

Aripiprazole Once-Monthly in the Acute Treatment of Schizophrenia: Findings From a 12-Week, Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Objective: To evaluate aripiprazole once-monthly (AOM), a long-acting injectable suspension of aripiprazole, as acute treatment in patients with schizophrenia (*DSM-IV-TR*).

Method: Adults experiencing an acute psychotic episode were randomized to 12 weeks of double-blind treatment with AOM 400 mg or placebo (October 2012–August 2013). The primary efficacy outcome was change from baseline to endpoint (week 10) in Positive and Negative Syndrome Scale (PANSS) total score. The key secondary efficacy outcome was change from baseline in Clinical Global Impressions-Severity of Illness scale (CGI-S) score. Secondary efficacy outcomes included change from baseline in PANSS positive and negative subscale and Personal and Social Performance Scale (PSP) scores. The study took place from October 2012 through August 2013.

Results: Patients (N = 340; 79% male, 66% black) were randomized to AOM (n = 168) or placebo (n = 172). Least squares (LS) mean change from baseline to endpoint (week 10) favored AOM versus placebo in PANSS total (treatment difference, -15.1 [95% CI, -19.4 to -10.8]; $P < .0001$) and CGI-S (treatment difference, -0.8 [95% CI, -1.1 to -0.6]; $P < .0001$) scores, as it did at all other timepoints through 12 weeks (all $P \leq .0005$). LS mean change from baseline in PANSS positive and negative subscale and PSP scores favored AOM versus placebo ($P < .0001$). Common (> 10%) treatment-emergent adverse events (AOM vs placebo) were increased weight (16.8% vs 7.0%), headache (14.4% vs 16.3%), and akathisia (11.4% vs 3.5%).

Conclusions: Symptoms and functioning improved with AOM 400 mg versus placebo in patients with acute schizophrenia, with acceptable safety and tolerability. These data suggest that AOM 400 mg is a viable treatment option for patients experiencing an acute schizophrenia episode.

Trial Registration: ClinicalTrials.gov identifier: NCT01663532

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Oral antipsychotics are effective for treating patients with schizophrenia; however, nonadherence to prescribed oral antipsychotic medication is common^{1,2} and is associated with more hospitalizations, longer hospital stays, higher health care costs,¹ increased risk of suicide, and potential emergence of treatment resistance.³ Discontinuation of antipsychotic treatment is a strong predictor of relapse.⁴ Compared with oral antipsychotics, long-acting injectables (LAIs) have been shown in naturalistic⁵ and mirror-image^{6,7} studies to reduce rates of relapse and rehospitalization. Results from controlled trials and meta-analyses of such trials are mixed,^{8,9} possibly reflecting methodological challenges in studying nonadherence in randomized controlled trials.

Aripiprazole once-monthly (AOM), an extended-release injectable suspension for intramuscular use, is the first dopamine partial agonist available as an LAI and is approved for the treatment of schizophrenia.^{10–12} Findings from 2 randomized controlled trials demonstrated that maintenance treatment with AOM reduces the rate of impending relapse compared with placebo or a subtherapeutic dose of AOM^{13,14} and could be a valuable addition to the current options for maintenance therapy.

The question remains whether AOM can be used in acute settings. An acute exacerbation usually indicates that prior therapy is not working or not being taken, providing rationale for initiating a new therapy. The initial treatment to which a patient responds is often the treatment of choice for ongoing therapy. For patients with acute exacerbations, LAIs may be an important treatment option for ensuring continuous treatment exposure, regardless of the reason for relapse. This randomized, double-blind, placebo-controlled study evaluated the efficacy, safety, and tolerability of AOM for the treatment of acute exacerbations of psychotic symptoms in adults with schizophrenia.

METHOD

Study Design

In a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in adult patients with schizophrenia (NCT01663532), patients were enrolled from 41 trial sites (United States, 37; Croatia, 2; Latvia, 2). The study protocol was approved by the institutional review board/independent ethics committee of each site, and all patients provided written informed consent. The study took place from October 2012 through August 2013.

The study included 3 phases. Patients entered the screening phase for up to 13 days to assess eligibility. Patients with prior aripiprazole exposure entered a 7-day washout period from prior antipsychotics and other prohibited concomitant medications. Patients without

prior exposure received open-label treatment with oral aripiprazole 10 mg/d for 3 days to establish tolerability before the 7-day washout period. Hospitalization was required during the entire screening period. Patients who met the entrance criteria enrolled in the 12-week acute treatment phase.

