All safety data were tabulated and summarized using the Safety Sample. Patients meeting criteria for potentially clinically significant clinical laboratory abnormalities and vital sign abnormalities were summarized and listed.

**Substudy:** For the Substudy, it was anticipated that approximately 120 patients would be randomized to aripiprazole and that 30 patients would be randomized to standard of care at 30 selected investigational sites. This sample size was not based on statistical considerations.

The following samples and data sets were defined: the Substudy Randomized Sample included all patients in the Randomized Sample who had consented to participate in the Substudy or who had an evaluation pertaining to the Substudy; the Substudy Safety Sample included all patients in the Safety Sample who had consented to participate in the Substudy or who had an evaluation pertaining to the Substudy; and the Substudy Effectiveness Sample included all patients in the Substudy Safety Sample who had at least one post-baseline CGI-Improvement evaluation before the end of the Week 8 window, but not more than 7 days after the last day of dosing during the 8-week Treatment Phase.

CGI-Improvement results were summarized (including the mean, 95% CI for the mean, S.E. of the mean, range and median). Results from the Patient Self-Evaluation of Sexual Function assessment were collapsed into four subscores and the mean change to Weeks 4 and 8 were summarized for each subscore. Mean change in the FTND Total Score and in the EDS Total Score from baseline to each study visit were similarly summarized. In addition, frequency cross-tabulations by baseline and follow-up visits were calculated for five FTND dependency categories (ranging from very low to very high dependency) as well as item 4 of the FTND (which assessed the number of cigarettes used per day), and the number of patients who changed or continued their smoking status during the 8-week Treatment Phase was summarized. Patients who met criteria for Dysmetabolic Syndrome during the 8-week Treatment Phase were also summarized.

The incidence of treatment-emergent AEs occurring in the Substudy Safety Sample was tabulated, and the mean change from baseline in weight and BMI were summarized using the Substudy Safety Sample.

**EFFECTIVENESS RESULTS:**

**Main Study:** The effectiveness (ie, efficacy, safety and tolerability) of aripiprazole was demonstrated beginning Week 1 (as shown by the upper bound of the 95% CI for the mean CGI-Improvement Score of less than “4”, which corresponds to no change). By Weeks 4 and 8, the upper bound of the 95% CI was less than 3, indicating at least “minimal improvement” in aripiprazole patients. These results were observed with both the LOCF and OC data sets. Analysis of CGI-Improvement Scale results by rating (LOCF data set) indicated that 53% of aripiprazole patients were very much or much improved, and 73% were at least minimally improved by Week 8 of the open-label Treatment Phase. These results were supported by analysis of the OC data set which indicated that 69% of aripiprazole patients were very much or much improved, and 89% were at least minimally improved by Week 8.

Evaluation of POM results indicated that patients and their caregivers generally preferred aripiprazole over their prestudy medication(s). When the OC data set of the POM Sample was evaluated, 59% of patients
reported that aripiprazole was slightly better or much better than their prestudy medication at Week 1, and this percentage increased to 74, 78, and 86% of patients at Weeks 2, 4, and 8, respectively. Consistent with these results, when the LOCF data set at Week 8 was evaluated, 71% of aripiprazole patients reported that aripiprazole was slightly better or much better than their prestudy medication. Similarly, 60% of patients’ caregivers reported that aripiprazole was slightly better or much better than the prestudy medication at Week 1, and this percentage increased to 74, 77, and 86% at Weeks 2, 4, and 8, respectively (OC data set). When the LOCF data set at Week 8 was evaluated, 72% of aripiprazole patients’ caregivers reported that aripiprazole was slightly better or much better than the prestudy medication.

Evaluation of Investigator’s Assessment Questionnaire results indicated that investigators’ assessments of patients’ responses to aripiprazole (in comparison to prestudy medication) were generally very positive. When the LOCF data set was examined, 60% percent or more of aripiprazole patients were rated as doing slightly or much better on aripiprazole at Week 8 in comparison to their prestudy medication on seven of the 12 items assessed including: positive symptoms, negative symptoms, somnolence, weight gain, cognition, energy level and mood. For the remaining items including: other symptoms (efficacy); signs and symptoms of prolactin elevation, akathisia, EPS, and other safety/tolerability issues, the majority of patients were rated as doing about the same, slightly better or much better on aripiprazole in comparison to their prestudy medication. Similar findings were observed with the OC data set.

When the results of the Investigator’s Assessment Questionnaire at Week 8 were analyzed by the patients’ initial reason(s) for medication change, the results were generally consistent with those noted above; however, greater improvement at Week 8 was reported (ie, a greater percentage of aripiprazole patients were rated as doing slightly or much better) on signs and symptoms of prolactin elevation, akathisia, and EPS in patients who had changed from their prestudy medication(s) for these reasons.

Substudy: Consistent with results from the Main Study, the effectiveness of aripiprazole in patients who participated in the Substudy was apparent beginning Week 1 (as shown by the upper bound of the 95% CI of the mean CGI-Improvement Score of less than “4”), and maintained throughout the duration of the 8-week Treatment Phase (LOCF and OC data sets). Aripiprazole did not appear to impact overall sexual function, the desire/satisfaction/frequency of sex, or difficulty in male or female sexual functioning (as measured by the Patient Self-Evaluation of Sexual Function Scale). Similarly, aripiprazole did not appear to impact the FTND Total Score, the number and percentage of patients falling into a range of smoking dependency categories, the number of cigarettes smoked per day, or the smoking status of patients (as assessed by the FTND). However, aripiprazole did reduce the degree of daily somnolence over the course of the 8-week Treatment Phase (as measured by the EDS). Only one of 63 evaluable aripiprazole patients met criteria for Dysmetabolic Syndrome during the 8-week Treatment Phase.

