Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled, 52-Week Randomized Withdrawal Study

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ABSTRACT

Objective: To evaluate efficacy, safety, and tolerability of long-acting injectable antipsychotic aripiprazole once-monthly 400 mg (AOM 400) as maintenance treatment for bipolar I disorder (BP-I).

Methods: In a double-blind, placebo-controlled, 52-week randomized withdrawal study conducted from August 2012 to April 2016, patients with a *DSM-IV-TR* diagnosis of BP-I currently experiencing a manic episode were stabilized sequentially on oral aripiprazole and AOM 400 and then randomized to AOM 400 or placebo. The primary end point was time from randomization to recurrence of any mood episode. Other end points included proportion of patients with recurrence of any mood episode and recurrence by mood episode type.

Results: Of 266 randomized patients, 64 (48.1%) of 133 in the AOM 400 group and 38 (28.6%) of 133 in the placebo group completed the study. AOM 400 significantly delayed the time to recurrence of any mood episode compared with placebo (hazard ratio: 0.45; 95% CI, 0.30 to 0.68; $P < .0001$). Significantly fewer patients ($P < .0001$) experienced recurrence of any mood episode with AOM 400 (35/132; 26.5%) compared with placebo (68/133; 51.1%), with the effects observed predominantly on manic episodes ($P < .0001$). Patients were not depressed at study entry, and between-group differences in depressive episodes were not significant ($P < .864$). The treatment-emergent adverse events (incidence > 5%) that were reported at higher rates with AOM 400 than placebo were weight increase, akathisia, insomnia, and anxiety.

Conclusions: AOM 400 delayed the time to and reduced the rate of recurrence of mood episodes and was generally safe and well tolerated. These findings support the use of AOM 400 for maintenance treatment of BP-I.

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Bipolar I disorder (BP-I) is characterized by manic, depressive, and mixed mood episodes interspersed with periods of remission.[1] Long-term pharmacologic treatment is required to prevent relapse of symptoms.[1–3] Patients often experience persistent symptoms leading to social and functional impairment.[4–7] Episodes of mania are recurrent and commonly associated with unfavorable outcomes, including poorer cognitive performance and greater number of hospitalizations.[8] The chronic nature of the disorder and the negative consequences of unremitted or recurrent symptoms underscore the need for effective long-term treatment.

The highly recurrent nature of bipolar disorder can be very difficult to manage. Compounds that possess prophylactic efficacy during maintenance therapy are the mainstay treatment for BP-I; however, their use is limited by side effect burden and the need for therapeutic blood monitoring.[1,9,10] Multiple studies support the use of atypical antipsychotics in BP-I.[1,11] The efficacy and safety of oral aripiprazole, as monotherapy and adjunctive therapy, in both acute and maintenance treatment of BP-I, have been established in randomized controlled studies.[2,12–16]

Poor adherence to treatment is a significant problem in BP-I, resulting in suboptimal outcomes.[5,17–19] Nonadherence rates can be as high as 79%.[20–22] Long-acting injectable (LAI) antipsychotics have the potential to improve medication adherence.[23] Currently, risperidone injection every 2 weeks is the only LAI atypical antipsychotic approved by the US Food and Drug Administration for the maintenance treatment of BP-I.[24] In a randomized study,[25] risperidone LAI (RLAI) significantly delayed the time to recurrence of mood episodes versus placebo in patients with BP-I. Aripiprazole once-monthly 400 mg (AOM 400), an LAI formulation of aripiprazole, has demonstrated efficacy in schizophrenia in multiple randomized clinical studies.[26–29] Findings from these studies, the established efficacy of oral aripiprazole in BP-I, and the potential for improved adherence formed the basis for evaluating AOM 400 as maintenance treatment of BP-I.

The primary objective of this study was to evaluate the efficacy of AOM 400 in preventing recurrence of any mood episode in patients with BP-I. Safety and tolerability of AOM 400 were also evaluated.

METHODS

Study Design

This multicenter, double-blind, placebo-controlled, randomized withdrawal study (ClinicalTrials.gov: NCT01567527) assessed time

Clinical Points

- Long-acting injectable antipsychotics have the potential to improve medication adherence, a challenge in bipolar I disorder (BP-I).
- The established efficacy and safety of oral aripiprazole in BP-I led to the evaluation of aripiprazole once-monthly 400 mg (AOM 400) in BP-I.
- In a 52-week randomized controlled trial, AOM 400 significantly delayed the time to recurrence of mood episodes and was generally safe and well tolerated as maintenance treatment for BP-I.

to recurrence of any mood episode in patients with BP-I who had maintained stability on AOM 400 for ≥ 8 consecutive weeks, having also received ≥ 3 injections. The trial was conducted from August 2012 to April 2016 at 103 sites in 7 countries (Canada, Japan, Republic of Korea, Poland, Romania, Taiwan, and the United States) in compliance with the International Conference of Harmonization and Good Clinical Practice consolidated guideline.[30] The protocol was approved by an institutional review board or independent ethics committee, as appropriate. Informed consent was obtained from patients or their guardians or legal representatives.

The trial consisted of 4 treatment phases (Supplementary eFigure 1). During the first 2 phases (conversion to oral aripiprazole, 4–6 weeks; and oral aripiprazole stabilization, 2–8 weeks), patients were converted to oral aripiprazole monotherapy, if not currently receiving it (target dose, 15–30 mg/day), and then assessed for stability. During the subsequent single-blind AOM 400 stabilization phase (12–28 weeks), patients received AOM 400 injections every 4 weeks. Patients who met a priori stability criteria for ≥ 8 consecutive weeks were randomized at a 1:1 ratio to 52 weeks of double-blind treatment with AOM 400 or placebo in the maintenance phase (randomization stratified by region: United States and Canada, Europe, Japan, and other Asian countries). At the completion of 52 weeks, patients were invited to enroll in an open-label extension study.