At baseline, patients were randomized 1:1 in a double-blind fashion to either AOM 400 mg (injected into a gluteal muscle once every 4 weeks) or placebo. Because the AOM 400 mg and placebo solutions had different appearances, injections were administered by an independent, unblinded drug manager at each study site so that investigators remained blinded to study treatment. A single dose decrease to AOM 300 mg was permitted for tolerability per the investigator's judgment; a single return to the 400-mg dose was permitted for efficacy. On the basis of simulation data, median plasma levels of aripiprazole reach a therapeutic level ~ 3 days after injection of aripiprazole 400 mg.¹⁵ Because therapeutic levels may take longer to achieve in some patients, patients randomized to AOM received concomitant oral aripiprazole (10–20 mg/d, dose based on clinical judgment), and patients randomized to placebo received concomitant oral placebo for 14 days beginning on the day of the first injection. Patients were randomized via an interactive voice response system following computer-generated randomization codes. During the first 2 weeks of the acute treatment phase, patients were required to remain as inpatients, after which hospitalization status was determined on the basis of the investigator's judgment of the patient's clinical status. Outpatients returned to the clinic for study visits biweekly through week 12 (even-numbered weeks) and were contacted by phone biweekly (odd-numbered weeks). During the safety follow-up phase, all patients were contacted by phone 14 (\pm 2) days after the final study visit.

Patients

Eligible patients were 18 to 65 years of age and diagnosed with schizophrenia as defined by the *DSM-IV-TR* and confirmed by the Mini-International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies.¹⁶ All patients were currently experiencing an acute psychotic episode at screening and baseline, defined as (1) acute exacerbation of psychotic symptoms accompanied by significant deterioration in clinical and/or functional status from their baseline clinical presentation with a Positive and Negative Syndrome Scale (PANSS)¹⁷ total score \geq 80 and (2) specific psychotic symptoms on the PANSS with a score $>$ 4 on each of 4 specific items (conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, unusual thought content; possible scores ranged from 1 to 7 for each item). All patients resided in a stable living environment when not hospitalized, had demonstrated a good response to antipsychotic treatment (other than clozapine) in the last 12 months (investigator's opinion), and were not treatment resistant.

Patients with a first episode of schizophrenia, who had been hospitalized for \geq 30 days of the 90 days preceding the

- Initial treatment of acute exacerbation of schizophrenia with a long-acting injectable antipsychotic may enable long-term continuity of treatment, potentially improving adherence and outcomes.
- This randomized, controlled study demonstrated the efficacy, safety, and tolerability of aripiprazole once-monthly 400 mg for acute treatment of schizophrenia exacerbation.
- Patients with acute exacerbation of schizophrenia should be monitored for known and potential adverse events when initiating treatment with aripiprazole once-monthly or other long-acting injectable antipsychotics.

screening visit, had a comorbid *DSM-IV-TR* Axis I diagnosis (eg, major depressive disorder or bipolar disorder), or had evidence of substance abuse were excluded. Patients were also excluded if total PANSS score improved by \geq 30% between screening and baseline.

Assessments

The primary efficacy outcome was change from baseline to endpoint (week 10) in PANSS total score¹⁷; the key secondary efficacy outcome was change from baseline to endpoint in Clinical Global Impressions-Severity of Illness scale (CGI-S)¹⁸ score. Week 10 was chosen as the primary study endpoint (blinded to patients and investigators) to minimize potential rater/scoring bias associated with a final study visit; week 12 efficacy assessment data are also presented.

