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Enclosure:

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Efficacy of Aripiprazole Once-Monthly And Aripiprazole 2-Month Ready-To-Use on Illness Insight in Bipolar I Disorder: Post Hoc Analysis of Data From Two Randomized Controlled Trials

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Background

In bipolar I disorder (BP-I), level of insight is the degree to which a patient is consciously aware of their condition, recognizes symptoms as an indicator of the condition, and accepts that these symptoms require treatment.[1,2] Patients diagnosed with BP-I may experience impaired insight during both acute episodes and periods of remission.[3-8]

- Up to 94% of patients are reported to have impaired insight during depressed, manic, or subsyndromal states, compared with 47% of patients in remission.[3]
- Evidence suggests that insight impairment is worse during manic phases compared with periods of depression and remission.[4-8]
- Poorer insight is associated with several factors, including a higher number of previous episodes, more time spent in acute episodes, and higher residual symptoms.[8]
- Poor patient insight in BP-I results in worse clinical outcomes and treatment adherence.[9,10] Gains in patient insight are directly correlated with increased medication adherence.[10]

The Young Mania Rating Scale (YMRS) assesses insight as 1 of 11 items that, together, can be used to measure the severity of mania.[11]

YMRS data from clinical trials of 2 long-acting injectable (LAI) antipsychotic formulations – aripiprazole once-monthly 400 mg (AOM 400) and aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) – in patients diagnosed with BP-I provide an opportunity to examine whether insight improves with aripiprazole LAI treatment.

The objective of these exploratory post hoc analyses was to assess the effect of AOM 400 and Ari 2MRTU 960 on insight in patients diagnosed with BP-I

Methods

Study design

- These post hoc analyses were performed using data from 2 previously completed controlled trials.[12,13]
  - Data for AOM 400 were from a double-blind, randomized withdrawal trial conducted in patients diagnosed with BP-I who were currently experiencing a manic episode. Included patients were first stabilized on oral aripiprazole, followed by stabilization on AOM 400, before being randomized to continue AOM 400 or switch to placebo for 52 weeks (NCT01567527; Study 250).[12]
  - Data for Ari 2MRTU 960 were from an open-label trial conducted in clinically stable patients diagnosed with schizophrenia or BP-I who were randomized to Ari 2MRTU 960 or AOM 400 for 32 weeks (NCT04030143; Study 181).[13]
  - For study design figures, please refer to **Supplementary Figures 1 and 2**, which can be accessed via the QR code.

Post hoc analyses

- Study 250 and Study 181 used a range of clinical measures to assess symptoms; the YMRS 'insight' item (scale 0-4) assessed awareness and acceptance of illness in patients diagnosed with BP-I (**Box 1**).

Box 1: Illness insight measured using the YMRS

Higher scores = Worse insight

YMRS 'insight' item[11]
0. Present; admits illness; agrees with need for treatment
1. Possibly ill
2. Admits behavior change, but denies illness
3. Admits possible change in behavior, but denies illness
4. Denies any behavior change

YMRS, Young Mania Rating Scale

Results

Study 250 (AOM 400 versus placebo)

