Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient:		

SYNOPSIS

Clinical Study Report CN138008

TITLE OF STUDY: A Multicenter, Randomized, Double-Blind Study of Aripiprazole and Haloperidol in the Maintained Response to Treatment for an Acute Manic Episode (Protocol CN138008)

INVESTIGATORS AND STUDY CENTERS: Seventy-six investigators participated in the conduct of this study (1 in Australia, 2 in Austria, 3 in Belgium, 2 in Brazil, 4 in Croatia, 2 in the Czech Republic, 3 in Estonia, 10 in France, 5 in Germany, 8 in Italy, 2 in Latvia, 2 in Lithuania, 4 in Mexico, 8 in Poland, 1 in Portugal, 12 in Russia, 2 in South Africa, 3 in Spain, and 2 in the United Kingdom).

PUBLICATIONS: None

STUDY PERIOD: Date first patient enrolled: 20-Nov-2000

Date last patient completed: 08-Jan-2002

CLINICAL PHASE: III

OBJECTIVES:

Primary: The primary objective of this study was to compare the number of aripiprazole-treated patients with the number of haloperidol-treated patients who continued on treatment and maintained response after 12 weeks of study medication.

Secondary: The secondary objectives were to compare the response rates at the end of Week 3, to compare the numbers of patients maintained on treatment and responding at the end of Week 12 (in the subgroup of patients who continued in the study after Week 3), to assess the safety of aripiprazole and haloperidol in all patients, and to obtain data required for reimbursement filings.

METHODOLOGY: This was a multicenter, randomized, double-blind study comparing aripiprazole (15 to 30 mg per day) with haloperidol (10 to 15 mg per day) in patients experiencing an acute manic episode. After informed consent was obtained, patients underwent a 1- to 7-day screening period (screening could be extended to 14 days with permission from Bristol-Myers Squibb Company [BMS]). Patients met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for Bipolar I Disorder and were experiencing an acute manic or mixed episode. Patients were excluded if they had rapid-cycling Bipolar I Disorder.

Patients fulfilling entrance criteria were evenly randomized to aripiprazole or haloperidol treatment. Patients could have entered this study while hospitalized or as outpatients. Patients assigned to aripiprazole started at a dose of 15 mg daily. Patients assigned to haloperidol started at 10 mg daily. If patients had a Clinical Global Impression-Bipolar Scale (CGI-BP [mania]) Improvement Score of 3 or more at the end of Weeks 1 or 2, aripiprazole could be increased to 30 mg daily and haloperidol to 15 mg daily. If the higher dose was not tolerated, the study medication could be decreased to the initial dose. If the lowest dose of

aripiprazole or haloperidol was not tolerated, patients were discontinued from the study. Patients with a CGI-BP (mania) Severity Score ≥ 4 (moderately ill or worse) or a Montgomery-Asberg Depression Rating Scale (MADRS) Score of ≥ 18 at the end of Week 3 were discontinued from the study. Patients who discontinued at or prior to the end of Week 3 due to lack of response or adverse events (AEs) received alternative treatment.

At the conclusion of the initial 3-week period, patients meeting eligibility criteria continued in the same treatment group at the same dose level. The dose of study medication could not be increased during this phase of the study, but could be decreased from 30 to 15 mg daily for aripiprazole and from 15 to 10 mg daily for haloperidol, if necessary for tolerability. If these lowered doses of aripiprazole or haloperidol were not tolerated, patients were discontinued from the study. Patients were evaluated at scheduled treatment visits.

During Weeks 4 to 12, patients were discontinued from the study for any of the following reasons: increase in the CGI-BP (mania) Severity Score from previous assessment, which was confirmed at two consecutive visits; hospitalized for manic or depressive symptoms; required an addition to or increase in psychotropic medications; MADRS Score ≥ 18; did not tolerate the study medication at the lowest allowed dose; or required concomitant medication for symptomatic treatment of side effects.

Patients who completed the 12-week study and who met prespecified criteria could continue treatment in a 14-week double-blind Extension Phase. The results of the Extension Phase will be presented in a separate report. In addition, quality of life and pharmacoeconomic results will be presented in a separate report.

