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Enclosure:

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Efficacy of Aripiprazole Once-Monthly and Aripiprazole 2-Month Ready-To-Use on Insight in Schizophrenia: Post Hoc Analyses of Three Trials

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Background



Poor insight is common among patients diagnosed with schizophrenia, and broadly refers to a patient's lack of awareness of their illness, capacity to acknowledge when their behavior is abnormal, and understanding

 It has been reported that at least 80% of patients diagnosed with schizophrenia demonstrate some level of impaired insight.^{3,4}

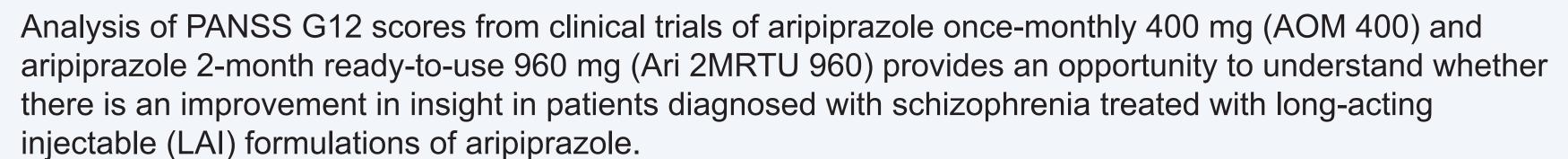


indeed, having better insight is associated with a reduced risk of these outcomes.⁵⁻⁹ The Positive and Negative Syndrome Scale (PANSS) Item G12 (lack of judgment and insight)¹⁰ is a



commonly used measure of insight in clinical studies.²

Evidence suggests that antipsychotics may improve insight in patients diagnosed with schizophrenia based on changes in PANSS G12 score.11





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

Methods

Study design

 These post hoc analyses were performed using data from three previously completed controlled trials (primary results reported elsewhere).¹²⁻¹⁵

- Two double-blind, randomized controlled trials provided data for AOM 400: these studies included adults (18-60 years) with a diagnosis of schizophrenia for ≥3 years who had a history of worsening symptoms or relapse when not receiving antipsychotic treatment. 12,13
- In Study 246 (NCT00705783), patients were stabilized on oral aripiprazole and then AOM 400, before randomization to continue AOM 400 or switch to placebo for 52 weeks (Supplementary Figure 1; scan the QR code to access supplementary content). 12
- In Study 247 (NCT00706654), patients stabilized on oral aripiprazole were randomized to AOM 400. oral aripiprazole 10-30 mg/day or aripiprazole once-monthly 50 mg (AOM 50; a subtherapeutic dose) for 38 weeks (Supplementary Figure 2).¹³
- Study 181 (NCT04030143) provided data for Ari 2MRTU 960; in this open-label, randomized trial,
- or bipolar I disorder (BP-I) were randomized to Ari 2MRTU 960 or AOM 400 for 32 weeks

clinically stable patients diagnosed with schizophrenia

(Supplementary Figure 3).14 A plain language summary of this study has been previously published. 16

Post hoc analyses

 Insight was assessed using the PANSS item G12 (lack of judgment and insight) (Box 1).

 Mean PANSS G12 score was assessed over the duration of Study 246 and Study 247.

 Least squares mean (LSM) change in PANSS G12 score was assessed over the duration of Study 181.

Box 1: PANSS item G12 (lack of judgment and insight) score description

PANSS G12 item score

. Absent: The patient fully acknowledges having a psychiatric illness, recognizes symptoms as abnormal, accepts need for treatment, and understands social consequences.

. **Minimal:** The patient accepts the presence of an illness and need for treatment, but may rationalize minor symptoms or show trivial misinterpretation.

Mild: The patient acknowledges some mental difficulties but minimizes the illness, explains away symptoms, or questions the need for treatment.

 Moderate: The patient shows clear denial of illness for significant symptoms, shows poor understanding of the need for treatment, or consistently rationalizes abnormal experiences.

Moderate-severe: Patient mostly denies having an illness, rejects treatment, or consistently misattributes symptoms to non-illness explanations.

6. Severe: Patient has almost total lack of insight: strongly denies illness, adamantly refuses treatment, or sees no link between symptoms and illness.

Extreme: Complete denial of any mental disorder or need for treatment; firmly rejects all explanations other than external or normal variation.