Stability was defined as meeting all of the following criteria: outpatient status, Young Mania Rating Scale (YMRS)[31] total score ≤ 12, Montgomery-Asberg Depression Rating Scale (MADRS)[32] total score ≤ 12, and no active suicidality (defined as score ≥ 4 on MADRS item 10 or "yes" on question 4 or 5 of the Columbia Suicide Severity Rating Scale [C-SSRS]).[33] Patients were randomly assigned via an interactive voice or web response system. In both AOM 400 stabilization and randomized phases, a single decrease to 300 mg was permitted for tolerability, as was a single return to 400 mg, if required. To maintain the blind, study drug was administered by unblinded site personnel, independent from those conducting the trial. Patient evaluations occurred every 2 weeks for the first 28 weeks and every 4 weeks thereafter.

Patients

Study participants were men or women, inpatient or outpatient at entry, aged 18 to 65 years, with a diagnosis of BP-I according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[34] criteria and confirmed by the Mini-International Neuropsychiatric Interview.[35] Eligible patients had experienced ≥ 1 previous manic or mixed episode with manic symptoms of sufficient severity to require hospitalization, treatment with a mood stabilizer, or treatment with an antipsychotic agent. Patients were required to be currently experiencing a manic episode (per *DSM-IV-TR* criteria) with YMRS total score ≥ 20. Those who experienced ≥ 9 episodes in the past year (rapid cycling) were excluded.

The use of cytochrome P450 (CYP) 3A4 or CYP2D6 inhibitors or CYP3A4 inducers was not allowed during the study. Benzodiazepine use was allowed at ≤ 2 mg/day lorazepam equivalent, but not within 8 hours of a rating scale assessment. Anticholinergics were allowed at ≤ 4 mg/day benztropine or equivalent but not within 12 hours of a rating scale assessment.

Efficacy Endpoints

The primary efficacy end point was time from randomization to recurrence of any mood episode, which was defined as meeting any of the following criteria: hospitalization for any mood episode; YMRS total score ≥ 15; MADRS total score ≥ 15; Clinical Global Impressions for Bipolar Disorder–Severity (CGI-BP-S) scale[36] overall score > 4; serious adverse event (AE) of worsening BP-I; discontinuation due to lack of efficacy or an AE of worsening of BP-I; clinical worsening with the need for addition of a mood stabilizer, antidepressant treatment, antipsychotic medication, or increase in benzodiazepine dose above the highest permitted dose; or active suicidality (score ≥ 4 on MADRS item 10 or "yes" answer to question 4 or 5 on the C-SSRS).

The key secondary efficacy end point was the proportion of patients meeting criteria for recurrence of any mood episode. Additional end points included change from randomization in YMRS and MADRS total scores. For the randomized phase, baseline was defined as the last visit in the AOM 400 stabilization phase.

Safety

All AEs were coded based on the *Medical Dictionary for Regulatory Activities*. A treatment-emergent AE (TEAE) was defined as an AE that occurred after the start of treatment or an AE that continued from baseline of one phase and became serious; was drug related; or resulted in death, discontinuation, interruption, or reduction of dosage during the subsequent phase. Suicidality was assessed using C-SSRS. Injection site pain was evaluated using the patient-reported Visual Analog Scale and investigator ratings. Extrapyramidal symptoms were reported as the change from baseline in Simpson-Angus Scale (SAS[37]; used in countries other than Japan), Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS[38]; used in Japan), Abnormal Involuntary Movement Scale (AIMS),[39] and Barnes Akathisia Rating Scale (BARS)[40] scores. Standard safety measurements included clinical laboratory tests, vital

signs, electrocardiogram (ECG), body weight, and physical examination. In addition, serum prolactin concentrations were monitored. Central laboratories designated by the sponsor were used for all laboratory tests and ECG review.

Statistical Analyses

Sample size estimates assumed that ≥55% of placebo-treated patients and ≤30% of AOM 400–treated patients would experience a recurrence. With an estimated attrition rate of 25%, 1:1 randomization of 238 subjects would provide at least 90% power to detect a 25% between-group difference in the proportion of patients having a recurrence using Fisher exact test at .049.

The safety sample included all patients who received ≥1 injection in that phase, and the efficacy sample included those who received ≥1 injection and had ≥1 postbaseline efficacy assessment in that phase.

Time to recurrence and time to discontinuation were plotted as Kaplan-Meier curves and analyzed using the log-rank test, and hazard ratios (HRs; AOM 400 vs placebo) and their 95% CIs were estimated using a Cox proportional hazards model with treatment as term. To assess the sensitivity of the primary efficacy analysis due to potentially informative withdrawal (missing not at random), worst-case analysis, Kaplan-Meier multiple imputations, and worst-comparison analysis using multiple imputation were performed (see Supplementary eFigure 2 for details). The proportion of patients with recurrence of any mood episode was analyzed using Fisher exact test. Changes from baseline in YMRS and MADRS scores were analyzed using mixed model repeated measures (MMRM), with treatment, region, trial week, and treatment-by-week interaction as terms, as well as the covariates of baseline-score-by-week interaction.

All statistical analyses used Statistical Analysis Software, version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patients

Of 1,175 patients screened, 731 met eligibility criteria. Figure 1 details the patient disposition during the 4 treatment phases. A total of 266 patients entered the double-blind withdrawal phase and were randomly assigned to AOM 400 (n = 133) or placebo (n = 133). Of these, 102 (38.3%) completed the study, 48.1% in the AOM 400 group and 28.6% in the placebo group. The most common reasons for discontinuation were recurrence of any mood episode without AE (AOM 400, 19 [14.3%]; placebo, 35 [26.3%]) and recurrence of any mood episode with AE (AOM 400, 16 [12.0%]; placebo, 33 [24.8%]).