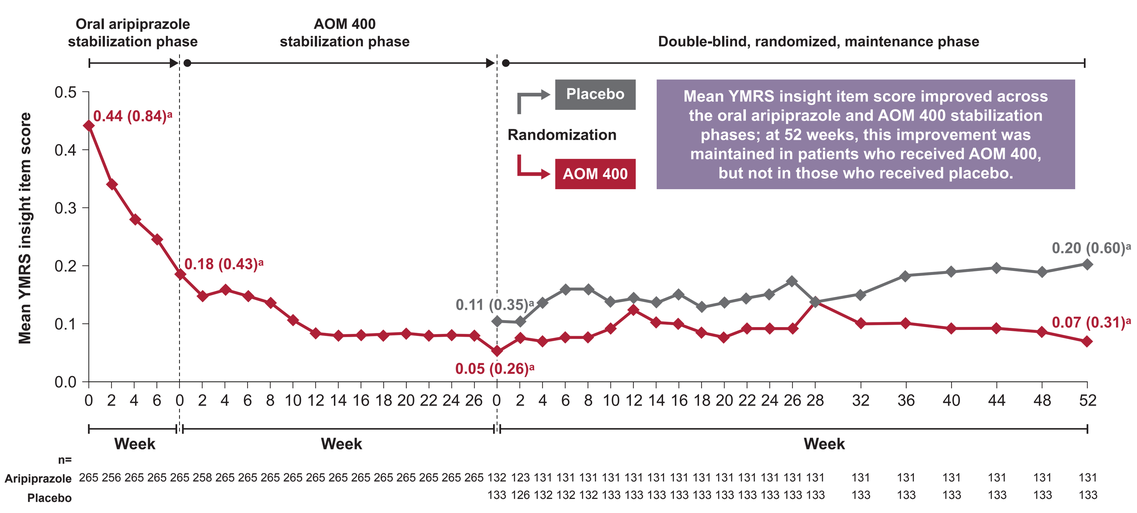
- In total, 265 patients were stabilized on oral aripiprazole and then AOM 400 before receiving randomized treatment with either AOM 400 or placebo. Demographics and baseline clinical characteristics for the randomized population are shown in **Table 1**; for this analysis, baseline was defined as the start of the oral aripiprazole stabilization phase.
- Mean YMRS insight item score over time is shown in **Figure 1**; change over time in the proportions of patients with YMRS insight item scores 0-4 is shown in **Figure 2**.
- Efficacy outcomes in the subpopulation of patients with a YMRS insight item score >0 at baseline (27.2% of the randomized population) are shown in **Table 2**.
- Change over time in YMRS insight item individual response category for all patients and in those patients with a YMRS insight item score >0 at baseline are shown in **Supplementary Figure 3** and **Supplementary Figure 4**, respectively.

Table 1: Study 250: Demographics and baseline clinical characteristics

	AOM 400 (N=132)	Placebo (n=133)
Demographic characteristics		
Age, years	40.2 (10.8)	40.0 (11.2)
Female, n (%)	82 (62.1)	70 (52.6)
BMI, kg/m²	30.5 (7.6)	29.8 (6.7)
Clinical characteristics		
YMRS total score	15.8 (10.5)	15.8 (10.9)
YMRS insight item score	0.5 (0.9)	0.4 (0.8)
YMRS insight item score >0, n (%)	35 (26.5)	37 (27.8)
MADRS total score	5.4 (5.5)	3.8 (4.1)
CGI-BP-S overall score	3.3 (1.1)	3.1 (1.3)
CGI-BP-S mania score	3.1 (1.2)	3.1 (1.3)
CGI-BP-S depression score	1.6 (0.8)	1.3 (0.6)

Data are shown as mean (standard deviation), unless otherwise stated
Baseline was defined as the start of the oral aripiprazole stabilization phase
AOM 400, aripiprazole once-monthly 400 mg; BMI, body mass index; CGI-BP-S, Clinical Global Impression – Bipolar Version-Severity; MADRS, Montgomery–Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale

Figure 1: Study 250: Mean YMRS insight item score over time



Mean YMRS insight item score improved across the oral aripiprazole and AOM 400 stabilization phases; at 52 weeks, this improvement was maintained in patients who received AOM 400, but not in those who received placebo.

[a]Data are shown as mean (standard deviation)
Data refer to all patients in Study 250 who entered the oral aripiprazole stabilization phase and who received randomized treatment (last observation carried forward dataset). The frequency of data collection reduced from every 2 weeks to every 4 weeks after Week 28 of the double-blind, randomized maintenance phase. Presented data reflect the results of a post hoc analysis and should be treated as exploratory and interpreted with caution
AOM 400, aripiprazole once-monthly 400 mg

Table 2: Study 250: Change in efficacy outcomes during the randomized phase in patients with a YMRS insight item score >0 at baseline

