SYNOPSIS

Clinical Study Report CN138-166

TITLE OF STUDY: A Prospective, Multicenter, Open-label Study to evaluate the Effectiveness and the Effect on Cognitive Functioning of a Treatment with Aripiprazole in a Broad Range of Schizophrenic Patients

STUDY CENTERS: 55 centers in Belgium and 1 center in Luxembourg enrolled at least one patient.

PUBLICATIONS: None

STUDY PERIOD: Date first patient enrolled: 10-Mar-2005
Date last patient completed: 23-Mar-2006

CLINICAL PHASE: IV

OBJECTIVES:

Primary:
To evaluate the effectiveness of a 12-week treatment with Aripiprazole in a broad range of schizophrenic patients. The overall effectiveness will be evaluated by the Clinical Global Impression- Improvement (CGI-I) scale at Week 12.

Secondary:
1) To evaluate treatment effectiveness by:
   a) Physicians: CGI-Severity (CGI-S) scale, CGI Therapeutic Index scale, Investigator Assessment Questionnaire (IAQ)
   b) Patients: Patient Global Impression – Improvement (PGI-I) scale, Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ) and Preference of Medication (POM) questionnaire
   c) Care givers and/or family: PGI-I scale and POM questionnaire
2) To evaluate cognitive function by California Verbal Learning Test and Verbal Fluency
3) To evaluate compliance by drug accountability records and by Drug Attitude Inventory (DAI) questionnaire.
4) To evaluate safety and tolerability by the incidence and severity of adverse events, serious adverse events, discontinuation from study due to adverse events and weight changes.

METHODOLOGY: This was a prospective, multi-center, open-label, non comparative study of Aripiprazole in the treatment of schizophrenic patients in an in-patient or out-patient setting.
Qualified patients were assigned to an open-label Aripiprazole treatment phase for 12 weeks with Aripiprazole 15 mg/day. In case of insufficient response the dose could be increased to 30 mg/day; in case of important adverse event, the dose could be decreased to 10 mg/day. Dose adjustments were to be based on the clinical judgment of the investigator. Patients started taking Aripiprazole at study Day 1. Discontinuation of the potential pre-study antipsychotic treatment was allowed during the first two weeks of the treatment phase. (A maximum of 14 days after the study start (Day 1) was allowed for dose tapering of pre-study antipsychotic medication).

All patients who complete the 12-week Treatment Phase were allowed to enter an Extension Phase and to continue treatment with open-label Aripiprazole until the drug was commercially available in Belgium for Belgium and in Luxembourg for Luxembourg.

**NUMBER OF PATIENTS:** 363 patients were enrolled; 361 patients received at least 1 dose of aripiprazole; 238 patients completed the 12-week treatment phase and 123 discontinued treatment.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** Males or females, aged ≥ 18 years; having a DSM-IV-TR diagnosis of schizophrenia; stabilized or not stabilized, in or out-patients, in whom an antipsychotic treatment is initiated or for whom, in the clinical judgment of the investigator, a change in antipsychotic treatment was warranted (for lack of efficacy of the current treatment or for the occurrence of adverse event under the current treatment).

**TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:** Aripiprazole 15 mg/day (10 - 30 mg) administered orally; batch numbers 4L81978 (10 mg), 4L81975 (15 mg) and 4L81979 (30 mg).

**DURATION OF TREATMENT:** Patients were treated for 12 consecutive weeks and were allowed to participate in an extension phase until Aripiprazole was commercially available in Belgium and in Luxembourg.

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:** No reference therapy was used in this study.

**CRITERIA FOR EVALUATION:**

- **Effectiveness:** Clinical Global Impression – Improvement (CGI-I), CGI-Severity (CGI-S), CGI-Therapeutic Index (CGI-TI), Investigator Assessment Questionnaire (IAQ), Patient Global Impression – Improvement (PGI-I), Preference of medication (POM), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

- **Cognition:** California Verbal Learning Test (CVLT) and Verbal Fluency (VF).

- **Compliance:** drug accountability records and Drug Attitude Inventory (DAI),

- **Safety:** adverse events (AEs), serious adverse events (SAEs), discontinuation from study due to AEs and weight changes.

**STATISTICAL METHODS:**

The primary effectiveness analysis was a comparison of the upper bound of the 95% confidence interval (CI) for the mean score of the CGI-I at Week 12 Last Observation Carried Forward (LOCF) to 4 (=no change) using the Effectiveness Sample. An upper 95% confidence bound less than 4 is considered as a proof of the effectiveness of Aripiprazole.

The percentage of patients with beneficial CGI - Therapeutic Index was presented. Changes from Baseline in CGI - S, cognitive assessments, Q-LES-Q total score, and DAI total score were summarized using
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Descriptive statistics. The PGI-I and the POM score (both assessed by patients and caregivers) as well as IAQ total score were also summarized.