Demographic and disease characteristics for AOM 400 and placebo groups are reported in Supplementary eTable 1.

Efficacy

Time to recurrence of any mood episode was significantly delayed with AOM 400 compared with placebo (log-rank test $P < .0001$; Figure 2). The risk of recurrence of any mood episode over 1 year was reduced by approximately half with AOM 400 compared with placebo (HR = 0.45; 95% CI, 0.30 to 0.68). Sensitivity analyses confirmed the robustness of the primary efficacy end point result (Supplementary eFigure 2).

The proportion of patients with recurrence of any mood episode in the randomized phase was significantly lower (Fisher exact test $P < .0001$) in the AOM 400 group (35/132; 26.5%) than in the placebo group (68/133; 51.1%; Figure 3). When treatment groups were assessed by type of mood episode, the difference between treatment groups was statistically significant for recurrence of manic episodes (52 episodes total; $P < .0001$). While the number of mixed-mood recurrences was small (11 episodes total), the relative proportion of patients with mixed episodes (AOM 400, 1.5% vs placebo, 6.8%; Fisher exact test $P = .06$) was similar to that observed for manic recurrences. There was no difference between treatments for recurrence of depressive episodes (39 episodes total; Fisher exact test $P = .864$).

Mean (standard deviation [SD]) YMRS scores in AOM 400 and placebo groups were 3.95 (6.08) and 7.99 (9.03) at week 52, respectively. Adjusted mean change in YMRS total score from baseline to week 52 significantly favored AOM 400 over placebo (–3.09; 95% CI, –5.01 to –1.17; $P = .002$; MMRM), with consistently significant differences between treatment groups starting at week 14. The mean MADRS total score varied by < 1 point in each group during the randomized phase; no statistical differences in change from baseline were observed between the treatment groups (AOM 400 vs placebo, –0.04; 95% CI, –1.1 to 0.97; $P = .935$; MMRM).

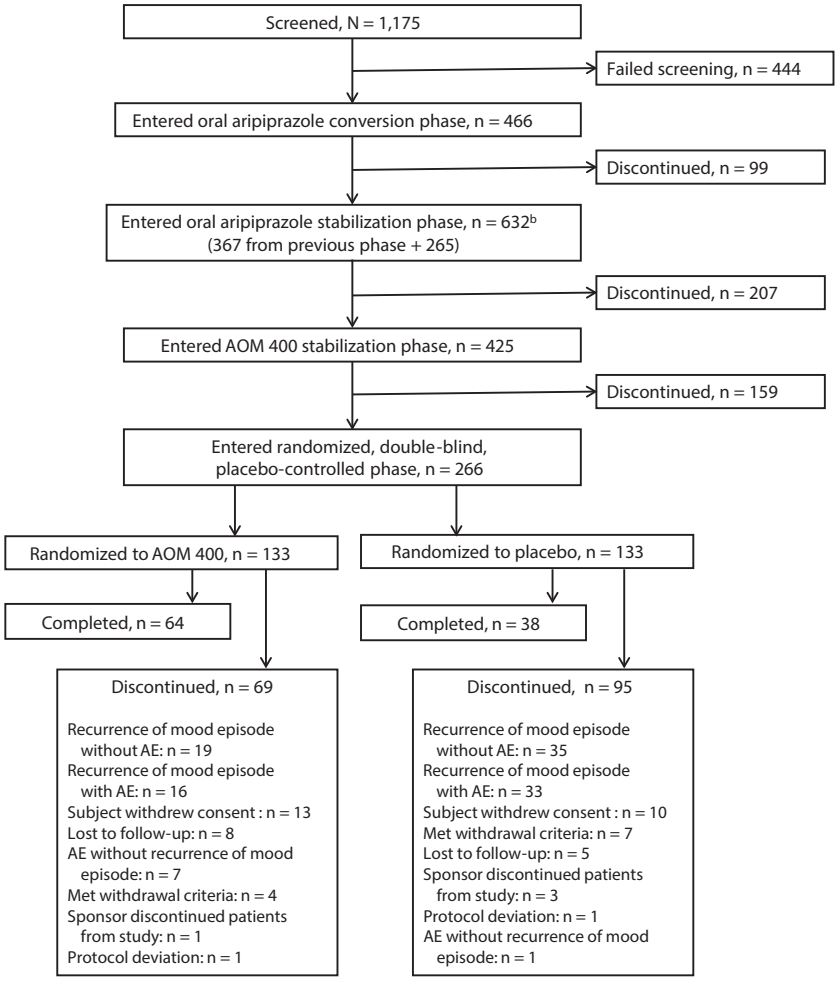
Median time to discontinuation from all causes was significantly longer with AOM 400 treatment (345 days) compared with placebo (170 days, log-rank test $P = .0026$; Figure 4). The risk of discontinuation over 1 year was reduced by almost 40% with AOM 400 treatment versus placebo (HR = 0.62; 95% CI, 0.46 to 0.85).

Safety and Tolerability

In the randomized phase, patients received injections every 4 weeks, for a total of up to 13 injections. Of 132 patients who received ≥1 injection of AOM 400 in the randomized phase, 113 (85.6%) received an initial dose of 400 mg and 19 (14.4%) received an initial dose of 300 mg; at each injection visit, >80% of patients received a dose of 400 mg. Mean dose of the last injection was 380.3 mg. Concomitant use of anticholinergics (AOM 400, 18.0%; placebo, 14.3%) and benzodiazepines (AOM 400, 27.8%; placebo, 24.1%) was similar between groups.