PANSS, Positive and Negative Syndrome Scale

Results

Study 246 (AOM 400 versus placebo)

- In total, 403 patients diagnosed with schizophrenia were stabilized on oral aripiprazole, followed by AOM 400, before randomization to continue AOM 400 (n=269) or switch to placebo (n=134). 12
- Participant demographics and clinical characteristics at baseline were similar between patients in the AOM 400 group and those in the placebo group (Supplementary Table 1).12 Across both groups, patients were mostly male (59.8%), with mean age of 40.6 years, and mean PANSS total score of 54.5. Mean PANSS G12 score was 2.05 in the AOM 400 group and 2.13 in the placebo group.
- Mean PANSS G12 scores over the study period are shown in Figure 1.

Study 247 (AOM 400 versus oral aripiprazole 10-30 mg or AOM 50)

- Overall, 662 patients diagnosed with schizophrenia and stabilized on oral aripiprazole were randomized to AOM 400 (n=265), oral aripiprazole 10-30 mg/day (n=266), or AOM 50 (n=131).¹³
- Baseline demographics and characteristics of the patients were similar between the randomized treatment groups (Supplementary Table 2).13 Patients were mostly male (61.3%), with mean age of 41.2 years and mean PANSS total score of 57.1. Mean PANSS G12 score was 2.22 in the AOM 400 group, 2.21 in the oral aripiprazole group, and 2.19 in AOM 50 group.
- Mean PANSS G12 scores over the study period are shown in Figure 2.

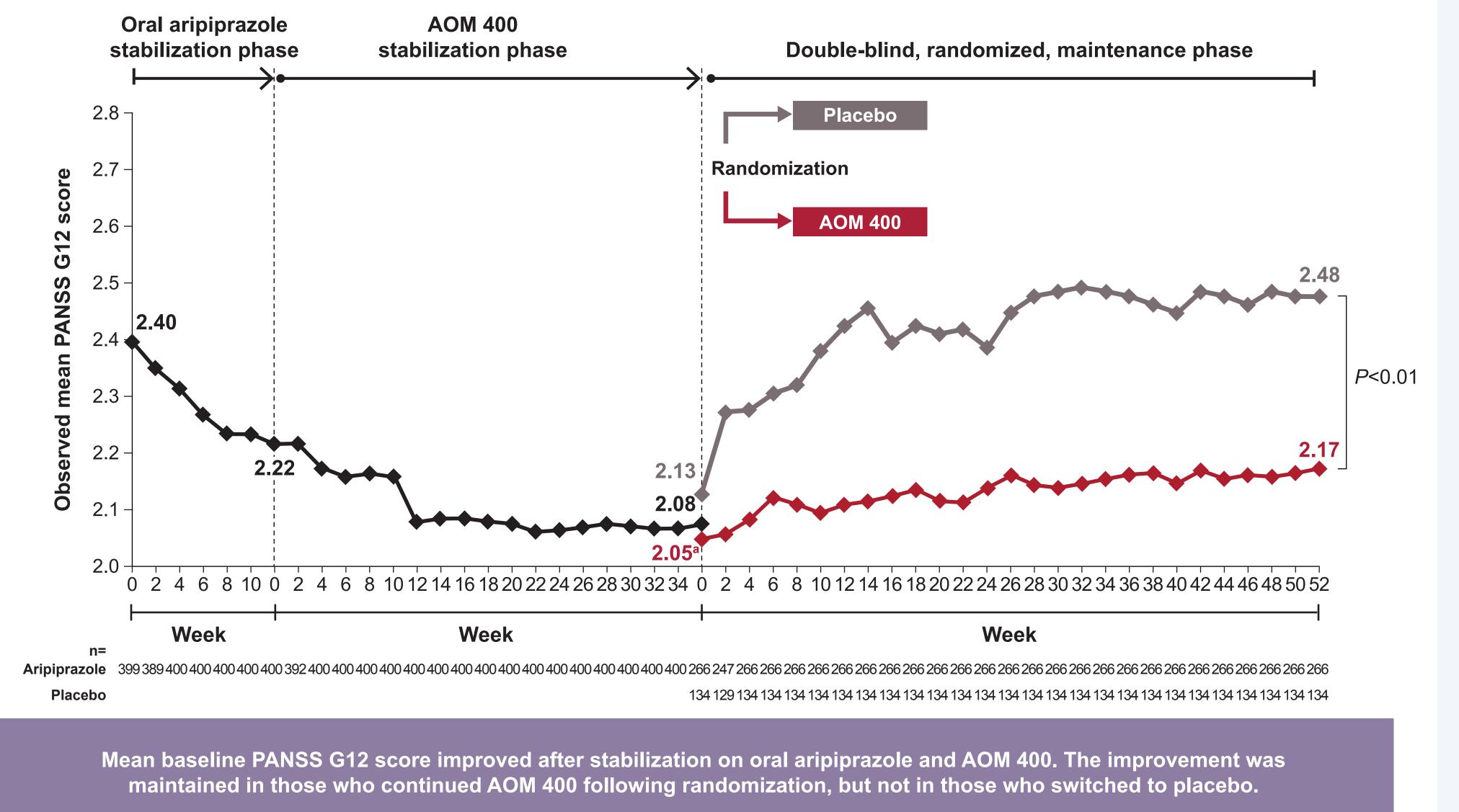
Study 181 (Ari 2MRTU 960 versus AOM 400) – Patients diagnosed with schizophrenia