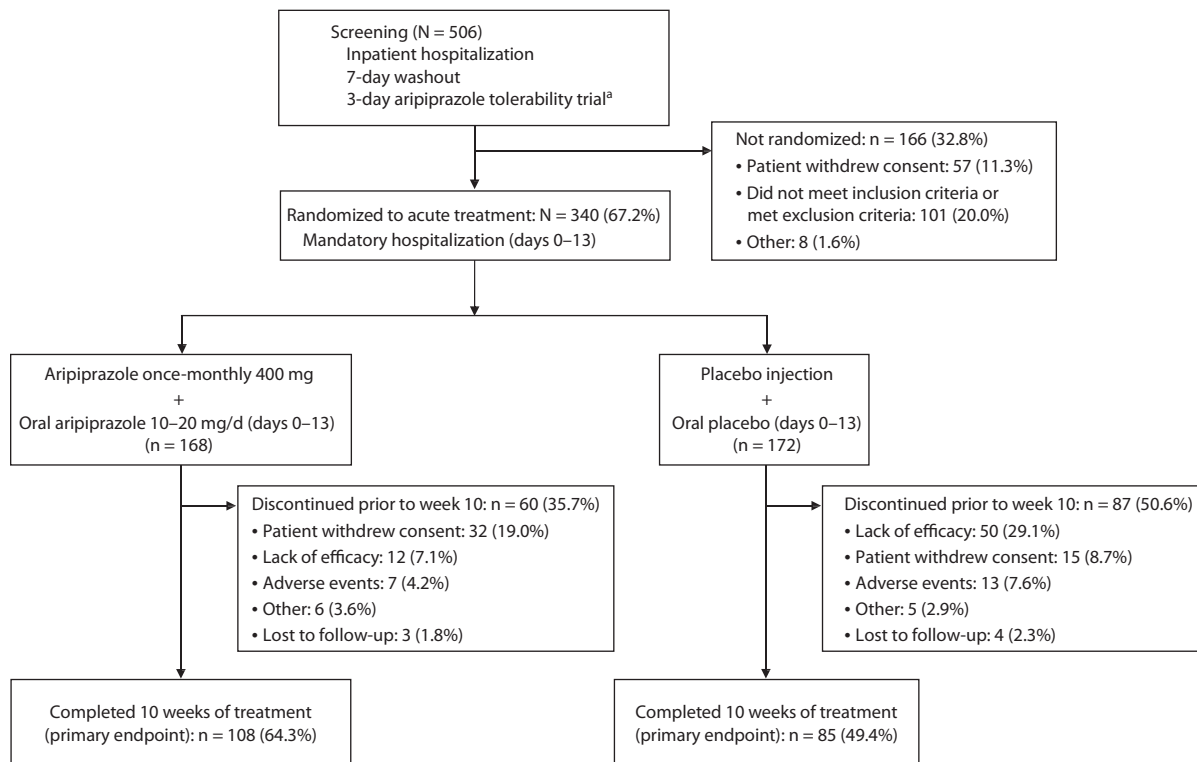
Other secondary efficacy outcomes included change from baseline to endpoint in PANSS positive and negative subscale scores, PANSS responder rate (\geq 30% reduction in PANSS total score) at endpoint, change from baseline to endpoint in Personal and Social Performance Scale (PSP) score,¹⁹ Clinical Global Impressions-Improvement scale (CGI-I)¹⁸ score at endpoint, and time to all-cause discontinuation. After patients entered the acute treatment phase, PANSS and CGI-S assessments were conducted at weeks 1 and 2 and every 2 weeks thereafter until week 12 (last scheduled visit) and/or last visit (last assessment visit in the acute treatment phase [scheduled or unscheduled]). PSP total score was assessed at endpoint and week 12 or last visit.

Safety variables included treatment-emergent adverse events (TEAEs), extrapyramidal symptoms (EPS; Simpson Angus Scale [SAS]),²⁰ Abnormal Involuntary Movement Scale [AIMS],²¹ and Barnes Akathisia Rating Scale [BARS]²², weight, clinical laboratory assessments, (eg, metabolic parameters [glucose, cholesterol, triglycerides], prolactin), vital signs, and electrocardiograms (ECGs).

The correlation between patient in-hospital days and weight gain at week 12 was evaluated as an exploratory post hoc analysis.

Statistical Analyses

An estimated sample size of 310 patients for randomization (1:1) was determined to achieve at least 90% power at an α

Figure 1. Patient Disposition

^aTolerability trial only in patients without prior exposure to aripiprazole.

level of .05 (2-sided z test) to detect a treatment difference of -7.5 points with a standard deviation (SD) of 20 points in change from baseline in PANSS total score between AOM 400 mg and placebo.

The efficacy sample was defined as the modified intent-to-treat (mITT) population, which included all randomized patients who received ≥ 1 injection of AOM or placebo and had ≥ 1 postbaseline efficacy assessment. The safety sample included all patients who received ≥ 1 injection of AOM or placebo. Baseline values were defined as the last observation before the first injection of study medication.

The primary and key secondary efficacy outcome comparisons were performed using a mixed-model repeated measures (MMRM) analysis with an unstructured variance-covariance matrix for the repeated measures based on the observed cases (OC) dataset. This model included fixed class effect terms for treatment, geographic region, visit week, and an interaction term of treatment by visit week (covariate). Sensitivity analyses were performed using the pattern mixture approach with multiple imputations (based on the discontinuation reasons) under the assumption of missing not at random.

