SYNOPTIC CLINICAL STUDY REPORT


INVESTIGATORS AND STUDY CENTERS: Seven sites enrolled patients; these comprised six study centers in the United States of America and one study center in Argentina. A list of centers and investigators who received drug shipment and the number of patients enrolled in each center is provided in Appendix 1.

PUBLICATIONS: None

STUDY PERIOD: Date first patient enrolled: 17-Jun-2002

Date last patient completed: 02-Apr-2003

Bristol-Myers Squibb (BMS) discontinued enrollment and closed the study early because sufficient data were available from other studies to support the safety and efficacy of aripiprazole in the treatment of acute mania in Bipolar I Disorder. The last patient was enrolled in the study on 06-Mar-2003, and enrollment for the study was closed on 10-Mar-2003. The study was closed (last patient visit) on 02-Apr-2003.

CLINICAL PHASE: III

OBJECTIVES:

Primary: The primary objective of this study was to compare the efficacy of aripiprazole with placebo as measured by the Young-Mania Rating Scale (Y-MRS) in the treatment of acutely manic patients with a diagnosis of Bipolar I Disorder, manic or mixed.

Secondary: The secondary objective was to evaluate the safety of aripiprazole in the same population.
METHODOLOGY:

This study was a multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in hospitalized patients diagnosed with Bipolar I Disorder (current episode manic or mixed).

After informed consent was obtained, patients were screened for 1 - 7 days (screening could be extended to a maximum of 14 days with permission from Bristol-Myers Squibb).

Patients who met the eligibility criteria were randomized to receive either aripiprazole or placebo for 3 weeks. The starting dose of aripiprazole was 30 mg/day; the dose could be reduced to 15 mg/day and could be subsequently increased to 30 mg/day based on tolerability and clinical response, respectively. Patients unable to tolerate study medication were discontinued from the study. All patients were to remain hospitalized for a minimum of 2 weeks. Patients were eligible to be discharged from the hospital at the end of the second week and continue in the study (receiving double-blind treatment) as outpatients if they met the following criteria:

- Clinical Global Impression-Bipolar Version (CGI-BP)$^2$ Severity of Illness (mania, depression, overall) score $\leq 3$ (mildly ill, minimally ill, not ill), and
- CGI-BP Change from Preceding Phase (mania) score $\leq 2$ (much improved, very much improved)$^2$

Patients who did not meet the above criteria remained hospitalized for the duration of the 3-week treatment phase.

The concomitant use of lorazepam was allowed during this study as follows: up to 6 mg/day on Days 1 to 4, up to 4 mg/day on Days 5 to 7 and up to 2 mg/day on Days 8 to 10, none thereafter. Treatment with lorazepam within 4 hours prior to rating scale administration was prohibited, with the exception of the screening visit. Other psychotropic medications including mood stabilizers were prohibited.

Additional Provisions for Stabilization and Aftercare: Patients who discontinued from the study due to lack of clinical response or an adverse event (AE) could receive up to one additional week of hospitalization for stabilization. Patients who completed the 3-week study prior to 16-Sep-2002 were eligible to enter into a long-term study.
After this date, patients who completed the 3-week study were eligible to receive limited outpatient aftercare provided by the investigator. Patients who discontinued prior to Week 3 of the study due to an AE or lack of clinical response were not eligible to enter into a long-term study or receive outpatient aftercare by the investigator.

Appendix 2A contains the most recent version of the protocol incorporating amendments 2 and 3. Appendix 2B and 2C contain protocol amendment 1, and protocol administrative letters, respectively. Sample Case Report Form (CRF) is provided in appendix 3.

A list of Institutional Review Boards and Chairpersons is provided in appendix A.1 and sample Subject Information and Consent Form is provided in appendix A.2. Both of these appendices are available upon request.

