Long-Term Safety and Symptom Trajectory With Aripiprazole Lauroxil in Female Patients With Schizophrenia: A Post Hoc Subgroup Analysis

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INTRODUCTION

- The efficacy and tolerability of antipsychotic medications may differ between female and male patients with schizophrenia; however, evidence of sex differences is inconsistent in clinical trial data and may vary depending on the medication used[1,2]
- Because most clinical studies of antipsychotics enroll substantially greater proportions of male versus female patients,[2,3] there is a dearth of antipsychotic efficacy and safety information specific to female patients with schizophrenia
- The long-acting injectable (LAI) antipsychotic aripiprazole lauroxil (AL; 441 mg or 882 mg monthly) significantly reduced Positive and Negative Syndrome Scale (PANSS)[4] total score from baseline compared with placebo in patients with schizophrenia in a pivotal 12-week efficacy study[5]
- Long-term effects of AL were evaluated in patients with schizophrenia in 2 successive open-label extension studies following the pivotal study[6,7]
  - The first extension study (EXT-1; ClinicalTrials.gov identifier, NCT01626456) was 52 weeks in duration[6,8]
  - The second (EXT-2; ClinicalTrials.gov identifier, NCT01895452) provided up to 128 weeks of additional AL treatment[7]

OBJECTIVE

- The objective of this post hoc analysis was to assess symptom trajectory and safety outcomes in the subgroup of female patients with schizophrenia who received AL treatment in the EXT-1 and EXT-2 clinical trials

METHODS

Study Design

- The phase 3, 52-week EXT-1 trial enrolled patients who either completed the 12-week, randomized, double-blind, placebo-controlled phase 3 pivotal AL trial or were enrolled de novo while receiving a stable dose of oral antipsychotic medication
- Patients received AL 441 mg or 882 mg via intramuscular injections starting on study day 1 and then every 4 weeks thereafter (last injection, week 48)
  - Patients assigned to receive 441 or 882 mg AL treatment in the lead-in study continued their previously assigned AL dose
  - Patients previously assigned to receive placebo started AL 441 mg or 882 mg every 4 weeks based on their placebo assignment (matched to either a low- or high-volume placebo injection, respectively)
  - Patients who enrolled de novo were assigned to receive AL 882 mg every 4 weeks
- Following the completion of EXT-1, patients could enroll in the phase 3, 128-week EXT-2 study to continue the evaluation of long-term treatment with AL
- Patients entering EXT-2 continued the same dose of AL they received in EXT-1

Study Population

- Patients enrolled in EXT-1 had either completed the pivotal study or met the following criteria:
  - Adult outpatients aged ≥18 to ≤70 years at screening with a diagnosis of chronic schizophrenia according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition text revision) criteria
  - On a stable dose of oral antipsychotic medication with a potential benefit from converting to an LAI antipsychotic
  - PANSS total score <70 and Clinical Global Impression–Severity (CGI-S)[9] score ≤3 at screening
  - No hospitalizations for acute exacerbations of schizophrenia ≤3 months before screening

Assessments and Analysis

- Symptom trajectory outcomes: PANSS total score (range 30–210) and PANSS anxiety item (G2) analysis (range 1–7)
  - PANSS total score was assessed separately in patients ≤40 years or >40 years of age and in patients with mild (CGI-S score ≤3) or moderate or worse (CGI-S score ≥4) severity of illness[9]
  - PANSS total and anxiety scores were assessed over time in EXT-1; changes from baseline in scale scores were assessed in EXT-2
- Safety outcomes: Body mass index (BMI; assessed separately in patients with BMI <25 kg/m^2 or ≥25 kg/m^2 at baseline), injection site reactions (ISRs), adverse events (AEs), and AEs potentially related to prolactin (EXT-1 only)
  - AEs potentially related to prolactin were based on a Customized Medical Dictionary for Regulatory Activities Query (CMQ) prespecified in the statistical analysis plan
- Outcomes are reported descriptively for female patients and for the overall population; no statistical comparisons were made

RESULTS

Patients

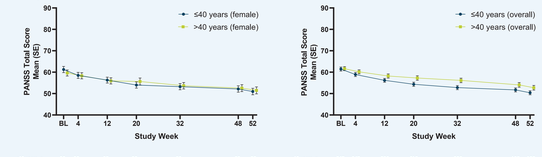
- The safety population in EXT-1 included 478 patients (42.5% female), and 291 patients continued into EXT-2 (46.4% female; **Table 1**)

Table 1. Demographics, Baseline Characteristics, and Disposition (Safety Population)

Demographics and Baseline Characteristics: All Patients	EXT-1 (N=478)	EXT-2 (N=291)
Age, mean (SD), years	39.4 (11.6)	39.6 (11.5)
Female, n (%)	203 (42.5)	135 (46.4)
BMI, mean (SD), kg/m^2	27.0 (6.3)	26.6 (5.0)
PANSS total score, mean (SD)[a]	61.5 (14.4)	50.6 (13.2)
Disposition: Females	**EXT-1 (n=203)**	**EXT-2 (n=135)**
Completed, n (%)	152 (74.9)	119 (88.1)
Discontinued, n (%)	51 (25.1)	16 (11.9)
Reason for discontinuation, n (%)		
Withdrawal by subject	24 (11.8)	12 (8.9)
Adverse event	13 (6.4)	1 (0.7)
Lost to follow-up	10 (4.9)	1 (0.7)
Lack of efficacy	3 (1.5)	0
Other	1 (0.5)	1 (0.7)
Pregnancy	0	1 (0.7)