Changes from baseline in PANSS positive and negative subscale scores were compared using the same analytic approach described for the primary efficacy outcome (MMRM; OC dataset). Responder rate ($\geq 30\%$ reduction in PANSS total score) was analyzed in the mITT population

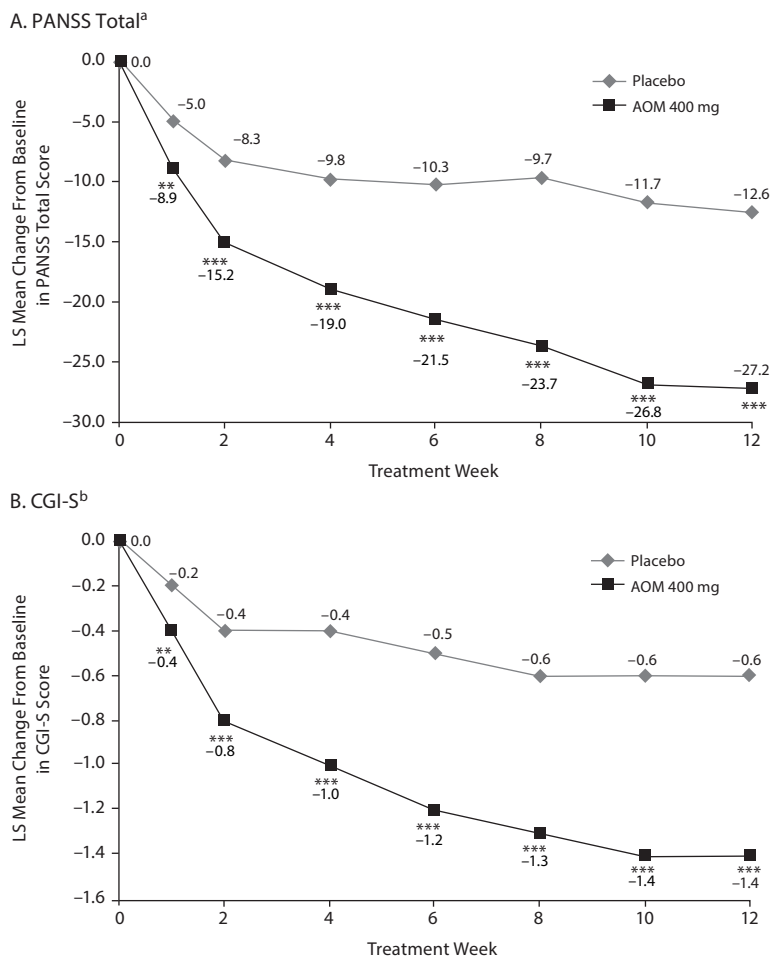
Table 1. Patient Demographics and Baseline Characteristics

	AOM 400 mg (n = 168)	Placebo (n = 172)
Age, mean (SD), y	42.1 (11.0)	42.7 (10.9)
Sex, n (%)		
Male	130 (77.4)	139 (80.8)
Race, n (%)		
White	52 (31.0)	55 (32.0)
Black or African American	110 (65.5)	113 (65.7)
Asian	2 (1.2)	0 (0)
Other	4 (2.4)	4 (2.3)
Weight, mean (SD), kg	86.0 (17.7)	86.6 (16.7)
BMI, mean (SD), kg/m ²	28.4 (5.6)	28.5 (5.2)
Age at first diagnosis, mean (SD), y	24.4 (8.3)	24.0 (9.3)
PANSS score, mean (SD)		
Total	103.0 (11.3)	104.0 (11.0)
Positive subscale	29.5 (3.3)	29.4 (3.0)
Negative subscale	23.8 (4.8)	24.6 (4.5)
CGI-S score, mean (SD)	5.2 (0.5)	5.2 (0.5)
PSP total score, mean (SD) ^a	43.1 (9.9)	42.2 (10.0)

^aSample size for baseline PSP total score was 167 for AOM 400 mg and 170 for placebo.

Abbreviations: AOM = aripiprazole once-monthly, BMI = body mass index, CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale, PSP = Personal and Social Performance Scale.

with the Fisher exact test (last observation carried forward [LOCF]). CGI-I score was analyzed in the mITT population with the Cochran-Mantel-Haenszel row mean score test (van Elteren test) controlling for geographical region (LOCF). Change from baseline in PSP total score was analyzed using analysis of covariance (ANCOVA) with treatment group as a factor and baseline as a covariate (LOCF). Time to all-

Figure 2. LS Mean Change From Baseline (MMRM) in (A) PANSS Total Score and (B) CGI-S Score

^aMean baseline score: placebo (n = 167), 103.4; AOM 400 mg (n = 162), 102.4.