Note that the Substudy was added to the Main Study after patient enrollment had begun, was only conducted by investigators having previous clinical research experience (N = 27), and had a limited target N of 150. The resulting small sample size (N = 139) makes it difficult to draw conclusions regarding the results.

SAFETY RESULTS:

Main Study: The mean dose of aripiprazole at endpoint (ie, last day of dosing for all patients) was 20 mg per day; almost one half of the patients (47%) who completed the study were receiving 15 mg aripiprazole per day at Week 8, and 29% were receiving 30 mg aripiprazole per day at Week 8.

Thirty-six percent (36%) of aripiprazole patients used new concomitant CNS medications and 3% used new EPS concomitant medications during the 8-week Treatment Phase. A new concomitant medication was any medication (other than study medication) used at any time during the study, excluding medications started prior to entering the study which were continued during the study. The most frequently prescribed new concomitant CNS medications (ie, those prescribed in at least 5% aripiprazole patients) were hypnotics and sedatives, analgesics and antipyretics, anxiolytics and antiepileptics.
Nine hundred and one (72%) of the 1255 patients in the aripiprazole group reported at least one AE during the 8-week Treatment Phase. Most of these events were mild to moderate in intensity. The most frequently occurring AEs in aripiprazole-treated patients (ie, those with ≥10% incidence in the aripiprazole group) included: insomnia (24%), nausea (16%), headache (11%), and anxiety (10%). Importantly, these AEs led to discontinuation in 2% or fewer of aripiprazole patients.

Five aripiprazole-treated patients died during the course of this study. All of the deaths were considered not likely related or unrelated to study medication. One patient died due to an accidental injury (homicide), and another patient, with a long history of cardiac disease, died due to Coronary Artery Disorder. The cause(s) of death for the three other patients with multiple comorbid medical histories were not clearly identified as autopsy reports could not be obtained.

One hundred twenty-two (10%) patients in the aripiprazole group experienced at least one SAE during the study (or within 30 days of the study). Most of these were considered not likely related or unrelated to study medication by the investigator. The most frequently reported SAE in aripiprazole patients was psychosis (3%), which is related to the underlying disease being treated. Non-psychiatric SAEs were varied.

A total of 221 (18%) patients in the aripiprazole group discontinued from the study due to an AE. The most frequently occurring AEs leading to discontinuation in the aripiprazole group were related to the patients’ underlying illness (eg, psychosis, insomnia, anxiety, agitation, hallucination), and gastrointestinal symptoms (eg, nausea, dyspepsia, vomiting, and diarrhea).

EPS-related AEs occurred in 126 (10%) patients in the aripiprazole group. The most frequently reported EPS-related AE in aripiprazole patients was akathisia, which was reported by 5% of patients, and led to discontinuation in only 1% of patients.

Analysis of laboratory and vital signs data did not reveal any significant safety concerns regarding aripiprazole.

There were two pregnancies in the aripiprazole group during this study. One patient had a positive serum pregnancy test on Study Day 9, discontinued aripiprazole on Day 9, and had an elective abortion on Day 11. The other had a positive urine pregnancy test on Study Day 11, discontinued aripiprazole on Day 11, and gave birth to a healthy baby on day 251.

Substudy: The mean weight and BMI of aripiprazole patients who participated in the Substudy decreased over the course of the 8-week Treatment Phase.

Conclusions:

- The effectiveness (ie, efficacy, safety and tolerability) of aripiprazole in this broad effectiveness trial, which was conducted in the general psychiatric setting under naturalistic conditions, was demonstrated as early as Week 1, and was maintained throughout the 8-week Treatment Phase.
- Aripiprazole was preferred by the majority of patients and their caregivers over prestudy medication.
- Investigators reported that 60% or more of aripiprazole patients were doing slightly or much better at Week 8 on seven of the 12 items assessed (positive symptoms, negative symptoms, somnolence, weight gain, cognition, energy level, and mood) in comparison to their prestudy medication (LOCF data set). For the remaining items including: other symptoms (efficacy); signs and symptoms of prolactin elevation, akathisia, EPS, and other safety/tolerability issues, the majority of patients were rated as doing about the same, slightly better or much better on aripiprazole in comparison to their prestudy medication (LOCF data set).
- Consistent with controlled Phase II and III clinical trials, aripiprazole was safe and well tolerated.
• The mean dose of aripiprazole at endpoint (ie, last day of dosing for all patients) was 20 mg per day; almost one half of the patients (47%) who completed the study were receiving 15 mg aripiprazole per day at Week 8, while 29% were receiving 30 mg aripiprazole per day at Week 8.

• Thirty-six percent (36%) of aripiprazole patients used new concomitant CNS medications and 3% used new EPS concomitant medications during the 8-week Treatment Phase.

• The limited number of patients enrolled into the Substudy (N = 139) made it difficult to draw conclusions regarding the results of the Substudy.

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