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Efficacy of Aripiprazole Once-Monthly and Aripiprazole 2-Month Ready-to-Use on Sleep Disruption in People With Bipolar I Disorder: *Post Hoc* Analyses of Data From Two Randomized Controlled Trials

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Background

Disruption in sleep and circadian rhythms is common during and between mood episodes in people living with bipolar disorder,[1–3] and can impair quality of life and functioning.[3–6] Sleep disturbances may include waking up often during the night, poor sleep quality, unusually short or unusually long sleep durations, and nightmares.[6,8,9]

Sleep disturbances in bipolar disorder can be both a symptom of, and a risk factor for, mood episodes.

- A decreased need for sleep is observed in approximately 69–99% of individuals experiencing a manic episode,[9] while insomnia or hypersomnia may be present during episodes of depression.[9]
- A short sleep duration is associated with more severe symptom presentation,[8] with a change of >3 hours in sleep duration from the previous pattern linked to a greater likelihood of hypomanic or manic symptoms.[10]
- People living with with bipolar I disorder (BP-I) are nearly three times more likely than those with bipolar II disorder to report sleep loss as a trigger for elevated mood.[11]

The impact of manic and depressive episodes on sleep in people living with BP-I can be assessed using sleep-specific items in the Young Mania Rating Scale (YMRS) and the Montgomery–Åsberg Depression Rating Scale (MADRS), respectively.[12,13]

Achieving and maintaining symptom control in people living with BP-I may involve antipsychotic treatment.[14,15] This includes long-acting injectable (LAI) antipsychotics, which have been associated with improved treatment adherence and decreased risk of rehospitalization, compared with oral antipsychotic formulations.[16,17]

The LAI formulation of the second-generation antipsychotic aripiprazole – aripiprazole once-monthly 400 mg (AOM 400) – reduces the recurrence of mood episodes in people living with BP-I compared with placebo.[18] Aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) has a similar pharmacokinetic, safety, and efficacy profile to AOM 400.[19]

Currently available evidence is limited, but suggests that second-generation antipsychotic treatments may improve sleep disturbances in people living with BP-I.[20] Although such data are so far lacking for AOM 400 and Ari 2MRTU 960, the collection of YMRS and MADRS data in clinical trials of these two LAIs in people living with BP-I provides an opportunity for item-level analyses, to examine whether sleep items stabilize or change with therapy.

The objective of these exploratory *post hoc* analyses was to assess the effect of AOM 400 and Ari 2MRTU 960 on sleep disturbance in BP-I

Methods

Study design

- These *post hoc* analyses were performed using data from two previously completed controlled trials.[18,19]
  - 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[18] (NCT01567527; Study 250).
  - 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[19] (NCT04030143; Study 181).
    - For study design figures, please refer to supplementary **Figures S1** and **S2**, 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 'sleep' and the MADRS 'reduced sleep' items (scales 0–4 and 0–6, respectively) both assess sleep-associated symptoms (**Box 1**).
- In the current *post hoc* analyses, sleep-associated data collected using the YMRS and MADRS scales were used to examine sleep-related outcomes following treatment with Ari 2MRTU 960 or AOM 400.
- For a per-study description of the analysis population and endpoints for the *post hoc* analyses, please refer to **Box S1**, which can be accessed via the QR code.

Box 1. Overview of sleep-associated symptoms measured using the YMRS and MADRS

Higher scores = Worse symptoms

YMRS 'sleep' item[12]	MADRS 'reduced sleep' item[13]
0. Reports no decrease in sleep	0. Sleeps as usual
1. Sleeping less than normal amount by up to 1 hour	1.
2. Sleeping less than normal by more than 1 hour	2. Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep
3. Reports decreased need for sleep	3.
4. Denies need for sleep	4. Sleep reduced or broken by at least 2 hours
	5.
	6. Less than 2 or 3 hours of sleep
Measures a decreased need for sleep, as a symptom of mania	**Measures reduced sleep, as an aspect of depression**

Collectively, the different items provide information about whether an individual is getting less sleep, and whether this is associated with manic or depressive symptoms

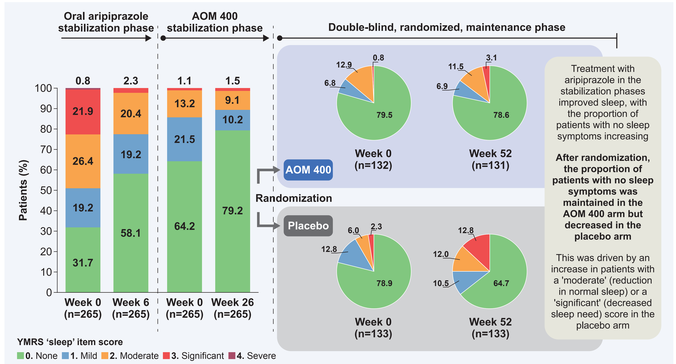
MADRS=Montgomery–Åsberg Depression Rating Scale; YMRS=Young Mania Rating Scale