^bMean baseline score: placebo (n = 168), 5.2; AOM 400 mg (n = 162), 5.2.

***P* < .001.

****P* < .0001.

Abbreviations: AOM = aripiprazole once-monthly, CGI-S = Clinical Global Impressions-Severity of Illness scale, LS = least squares, MMRM = mixed-model repeated measures, PANSS = Positive and Negative Syndrome Scale.

cause discontinuation was estimated using Kaplan-Meier and compared with a log-rank test.

Descriptive statistics were generated for all safety variables. Changes from baseline to week 12 (OC dataset) in EPS scale scores (SAS, AIMS, BARS), body weight, and prolactin levels were analyzed using ANCOVA with treatment group as a factor and baseline as a covariate.

Because observed weight changes did not align with those from earlier long-term outpatient studies, correlations between patient in-hospital days and weight gain in the safety sample at week 12 were explored using Pearson correlation coefficients.

RESULTS

Patient Disposition and Characteristics

Of 506 patients screened, 340 patients were randomized to double-blind treatment with AOM 400 mg (n = 168) or placebo (n = 172; Figure 1); no patient failed screening due

to intolerance of aripiprazole. A total of 64.3% (AOM 400 mg) and 49.4% (placebo) of patients completed 10 weeks of treatment. The most common reason for discontinuation was patient withdrawal of consent in the AOM group (n = 32/168 [19.0%]) and lack of efficacy in the placebo group (n = 50/172 [29.1%]; Figure 1).

Baseline demographic and disease characteristics were similar between treatment groups in the randomized population (Table 1). Mean patient age was approximately 42 years; ~79% were men, and ~66% were black. Before enrollment, 6.5% and 6.4% of patients randomized to AOM and placebo, respectively, had taken oral aripiprazole.

Treatment Exposure

Of 340 randomized patients, 195 received oral aripiprazole (10 mg/d for 3 days) during the screening phase to establish tolerability to aripiprazole. During the first 2 weeks of the acute treatment phase, patients randomized to AOM received a mean (SD) average daily dose of 12.8 (3.2) mg oral aripiprazole. Almost all patients remained at their starting injection dose (AOM 400 mg, 161/167 [96.4%]; placebo, 168/172 [97.7%]). Use of concomitant benzodiazepines was comparable between treatment arms (139/167 [83.2%] AOM, 144/172 [83.7%] placebo), with similar mean average daily doses.

Primary and Key Secondary Efficacy Outcomes

Least squares (LS) mean change from baseline at endpoint was significantly greater with AOM versus placebo for PANSS total score (Figure 2A; treatment difference, -15.1 [95% CI, -19.4 to -10.8]; *P* < .0001) and for CGI-S (Figure 2B; treatment difference, -0.8 [95% CI, -1.1 to -0.6]; *P* < .0001). MMRM results were confirmed by ANCOVA with both OC and LOCF data. Sensitivity analyses demonstrated that the superiority of AOM to placebo at endpoint was maintained up to a deduction of 140% (PANSS total) and 160% (CGI-S) estimated treated difference from the imputed data after discontinuation for all discontinued patients in the AOM group. Subgroup analysis by sex showed a similar pattern of improvement at endpoint with AOM on primary and key secondary efficacy measures for men (PANSS total score and CGI-S, AOM vs placebo, both *P* < .05) and women (PANSS, *P* = .053; CGI-S, *P* < .05). At all time points assessed, AOM significantly improved both PANSS total and CGI-S scores (Figure 2A and 2B).

Secondary Efficacy Outcomes

LS mean change from baseline in PANSS positive and negative subscale scores was significantly improved

with AOM versus placebo at each time point ($P < .0001$; Figure 3A and 3B). PANSS responder rate ($\geq 30\%$ reduction in total score) was significantly higher with AOM versus placebo at endpoint (60/162 [37.0%] vs 24/167 [14.4%]; $P < .0001$) and week 12 (56/162 [34.6%] vs 26/167 [15.6%]; $P < .0001$).