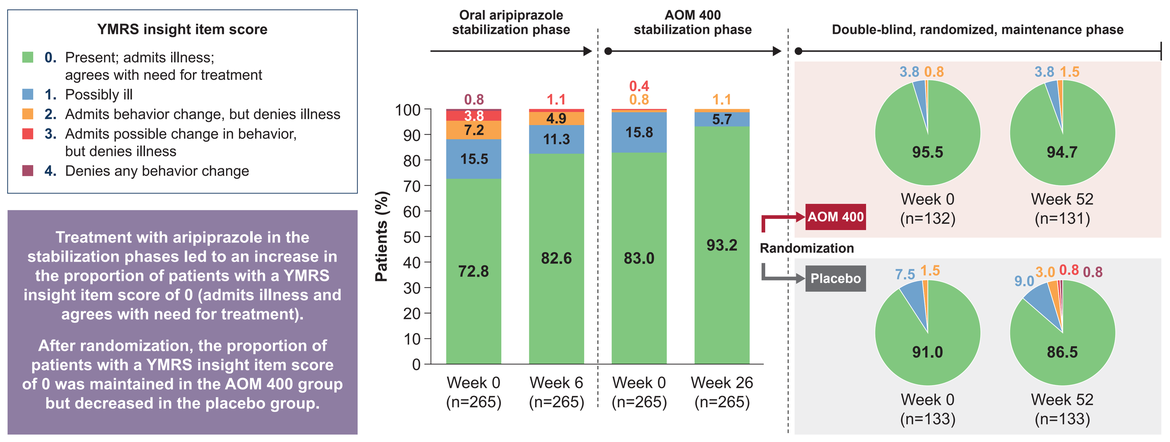
	AOM 400 (n=35)		Placebo (n=37)	
	Week 0 of randomized phase	Week 52 of randomized phase	Week 0 of randomized phase	Week 52 of randomized phase
YMRS total score	3.34 (3.54)	4.34 (7.74)	3.19 (3.09)	8.73 (9.52)
CGI-BP-S overall score	1.94 (0.73)	2.11 (1.11)	1.73 (0.65)	2.70 (1.54)
CGI-BP-S mania score	1.66 (0.76)	1.80 (1.08)	1.57 (0.65)	2.27 (1.50)
MADRS score	2.63 (3.26)	3.89 (6.30)	2.84 (3.50)	6.19 (10.81)

Mean YMRS total, CGI-BP-S overall, and CGI-BP-S mania scores were lower in the AOM 400 group compared with the placebo group at the end of the randomized phase. Mean MADRS score increased at the end of the randomized phase in both groups, but remained within the normal range for patients treated with AOM 400 and was lower than patients who received placebo. These results indicate better symptom control with AOM 400 versus placebo in the subpopulation of patients with a YMRS insight item score >0 at baseline.

Data are shown as mean (standard deviation)
Data refer to all patients in Study 250 with a YMRS insight item score >0 at baseline (last observation carried forward dataset). Presented data reflect the results of a post hoc analysis and should be treated as exploratory and interpreted with caution
AOM 400, aripiprazole once-monthly 400 mg; CGI-BP-S, Clinical Global Impression – Bipolar Version-Severity; MADRS, Montgomery–Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale

Results (continued)

Figure 2: Study 250: Change over time in the proportions of patients with YMRS insight item scores 0-4



Treatment with aripiprazole in the stabilization phases led to an increase in the proportion of patients with a YMRS insight item score of 0 (admits illness and agrees with need for treatment).

After randomization, the proportion of patients with a YMRS insight item score of 0 was maintained in the AOM 400 group but decreased in the placebo group.

Data refer to all patients in Study 250 who entered the oral aripiprazole stabilization phase and who received randomized treatment (last observation carried forward dataset)
Presented data reflect the results of a post hoc analysis and should be treated as exploratory and interpreted with caution
AOM 400, aripiprazole once-monthly 400 mg; YMRS, Young Mania Rating Scale