Results

Study 250 (AOM 400 versus placebo)

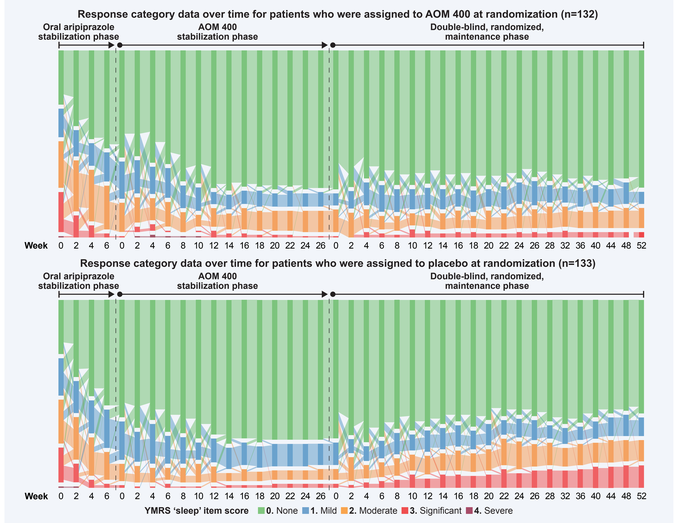
- In total, 265 patients entered the oral aripiprazole stabilization phase of Study 250:
  - 57.4% of patients were female, mean (standard deviation [SD]) age was 40.1 (11.0), and mean (SD) body mass index (BMI) was 30.1 (7.2). For further baseline demographic and disease characteristics, please refer to supplementary **Table S1**, which can be accessed via the QR code.
  - 84 patients (31.7%) had no reduction in sleep (i.e., a score of 0 for the YMRS 'sleep' item) and 181 patients (68.3%) had a mild-to-severe reduction in sleep/sleep need (i.e., a score of 1–4 for the YMRS 'sleep' item).
- YMRS data showed an improvement in sleep outcomes across the oral aripiprazole and AOM 400 stabilization phases. This improvement was maintained in patients who were subsequently randomized to AOM 400 but not in those randomized to placebo. This was demonstrated by a reduction in the proportion of patients with a YMRS 'sleep' score of 1–4 (indicating a mild-to-severe reduction in sleep/sleep need; **Figure 1**; **Figure 2**).
  - Regression analyses indicated a significant between-treatment difference in the change in YMRS 'sleep' item scores during the double-blind, randomized, maintenance phase, driven by well-maintained efficacy with AOM 400 versus placebo (**Table 1**).
- Mean (SD) MADRS 'reduced sleep' item score was low at baseline (0.7 [1.3]), but a small reduction in mean scores was observed during the oral aripiprazole and AOM 400 stabilization phases; during the double-blind, randomized, maintenance phase there was a small increase in mean score in both treatment groups (**Figure 3**).

Figure 1. Study 250: Change over time in sleep/sleep need based on YMRS 'sleep' item score



Data refer to all patients in Study 250 who entered the oral aripiprazole stabilization phase (last observation carry 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

Figure 2. Study 250: Change over time in YMRS 'sleep' item individual response category



Data refer to all patients in Study 250 who entered the oral aripiprazole stabilization phase (last observation carry 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; YMRS=Young Mania Rating Scale

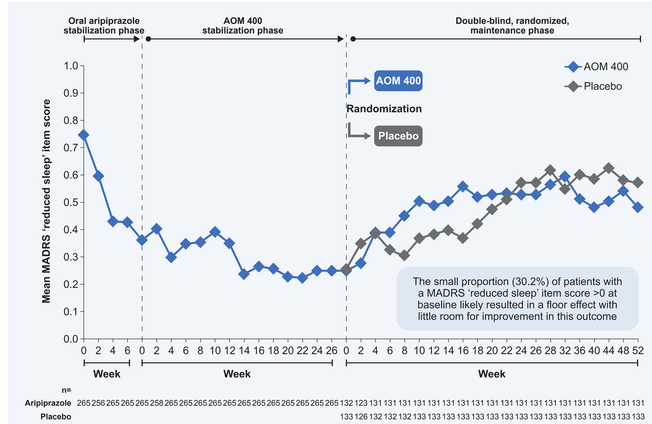
Table 1. Study 250: Change in efficacy outcomes with AOM 400 and placebo in the double-blind, randomized, maintenance phase