LS mean (SE) change from baseline in PSP total score was significantly greater with AOM versus placebo at endpoint (12.3 [1.2] vs 5.2 [1.2], respectively; $P < .0001$) and week 12 (13.0 [1.2] vs 5.5 [1.2]; $P < .0001$). Mean (SD) CGI-I score was significantly better with AOM versus placebo at each assessment ($P < .0001$), including endpoint (2.7 [1.2] vs 3.7 [1.3]) and week 12 (2.6 [1.2] vs 3.7 [1.3]).

Estimated median time to discontinuation due to all reasons was longer in the AOM 400 mg group than in the placebo group (92 vs 60 days; $P = .0029$).

Exploratory Post Hoc Analysis

A statistically significant correlation was found between in-hospital days and weight change at week 12 with AOM ($r = 0.2340$; $P = .0197$) but not placebo ($r = 0.1496$; $P = .2306$).

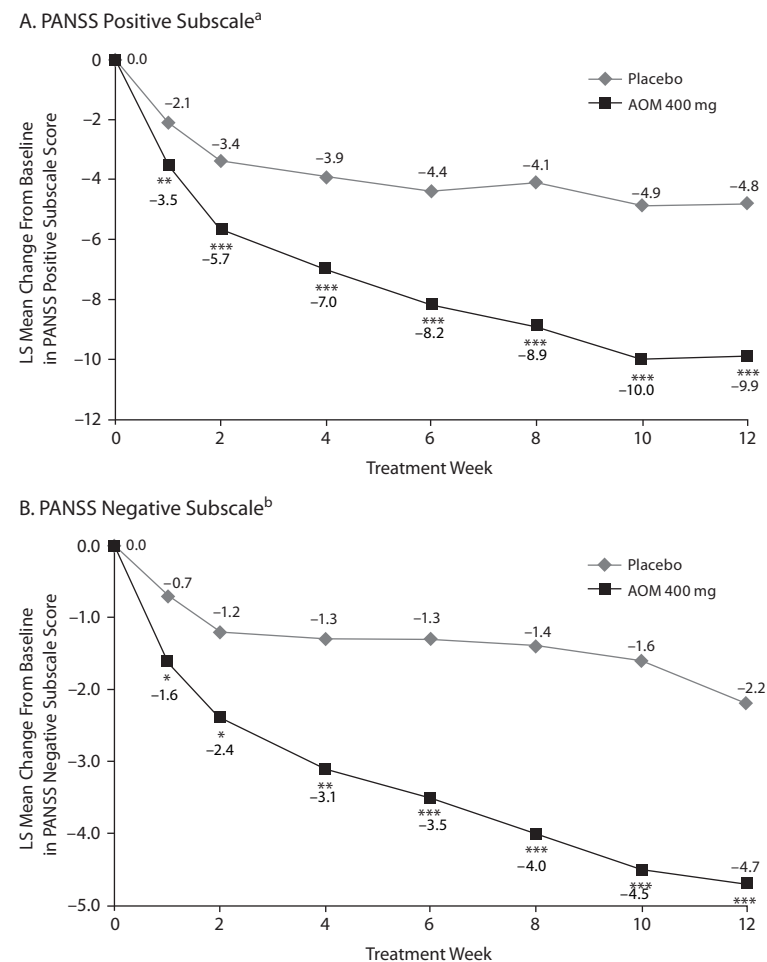
Safety and Tolerability

TEAEs through week 12 are summarized in Table 2; the most common ($> 10\%$) were weight increase, headache, and akathisia in the AOM group and headache in the placebo group. No patient discontinued due to weight gain, headache, or akathisia. Serious TEAEs were observed in 8/167 (4.8%) patients in the AOM group and 6/172 (3.5%) in the placebo group. Serious TEAEs observed in $\geq 1\%$ of patients were schizophrenia (AOM, 3/167 [1.8%]; placebo, 3/172 [1.7%]) and psychotic disorder (AOM, 2/167 [1.2%]; placebo, 2/172 [1.2%]). No other serious TEAEs were observed in > 1 patient in either group, and all serious TEAEs resolved. No deaths occurred.

On average, minimal changes from baseline to week 12 in EPS scales were observed, with no statistically significant differences between groups. EPS scale LS (SE) mean changes from baseline to week 12 for the AOM and placebo groups were as follows: SAS total score, -1.0 (0.1) and 0.1 (0.2), respectively; AIMS movement rating score, 0.1 (0.1) and 0.1 (0.1); and BARS global score, -0.1 (0.1) and -0.1 (0.1).