NUMBER OF PATIENTS: Three hundred seventy-two patients were enrolled in the study and 347 patients were randomized to double-blind treatment: 172 (49.6%) to the haloperidol group and 175 (50.4%) to the aripiprazole group. There were 133 (38.3%) men and 214 (61.7%) women between 18 and 68 years of age randomized to treatment. Of the 347 patients randomized to treatment, 344 were included in the Safety Sample and 338 were in the Efficacy Sample. Two hundred twenty-nine (66.0%) and 139 (40.1%) of the 347 randomized patients completed Weeks 3 and 12 of the study, respectively.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Weeks 1 to 3 Treatment Phase: Patients must have had a DSM-IV diagnosis of Bipolar I Disorder, Manic or Mixed, and have been in acute relapse. Patients must also have had a Young Mania Rating Scale (Y-MRS) Score ≥ 20.

Weeks 4 to 12 Treatment Phase: Patients must have had a score of < 4 on the CGI-BP (mania) Severity Scale and a score of < 18 on the MADRS at the end of Week 3.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Aripiprazole 15-mg tablet, one or two tablets daily, administered orally, batch numbers 99H93A015A and 99L77A015.

DURATION OF TREATMENT: 12 weeks.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Haloperidol 5-mg capsules, two or three capsules daily, administered orally, batch numbers 102924-03 and 102920-03; placebo capsules for haloperidol, two or three capsules daily, administered orally, batch numbers 102924-02 and 102920-02; placebo tablets for aripiprazole, one or two tablets daily, administered orally, batch number 99K77P000B.

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy measure was the number of patients who completed Week 12 and were in response at the end of Week 12 (at least 50% improvement from baseline Y-MRS). Efficacy rating scales completed during this study included the Y-MRS, MADRS, the Positive and Negative Syndrome Scale (PANSS), and the CGI-BP.

Safety: Safety assessments included medical review of AE reports (including intercurrent illness), vital sign measurements, electrocardiograms (ECGs), body weight, concomitant medications, and results of physical examination and clinical laboratory tests. Extrapyramidal syndrome (EPS) rating scales completed during this study were the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale.

STATISTICAL METHODS: The planned sample size of 306 patients (153 per treatment group) was estimated to yield 90% power to detect a treatment difference of 54% of patients completing the study in the aripiprazole group versus 35% of patients completing the study in the haloperidol group, assuming a two-sided test at the 0.05 level. The estimated percentages of patients completing the study were derived from an estimated response rate at end of Week 3 of 60% in the aripiprazole group versus 50% in the haloperidol group, and the estimated number of patients who either dropped out after end of Week 3 or were not in response at end of Week 12 (10% in the aripiprazole group and 30% in the haloperidol group).

The Safety Sample included patients who received at least one dose of study medication as indicated on the dosing record. The Efficacy Sample included patients in the Safety Sample who had at least one efficacy evaluation (ie, evaluable patients) who received at least one dose of study medication.

The primary efficacy endpoint was the response rate at Week 12, defined as the proportion of patients who completed the 12-week phase (as stated on the Week 12 end-of-study form) and who had at least a 50% improvement from baseline in the Y-MRS Total Score. Patients who discontinued from the study during the 12-week phase and patients without a Week-12 Y-MRS Total Score were considered non-responders. The primary outcome measure was analyzed within the framework of the Cochran-Mantel Haenszel (CMH) test, controlling for treatment, and was performed on the Safety Sample. Relative risk (RR) versus haloperidol, P-values, and 95% confidence intervals (CIs) for the relative risk were presented. The same analysis was performed on the OC data set. A sensitivity analysis was performed, similar to the primary analysis but with adjustment for the current episode (manic, mixed).

The secondary outcome measures were the response rate at Week 3 and the response rate at Week 12 in the subgroup of patients who had a CGI-BP (mania) Severity Score < 4 and a MADRS Total Score < 18 at Week 3. Secondary measures were analyzed with the same methods as those used for the primary outcome measure.

Remission rate at Week 3 (Week 12), defined as the proportion of patients who completed Week 3 (Week 12) with a Y-MRS Total Score < 12, was analyzed within the framework of the CMH test, controlling for treatment, and was performed on the Safety Sample. Relative risk versus haloperidol, P-values, and 95% CIs for the relative risk were presented. The same analysis was performed on the OC data set.

Time to discontinuation and time to discontinuation due to lack of efficacy were evaluated using the log-rank test to compare survival distributions. The parameter estimates and 95% CI for the hazard ratio were obtained from the Cox regression model, with treatment as covariate. The Safety Sample was used for these analyses.