	LS mean change (SE) from baseline to Week 52		LS mean difference (SE) in change with AOM 400 vs placebo[a]
	AOM 400	Placebo	
YMRS 'sleep' item score	0.00 (0.11) [p=0.965]	0.35 (0.12) [p=0.003]	−0.35 (0.11) [p=0.0026]
MADRS 'reduced sleep' item score	0.19 (0.15) [p=0.215]	0.27 (0.15) [p=0.074]	−0.09 (0.15) [p=0.565]
YMRS Total score	1.20 (0.90) [p=0.182]	5.42 (0.90) [p<0.0001]	−4.22 (0.91) [p<0.0001]
CGI-BP-S overall score	0.43 (0.15) [p=0.004]	0.92 (0.15) [p<0.0001]	−0.49 (0.15) [p=0.001]
CGI-BP-S mania score	0.18 (0.12) [p=0.141]	0.78 (0.13) [p<0.0001]	−0.60 (0.13) [p<0.0001]
	P-values >0.05 indicated well-maintained efficacy from the start to the end of the double-blind, randomized, maintenance phase	P-values values <0.05 indicated significant worsening during the double-blind, randomized, maintenance phase	Larger negative LS mean differences indicated greater worsening with placebo vs AOM 400; P-values <0.05 indicated a statistically significant difference with AOM 400 versus placebo

An analysis of data from the start of the AOM 400 stabilization phase to the end of the double-blind, randomized, maintenance phase showed a strong correlation between the YMRS 'sleep' item and the other efficacy endpoints of YMRS Total score, and CGI-BP-S overall and mania scores

[a]Treatment differences were assessed using analysis of covariance, with covariates of baseline age, gender, body mass index, region (stratification factor), and concomitant medication use (sleep aid use at baseline [AOM 400, 49.6% (n/N=65/131); placebo, 54.1% (n/N=72/133)] was included as an additional covariate for the YMRS 'sleep' and the MADRS 'reduced sleep' items only)
Data refer to all patients in Study 250 who entered the oral aripiprazole stabilization phase (last observation carry 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; LS=least squares; MADRS=Montgomery–Åsberg Depression Rating Scale; SE=standard error; YMRS=Young Mania Rating Scale

Figure 3. Study 250: Change over time in reduced sleep based on MADRS 'sleep' item score



Data refer to all patients in Study 250 who entered the oral aripiprazole stabilization phase (last observation carry 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; MADRS=Montgomery–Åsberg Depression Rating Scale

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

- In total, 266 clinically stable patients were enrolled and randomized to receive Ari 2MRTU 960 or AOM 400.
- Of the 266 patients, 185 (69.5%) were diagnosed with schizophrenia and 81 patients (30.5%) were diagnosed with BP-I. Data for the patients with schizophrenia will be considered in a separate *post hoc* analysis.
- Of the 81 patients with BP-I, YMRS data were available for 39 patients treated with Ari 2MRTU 960 and 40 patients treated with AOM 400 and, comprising the analysis population for this *post hoc* analysis.
  - In the Ari 2MRTU 960 group with BP-I, 38.5% of patients were female, mean (SD) age 47.9 (11.1) years, and mean (SD) BMI was 28.4 (3.9); in the AOM 400 group with BP-I, 52.5% of patients were female, mean (SD) age was 45.1 (11.2) years, and mean (SD) BMI was 27.0 (4.8). For further baseline demographic and disease characteristics, please refer to supplementary **Table S2**, which can be accessed via the QR code.
- Treatment with Ari 2MRTU 960 or AOM 400 resulted in improvements from baseline to Week 32 in the YMRS 'sleep' item score, and the MADRS 'reduced sleep' item scores (please refer supplementary **Figures S3** and **S4** which can be accessed via the QR code).
- Regression analyses indicated significant improvements from baseline in YMRS and MADRS sleep item scores with Ari 2MRTU 960 and AOM 400, with no significant between-treatment difference observed (**Table 2**).

Table 2. Study 181: Change in efficacy outcomes with Ari 2MRTU 960 and AOM 400

	LS mean change (SE) from baseline to Week 32		LS mean difference (SE) in change with Ari 2MRTU 960 vs AOM 400[a]
	Ari 2MRTU 960	AOM 400	
YMRS 'sleep' item score	−0.37 (0.18) [p=0.0465]	−0.55 (0.20) [p=0.008]	−0.178 (0.22) [p=0.416]
MADRS 'reduced sleep' item score	−0.78 (0.31) [p=0.0136]	−0.93 (0.35) [p=0.0096]	−0.152 (0.38) [p=0.6902]
	A significant improvement from baseline was observed in sleep outcomes with both Ari 2MRTU 960 and AOM 400		No statistically significant difference was observed with Ari 2MRTU 960 vs AOM 400

[a]Treatment differences were assessed using analysis of covariance, with baseline age, gender, body mass index, pharmacokinetic sampling schedule (stratification factor), and concomitant medication use (prior sleep aid use) as covariates
Data refer to the subset of patients in Study 181 diagnosed with BP-I and with available data relating to YMRS assessments (last observation carry 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; BP-I=bipolar I disorder; LS=least squares; MADRS=Montgomery–Åsberg Depression Rating Scale; SE=standard error; 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.
- Heterogeneity between patient populations in Study 250 and Study 181 may limit an overall interpretation of the results. That said, observed improvements in sleep symptoms across both trials suggest a treatment effect for AOM 400 and Ari 2MRTU 960 across a diverse group of patients.
- Sleep-related outcomes for Study 250 predominantly focused on the YMRS 'sleep' item, as a symptom of mania. This was driven by the study design, which required that patients be experiencing a current manic episode. Study 181 included patients with moderately elevated scores for both YMRS and MADRS sleep items, making any change in the MADRS 'reduced sleep' item more measurable than in Study 250.
- The open-label design and lack of a placebo comparator may limit conclusions about treatment effects in Study 181. Similarly, the lack of sleep-related patient-reported outcomes in both studies limits insight into patients' subjective experiences of sleep improvement or worsening.