During the AOM 400 stabilization phase (single-blind AOM 400), 291 (68.5%) of 425 patients experienced TEAEs; of these, 8.5% had ≥1 serious TEAE, 6.6% had ≥1 severe TEAE, and 8.7% had ≥1 TEAE resulting in treatment discontinuation. The most frequently occurring TEAEs (≥5%) were akathisia (17.4%), weight increase (11.1%), insomnia (9.6%), anxiety (7.1%), restlessness (5.6%), fatigue (5.2%), and nasopharyngitis (5.2%). Mean (SD) increase in weight from baseline to the last visit in AOM stabilization

Figure 1. Patient Disposition Across the Study[a]



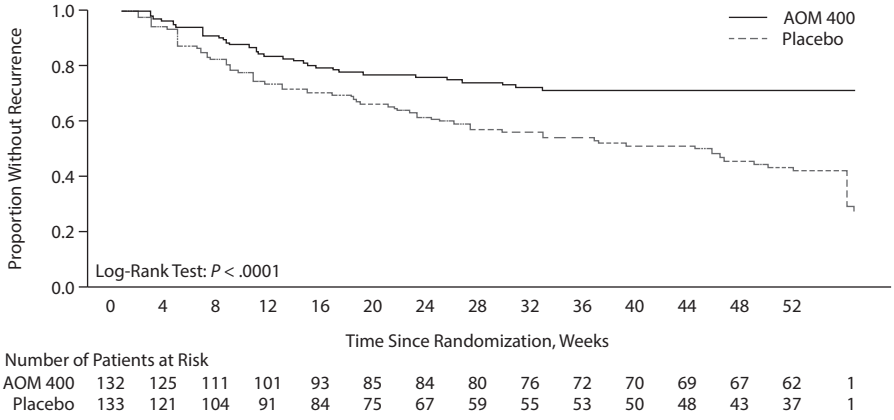
[a]Patients entered the oral aripiprazole conversion phase if they were not already receiving aripiprazole.
[b]Patients who successfully converted to oral aripiprazole monotherapy and those who were already receiving aripiprazole as monotherapy for bipolar I disorder (BP-I) at screening or who had a lapse in their BP-I treatment (such that washout of prior treatment would not be required) entered the oral stabilization phase.
Abbreviations: AE = adverse event, AOM 400 = aripiprazole once-monthly 400 mg.

phase was 1.0 kg (4.0 kg), with potentially clinically relevant weight gain at any time during the randomized phase observed in 44 (10.9%) patients.

In the randomized phase, 208 (78.5%) of 265 patients experienced ≥ 1 TEAE: 101 (76.5%) of 132 in the AOM 400 group and 107 (80.5%) of 133 in the placebo group (Table 1). The majority of TEAEs were mild or moderate in intensity. Serious TEAEs occurring in ≥ 1 patient, all related to the underlying disease, occurred at a lower rate with AOM 400 than placebo (bipolar disorder, 0.8% vs 2.3%, respectively; BP-I, 1.5% vs 2.3%; major depression, 0.0% vs 1.5%; and mania, 1.5% vs 7.5%). Two deaths were reported, 1 in the oral stabilization phase (myocardial infarction) and 1 in the randomized phase (AOM 400 group, anoxic brain injury and respiratory failure secondary to asthma), neither of which was considered drug related by the investigator.

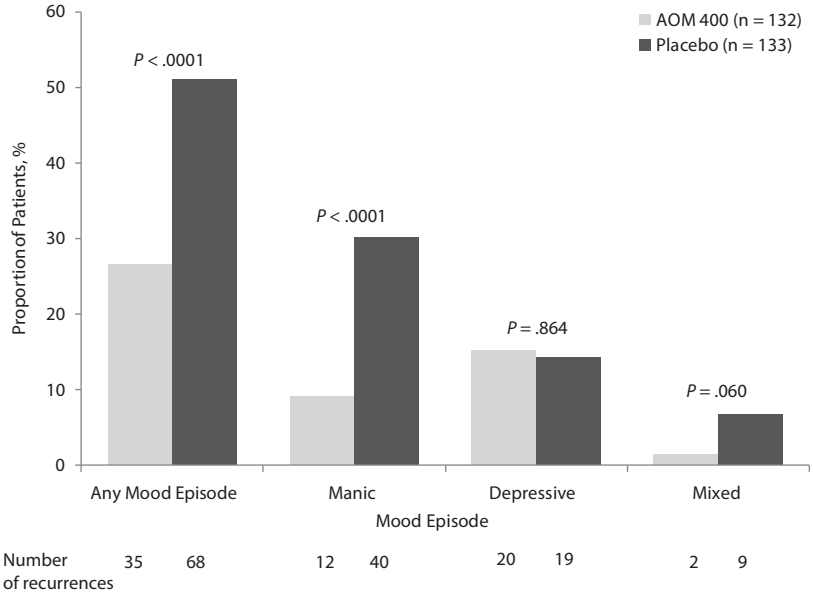
Treatment-emergent extrapyramidal symptoms and extrapyramidal symptom–related AEs are reported in Table 1. There was minimal variation from baseline and between groups in extrapyramidal symptoms as assessed by SAS, BARS, DIEPSS, or AIMS total scores. Mean (SD) increase in weight from baseline to week 52 was 1.3 kg (5.9 kg) and 1.5 kg (6.1 kg) in the AOM 400 and placebo groups, respectively, with a numerically higher proportion of patients in the AOM 400 group (18.0% vs 12.9% for placebo) experiencing potentially clinically significant weight gain (increase ≥ 7% from baseline; Table 1). No clinically meaningful changes in the mean levels of fasting serum glucose, lipids, or prolactin were observed within or between groups. One patient in each group had a prolactin concentration more than twice the upper limit of normal during the randomized phase. Additionally, mean C-SSRS suicidal ideation intensity total scores showed minimal change from baseline, which was not considered clinically meaningful. Injection site pain assessed using patient-reported Visual Analog Scale scores and investigator ratings

Figure 2. Kaplan-Meier Curve of Time From Randomization to Recurrence of Any Mood Episode[a]



[a]Time to recurrence was analyzed using a log-rank test in the efficacy sample of the randomized, double-blind, placebo-controlled phase.
Abbreviation: AOM 400 = aripiprazole once-monthly 400 mg.

