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ORIGINAL RESEARCH ARTICLE

A Randomized, Open-Label, Multiple-Dose, Parallel-Arm, Pivotal Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Aripiprazole 2-Month Long-Acting Injectable in Adults With Schizophrenia or Bipolar I Disorder

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Abstract

Background Aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) is a new long-acting injectable antipsychotic formulation for gluteal administration every 2 months, currently being investigated for the treatment of schizophrenia and bipolar I disorder (BP-I). The objectives of this trial were to evaluate the safety and tolerability of Ari 2MRTU 960, and the similarity of aripiprazole plasma concentrations following administration of Ari 2MRTU 960 or aripiprazole once-monthly 400 mg (AOM 400), in adults with schizophrenia or BP-I.

Methods This was a 32-week open-label study. Eligible participants were randomized 1:1 to receive Ari 2MRTU 960 every 56 ± 2 days (four injections scheduled) or AOM 400 every 28 ± 2 days (eight injections scheduled). Participants received overlapping oral antipsychotic treatment with the first administration of study drug (there was no oral overlap for participants stabilized on AOM 400). Safety, tolerability, and pharmacokinetics (PK) were evaluated throughout the study. Primary safety endpoints included reported adverse events, injection site reactions, and extrapyramidal symptoms. Primary PK endpoints were plasma concentration of aripiprazole 56 days after the fourth dose of Ari 2MRTU 960 and 28 days after the eighth dose of AOM 400, and area under the concentration–time curve (AUC) from Day 0 to 56 postdose after the fourth dose of Ari 2MRTU 960, or AUC from Day 0 to 28 after the seventh and eighth doses of AOM 400.

Results Of the 266 participants enrolled (schizophrenia, $n = 185$; BP-I, $n = 81$), 132 were randomized to receive Ari 2MRTU 960 and 134 were randomized to receive AOM 400. The majority (66.2%) of participants were male; 72.9% were Black or African American, and mean age was 47.3 years; demographic characteristics and baseline disease characteristics were generally well balanced between groups. Study completion rate was 77.3% in the Ari 2MRTU 960 group and 68.7% in the AOM 400 group. The incidence of treatment-emergent adverse events (TEAEs) was similar between Ari 2MRTU 960 (71.2%) and AOM 400 (70.9%). The most frequently reported TEAEs were increased weight (Ari 2MRTU 960: 22.7%; AOM 400: 20.9%) and injection-site pain (Ari 2MRTU 960: 18.2%; AOM 400: 9.0%). The geometric means ratio (GMR) of aripiprazole plasma concentrations on the last day following the final dosing for Ari 2MRTU 960 versus AOM 400 was 1.011 (90% confidence interval [CI] 0.893–1.145), and the GMR of aripiprazole plasma exposure (area under the concentration–time curve) over the fourth Ari 2MRTU 960 dosing interval versus the seventh and eighth AOM 400 dosing intervals was 1.006 (90% CI 0.851–1.190).

Conclusions Ari 2MRTU 960 was generally well tolerated in adults with schizophrenia or BP-I, with a safety profile comparable with that of AOM 400, and aripiprazole exposure equivalent to that with AOM 400 (ClinicalTrials.gov identifier: NCT04030143, registered on 23 July 2019).

Plain Language Summary

Aripiprazole is a medication used to treat psychotic symptoms in schizophrenia or bipolar I disorder (BP-I) that can be taken orally or injected into the muscle. Aripiprazole once-monthly 400 mg (AOM 400) is a long-acting injectable formulation administered every 28 days, used in the treatment of schizophrenia or BP-I. A new 2-month ready-to-use formulation

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containing 960 mg of aripiprazole (Ari 2MRTU 960) is currently being investigated for the treatment of schizophrenia or BP-I. This 32-week study compared Ari 2MRTU 960 with AOM 400 in adults with schizophrenia or BP-I stabilized on their current medication. Study participants were randomly assigned to receive either Ari 2MRTU 960 every 56 ± 2 days (four injections scheduled in total) or AOM 400 every 28 ± 2 days (eight injections scheduled in total). Safety, tolerability, and concentration of aripiprazole in the blood were evaluated throughout the study. The incidence of adverse events emerging during the treatment period was similar between Ari 2MRTU 960 and AOM 400 (71.2% and 70.9%, respectively), with the most frequently reported events being increased weight (Ari 2MRTU 960: 22.7%; AOM 400: 20.9%) and injection-site pain (Ari 2MRTU 960: 18.2%; AOM 400: 9.0%). At the end of the study, aripiprazole concentrations were similar between treatment groups, based on the reported pharmacokinetic parameters. Participants remained clinically stable throughout the study. Ari 2MRTU 960 was generally well tolerated in adults with schizophrenia or BP-I.

Key Points

Aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) is a new long-acting injectable antipsychotic formulation for injection into the gluteal muscle every 2 months, currently in development for the treatment of schizophrenia or bipolar I disorder (BP-I).

The safety, efficacy, and pharmacokinetic profile of Ari 2MRTU 960 are similar to those of aripiprazole once-monthly 400 mg (AOM 400), a long-acting injectable antipsychotic medication used in the treatment of schizophrenia or BP-I in adults.