Conclusions

- Sleep problems were common in patients enrolled in Study 250, i.e., people living with BP-I experiencing a current manic episode; over two-thirds of patients had YMRS scores indicating mild-to-severe reduction in sleep/sleep need at study initiation, consistent with previous evidence.[1,2]
- In the *post hoc* analysis of Study 250, aripiprazole improved YMRS sleep-associated symptoms in patients diagnosed with BP-I. When AOM 400 was withdrawn, YMRS sleep scores worsened, potentially indicating a loss of sleep stability.
- In the *post hoc* analysis of Study 181, Ari 2MRTU 960 and AOM 400 were associated with improvements in YMRS and MADRS sleep-associated symptoms in clinically stable patients diagnosed with BP-I.
- As Ari 2MRTU 960 and AOM 400 have comparable pharmacokinetic, safety, and efficacy profiles,[19] Ari 2MRTU 960 is expected to provide similar sleep benefits to AOM 400, with fewer injections per year.

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Disclosures

Karimah S Bell Lynum, **Norman Atkins**, and **Zhen Zhang** are full-time employees of Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA
Anne Walker is a full-time employee of Lundbeck LLC, Deerfield, IL, USA.
Craig Chepke has served on advisory boards for AbbVie, Acadia, Alkermes, Axsome, Biogen, Corium, Eisai, Idorsia, Intra-Cellular, Ironshore, Janssen, Jazz, Lundbeck, Karuna, Neurocrine, Noven, Otsuka, Takeda and Teva (his spouse has served on advisory boards for Otsuka); has served as consultant for AbbVie, Acadia, Alkermes, BioXcel, Corium, Eisai, Genomind, Intra-Cellular, Janssen, Jazz, Karuna, Lundbeck, MedinCell, Merck, Neurocrine, Noven, Otsuka, Sage Therapeutics and Sunovion; has received grants or research support from Acadia, Axsome, Biohaven, Harmony, Neurocrine and Teva; is on the Speakers' bureau for AbbVie, Acadia, Alkermes, Corium, Eisai, Genomind, Intra-Cellular Therapies, Ironshore, Janssen, Jazz, Lundbeck, Merck, Neurocrine Biosciences, Noven, Otsuka, Sunovion, Takeda and Teva; and has no stocks or ownership interests.
Joseph F. Goldberg 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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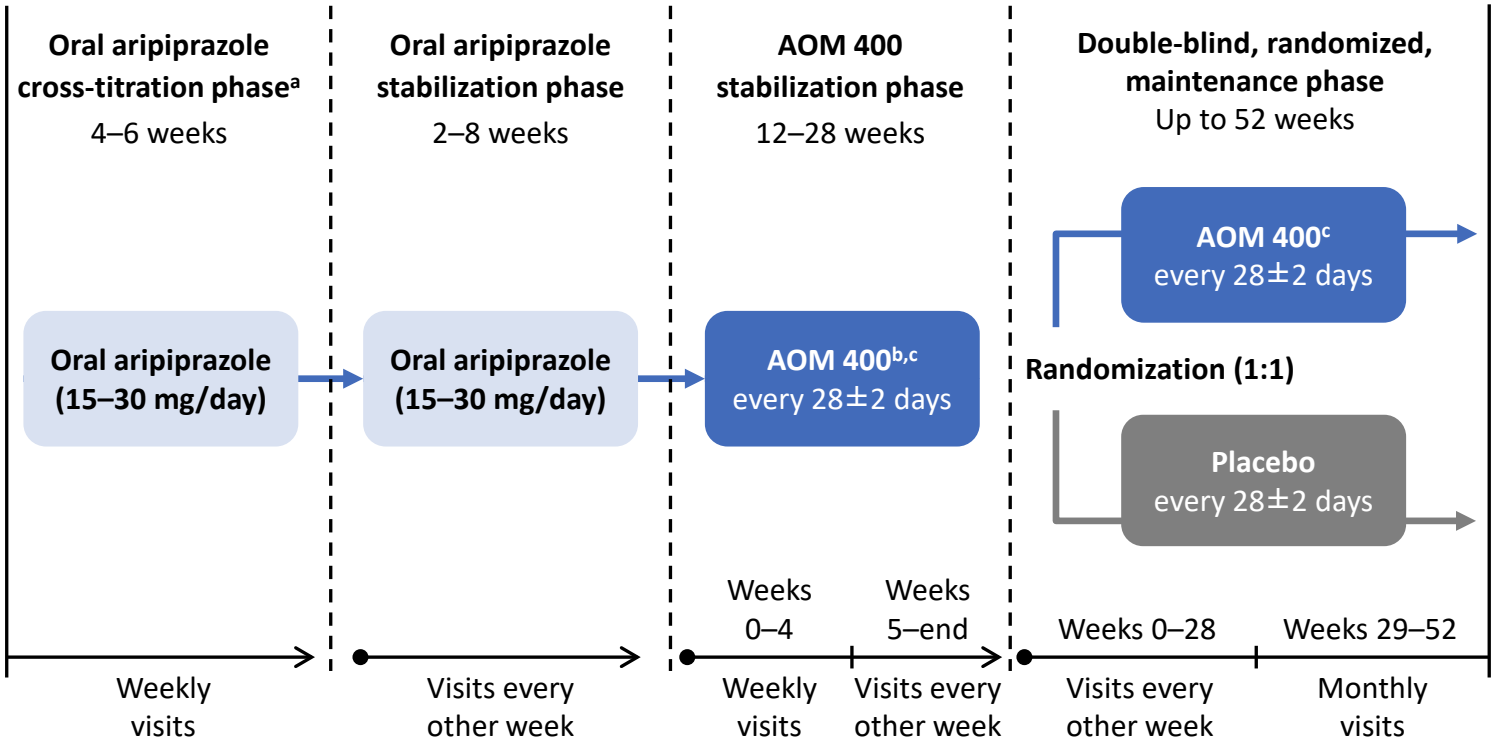
Figure S1. Study 250 design and eligibility (NCT01567527)

