SYNOPSIS

Clinical Study Report CN138131

TITLE OF STUDY: A Double-Blind Placebo Controlled Pilot Tolerability Study of Intramuscular Aripiprazole in the Treatment of Acutely Agitated Patients with a Diagnosis of Alzheimer’s, Vascular or Mixed Dementia

INVESTIGATORS AND STUDY CENTERS: Investigators at 16 study centers in the United States of America (US).

PUBLICATIONS: None

STUDY PERIOD: Date first patient enrolled: 17-Dec-2003
Date last patient completed: 25-Mar-2005

CLINICAL PHASE: 3

HYPOTHESIS: Intramuscular (IM) aripiprazole will be well tolerated in acutely agitated patients with a diagnosis of Alzheimer’s, vascular or mixed dementia.

OBJECTIVES:
Primary: To assess the tolerability and determine the maximum tolerated dose of multiple injections of IM aripiprazole at total doses of 5 mg, 10 mg and 15 mg in agitated patients diagnosed with Alzheimer’s, vascular or mixed dementia.

Secondary: To obtain preliminary data regarding the efficacy of IM aripiprazole in treating agitation in patients with Alzheimer’s, vascular or mixed dementia and to gather pharmacokinetic information on the IM formulation in this patient population.

METHODOLOGY: This was a multicenter, double-blind, placebo-controlled, pilot tolerability study of IM aripiprazole in agitated patients diagnosed with Alzheimer’s, vascular or mixed dementia. A total of 128 inpatients were treated with IM aripiprazole or placebo in a 4:1 randomization ratio.

The study began with a minimum 2-hour screening period (maximum 30 days) prior to initiation of baseline assessments. Baseline assessments were performed within 1 hour prior to the first dose of study drug. An inpatient evaluation period of 24 hours after administration of the first IM dose of study medication followed.

Patients were enrolled in up to 3 sequential cohorts each beginning with 15 patients. Four out of 5 patients in each cohort were randomized to receive 2 injections of aripiprazole and 1 out of 5 was randomized to receive 2 injections of placebo, as described below. The dosage strength of aripiprazole for injection was 7.5 mg/mL. Once a maximally-tolerated dose was established from 1 cohort, additional patients were to be enrolled into that cohort to bring total enrollment to at least 125 patients. Based on a blinded review of tolerability by the study director, and using a conservative approach to patient care, Cohort 2 (aripiprazole
10 mg or placebo) was chosen for additional enrollment. Overall, tolerability was similar between Cohorts 2 and 3; however, a slight increase was found in the incidence of somnolence (4 of 15 patients in Cohort 3 versus 3 of 15 patients in Cohort 2) and Cohort 3 had the only patient who experienced a Grade IV AE (femoral neck fracture resulting from a fall).

Cohort 1  Dose  # of Injections  Maximum Dose
- 15 patients  2.5 mg aripiprazole or placebo  2  5 mg

Cohort 2
- 15 patients  5 mg aripiprazole or placebo  2  10 mg

Cohort 3
- 15 patients  10 mg aripiprazole or placebo  1
  5 mg aripiprazole or placebo  1  15 mg

NUMBER OF SUBJECTS/PATIENTS: 128 total treated patients / 103 aripiprazole : 25 placebo

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Acute agitation with a diagnosis of Alzheimer’s, vascular or mixed dementia as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Aripiprazole 2.5 mg, 5 mg, and 10 mg, intramuscular (IM) formulation; batch number 3C7414.

DURATION OF TREATMENT: 24 hours (treatment and observation period) from first IM injection.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Placebo, IM administration; batch number C01044.

CRITERIA FOR EVALUATION: Laboratory assessments, adverse events (AEs), concomitant medication, Positive and Negative Symptom Scale (PANSS) Excited Component (PEC), Agitation Calmness Evaluation Scale (ACES), Clinical Global Impressions-Severity (CGI-S), Clinical Global Impressions-Improvement (CGI-I), Mini Mental State Examination (MMSE), Simpson-Angus Scale (SAS) and Barnes Akathisia Rating Scale (Barnes).

STATISTICAL METHODS: It was anticipated that approximately 125 patients would receive double-blind study medication. Although the sample size was not based on statistical considerations, administration of IM aripiprazole to 100 patients provided an 80% probability of observing at least 1 occurrence of any AE that occurred with an incidence of 1.6% in the population, and a 95% probability of observing at least 1 occurrence of any AE that occurred with an incidence of 3.0% in the population.

The Enrolled Sample comprised all patients who were enrolled in the study. The Randomized Sample comprised all patients who were randomized to receive treatment. The Safety Sample included all patients in the Randomized Sample who received at least 1 dose of study medication as indicated on the dosing record. The Efficacy Sample comprised all patients in the Safety Sample who had at least 1 postrandomization efficacy evaluation and a corresponding baseline value (not applicable to the CGI-I). The last observation carried forward (LOCF) data set included data recorded at a scheduled timepoint or, if no observation was recorded at that timepoint, data carried forward from the previous timepoint with available data. The observed cases (OC) data set consisted of the actual observations at each timepoint.