PATIENT DISPOSITION AND DEMOGRAPHIC CHARACTERISTICS:

The disposition of all patients is summarized in Table 1 and the number of patients in each randomized group is shown in Table 2. The demographic characteristics are shown in Table 3. A total of 80 patients were enrolled: 24 did not meet eligibility criteria and 56 (23 men and 33 women, 21-75 years old) were randomized (29 to aripiprazole and 27 to placebo). All 56 patients were included in the safety evaluations (Safety Sample). Twenty-nine (51.7%) of the 56 randomized patients completed the study. Summaries of the demographic characteristics, psychiatric histories, and end-of-baseline ratings are presented in Tables 3, 4 and 5, respectively. Appendices 4, 5, 6, 7, and 8 present by-patient listings of final disposition, patients by batch number, demography, medical history, and psychiatric history, respectively. Appendix A.3 (available upon request) contains the randomization scheme and codes.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

For enrollment into the study, patients must have met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for Bipolar I Disorder (manic or mixed), be in acute relapse, and require inpatient hospitalization. Patients must also have had a history of a previous hospitalization for the treatment of acute mania. To be eligible for randomization into the double-blind treatment phase, patients had to meet all entry criteria including a Y-MRS score ≥ 20 prior to randomization.
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Aripiprazole 15 mg tablet, one or two tablets daily, administered orally, batch number 98B85A015D.

DURATION OF TREATMENT: The total duration of treatment was 21 days and included a minimum of 14 days of inpatient hospitalization.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Placebo tablet, one or two tablets daily, administered orally, batch number 00F82P000.

DOSAGE AND ADMINISTRATION: Study medications were administered orally once a day at approximately the same time each day. The starting dose was 30 mg/day and could be reduced to 15 mg/day and subsequently increased to 30 mg/day based on tolerability and clinical response. The number of patients in the Safety Sample who received study medication during each of the study weeks (Week 1, Week 2, and Week 3), the mean daily dosage per week, and the range of dose is given in Table 6. A listing of patients by batch number of drug is provided in Appendix 5. Appendix 9 displays a by-patient listing of study medication dosage and the start and end days.

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy outcome measure was the mean change from baseline to Week 3 in the Y-MRS Total Score.1 Secondary efficacy measures include response rate on the Y-MRS Total Score at Week 3 (response is defined as a 50% decrease from baseline on the Y-MRS Total Score), the mean change from baseline to Week 3 in the CGI-BP Severity of Illness Score (mania, depression, overall)2, the mean CGI-BP Change from Preceding Phase Score (mania, depression, overall), and the percentage of discontinuations due to lack of efficacy.

Additional exploratory efficacy measures included the mean change from baseline to Week 3 on the Positive and Negative Syndrome Scale (PANSS) Hostility Subscale Score,5 mean change from baseline to Week 3 in the PANSS Total Score, the PANSS Cognitive Sub-Scale Score, and the mean change from baseline to Week 3 in the Montgomery Asberg Depression Rating Scale (MADRS) Total Score.6
**Safety:** Safety assessments include medical review of reports of AEs including intercurrent illness, vital sign measurements, electrocardiograms (ECG), body weight, concomitant medications, and results of physical examinations and clinical laboratory tests (including serum prolactin levels). Extrapyramidal Syndrome rating scales completed during this study included the Simpson-Angus Scale (SAS),\(^7\) the Abnormal Involuntary Movement Scale (AIMS),\(^8\) and the Barnes-Akathisia Rating Scale.\(^9\)

**STATISTICAL METHODS**

A sample size of 250 evaluable patients (125 per treatment group) was planned to yield 90% power to detect a difference of 5.5 between aripiprazole and placebo in the change from baseline to Week 3 in the Y-MRS Score. This assumed a standard deviation of 13.4 and that the testing would be two-sided at the 0.05 significance level. Efficacy measures, including the primary outcome measure of mean change from baseline visit on the Y-MRS, were not analyzed because the early closure of the study resulted in a much smaller sample size that was not adequate to answer the primary clinical research question.

The Randomized Sample included all patients who were randomized to treatment. The Efficacy Sample included all patients who were randomized to treatment, took at least one dose of study medication (as indicated on the dosing record), and had at least one on-study efficacy evaluation. The Safety Sample included all patients in the Randomized Sample who took at least one dose of study medication as indicated on the dosing record. The Safety Sample was used in the analysis of all safety data, the extent of medication exposure, and concomitant medications.

The Last Observation Carried Forward (LOCF) data set included data recorded at a given visit or, if no observation is recorded at that visit, data carried forward from the previous on-study visit. Baseline data were not carried forward or averaged with treatment data to impute missing values for the LOCF data set.