Design: International, multicenter, randomized withdrawal study in patients diagnosed with BP-I[18]



Eligibility criteria

- Age 18–65 years
- Diagnosis of BP-I per DSM-IV-TR and MINI criteria
- ≥1 previous manic or mixed episode[d]
- A current manic episode (YMRS total score ≥20)
- ≥9 episodes in the past year

Endpoints

Primary: Time from randomization to recurrence of any mood episode[e]

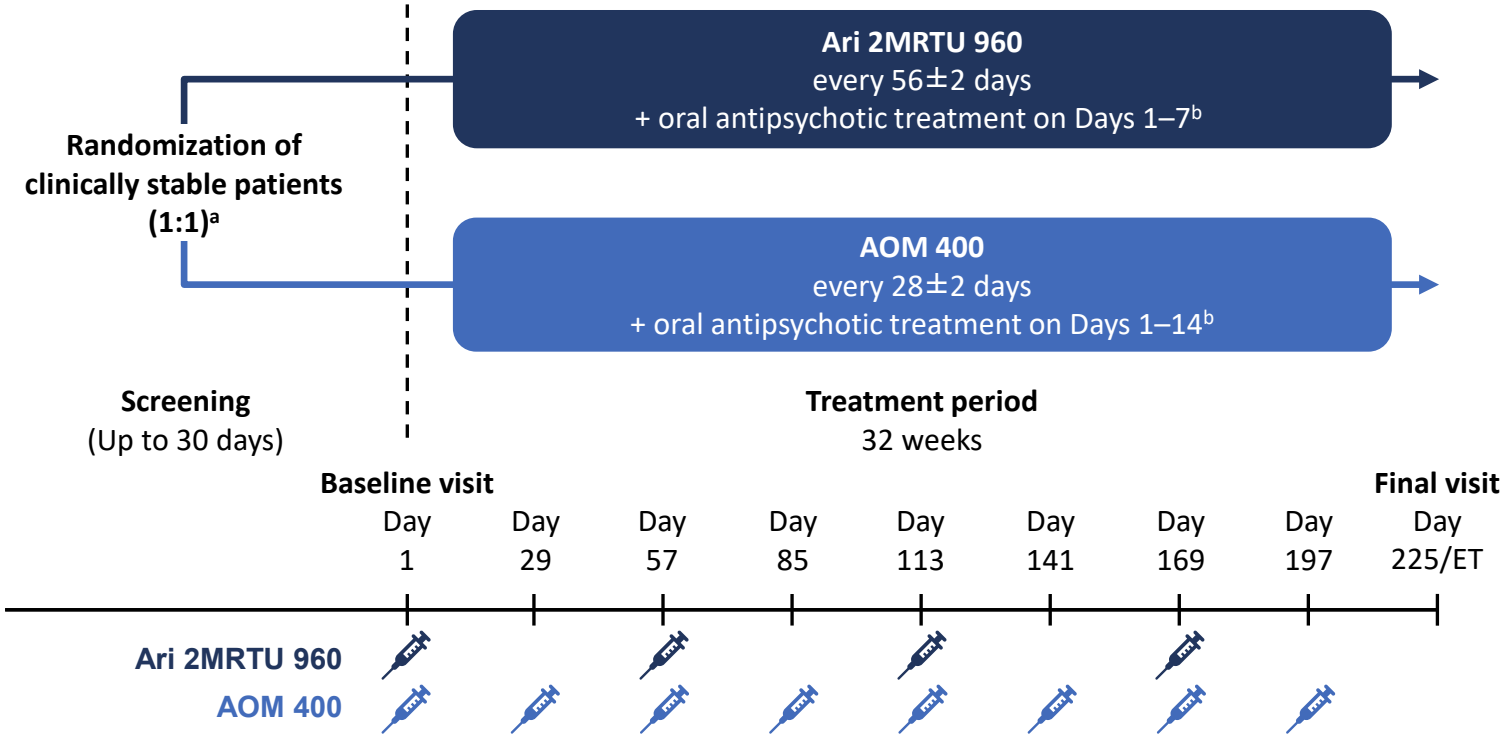
Key secondary: Proportion of patients meeting criteria for recurrence of any mood episode[e]