Mean (SD) weight increases from baseline to week 12 (completer analysis) were significantly larger with AOM (3.5 [5.8] kg) versus placebo (0.8 [4.3] kg; $P = .0018$). The incidence of potentially clinically relevant weight gain ($\geq 7\%$ change from baseline) at any time during the acute treatment phase was 31/144 (21.5%) for AOM and 12/141 (8.5%) for placebo. At week 12, African American patients receiving AOM ($n = 59$) gained a mean (SD) of 4.9 (5.4) kg, whereas

Figure 3. LS Mean Change From Baseline (MMRM) in (A) PANSS Positive Subscale Score and (B) PANSS Negative Subscale Score



^aMean baseline score: placebo ($n = 167$), 29.4; AOM 400 mg ($n = 162$), 29.5.

^bMean baseline score: placebo ($n = 167$), 24.6; AOM 400 mg ($n = 162$), 23.7.

* $P < .01$.

** $P < .001$.

*** $P < .0001$.

Abbreviations: AOM = aripiprazole once-monthly, LS = least squares, MMRM = mixed-model repeated measures, PANSS = Positive and Negative Syndrome Scale.

white patients ($n = 34$) gained 0.7 (5.6) kg. Mean changes from baseline to week 12 in fasting metabolic parameters and shifts in metabolic parameters from normal levels at baseline to abnormal at any time during treatment were generally comparable between groups, although fasting glucose levels showed numerically greater changes with AOM versus placebo (Table 2).

Mean prolactin levels decreased in both groups; the mean (SD) reduction from baseline to week 12 was significantly larger with AOM (-6.4 [13.5]) than placebo (-1.1 [14.5]; $P = .0176$).

No clinically relevant mean changes from baseline were observed in vital signs or ECG parameters (data not shown).

DISCUSSION

These data demonstrate the efficacy, safety, and tolerability of AOM 400 mg with concomitant oral aripiprazole for

Table 2. Incidence of TEAEs^a and Summary of Metabolic Measures

	AOM 400 mg (n = 167)	Placebo (n = 172)
TEAEs, n (%)		
Any TEAE	133 (79.6)	122 (70.9)
Weight increased	28 (16.8)	12 (7.0)
Headache	24 (14.4)	28 (16.3)
Akathisia	19 (11.4)	6 (3.5)
Constipation	16 (9.6)	12 (7.0)
Cough	10 (6.0)	10 (5.8)
Dyspepsia	10 (6.0)	11 (6.4)
Agitation	9 (5.4)	11 (6.4)
Injection site pain	9 (5.4)	1 (0.6)
Sedation	9 (5.4)	2 (1.2)
Toothache	9 (5.4)	8 (4.7)
Schizophrenia	4 (2.4)	10 (5.8)
Metabolic measures^b		
Glucose		
Fasting level at baseline, mean, mg/dL	93.68	96.03
Fasting change from baseline at week 12, mean (SD), mg/dL	9.82 (41.97)	0.69 (19.59)
New-onset abnormality at any time, n/N (%) ^c	7/88 (8.0)	0/75 (0)
Total cholesterol		
Fasting level at baseline, mean, mg/dL	182.69	190.56
Mean (SD) fasting change from baseline at week 12, mg/dL	3.34 (31.46)	-6.75 (33.51)
New-onset abnormality at any time, n/N (%) ^c	3/83 (3.6)	2/73 (2.7)
LDL cholesterol		
Fasting level at baseline, mean, mg/dL	103.43	107.45
Fasting change from baseline at week 12, mean (SD), mg/dL	4.13 (26.90)	-1.56 (26.50)
New-onset abnormality at any time, n/N (%) ^c	1/59 (1.7)	1/51 (2.0)
HDL cholesterol		
Fasting level at baseline, mean, mg/dL	53.39	54.14
Fasting change from baseline at week 12, mean (SD), mg/dL	-1.90 (10.09)	-4.81 (12.56)
New-onset abnormality at any time, n/N (%) ^c	14/104 (13.5)	11/87 (12.6)
Triglycerides		
Fasting level at baseline, mean, mg/dL	127.75	139.10
Fasting change from baseline at week 12, mean (SD), mg/dL	8.97 (61.57)	6.73 (67.95)
New-onset abnormality at any time, n/N (%) ^c	7/98 (7.1)	4/78 (5.1)

^aReported by $\geq 5\%$ of patients in either treatment group.

^bFor LDL cholesterol, AOM 400 mg group n = 87, placebo group n = 55. For all other metabolic measures, AOM 400 mg group n = 88, placebo group n = 59.