The Observed Cases (OC) data set consisted of the actual observations at each visit.
EXTENT OF EXPOSURE:

Of the 56 patients who received double-blind treatment, 27 received placebo and 29 received aripiprazole. The number of patients receiving study medication as a function of study week is presented in Table 6 with the range and dose of study medication that they received during that period. A by-patient listing of study medication is presented in Appendix 9.

PROTOCOL DEVIATIONS: Protocol deviations of clinical significance are listed in Supplemental Table S.1, and further information is available in Appendix 10.

EFFICACY RESULTS:

The clinical research hypothesis was that aripiprazole (15 mg or 30 mg) would have a greater mean change from baseline to Week 3 on the Y-MRS Score than placebo in the treatment of acutely manic patients with a diagnosis of Bipolar I Disorder, manic or mixed. However, efficacy analyses were not performed due to the early closure of the study and, consequently, the small sample size.

The following tables are summary presentations of the outcome measures of the study (Efficacy Sample) that were specified in the Statistical Analysis Plan (SAP), prior to unblinding, as the most appropriate: The mean change from baseline in the Y-MRS Total Score of the Efficacy Sample, LOCF data set (Table 7) and OC data set (Table 8); the mean change from baseline in CGI-BP Severity of Illness (mania) Score, LOCF data set (Table 9) and OC data set (Table 10); the response rate for the Y-MRS Total Score, LOCF data set (Table 11) and OC data set (Table 12). The SAP is provided in appendix A.4 and is available upon request.

SAFETY FINDINGS:

All patients who took at least one dose of study medication, as indicated on the dosing record, are included in the Safety Sample. A physician from BMS reviewed safety findings of any potential significance. A summary of the safety findings is presented below.

Adverse Events: Table 13 shows the incidence of treatment-emergent AEs that occurred in ≥ 5% of all patients in the Safety Sample. Forty-six (82.1 %) of the 56 patients in the
Safety Sample reported at least one AE during the study; these were comprised of 26 (89.7 %) of 29 patients in the aripiprazole group, and 20 (74 %) of 27 patients in the placebo group. The most frequently occurring treatment-emergent AEs (≥ 10% incidence) for the aripiprazole group were: headache (31%), nausea (17.2%), insomnia (17.2%), constipation (13.8%), dyspepsia (13.8%), pain (10.3%), agitation (10.3%), and akathisia (10.3 %). The most frequently occurring treatment-emergent AEs (≥ 10% incidence) for the placebo group were: diarrhea (14.8 %), headache (11.1%), nausea (11.1%), reflux gastroesophageal (11.1%), and disorder personality (11.1%). The patients in the aripiprazole group displayed a wider range of symptoms and tended to have higher rates of headache, constipation, dyspepsia, and insomnia. The incidence of all adverse events by body system and treatment group in the Safety Sample is shown in Supplemental Table S.2.

**EPS Scales:** In general, minimal changes from baseline to Week 3 (LOCF endpoint) or highest score were noted among the groups for the three EPS-rating scales (SAS, AIMS, and Barnes-Akathisia Global Clinical Assessment). No statistical testing was performed on these variables.

Tables 14, 15, and 16 summarize mean change from baseline to LOCF endpoint results for the SAS, AIMS, and Barnes-Akathisia Clinical Global Assessment scores, respectively, for patients in the double-blind phase, OC data set, Safety Sample. Appendices 15, 16, and 17 present by-patient listings of SAS, AIMS, and Barnes-Akathisia Clinical Global Assessment scores, respectively.

Table 17 presents the incidence of EPS-related AEs for the Safety Sample. EPS-related AEs were noted in 7 (25.9%) of patients in the placebo group and 6 (20.7%) of patients in the aripiprazole group. Akathisia was the most frequently encountered EPS symptom (7.4% placebo, 10.3% aripiprazole). Appendices 13 and 14 present a by-patient listing of AEs and a listing of the number of AEs observed with patient identification, respectively.

**Concomitant Medications:** Fifty-three (94.6%) of the 56 patients in the Safety Sample had concomitant use of a central nervous system (CNS) medication during the study; these comprised 24 (88.9%) patients in the placebo group and 29 (100%) patients in the aripiprazole group (Table 18). The most common CNS concomitant medications taken by all treatment groups were anxiolytics (91%), other analgesics and antipyretics (66 %),
and anticholinergics (23%). Other less frequent concomitant medications used were hypnotics and sedatives, antiepileptics, antimigraines, antipsychotics, and opioids. A by-patient listing of concomitant medications taken during the study is provided in Appendix 18, and a summary of concomitant medications is displayed in Appendix 19. A by-patient listing of previous medications is given in Appendix 20.