Other: Change from randomization in YMRS and MADRS total scores

[a]Patients only entered this phase of the study if they were not already receiving oral aripiprazole; [b]for the first 2 weeks, AOM 400 was administered with oral aripiprazole (15–30 mg/day); [c]patients received a starting dose of 400 mg but modification to 300 mg with a return to 400 mg was allowed at any point; [d]of sufficient severity to require hospitalization, treatment with a mood stabilizer, or treatment with an antipsychotic agent; [e]defined as meeting any of the following criteria: hospitalization for any mood episode; YMRS total score ≥15; MADRS total score ≥15; CGI-BP-S scale overall score >4; serious AE of worsening BP-I; discontinuation due to lack of efficacy or AE of worsening of BP-I; clinical worsening with the need for addition of a mood stabilizer, antidepressant treatment, antipsychotic medication, or increase in the benzodiazepine dose above the highest permitted dose; or active suicidality (score ≥4 for MADRS item 10 or "yes" answer to question 4 or 5 on the Columbia Suicide Severity Rating Scale)
AE=adverse event; AOM 400=aripiprazole once-monthly 400 mg; BP-I=bipolar I disorder; CGI-BP-S=Clinical Global Impression – Bipolar Version-Severity; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text revision; MADRS=Montgomery–Åsberg Depression Rating Scale; MINI=Mini-International Neuropsychiatric Interview; YMRS=Young Mania Rating Scale

Figure S2. Study 181 design and eligibility (NCT04030143)

Design: United States-based, multicenter, open-label study in patients diagnosed with BP-I or schizophrenia[19]



Eligibility criteria

- Age 18–64 years
- Diagnosis of BP-I or schizophrenia per DSM-5 criteria
- BMI 18–35 kg/m^2
- Stable on an atypical antipsychotic[a] for ≥2 months prior to screening

Endpoints

Primary:

- Safety and tolerability
- Aripiprazole plasma concentration and exposure

Secondary:

- Efficacy (YMRS, MADRS, CGI-BP [BP-I only])[c]

[a]Participants could have been stabilized on an oral antipsychotic (excluding clozapine), or AOM 400; [b]participants previously treated with an oral antipsychotic received overlapping oral antipsychotic treatment with the first study drug dose to ensure antipsychotic treatment continuity (no overlapping oral antipsychotic treatment was administered to participants stabilized on AOM 400); [c]additional secondary endpoints included various pharmacokinetic parameters, the Clinical Global Impression – Improvement, the Subjective Well-being under Neuroleptic Treatment—Short Form (assessed in all participants), and the Positive and Negative Syndrome Scale and Clinical Global Impression—Severity (assessed in the subset of patients diagnosed with schizophrenia)

AOM 400=aripiprazole once-monthly 400 mg; Ari 2MRTU 960=aripiprazole 2-month ready-to-use 960 mg; BMI=Body Mass Index; BP-I=bipolar I disorder; CGI-BP=Clinical Global Impression – Bipolar Version; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ET=early termination; MADRS=Montgomery–Åsberg Depression Rating Scale; YMRS=Young Mania Rating Scale

Box S1. Description of the *post hoc* analysis populations and endpoints

Study 250

Analysis population

- All patients entering the oral aripiprazole stabilization phase

Endpoints

- Change from baseline in:
  - YMRS 'sleep' item score
  - MADRS 'reduced sleep' item score
  - YMRS total score
  - CGI-BP-S overall score
  - CGI-BP-S mania score

Study 181

Analysis population

- Subset of patients diagnosed with BP-I[a] and with available data for YMRS and MADRS sleep-associated items

Endpoints

- Change from baseline in:
  - YMRS 'sleep' item score
  - MADRS 'reduced sleep' item score

[a]Study 181 included patients with schizophrenia or BP-I, but endpoints for this *post hoc* analysis were assessed in only the subset of patients diagnosed with BP-I