Study 181 (Ari 2MRTU 960 versus AOM 400) – All patients diagnosed with BP-I

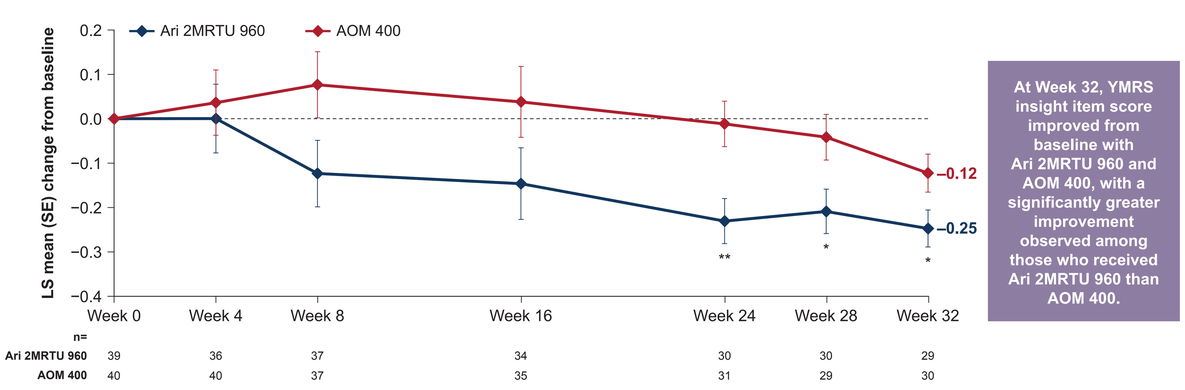
- In total, 266 clinically stable patients diagnosed with BP-I or schizophrenia were enrolled and randomized to receive Ari 2MRTU 960 or AOM 400. Of these, 81 patients (30.5%) were diagnosed with BP-I, with YMRS data available for 39 patients treated with Ari 2MRTU 960 and 40 patients treated with AOM 400, comprising the analysis population for this post hoc analysis. Demographics and baseline clinical characteristics for these patients are shown in **Table 3**.
- Least squares (LS) mean change from baseline in YMRS insight item score over time is shown in **Figure 3**.
- Efficacy outcomes in the subpopulation of patients with a YMRS insight item score >0 at baseline are shown in **Table 4**.

Table 3: Study 181: Demographics and baseline clinical characteristics

	Ari 2MRTU 960 (n=39)	AOM 400 (n=40)
Demographic characteristics		
Age, years	47.9 (11.1)	45.1 (11.2)
Female, n (%)	15 (38.5)	21 (52.5)
BMI, kg/m²	28.4 (3.9)	27.0 (4.8)
Clinical characteristics		
YMRS total score	6.6 (7.4)	9.4 (8.3)
YMRS insight item score	0.2 (0.5)	0.3 (0.7)
MADRS total score	11.0 (9.5)	13.0 (9.3)
CGI-BP-S overall score	2.3 (1.2)	2.8 (1.2)
CGI-BP-S mania score	1.7 (1.0)	2.3 (1.2)
CGI-BP-S depression score	2.2 (1.2)	2.5 (1.1)

Data are shown as mean (standard deviation), unless otherwise stated
Data are for the subset of patients in Study 181 diagnosed with BP-I and with available data relating to YMRS assessments
BMI, body mass index; CGI-BP-S, Clinical Global Impression – Bipolar Version-Severity; MADRS, Montgomery–Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale

Figure 3: Study 181: Change in YMRS insight item score



At Week 32, YMRS insight item score improved from baseline with Ari 2MRTU 960 and AOM 400, with a significantly greater improvement observed among those who received Ari 2MRTU 960 than AOM 400.

Data refer to the subset of patients in Study 181 diagnosed with BP-I and with available data relating to YMRS assessments (last observation carried forward dataset). Presented data reflect the results of a post hoc analysis and should be treated as exploratory and interpreted with caution
*P<0.05, **P<0.01 versus AOM 400 (*P* values for between-group comparison were derived from an MMRM analysis with fixed effects of treatment, pharmacokinetic sampling schedule for determining the concentration of aripiprazole in patients' plasma, week, treatment-by-week interaction, and baseline-by-week interaction as covariate)
AOM 400, aripiprazole once-monthly 400 mg; Ari 2MRTU 960, aripiprazole 2-month ready-to-use 960 mg; BP-I, bipolar I disorder; LS, least squares; MMRM, mixed model for repeated measures; SE, standard error; YMRS, Young Mania Rating Scale

Table 4: Study 181: Change in efficacy outcomes in patients with a YMRS insight item score >0 at baseline

	Ari 2MRTU 960		AOM 400	
	Week 0 of randomized phase (n=4)	Week 32 of randomized phase (n=4)	Week 0 of randomized phase (n=8)	Week 32 of randomized phase (n=7)
YMRS total score	16.00 (12.14)	4.00 (0.82)	20.00 (6.78)	6.43 (2.51)
CGI-BP-S overall score	3.00 (1.41)	1.50 (0.58)	3.88 (0.99)	2.57 (1.13)
CGI-BP-S mania score	2.75 (1.71)	1.50 (0.58)	3.25 (1.04)	1.71 (0.49)
MADRS score	13.50 (10.75)	1.75 (1.26)	20.13 (7.36)	11.29 (8.38)

For the few clinically stable patients who had a YMRS insight item score >0 at baseline, treatment with Ari 2MRTU 960 and AOM 400 improved mean YMRS total score, CGI-BP-S overall score, CGI-BP-S mania score, and MADRS score at Week 52 compared with baseline, suggesting an improvement in symptoms over the course of treatment.