^cIncidence of shift in metabolic parameters from normal at baseline to high at any time during randomized treatment, n/N (%). Shifts from normal to abnormal fasting metabolic parameters were defined as follows: glucose, < 100 to ≥ 126 mg/dL; total cholesterol, < 200 to ≥ 240 mg/dL; LDL cholesterol, < 100 to ≥ 160 mg/dL; HDL cholesterol, ≥ 40 to < 40 mg/dL; triglycerides, < 150 mg/dL to ≥ 200 mg/dL.

Abbreviations: AOM = aripiprazole once-monthly, HDL = high-density lipoprotein, LDL = low-density lipoprotein, n = number of reported patients, N = number of evaluated patients with baseline and ≥ 1 postbaseline result, TEAE = treatment-emergent adverse event.

the first 2 weeks for the treatment of adult patients with schizophrenia experiencing an acute exacerbation of psychosis. Both primary (PANSS total score change) and key secondary (CGI-S change) study endpoints were superior for AOM 400 mg over placebo. Results from other placebo-controlled studies of atypical LAIs were comparable to the present study.^{23,24} The significant reduction in both PANSS subscale scores as early as week 1 demonstrates that AOM

may rapidly resolve not only positive symptoms but also negative symptoms. Negative symptoms are often associated with functional deficits,²⁵ and low PSP scores at baseline in the present study indicated marked functional impairment. Improvements in PSP scores and PANSS negative symptoms indicated clinically significant improvement in patient function. Together with data showing that AOM 400 mg maintains stability of both symptoms and function over long-term treatment,^{13,14} the present data demonstrate the utility of AOM for acute treatment.

The overall safety and tolerability profile of AOM 400 mg in the current study was generally consistent with that observed in previous double-blind phase 3 studies.^{13,14} EPS and metabolic issues are important considerations with any antipsychotic treatment.²⁶ EPS scale scores indicated no significant difference between AOM and placebo, yet EPS-related TEAEs should be continuously monitored.

Mean change in weight and the incidence of clinically significant weight change were higher with AOM in the present study versus placebo and were higher with AOM in the present study compared with previous long-term AOM studies.^{13,14} Mean changes from baseline in AOM 400 mg treatment groups during the double-blind phase of a 52-week study¹⁴ and a 38-week study¹³ were -0.2 kg and +0.1 kg, respectively, suggesting that long-term outpatient treatment with AOM 400 mg is not associated with notable weight gain in most patients. One explanation for the difference between the current study and previous long-term studies, supported by the observed positive correlation between inpatient days and weight gain, could be that hospitalized patients receiving AOM experienced symptom improvements that potentially led to increased food intake given the provision of regular meals in the hospital setting. This may be particularly true for these patients who exhibited a full range of positive symptoms at enrollment. Another explanation may relate to patient demographics; ~66% of patients in the current study were African American compared with ~20% in previous AOM studies, and mean weight gain at 12 weeks was numerically greater in African American than in white patients.^{13,14} Increased risk for obesity and weight gain has been observed in African Americans with severe mental illness.²⁷ The prevalence of a risk allele (rs489693, genotype A/A) associated with antipsychotic drug-induced weight gain²⁸ is approximately twice as high in people of African ancestry compared with those of European ancestry.²⁹ Regardless of reason, continued treatment of patients experiencing weight gain should be based on clinical assessment of the patient in the context of the overall benefits and risks of treatment. All patients being treated with atypical antipsychotics should be monitored for changes in glucose, lipids, and body weight.³⁰

Several important study features may limit the generalizability of these findings to all patients treated in real-world clinical practice. These include the exclusion of patients with comorbid DSM-IV-TR Axis I diagnoses or substance abuse, the intense weekly follow-up, and the use of objective assessments.

In conclusion, treatment of acute schizophrenia with AOM 400 mg with 2 weeks of concomitant oral aripiprazole significantly improved patient symptoms and functioning compared with placebo. Treatment discontinuation in the AOM group was notably lower than in the placebo group, and almost all patients stayed on their starting dose of 400 mg. Safety and tolerability were generally as expected on the basis of previous studies of AOM in stable patients with schizophrenia.^{13,14} Collectively, the results suggest that AOM 400 mg is a viable treatment option for patients who experience an acute exacerbation of schizophrenia.

Drug names: aripiprazole once-monthly (Abilify Maintena), clozapine (Clozaril, FazaClo, and others).

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