The number of patients in the Safety Sample who required concomitant medication (benztropine) for potential treatment of EPS-related symptoms is shown in Table 19 (placebo group 11.1%; aripiprazole 34.5%).

**Deaths:** No deaths were reported in this study.

**Serious Adverse Events (SAEs):** The incidence of SAEs are shown in Table 20. Three patients in the aripiprazole group had at least one serious adverse event (SAE) during the study or up to 30 days after the last day of dosing; these were severe psychosis, severe reaction manic depressive, severe reaction manic, and severe thought suicidal. All began after the last day of dosing, and all were considered unrelated to study medication (Table 21). There were no SAEs in the placebo group. A by-patient listing of SAEs is found in Appendix 21 and narratives for these patients are found in Supplemental Table S.3.

**Discontinuations:** Three patients in the Safety Sample discontinued from the study because of AEs, and all were in the placebo group. AEs that led to discontinuation of treatment were moderate anxiety and severe hematuria, and were considered not likely related and unrelated to study medication, respectively. Table 22 shows the incidence of treatment-emergent AEs that led to discontinuation of study therapy listed by body system. A by-patient listing of discontinuations due to AEs is found in Table 23 and narratives for these patients are found in Supplemental Table S.4. There were no discontinuations due to AEs in the aripiprazole group. One patient discontinued because of an AE prior to taking the first dose of study drug and is, therefore, excluded from the incidence table (Table 22).

**Pregnancies:** No pregnancies were reported during the study.

**Clinical Laboratory Evaluation:** Five (8.9%) of the 56 patients in the Safety Sample had at least one potentially clinically significant laboratory abnormality. These were
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comprised of one patient in the placebo group and 4 patients in the aripiprazole group (Table 24). In the placebo group one patient (138077-1-50) had an elevated creatine kinase (CK) level (baseline 210 U/L, 538 U/L on Day 23) and also a granular cast count of 2 on Day 23. Elevated prolactin levels were noted for 3 patients in the aripiprazole group (138077-1-41: baseline 12 U/L, 32 U/L on Day 6; 138077-5-17: baseline 49 U/L, 23 U/L on Day 20; 138077-6-77 baseline 9 U/L, 31 U/L on Day 21). One patient (138077-4-36) in the aripiprazole group had an elevated blood urea nitrogen (baseline 34 mg/dL, 33 mg/dL on Day 22). These values can be found in Supplemental Table S.5. By-patient listings of clinical laboratory values can be found in Appendix 22. In each of the 5 cases noted above, the investigator judged the laboratory abnormality to be of no clinical significance and follow-up measurements were not performed. No further information is available. The criteria for identifying potentially clinically significant laboratory values are listed in Supplemental Table S.6.

Vital Signs: There were no potentially clinically significant vital sign measurements recorded for any patient. A by-patient listing of vital sign values is provided in Appendix 23. The criteria used for identifying potentially significant vital sign measurements are shown in Supplemental Table S.7.

Electrocardiograms: One patient in the placebo group had a potentially significant ECG abnormality recorded on Day 11 classified as ventricular premature beat (Supplemental Table S.8). A by-patient listing of ECG values is provided in Appendix 24. The guidelines used for identifying potentially clinically significant ECG measurements are given in Supplemental Table S.9. Follow-up ECG measurements were not performed and no further information is available.

Physical Examination: Excluding trivial findings such as minor scars previously unrecorded on the baseline physical examination form, all treatment-emergent physical examination findings were recorded on the AE form. There was no evidence in this study of toxicity for different body systems, based on review of physical examination findings. Physical examination data are presented in Appendix 25.

SUMMARY:
The primary objective of this trial was to compare the efficacy of aripiprazole (15 mg or 30 mg) with placebo in the treatment of hospitalized acutely manic patients who had a
diagnosis of Bipolar I Disorder, manic or mixed episode. The study was terminated early since sufficient data were available from other studies to support the safety and efficacy of aripiprazole in the treatment of acute mania in Bipolar I Disorder.