- There were 185 clinically stable patients diagnosed with schizophrenia enrolled into the study, alongside 81 patients diagnosed with BP-I who were not included in this analysis. 14
- Overall, 115/185 (62.2%) patients diagnosed with schizophrenia had a baseline PANSS G12 score >2 (at least mild lack of insight) and ≥1 post-baseline PANSS assessment; 58 patients who received Ari 2MRTU 960 and 57 patients who received AOM 400 were subject
- Patient demographics and clinical characteristics at baseline were well balanced between treatment groups and are shown in
- Supplementary Table 3.14 Patients who had a baseline PANSS G12 score >2 were mostly male (70.7%-71.9%), with mean age of 48.9-49.1 years, mean PANSS total score of 63.5-64.3, and mean PANSS G12 score of 3.2-3.3.
- LSM change in PANSS G12 score for patients with baseline PANSS G12 score >2 and ≥1 post-baseline PANSS assessment treated with Ari 2MRTU 960 or AOM 400 is shown in Figure 3.

Figure 1: Study 246: Mean PANSS G12 scores over time

of a post hoc analysis and should be treated as exploratory and interpreted with caution

ANCOVA, analysis of covariance; AOM 400, aripiprazole once-monthly 400 mg; LOCF, last observation carried forward; PANSS, Positive and Negative Syndrome Scale



^aThere was no statistically significant difference between AOM 400 and placebo at randomization (*P*=0.457) Observed data. LOCF analysis. Dataset includes all patients diagnosed with schizophrenia who were randomized to double-blind maintenance treatment and had PANSS G12 data available. P values obtained from an ANCOVA model including treatment and

baseline PANSS G12 score as model terms to adjust for differences when comparing groups upon entry to the double-blind, randomized, maintenance phase. LOCF data at Week 52 were used to account for discontinuation. Presented data reflect the results