BP-I=bipolar I disorder; CGI-BP-S=Clinical Global Impression – Bipolar Version-Severity; MADRS=Montgomery–Åsberg Depression Rating Scale; YMRS=Young Mania Rating Scale

Table S1. Study 250: Demographics and characteristics at AOM stabilization

	Overall population[a] (N=265)
Demographic characteristics	
Age, years	40.1 (11.0)
Female, n (%)	152 (57.4)
BMI, kg/m^2	30.1 (7.2)
Disease characteristics	
YMRS total score	15.8 (10.7)
MADRS total score	4.6 (4.9)
CGI-BP-S overall score	3.2 (1.2)
CGI-BP-S mania score	3.1 (1.3)
CGI-BP-S depression score	1.5 (0.8)
YMRS 'sleep' item score	1.4 (1.2)
MADRS 'reduced sleep' item score	0.7 (1.3)
Prior use of sleep aids, n (%)	137 (51.9)

Data are shown as mean (standard deviation), unless otherwise stated

[a]Data refer to all patients in Study 250 who entered the oral aripiprazole stabilization phase

BMI=body mass index; CGI-BP-S=Clinical Global Impression – Bipolar Version-Severity; MADRS=Montgomery–Åsberg Depression Rating Scale; YMRS=Young Mania Rating Scale

Table S2. Study 181: Demographics and baseline characteristics of the BP-I analysis population

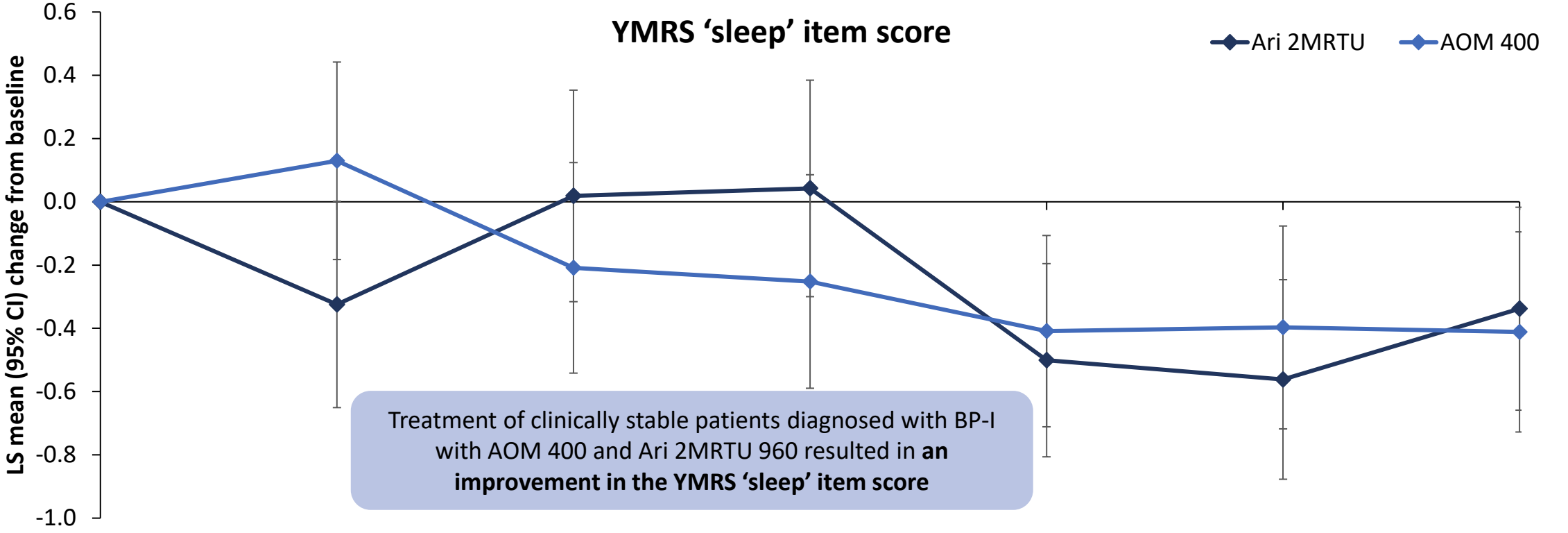
	AOM 400 (n=40)	Ari 2MRTU 960 (n=39)
Demographic characteristics		
Age, years	45.1 (11.2)	47.9 (11.1)
Female, n (%)	21 (52.5)	15 (38.5)
BMI, kg/m^2	27.0 (4.8)	28.4 (3.9)
Disease characteristics		
YMRS total score	9.4 (8.3)	6.6 (7.4)
MADRS total score	13.0 (9.3)	11.0 (9.5)
CGI-BP-S overall score	2.8 (1.2)	2.3 (1.2)
CGI-BP-S mania score	2.3 (1.2)	1.7 (1.0)
CGI-BP-S depression score	2.5 (1.1)	2.2 (1.2)
YMRS 'sleep' item score	1.2 (1.0)	0.7 (1.0)
MADRS 'reduced sleep' item score	2.7 (1.6)	1.7 (1.5)
Prior use of sleep aids, n (%)	3 (7.5)	8 (20.5)