Incidence of AEs, SAEs, and discontinuation due to AEs were presented for the Safety Sample. Also mean changes from baseline in weight were reported and summarized.

**DISPOSITION AND BASELINE CHARACTERISTICS**

In total, 363 patients were enrolled: on average patients were 36 years old, all but 19 were Caucasian, 2 patients were not included because of baseline failure. The mean CGI-S at baseline was 4.3 (moderately to markedly ill) and the majority of patients was taking antipsychotic medications (87%). The most common primary reasons to participate were lack of efficacy on positive or negative symptoms and weight gain while taking previous drug. Of the 361 patients who were included in the study, 238 (66%) completed the study and 123 (34%) discontinued. The most frequent primary reasons for discontinuation (% of patients) were adverse events (10%), lack of efficacy (8%), patient consent withdrawal (7%), and lost to follow up (7%).

**EFFECTIVENESS RESULTS:**

Since the CI boundaries are under the score 4 in the scale CGI-I, the effectiveness of Aripiprazole is demonstrated. The average improvement score decreased from 3.5 to 3.0, at Week 12 LOCF with CI of 2.84 to 3.15 (where CGI-I: 3 = minimal improvement; 4 = no change)

A decrease in the CGI-S at Week 12 (LOCF) was observed. In total 54% of patients had a beneficial therapeutic Index score (CGI-TI) at Week 12 (LOCF). Furthermore, the majority of the patients were rated doing “slightly better” or “much better” on 7/10 items of the IAQ: energy (73%), somnolence (71%), negative symptoms (68%), cognition (67%), mood (61%), weight gain (57%) and positive symptoms (50%).

PGI-I rated by patients and caregivers were consistent with each other. Through the Q-LES-Q, patients reported increases from baseline for 8 on the 10 sub-scales: ‘physical health’, ‘feelings of well-being’, ‘household duties’, ‘leisure time’, ‘social relations’, ‘overall-general’, ‘satisfaction with medication’ (from 2.8 to 3.4 (week 12 LOCF) on a 5 points scale) and ‘overall life satisfaction’ (from 2.8 to 3.2).

Both patients (71%) and caregivers (61%) reported that Aripiprazole was “slightly better” or “much better” than their prior antipsychotic medication (POM).

Patient performance increased for all CVLT indices (except discriminability) and Verbal Fluency during the 12 Week Treatment Phase.

**SAFETY RESULTS:**

A total of 207 patients on 361 patients (57%) presented with at least one adverse event. The most frequently reported adverse events were insomnia (14%), nausea (12%), akathisia (6%) and headache (6%) and the most frequent treatment-related AE’s were insomnia (14%) and nausea (11%).

One patient completed suicide by defenestration after 4 weeks of treatment, the investigator considered her death possibly related to study treatment.

A total of 23 other serious adverse events were reported by 19 other patients (5%) during the treatment phase. Most common serious adverse events were: psychotic disorder (5), delusion (3) and anxiety (2). Four cases of psychotic disorder, 2 cases of delusion and all cases of anxiety and insomnia were considered related in the investigator’s opinion.
One patient reported pregnancy at week 12, this event resulted in induced abortion at week 10 of gestational age.

A total of 37 patients on 361 patients (10.3%) experienced at least one adverse event which led to discontinuation of study therapy. In these 37 patients the most frequent discontinuation reasons were the following: 7 patients left because of insomnia, 5 because of akathisia, 4 because of agitation and another 4 because of nausea.

CONCLUSIONS

The ability to draw conclusions from this open-label, uncontrolled, naturalistic study is limited. Nevertheless, in this study population of relatively young patients, with mild to moderate schizophrenia, switching from another antipsychotic medication mainly because of lack of efficacy (positive as well as negative symptoms), Aripiprazole showed effectiveness as early as Week 1. The effectiveness was maintained throughout the 12-Week Treatment Phase.

- Aripiprazole showed effectiveness in a broad range of schizophrenic patients, as demonstrated by a significant improvement of patient’s condition (CGI-I).

- A positive effect of Aripiprazole was also demonstrated on all physician- and patient/caregiver-rated assessments of disease and patient’s condition, quality of life and antipsychotic medication preference (CGI-S, CGI-TI, IAQ, PGI-I, Q-LES-Q, POM).

- Cognitive function assessments (CVLT, VF) demonstrated an improvement over the 12-Week Treatment Phase. The existence and/or quantification of a potential practice effect should be clarified.

Treatment compliance and the patient’s attitude towards drug were moderately positive.

The mean weight loss observed in this study was consistent with the observed weight change in other Aripiprazole clinical trials.

Safety results showed a low number of patients (57%) presenting with at least one adverse event. The incidence of treatment-related adverse events and the incidence of serious adverse events was lower than expected in this patient population. The study results confirm the current safety profile of Aripiprazole.

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