Figure 3. Recurrence Rate by Type of Mood Episode[a]



[a]Proportion of patients in the efficacy sample of the randomized phase experiencing any mood episode and manic, depressive, or mixed mood episodes. *P* values were derived from Fisher exact test.
Abbreviation: AOM 400 = aripiprazole once-monthly 400 mg.

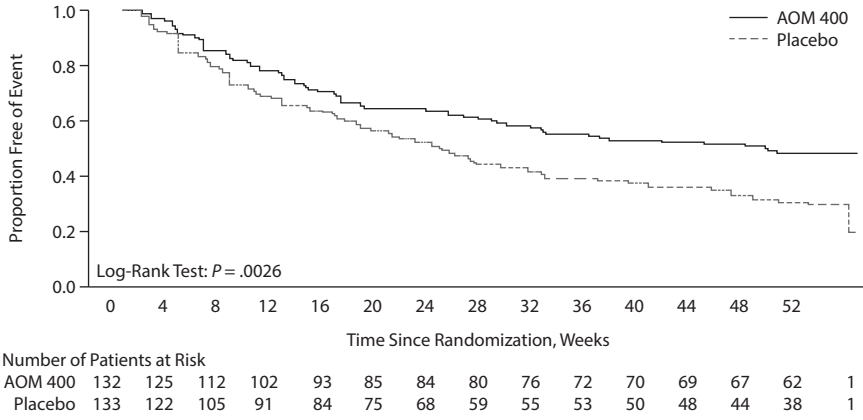
of injection site reactions remained low and decreased with subsequent injections.

DISCUSSION

There are multiple studies showing the efficacy of oral atypical antipsychotics in the treatment of BP-I[11]; however, literature on the use of LAIs in BP-I is scarce. The benefits of a once-monthly injection of aripiprazole (AOM 400) as maintenance treatment for BP-I were shown in the present double-blind, placebo-controlled, randomized withdrawal study. In patients with BP-I who had a manic episode at study enrollment, AOM 400 delayed the time to recurrence of mood episodes, primarily manic episodes, without increasing depressive episodes. Significantly fewer patients experienced any mood episode during 52 weeks with AOM 400 treatment compared with placebo. Effectiveness of AOM 400 was further supported by the improvement in mania symptom severity as assessed by YMRS. AOM 400 treatment was generally safe and well tolerated, as evidenced by the prolonged time to discontinuation and lower rate of discontinuation due to AEs versus placebo.

These efficacy results are consistent with the known efficacy of oral aripiprazole monotherapy in the maintenance treatment of BP-I.[13] The present efficacy results also are consistent with those of RLAI given every 2 weeks,

Figure 4. Kaplan-Meier Plot of Time to Discontinuation due to All Causes in the Randomized Phase[a]



[a]*P* value was derived from log-rank test.
Abbreviation: AOM 400 = aripiprazole once-monthly 400 mg.

Table 1. TEAEs During the Randomized, Double-Blind, Placebo-Controlled Phase

Variable	AOM 400 (n = 132)	Placebo (n = 133)
Any TEAE, n (%)	101 (76.5)	107 (80.5)
Any SAE, n (%)	10 (7.6)	25 (18.8)
TEAEs leading to discontinuation, n (%)	23 (17.4)	34 (25.6)
TEAEs occurring in ≥ 5% of patients in either group, n (%)		
Weight increase	31 (23.5)	24 (18.0)
Akathisia	28 (21.2)	17 (12.8)
Nasopharyngitis	10 (7.6)	13 (9.8)
Insomnia	10 (7.6)	10 (7.5)
Anxiety	9 (6.8)	6 (4.5)
Mania	3 (2.3)	14 (10.5)
Headache	4 (3.0)	9 (6.8)
Bipolar I disorder	2 (1.5)	8 (6.0)
TEAEs related to EPS, n (%)		
Any TEAEs related to EPS	36 (27.3)	22 (16.5)
Akathisia event	29 (22.0)	17 (12.8)
Parkinsonism events	7 (5.3)	5 (3.8)
Dyskinetic events	3 (2.3)	2 (1.5)
Dystonic events	3 (2.3)	0 (0.0)
Change in EPS scales at week 52, mean (SD)[a]		
AIMS	0.19 (1.01)	−0.03 (0.27)
BARS	0.05 (0.91)	−0.05 (0.58)
DIEPSS[b]	−0.56 (1.13)	−0.80 (1.40)
SAS[c]	0.05 (0.99)	−0.11 (0.87)
Potentially clinically relevant weight changes,[d] n (%)		
Weight gain ≥ 7%[e]	23 (18.0)	17 (12.9)
Weight loss ≥ 7%[e]	12 (9.4)	16 (12.1)

[a]Last observation carried forward.
[b]n = 9 (AOM 400), n = 10 (placebo).
[c]n = 122 (AOM 400), n = 120 (placebo).
[d]At any time during randomized phase.
[e]n = 128 (AOM 400), n = 132 (placebo).
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, AOM = aripiprazole once-monthly, BARS = Barnes Akathisia Rating Scale, DIEPSS = Drug-Induced Extrapyramidal Symptoms Scale, EPS = extrapyramidal symptoms, SAE = serious adverse event, SAS = Simpson Angus Scale, TEAE = treatment-emergent adverse event.