Other efficacy analyses included the mean change from baseline to each specified visit in the Y-MRS Total Score, the mean changes from baseline in the CGI-BP Severity of Illness (mania, depression, and overall) Scores, the mean change from baseline in the PANSS Total Score, the mean change from baseline in the PANSS Cognitive Subscale Score, the mean change from baseline in the PANSS Hostility Subscale Score,

and the mean change from baseline in the MADRS Total Score. The analysis model included the baseline measure as covariate and treatment as main effect. Baseline scores for these efficacy variables and mean CGI-BP change from preceding phase (mania, depression, and overall) scores were evaluated by analysis of variance (ANOVA), with treatment as main effect. These analyses were applied to the Efficacy Sample, and performed on the last observation carried forward (LOCF) and observed cases (OC) data sets.

Other efficacy measures analyzed within the framework of the CMH test were the proportion of patients with a MADRS Total Score ≥ 18 (evaluated at all time points), time to discontinuation for lack of efficacy, and proportion of patients with at least 70% improvement from baseline in Y-MRS Total Score at Week 3. These analyses were applied to the Efficacy Sample, and performed on the LOCF and OC data sets.

All analyses carried out on the OC data set were considered secondary.

EFFICACY RESULTS:

Primary Efficacy Endpoint: The analysis of the primary efficacy endpoint, the number of patients who continued on treatment and maintained response after 12 weeks of study medication, showed that patients in the aripiprazole group had a statistically significantly ($P < 0.001$) greater response rate (49.7%) than patients in the haloperidol group (28.4%) at Week 12, and the relative risk was 1.75 in favor of aripiprazole.

Secondary Efficacy Endpoints: For the secondary efficacy measure, response rate at the end of Week 3, the aripiprazole group showed greater response (50.9%) than the haloperidol group (42.6%), but the comparison was not statistically significant ($P = 0.126$). There was a statistically significantly ($P = 0.048$) greater proportion of patients in the aripiprazole group (68.8%) compared with the haloperidol group (54.6%) who were in response (for the subgroup of patients who continued in the study after Week 3 with a CGI-BP [mania] Severity of Illness Score <4 and a MADRS Score < 18 at Week 3, and who were in response at the end of Week 12).

Other Key Efficacy Endpoints: At Week 12, the proportion of patients in remission (Y-MRS Total Score < 12) was statistically significantly higher ($P < 0.001$) in the aripiprazole group (50%) than in the haloperidol group (27%). For time to discontinuation for any reason, the treatment comparison showed a highly statistically significant result ($p < 0.001$) in favor of aripiprazole. For the mean change from baseline in Y-MRS Total Score for the LOCF data set, none of the differences between the groups at any time point was statistically significant, and the largest difference was 1.71 points at Week 12 numerically in favor of aripiprazole ($P = 0.226$).

Other additional efficacy endpoints were analyzed. For time to discontinuation due to AE, the treatment comparison showed a highly statistically significant result ($P < 0.001$) in favor of aripiprazole. For time to discontinuation due to lack of efficacy ($P = 0.041$) and the proportion of patients who discontinued due to lack of efficacy ($P <0.001$), results were statistically significantly in favor of haloperidol. The only other additional efficacy analysis showing statistically significant treatment differences was the LOCF analysis of change from baseline in the CGI-BP Severity of Illness (overall) Score. The results from Week 6 to Week 12 ($P = 0.019$) favored aripiprazole. There were no differences between the groups on the MADRS Total Score, the proportion of patients with MADRS scores ≥ 18 at Week 12, the proportion of patients with at least 70% improvement from baseline in Y-MRS at Week 3, the CGI-BP Severity of Illness (mania and depression) Scores, the CGI-BP Change from Preceding Phase (mania, depression, and overall) Scores, and the PANSS Total Score, Cognitive Subscale Score, and Hostility Subscale Score.

Summary of Primary Efficacy Results at Endpoint, Safety Sample

Variable	Haloperidol N = 169	Aripiprazole N = 175
PRIMARY EFFICACY ENDPOINT[a]		
Number (%) of responders at Week 12,[b] Safety Sample	48 (28.4)	87 (49.7)
RR (95% CI on RR)[c]	1.75 (1.33, 2.30)	
P-value	< 0.001	

Protocol CN138008

RR = Aripiprazole/Haloperidol

[a] Analysis: CMH analysis and RR unstratified.

[b] A responder was a patient who had at least a 50% decrease from baseline on the Y-MRS Total Score and who did not discontinue at or before Week 12.

[c] A RR greater than 1 favors aripiprazole.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.