Eighty patients were enrolled in the study and 56 patients were randomized to treatment. Twenty-nine patients completed the 3-week double-blind phase and 27 patients discontinued from treatment (Table 1). Fifty-six patients were included in the Safety and Efficacy Samples for the double-blind phase (Table 2).

Sample sizes were small because of the early termination of the study and, consequently, no statistical testing was performed on the primary and secondary efficacy measures. Therefore, no conclusions regarding efficacy can be made from the results.

The safety of aripiprazole was supported using numerous assessments. The overall incidence of AEs was slightly higher for aripiprazole-treated patients than for placebo-treated patients, although the incidence of EPS-related AEs was comparable in the two groups. Additionally, the number of patients who discontinued from treatment because of an AE was lower in the aripiprazole-treated group. There were no deaths in this study.

None of the patients in either treatment group showed any potentially significant vital sign abnormalities. No potentially significant ECG abnormalities were observed in the aripiprazole group, while one patient in the placebo group experienced a ventricular premature beat. Although 3 patients in the aripiprazole group had abnormal on-study prolactin measurements, none of these resulted in an AE or in discontinuation from the study. It should also be noted that the prolactin level for one of these patients was high at baseline, but decreased while the patient was in the study. The incidence of other potentially significant lab abnormalities was similar between the two groups.

**CONCLUSIONS:**

Aripiprazole was found to be well-tolerated in this patient population. None of the patients in the aripiprazole group discontinued treatment because of AEs. The SAE incidence was slightly higher in the aripiprazole treatment group, but these events were judged by the investigators to be unrelated to the study medication. Furthermore, no
safety concerns for aripiprazole were demonstrated on physical examination, laboratory tests, vital sign measurements, EPS scales, or ECG assessments (including \( QT_c \)).
LIST OF ABBREVIATIONS

This list encompasses abbreviations relevant to all study reports for BMS-337039/OPC-14597.

ADCS-ADL-SEV  Alzheimer’s Disease Cooperative Study - Activities of Daily Living Scale (modified)

AE  adverse event

AIMS  Abnormal Involuntary Movement Scale

ALT (SGPT)  alanine aminotransferase (serum glutamate-pyruvate transaminase)

ANCOVA  analysis of covariance

ANOVA  analysis of variance

AST (SGOT)  aspartate aminotransferase (serum glutamic oxaloacetic transaminase)

AUC  area under the curve

A-v  atrioventricular

BID  bis in die (twice a day)

BMS  Bristol-Myers Squibb Company

BP  blood pressure

bpm  beats per minute

BPRS  Brief Psychiatric Rating Scale

BUN  blood urea nitrogen

CGI  Clinical Global Impression

CGI-BP  Clinical Global Impression-Bipolar Version

CMAI  Cohen-Mansfield Agitation Inventory

Cmax  Maximum Concentration

CMH  Cochran-Mantel-Haenszel

Cmin  Minimum Concentration

COSTART  Coding Symbols for Thesaurus of Adverse Reaction Terms

CPK  creatine phosphokinase

CRF  Case Report Form

dL  deciliter
DSMB  Data Safety Monitoring Board
DSM-IV  Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG  electrocardiogram
EPS  extrapyramidal symptoms
FDA  Food and Drug Administration
GCP  Good Clinical Practice
HCl  hydrochloride
IM  intramuscular
IU/L  International Unit Per Liter
kg  kilogram
L  liter
LDH  lactate dehydrogenase
LOCF  Last Observation Carried Forward
MAS  Medication Adherence Scale
mEq  milliequivalent
mg  milligram
mL  milliliter
mm³  cubic millimeter
mmHg  millimeters of mercury
MADRS  Montgomery-Asberg Depression Rating Scale
MMSE  Mini-Mental State Examination
NPI-NH  Neuropsychiatric Inventory-Nursing Home Version
OC  Observed Cases
OMRI  Otsuka Maryland Research Institute
OPC  Otsuka Pharmaceutical Company
PANSS  Positive and Negative Syndrome Scale
Q-LES-Q  Quality of Life Enjoyment and Satisfaction Questionnaire
QD  once daily
<table>
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<tr>
<td>RBBB</td>
<td>right bundle branch block</td>
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<tr>
<td>RBC</td>
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<td>SAE</td>
<td>serious adverse event</td>
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<td>Tmax</td>
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REFERENCES