Data are shown as mean (standard deviation), unless otherwise stated

Data refer to the subset of patients in Study 181 diagnosed with BP-I and with available data relating to YMRS assessments

AOM 400=aripiprazole once-monthly 400 mg; Ari 2MRTU 960 aripiprazole 2-month ready-to-use 960 mg; BMI=body mass index; BP-I=bipolar I disorder; CGI-BP-S=Clinical Global Impression – Bipolar Version-Severity; MADRS=Montgomery–Åsberg Depression Rating Scale; SD=standard deviation; YMRS=Young Mania Rating Scale

Figure S3. Study 181: Change from baseline in YMRS and MADRS sleep-related item scores

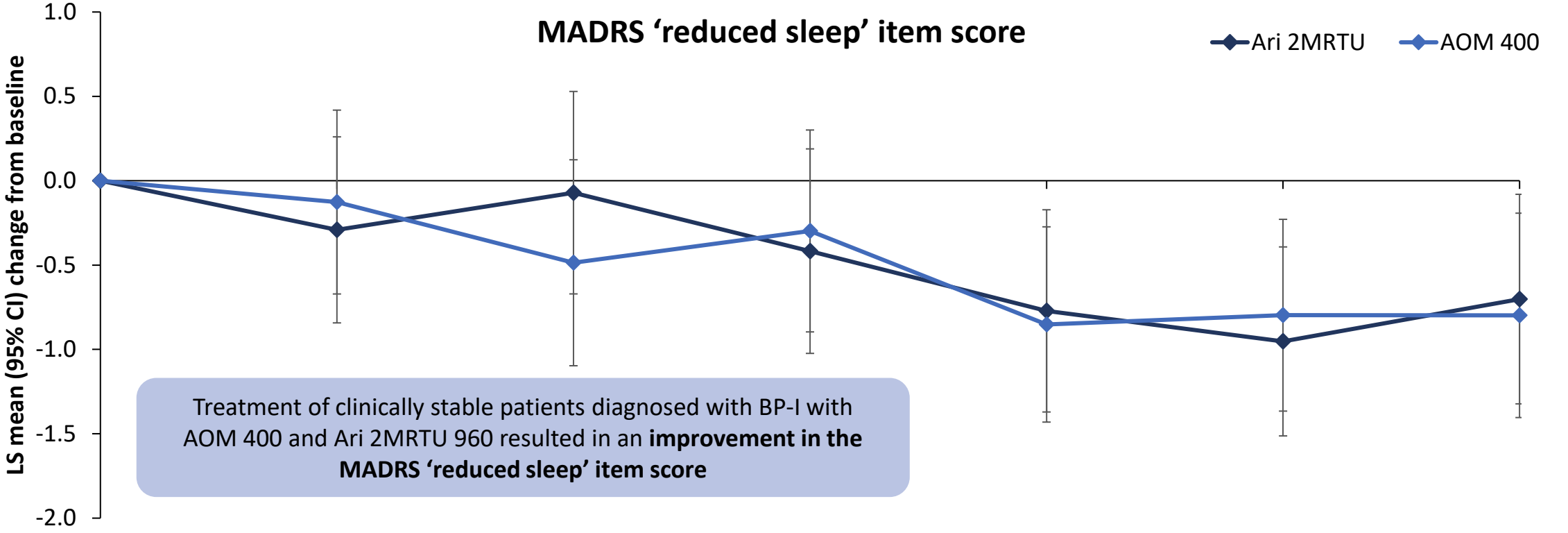


n=	Baseline	Week 4	Week 8	Week 16	Week 24	Week 28	Week 32
AOM 400	40	40	37	35	31	29	30
Ari 2MRTU 960	39	36	37	34	30	30	29

Data refer to the subset of patients in Study 181 diagnosed with BP-I and with available data relating to YMRS assessments (observed cases dataset [mixed model for repeated measures analysis]). 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; LS=least squares; MADRS=Montgomery–Åsberg Depression Rating Scale; YMRS=Young Mania Rating Scale

Figure S4. Study 181: Change from baseline in YMRS and MADRS sleep-related item scores



	Baseline	Week 4	Week 8	Week 16	Week 24	Week 28	Week 32
n=							
AOM 400	40	40	37	35	31	29	30
Ari 2MRTU 960	39	36	37	34	30	30	29

Data refer to the subset of patients in Study 181 diagnosed with BP-I and with available data relating to YMRS assessments (observed cases dataset [mixed model for repeated measures analysis]). 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; LS=least squares; MADRS=Montgomery–Åsberg Depression Rating Scale; YMRS=Young Mania Rating Scale