the only LAI atypical antipsychotic currently approved for maintenance treatment of BP-I.[24,41] In contrast to aripiprazole, which is a partial agonist at the D_2 receptor, risperidone is a high affinity D_2 receptor antagonist; thus, differences in side effect profiles may be anticipated and may differentially affect adherence.[42]

Adherence remains a significant challenge in the treatment of patients with BP-I.[18,19] Nonadherence leads to unfavorable outcomes such as increased risks of recurrence, hospitalization, and suicide.[23] LAI antipsychotics, by increasing treatment adherence, can potentially improve outcomes in patients with BP-I.[43] A meta-analysis[44] of randomized controlled trials demonstrated that the efficacy of LAI antipsychotics in BP-I was comparable with that of oral atypical antipsychotics. Available data on atypical LAI antipsychotics in BP-I are largely derived from controlled studies of RLAI[44]; thus, additional studies on the potential benefits of LAIs in bipolar disorder are needed, including comparisons with oral formulations.

Patients were required to have a manic episode at study entry. The YMRS thresholds used for determining manic episodes at study entry and for assessing recurrence are consistent with those used previously in the studies with oral aripiprazole and RLAI in BP-I.[13,25] Because the polarity of the BP-I index episode typically predicts the polarity of relapse and recurrence,[45] it was not surprising that the preponderance of mood events in the present study were manic. The present study shows robust evidence for the prophylactic efficacy of AOM 400 in preventing manic episodes. Patients had few-to-no depressive symptoms at study enrollment, the number of depressive episodes during the study was low, and a clinical benefit of AOM 400 in preventing depressive episodes was not evident. However, it should also be noted that maintenance treatment with AOM 400 did not result in an increase in depressive episodes. This finding contrasts with typical antipsychotics, which, although effective at reducing recurrence of manic

episodes, are associated with increased number of depressive episodes.[23,46,47]

The tolerability profile of a therapeutic agent is important in guiding long-term treatment decisions. In the current study, AOM 400 was generally safe and well tolerated by patients with BP-I during long-term treatment with few discontinuations because of TEAEs. The overall discontinuation rate during the 26-week randomized withdrawal phase in a study evaluating oral aripiprazole for maintenance treatment of BP-I was 50%,[13] similar to the 51.9% of patients on AOM 400 who discontinued during the longer 52-week randomized withdrawal phase of the present study. The majority of patients (> 80% at each injection visit) received the recommended dose of 400 mg. No new safety signals were noted, and observed TEAEs were mostly mild to moderate. Mean weight gain was low in the randomized phase and was similar between treatment groups. There were no clinically meaningful changes in extrapyramidal symptom scales, metabolic parameters, or vital signs. Prolactin elevation and the associated sexual dysfunction are troublesome consequences of antipsychotic treatment. Among the atypical antipsychotics, aripiprazole is known to be prolactin-sparing, whereas others, including risperidone, are considered to be prolactin-raising.[42,48] The present study did not reveal any clinically meaningful alterations in prolactin levels with AOM 400 versus placebo, and there were few TEAEs related to prolactin or sexual dysfunction.

The study has some limitations. Stringent criteria were followed to assess stability and recurrence. The study's randomized population included patients who had been previously stabilized on AOM 400 monotherapy, providing a population enriched in responders and those who tolerate AOM 400. Therefore, the clinical efficacy, tolerability, and safety of AOM 400 might be less robust in a clinical practice setting where patients were not previously exposed to aripiprazole or require adjunct treatment in addition to antipsychotics. Further, patients in the placebo group could have experienced AEs resulting from withdrawal of AOM 400 after having received it during the stabilization phase. Finally, patients were required to be experiencing a manic mood episode at study entry, which may limit the generalizability to other types of mood episodes.

CONCLUSIONS

AOM 400 demonstrated efficacy as maintenance treatment for BP-I by reducing the risk of recurrence of mood episodes. AOM treatment was generally safe and well tolerated. These findings support the role of AOM 400 as the first monthly LAI for the maintenance treatment of BP-I.

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Author contributions: All authors had full access to the data included in the paper, interpreted the data, critically reviewed drafts of the paper, and approved the final version for submission.

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Supplementary material: Available at Psychiatrist.com.

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Supplementary Material

Article Title: Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled, 52-Week Randomized Withdrawal Study

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List of Supplementary Material for the article

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Supplementary material for Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled, 52-Week Randomized Withdrawal Study

Supplementary eTable 1: Patient Demographics and Baseline Disease Characteristics of the Randomized Sample

Characteristics	AOM 400 (n=133)	Placebo (n=133)	Total (N=266)
Sex, n (%)			
Male	50 (37.6)	63 (47.4)	113 (42.5)
Female	83 (62.4)	70 (52.6)	153 (57.5)
Race, n (%)			
White	70 (52.6)	74 (55.6)	144 (54.1)
Black or African American	40 (30.1)	35 (26.3)	75 (28.2)
American Indian	1 (0.8)	1 (0.8)	2 (0.8)
Asian	19 (14.3)	18 (13.5)	37 (13.9)
Other	3 (2.3)	5 (3.8)	8 (3.0)
Age, y, mean (SD)	40.6 (10.8)	40.6 (11.2)	40.6 (11.0)
Weight, kg, mean (SD)	89.3 (24.1)	89.2 (22.6)	89.2 (23.3)
BMI, kg/m^2, mean (SD)	31.4 (7.7)	30.5 (7.0)	30.9 (7.3)
Last dose in AOM 400 stabilization phase, n (%)			
300 mg	19 (14.3)	16 (12.0)	35 (13.2)
400 mg	114 (85.7)	117 (88.0)	231 (86.8)