Data are shown as mean (standard deviation)
Data refer to the subset of patients in Study 181 diagnosed with BP-I and with a YMRS insight item score >0 at baseline (last observation carried forward dataset). Presented data reflect the results of a post hoc analysis and should be treated as exploratory and interpreted with caution
AOM 400, aripiprazole once-monthly 400 mg; Ari 2MRTU 960, aripiprazole 2-month ready-to-use 960 mg; CGI-BP-S, Clinical Global Impression – Bipolar Version-Severity; MADRS, Montgomery–Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale

Limitations

- These were post hoc analyses of Study 250 and Study 181; consequently, analyses were not fully powered for the endpoints measured and some subgroups had a limited number of patients.
- Result interpretation may be limited by heterogeneity between the populations of Study 250 and Study 181, and the open-label design of Study 181. However, the analyses suggest that treatment with Ari 2MRTU 960 or AOM 400 is associated with an improvement in insight across a diverse group of patients diagnosed with BP-I.

Conclusions

- In the post hoc analysis of Study 250, aripiprazole improved YMRS insight item scores in patients diagnosed with BP-I. When AOM 400 was withdrawn, YMRS insight scores worsened, potentially indicating a loss of insight.
- In the post hoc analysis of Study 181, Ari 2MRTU 960 was associated with significantly greater improvements in YMRS insight item scores compared with AOM 400 in clinically stable patients diagnosed with BP-I.
- Given that Ari 2MRTU 960 and AOM 400 have comparable pharmacokinetic, safety, and efficacy profiles,[13] Ari 2MRTU 960 is expected to provide similar or better insight benefits to AOM 400, with fewer injections per year.
- With evidence suggesting higher levels of insight are associated with greater adherence to treatment,[10] which in itself is associated with improved prognosis in patients diagnosed with BP-I,[14] these post hoc analyses suggest the potential benefit of greater insight leading to better outcomes with LAI antipsychotic treatments.

References

1. Crişan. IntechOpen; 2018. Available from: http://dx.doi.org/10.5772/intechopen.76286
2. Amador et al. Am J Psychiatry 1993; 150 (6): 873–879.
3. Varga et al. J Affect Disord 2006; 91 (1): 1–9.
4. Dell'Osso et al. Bipolar Disord 2002; 4 (5): 315–322.
5. de Assis da Silva et al. J Nerv Ment Dis 2014; 202 (5): 386–390.
6. Yen et al. J Affect Disord 2004; 78 (1): 57–60.
7. Choudhury et al. Nord J Psychiatry 2021; 75 (5): 378–388.
8. Grover et al. Indian J Psychiatry 2023; 65 (7): 767–773.
9. Yen et al. J Affect Disord 2008; 108 (1–2): 121–127.
10. Novick et al. BMC Psychiatry 2015; 15: 189.
11. Young et al. Br J Psychiatry 1978; 133 (5): 429–435.
12. Calabrese et al. J Clin Psychiatry 2017; 78 (3): 324–331.
13. Harlin et al. CNS Drugs 2023; 37 (4): 337–350.
14. Lage & Hassan. Ann Gen Psychiatry 2009; 8: 7.

Disclosures

KSBL, ZZ: employees of Otsuka Pharmaceutical Development & Commercialization Inc.
NA: consultant for Otsuka Pharmaceutical Development & Commercialization Inc.
AW: employee of Lundbeck LLC.
JFG: has served as a consultant for Alkermes, Genomind, Luye Pharmaceuticals, Neurelis, Neuroma, Otsuka, Sunovion, and Supernus. He is on the Speakers' bureau for AbbVie, Alkermes, Axsome, Bristol Myers Squibb, and Intra-Cellular Therapies. He has received royalties from American Psychiatric Publishing Inc., and Cambridge University Press.

Key contributors

All authors were involved in conception of the post hoc analyses, data interpretation, and reviewed and approved the content for poster presentation.

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