Figure 2: Study 247: Mean PANSS G12 scores over time

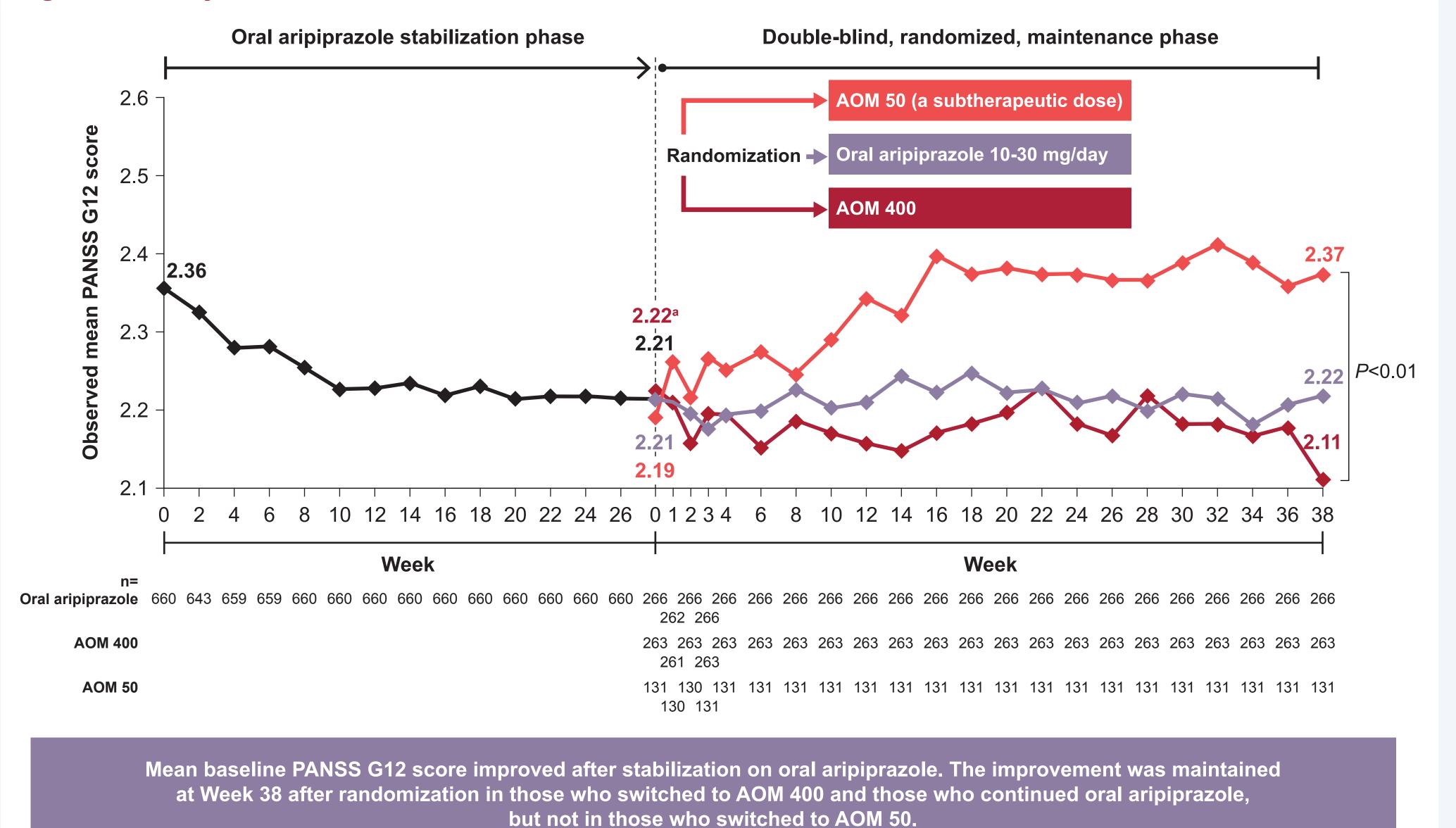
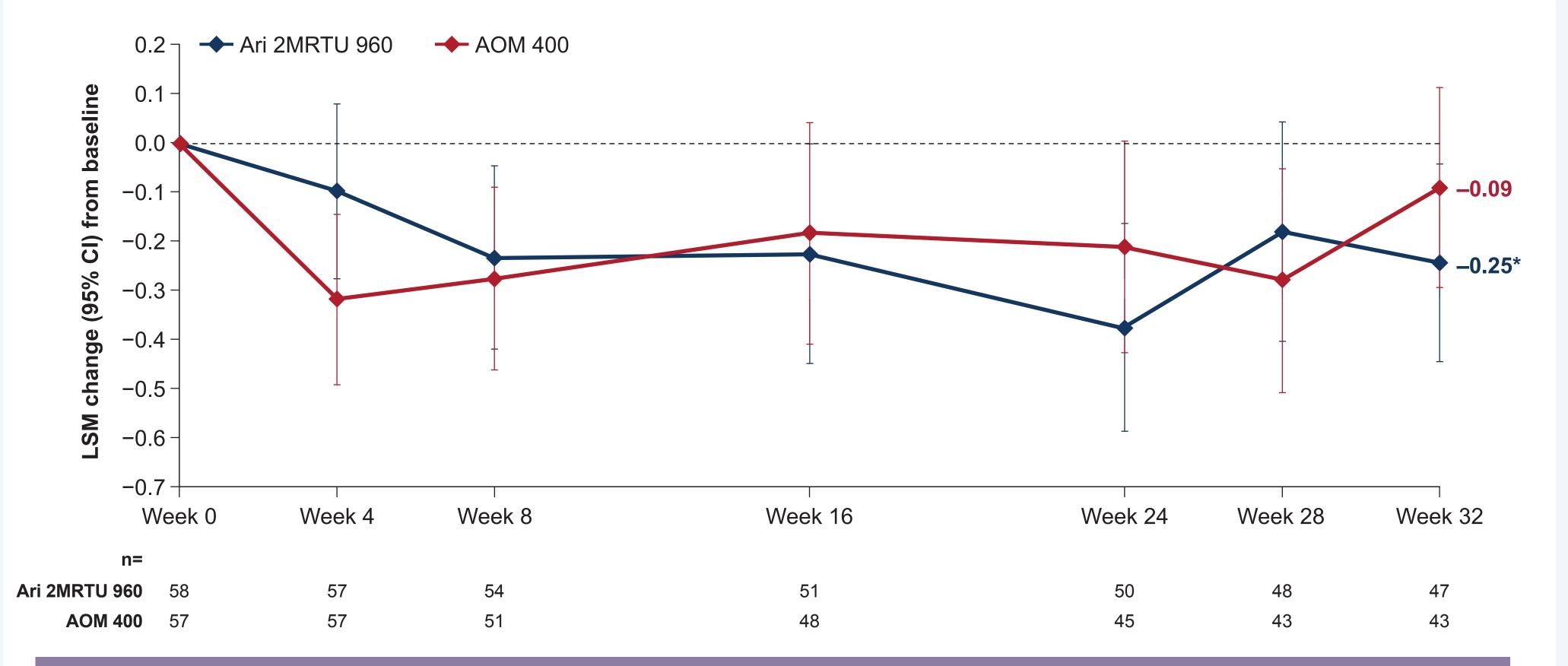