Disease characteristics			
Age at first manic episode, y, mean (SD)	25.2 (10.3)	24.8 (9.9)	25 (10.1)
Number of mood episodes in the past 12 mo, mean (SD)	2.2 (1.2)	2.2 (1.1)	2.2 (1.2)
Duration of disease prior to enrollment, y, mean (SD)	12.1 (9.2)	13.6 (9.8)	12.9 (9.5)
Number of previous hospitalizations for a mood episode, mean (SD)	3.5 (3.9)	3.5 (4.1)	3.5 (4.0)
YMRS total score, mean (SD)	2.9 (3.5)	2.6 (3.0)	2.8 (3.3)
MADRS total score, mean (SD)	3.0 (3.4)	2.4 (3.4)	2.7 (3.4)
CGI-BP-S, mania score, mean (SD)	1.5 (0.7)	1.4 (0.6)	1.5 (0.7)

AOM 400=aripiprazole once-monthly 400 mg; BMI=body mass index; CGI-BP-S=Clinical Global Impression for Bipolar Disorder–Severity; MADRS=Montgomery Åsberg Depression Rating Scale; YMRS=Young Mania Rating Scale.

YMRS[1] score ranges from 0 to 60, with higher scores indicating more severe manic symptoms. MADRS[2] total scores range from 0 to 60, with higher scores indicating more severe depressive symptoms. CGI-BP-S-Mania[3] score ranges from 1 to 7, with higher scores indicating greater severity of mania.

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2. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-389.
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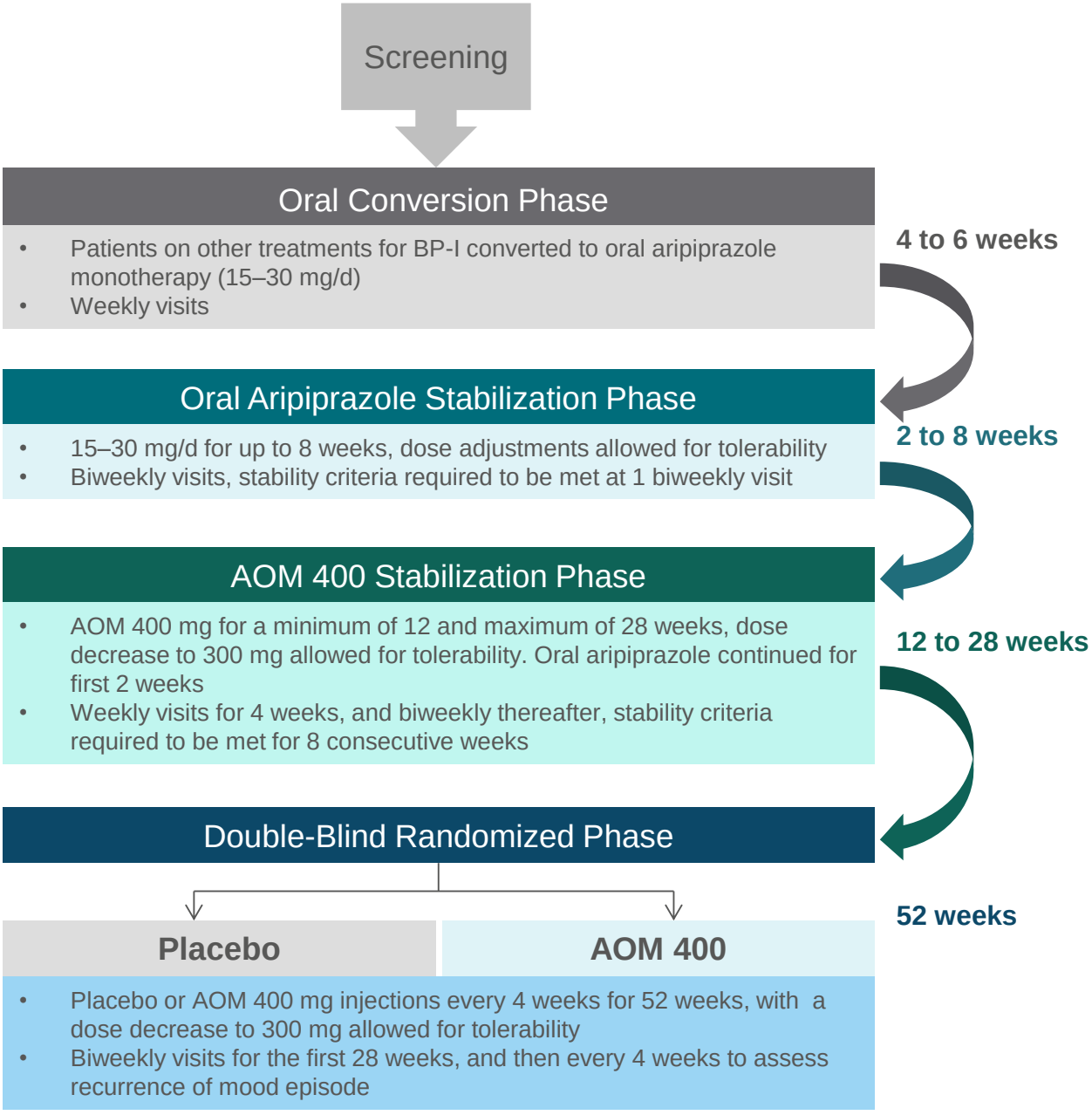
Supplementary eFigure 1: Study Design



AOM 400=aripiprazole once-monthly 400 mg.