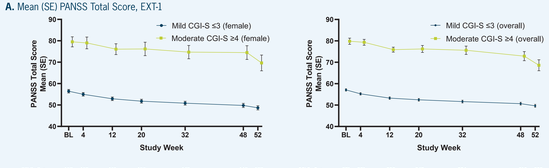
[a]Based on patients with ≥1 postbaseline PANSS assessment
BMI, body mass index; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

Figure 1. PANSS Total Score by Age (≤40 years or >40 years)



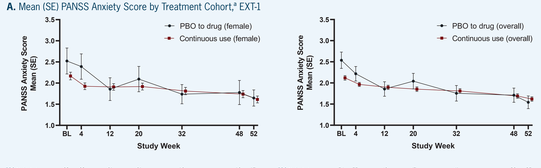
BL, baseline; LPV, last postbaseline visit; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

Figure 2. PANSS Total Score by Severity of Illness (CGI-S score ≤3 or ≥4)



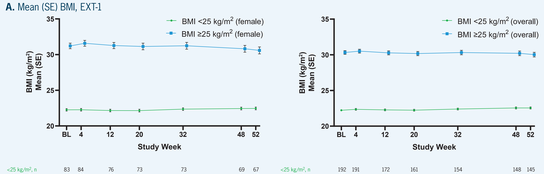
BL, baseline; CGI-S, Clinical Global Impression–Severity; LPV, last postbaseline visit; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

Figure 3. PANSS Anxiety Item (G2) Score



[a]Continuous use: AL 441 mg → AL 441 mg; AL 882 mg → AL 882 mg, and de novo AL 882 mg combined; PBO to drug: placebo → AL 441 mg and placebo → AL 882 mg combined.
BL, baseline; LPV, last postbaseline visit; PANSS, Positive and Negative Syndrome Scale; PBO, placebo; SE, standard error.

Figure 4. BMI by Baseline Value (BMI <25 kg/m^2 or ≥25 kg/m^2)



BL, baseline; BMI, body mass index; LPV, last postbaseline visit; SE, standard error.

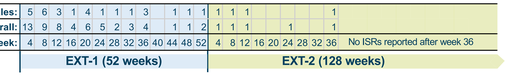
Symptom Trajectory

- Among females, PANSS total score improved (ie, decreased) over the course of EXT-1 and remained stable in EXT-2
- Results for females by age (**Figure 1**) and severity of illness (**Figure 2**) were consistent with the pattern of response in the overall study population
- PANSS anxiety scores improved (ie, decreased) during EXT-1 and were maintained through EXT-2 in females and the overall population (**Figure 3**)

Safety Outcomes

- Mean BMI was stable in EXT-1; variability in BMI increased with decreasing sample size during EXT-2 (**Figure 4**)
- AEs were reported in 49.3% of females (50.4% overall) in EXT-1 and 34.1% of females (39.5% overall) in EXT-2
- The 3 most common AEs for females in EXT-1 were insomnia (8.9%; 8.4% overall), increased weight (4.9%; 5.0% overall), and anxiety (4.9%; 4.4% overall); in EXT-2, the 3 most common AEs for females were insomnia (6.7%; 6.2% overall), headache (5.9%; 4.5% overall), and asthenia (4.4%; 3.1% overall)
- Rates of ISRs were comparable for female patients and for those in the overall population (**Figure 5**)
- Four potentially prolactin-related AEs reported for female patients were identified by CMQ in EXT-1 (libido decreased, amenorrhea, blood prolactin increased, and menstrual disorder in 1 female patient each); all were mild or moderate in severity

Figure 5. ISRs by Week, EXT-1 and EXT-2



ISR, injection site reaction.

LIMITATIONS

- These post hoc analyses were exploratory, and the subgroups were small; study discontinuations reduced group sizes substantially over time, particularly in EXT-2
- Both EXT-1 and EXT-2 were open-label AL safety studies with no placebo or active comparator group
- Neither EXT-1 nor EXT-2 was designed or powered to assess results in patient subgroups; no statistical comparisons between subgroups were conducted
- Because the study population in EXT-1 and EXT-2 was limited to those who met the inclusion and exclusion criteria, these results may not be generalizable to all patients with schizophrenia who are treated with LAI antipsychotics
- These analyses focused on a subset of safety outcomes, and the full results for both open-label safety studies have been reported[6,7]

CONCLUSIONS

- In analyses from 2 open-label extension studies (52 weeks and 128 weeks in duration), AL (441 mg or 882 mg monthly) was safe and effective in female patients with schizophrenia during long-term LAI antipsychotic treatment
- Clinical symptoms improved or remained stable over EXT-1 and EXT-2 in female patients, consistent with the overall study population
- For female patients who received long-term AL treatment, the safety profile related to weight gain and ISRs was consistent with the known safety profile of AL
- Female patients' results analyzed by age and by illness severity were similar to those in the overall study population

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AUTHOR DISCLOSURES

DLK has served on advisory boards for Alkermes, Sunovion, and Janssen. SY and JAM are employees of Alkermes and may be shareholders.

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