Figure 3: Study 181: Change in PANSS G12 score with Ari 2MRTU 960 and AOM 400 in patients with baseline PANSS G12 score >2



At Week 32, there was a statistically significant reduction in mean PANSS G12 score from baseline in patients diagnosed with schizophrenia and at least mild lack of insight treated with Ari 2MRTU 960; a numerical reduction was observed in those reated with AOM 400. Improvements in PANSS G12 score correlated with improvements in PANSS total score and CGI-S score.

*P<0.05 versus baseline. Mean (standard deviation) PANSS G12 score at baseline was 3.26 (0.48) in the Ari 2MRTU 960 group and 3.21 (0.41) in the AOM 400 group. Data refer to the subset of patients in Study 181 diagnosed with schizophrenia with a baseline PANSS G12 score >2 and ≥1 post-baseline PANSS assessment. 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; CI, confidence interval; CGI-S, Clinical Global Impressions – Severity; LSM, least squares mean; PANSS, Positive and Negative Syndrome Scale

Limitations

- These were exploratory, post hoc analyses of Study 246, Study 247, and Study 181; therefore, they were not fully powered to evaluate the endpoints measured.
- Study 181 analyzed patients with at least mild lack of insight (PANNS G12 score >2), making any changes in PANSS G12 score more
- The assessment of a subgroup of patients with PANSS G12 score >2 in Study 181 resulted in a small patient population for analysis,
- restricting the interpretation of data from this study. • A lack of blinding and placebo control in Study 181 limits conclusions that can be made regarding the effect of treatment in this trial.
- There is heterogeneity in the patient populations analyzed in Study 246, Study 247, and Study 181. However, results suggest an effect of AOM 400 and Ari 2MRTU 960 on insight across a diverse group of patients diagnosed with schizophrenia.

Conclusions



 In the post hoc analysis of Study 246, insight improved following stabilization on oral aripiprazole then AOM 400 in patients diagnosed with schizophrenia. This improvement was maintained when AOM 400 was continued, but was lost when treatment was withdrawn for those switched to placebo.



 In the post hoc analysis of Study 247, insight improved from baseline following stabilization on oral aripiprazole in patients diagnosed with schizophrenia. This was maintained after a switch to AOM 400, with level of insight remaining similar to patients continuing oral aripiprazole, but worsening among those switched to AOM 50 (a subtherapeutic dose), highlighting the importance of remaining adherent to licensed doses to achieve therapeutic concentrations.



In clinically stable patients diagnosed with schizophrenia and at least mild lack of insight included in the post hoc analysis of Study 181, there was an improvement in insight with Ari 2MRTU 960, and a trend towards improvement with AOM 400, after 32 weeks; this correlated with broader symptomatic improvement in both treatment groups, emphasizing the effect of aripiprazole LAIs on multiple disease domains.



 Together, results from these post hoc analyses highlight an important role of aripiprazole LAIs in improving and maintaining insight in patients diagnosed with schizophrenia. Given insight worsens with subtherapeutic dosing of aripiprazole, patients at risk of non-adherence may benefit most from treatment with a longer dosing interval, such as Ari 2MRTU 960.

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Disclosures

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AW: employee of Lundbeck LLC

NA: consultant for Otsuka Pharmaceutical Development & Commercialization Inc.

MY: employee of H. Lundbeck A/S.

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