Conversion phase: Patients on other treatments (mood stabilizers, antidepressants, antipsychotics, generic aripiprazole) for bipolar I disorder (BP-I) were converted to oral aripiprazole monotherapy over a minimum of 4 weeks and a maximum of 6 weeks.

Patients could be in-patient at screening and in the conversion phase, but were required to be outpatients by the time they reached the oral stabilization phase.

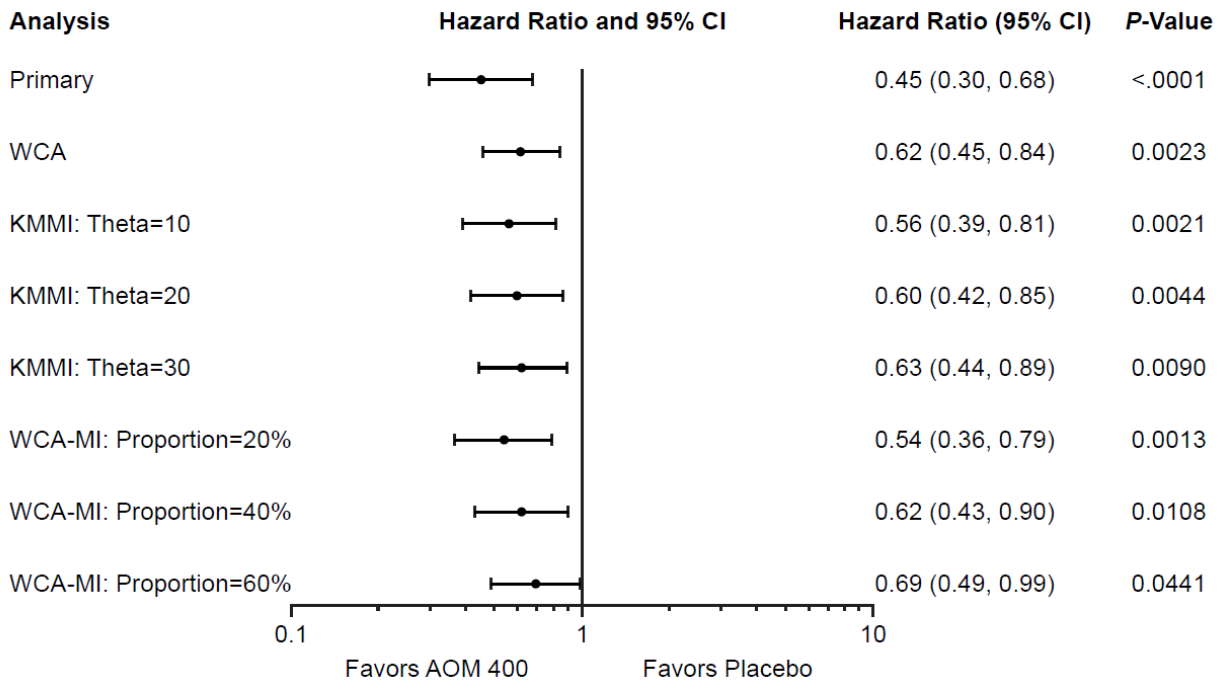
Oral aripiprazole stabilization phase: Patients who successfully converted to oral aripiprazole monotherapy and those who were already receiving aripiprazole as monotherapy for BP-I at screening or who had a lapse in their BP-I treatment (such that washout of prior treatment would not be required) entered the oral stabilization phase that lasted from 2 to 8 weeks. To proceed to the AOM 400 stabilization phase, patients needed to be on a minimum dose of 15 mg/d and were required to fulfill all of the following protocol-defined stability criteria at 1 biweekly visit: (1) outpatient status, (2) Young-Mania Rating Scale total score ≤ 12, (3) Montgomery Åsberg Depression Rating Scale (MADRS) total score ≤12, (4) No active suicidality; with active suicidality defined as a score of 4 or more on the MADRS item 10 or an answer of "yes" on Question 4 or 5 on the Columbia Suicide Severity Rating Scale.

Single-blind AOM 400 stabilization phase: Patients received AOM 400 mg as the initial dose in this phase, irrespective of the final dose in the oral-stabilization phase. Dose reduction to 300 mg was permitted for tolerability reasons as was a single-dose return to 400 mg, if required. Daily oral dosing with aripiprazole continued for the first 2 weeks in this phase. An unblinded site study drug manager administered the injections every 4 weeks. Patients were required to meet protocol-defined stability criteria for a minimum of 8 consecutive weeks, having received a

minimum of 3 injections; a period of up to 28 weeks was permitted to maximize the possibility of achieving the required duration of symptom stability.

Double-blind, placebo-controlled phase: Eligible patients were randomized 1:1 to 52 weeks of double-blind treatment with AOM 400 or placebo. A single decrease to 300-mg dose was permitted for tolerability as was a single dose return to 400 mg, if required. Patients were evaluated biweekly for the first 28 weeks and every 4 weeks thereafter.

Supplementary eFigure 2. Primary and Sensitivity Analysis of Time to Recurrence of any Mood Episode



AOM 400=aripiprazole once-monthly 400 mg; KMMI=Kaplan-Meier multiple imputations; WCA=worst-case analysis; WCA-MI=worst-comparison analysis using multiple imputations.

The following 3 sensitivity analyses were performed to impute the data for patients who discontinued without having a recurrence event: (1) worst-case analysis (discontinued patients were to have recurrences 1 day after discontinuation), (2) Kaplan-Meier multiple imputation (based on Kaplan-Meier estimators, discontinued patients had multiple imputations for their experience of recurrence during their unobserved remaining times until week 52), (3) worst-comparison analysis using multiple imputation (randomly selected specific discontinued patients only from the AOM 400 group had recurrences 1 day after discontinuation using multiple imputation methods).