No efficacy analyses were planned for this study; however, exploratory analyses were performed. Descriptive statistics were provided for the mean change from baseline at 2 hours and all other scheduled timepoints after the first IM injection for the PEC, ACES and CGI-S. For the CGI-I, descriptive statistics were provided for the actual mean score. These descriptive statistics were presented by pooled placebo-treated patients across cohorts, by IM aripiprazole-treated patients in each cohort, and by pooled IM aripiprazole-treated patients across cohorts.
For all safety analyses, the results were presented by pooled placebo-treated patients across cohorts, by IM aripiprazole-treated patients in each cohort, and by pooled IM aripiprazole-treated patients across cohorts. All safety analyses were performed on the Safety Sample.

EFFICACY RESULTS:

No formal efficacy analyses were planned for this study. Descriptive statistics showed numeric improvement on the PEC, CGI-I, CGI-S, and ACES for the aripiprazole group compared with the placebo group at 2 hours and 4 hours after the first injection.

SAFETY RESULTS:

Sixty-four (50.0%) of the 128 patients in the Safety Sample reported at least 1 AE at any time during the study: 8/25 (32.0%) in the placebo group, 6/12 (50.0%) in the 5-mg aripiprazole group, 41/76 (54.0%) in the 10-mg aripiprazole group, and 9/15 (60.0%) in the 15-mg aripiprazole group. AEs were mild or moderate in severity in the majority (> 91%) of patients. Somnolence was the only treatment-emergent and treatment-related AE that was reported at a higher incidence than placebo across all aripiprazole dose groups.

One death occurred during this study: a patient treated with 10-mg aripiprazole died of very severe dementia 24 days after completion of study treatment. Twelve patients (10 aripiprazole-treated and 2 placebo-treated) experienced an SAE. Most SAEs were related to the patient’s underlying illness and all were judged by the investigator to be either not related or not likely related to study medication. One patient in the aripiprazole 10-mg group was hospitalized on Day 17 for a probable stroke, which was rated by the investigator as severe in intensity and not likely related to study medication. Only 2 patients discontinued from the study: 1 had an AE of severe femoral neck fracture, judged by the investigator to be not related to study medication, and 1 no longer met study criteria.

No patient had an extrapyramidal symptom (EPS)-related AE. There were mean change decreases from baseline in the SAS Total Score at most timepoints for the 5-mg and 10-mg aripiprazole groups; there were mean change decreases on the Barnes Akathisia Global Clinical Assessment score for timepoints in the 10-mg and 15-mg aripiprazole groups; and all treatment groups except for the 5-mg aripiprazole group showed some improvement on the MMSE Total Score.

Overall, the incidence of somnolence was higher for aripiprazole-treated patients (35.9%) than for placebo-treated patients (8%). The incidence of sedation was low (≤1% for aripiprazole and 4% for placebo). An injection-site reaction AE was experienced by 1 placebo-treated patient and no aripiprazole-treated patients. Overall, somnolence, with an incidence of 10.2%, was the most common AE seen with first onset or increased severity after the second injection.

No aripiprazole-treated patient discontinued from the study because of a laboratory or vital sign abnormality. There were no clinical concerns raised by the assessments of laboratory abnormalities or vital sign measurements.

No patient discontinued from the study because of an ECG abnormality and there were no clinical concerns regarding ECG measurements of rate, rhythm, conduction, infarction, or increased ST/T morphology.

Given the baseline QTc and health status of this patient population, there were no noteworthy treatment differences versus placebo in any QTc intervals (QTcB, QTcN, and QTcF) with standard 12-lead ECGs or ambulatory 12-lead ECGs, and there was no clear pattern of treatment differences by timepoint, using either standard or ambulatory 12-lead ECGs. Furthermore, there were no clinically relevant differences versus placebo for the aripiprazole treatment groups on the mean change from baseline to highest and endpoint (LOCF) QTc results, regardless of correction formula (QTcB, QTcN, QTcF).

CONCLUSIONS:

• A maximum tolerated dose of IM aripiprazole was not identified for agitated, elderly patients diagnosed with Alzheimer's, vascular or mixed dementia.
Aripiprazole treatment was generally well tolerated at all 3 doses (each dose comprised 2 injections separated by 2 hours) and tolerability was similar for the 10- and 15-mg doses. Somnolence was the most common (> 5% and twice the incidence of placebo) AE. ECG changes were minimal and not clinically important.

Exploratory data on efficacy, using descriptive statistics for the PEC, CGI-I, CGI S, and ACES, showed numeric improvement that was generally greater for aripiprazole treatment than for placebo treatment.

DATE OF REPORT: 4-Aug-2005