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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)

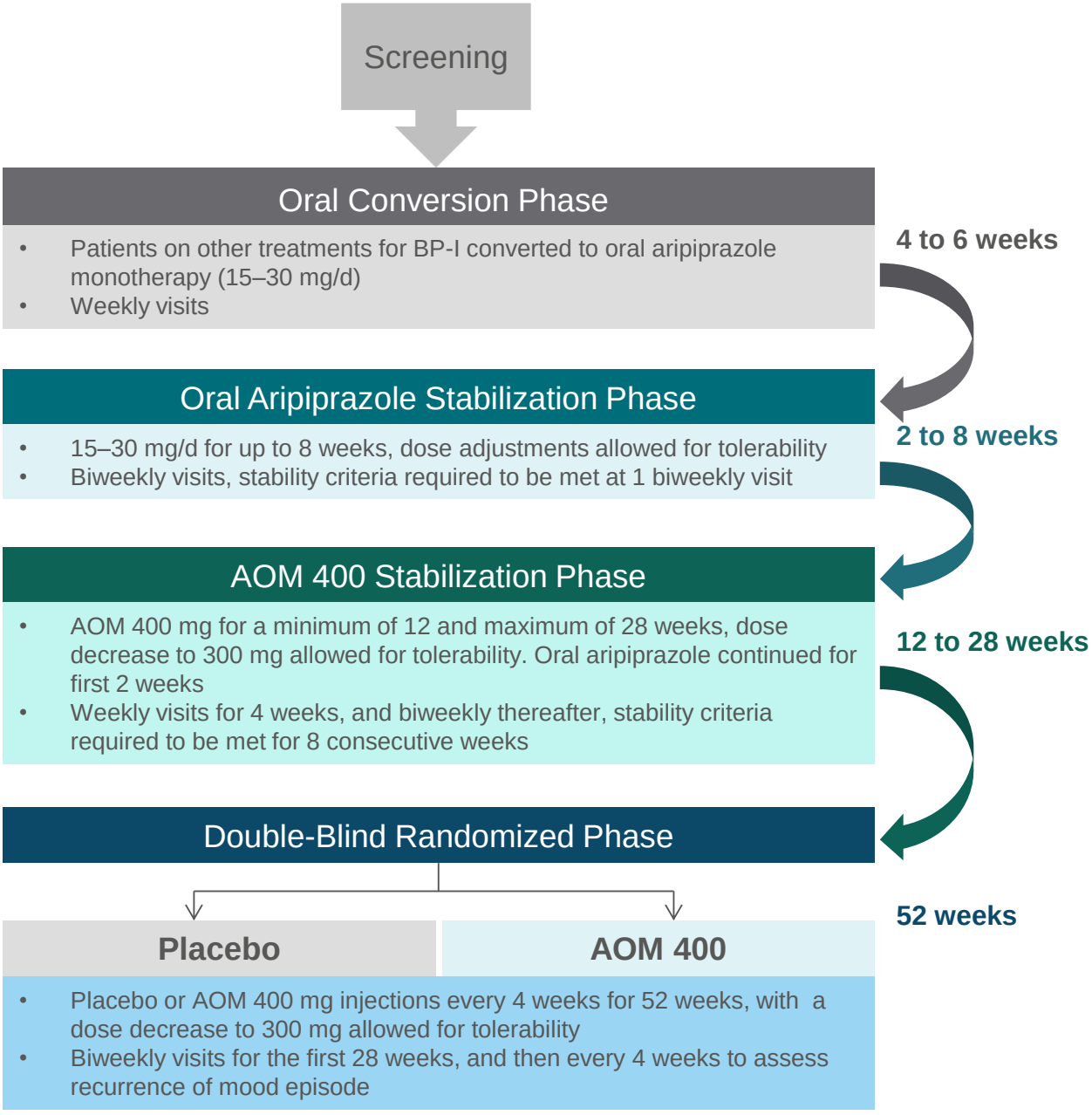
AOM 400=aripiprazole once-monthly 400 mg; BMI=body mass index; CGI-BP-S=Clinical Global Impression for Bipolar Disorder–Severity; MADRS=Montgomery Åsberg Depression Rating Scale; YMRS=Young Mania Rating Scale.

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.

References:

1. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429-435.
2. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-389.
3. Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res. 1997;73(3):159-171.

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.

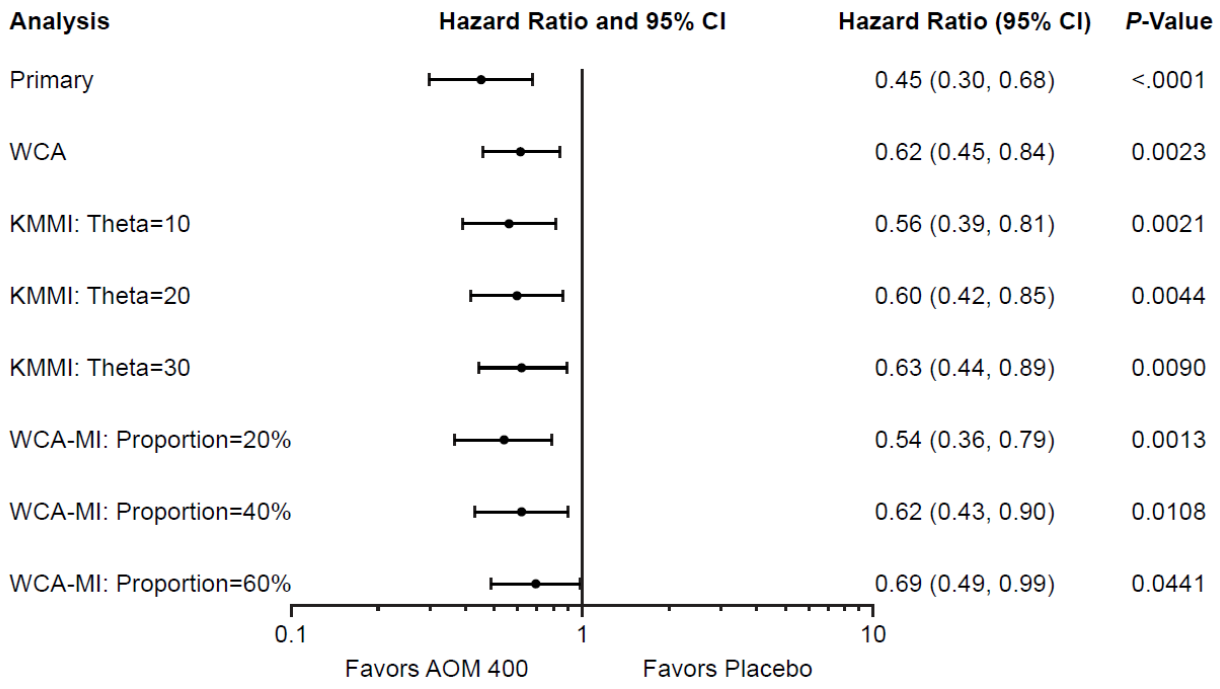
Oral aripiprazole stabilization phase: Patients who successfully converted to oral aripiprazole monotherapy and those who were already receiving aripiprazole as monotherapy for BP-I at screening or who had a lapse in their BP-I treatment (such that washout of prior treatment would not be required) entered 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).