1 Introduction

Schizophrenia is a chronic mental disorder characterized by continuous or relapsing episodes of psychosis [1]. Bipolar I disorder (BP-I) is a recurrent, episodic illness characterized by severe alterations in mood and behavior [1]. Pharmacological treatment is important for achieving and maintaining symptom control in schizophrenia and BP-I [2–4], but adherence to oral medication is often poor in these populations [5, 6]. Available data suggest that approximately 50% of people with schizophrenia or BP-I do not take their medication as prescribed [7–10]. Real-world evidence suggests that, compared with oral antipsychotics, long-acting injectable (LAI) formulations of antipsychotics are associated with significant improvements in treatment adherence [11–13], as well as clinical benefits such as lower rates of relapse [14], reduced risk of hospitalization [14], reduced length of hospitalization [15], and fewer visits to emergency rooms [14, 15], associated with improved functioning and improved quality of life [14].

Aripiprazole exhibits partial agonist activity at dopamine D_2 receptors and serotonin 5-HT_{1A} receptors [16–18], full agonist activity at dopamine D_3 receptors [17], and antagonist activity at serotonin 5-HT_{2A} receptors [19]. Exposure–response analysis has shown that a person with a diagnosis of schizophrenia and a predicted minimum aripiprazole plasma concentration (C_{min}) of ≥95 ng/mL is 4.41 times less likely to relapse compared with a person with a predicted C_{min} of < 95 ng/mL [20]. This minimum efficacy threshold aripiprazole plasma concentration was equivalent to the median model-predicted steady-state C_{min} ($C_{min,ss}$) for participants receiving a 10 mg dose of oral aripiprazole [20], the lowest recommended daily dose for the treatment of adults with schizophrenia [21, 22].

Aripiprazole once-monthly 400 mg (AOM 400) is an extended-release aripiprazole monohydrate suspension for administration every 28 days via intramuscular injection [23, 24]. In the US, AOM 400 has been approved by the US FDA for the treatment of schizophrenia in adults and the maintenance monotherapy treatment of BP-I in adults [23]. In Europe, AOM 400 has been approved for the maintenance treatment of schizophrenia in adult patients stabilized with oral aripiprazole [24].

Aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) is a new LAI formulation containing 960 mg of aripiprazole monohydrate for gluteal administration every 2 months. Ari 2MRTU 960 was designed to maintain efficacious aripiprazole plasma concentrations (≥ 95 ng/mL) [20] for a 2-month dosing interval. Given the established efficacy, safety, and tolerability profile of AOM 400 [25–28], the aim of this clinical study was to determine the safety and tolerability of multiple doses of Ari 2MRTU 960, and to establish the similarity of aripiprazole plasma concentrations and exposure following Ari 2MRTU 960 and AOM 400 administration, in adults with schizophrenia or BP-I.

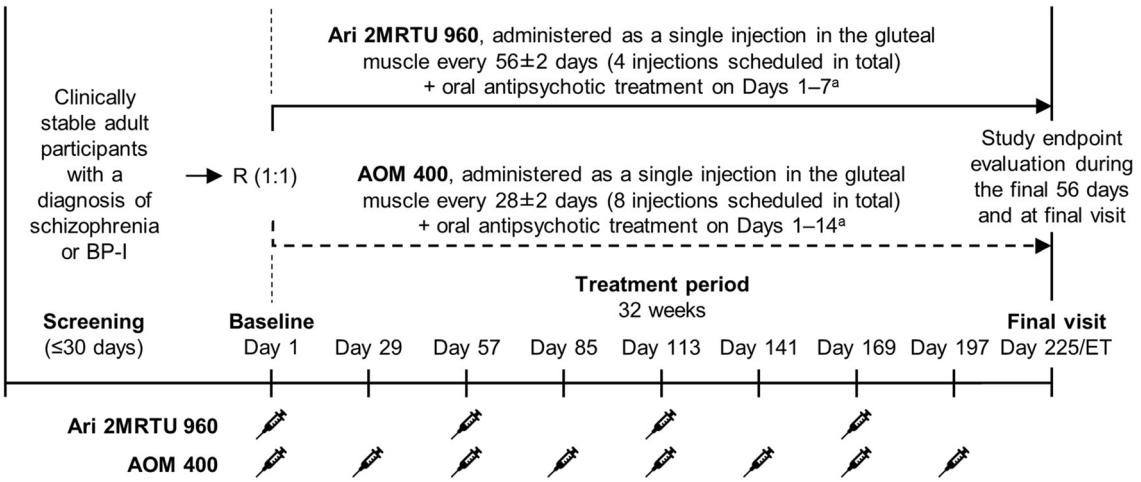

Fig. 1 Study design. [a] Participants received overlapping oral antipsychotic treatment with the first study drug dose to ensure antipsychotic treatment continuity. No overlapping oral antipsychotic treatment was administered to participants stabilized on AOM 400; these participants could not be enrolled to the robust sampling schedule. *AOM 400* aripiprazole once-monthly 400 mg, *Ari 2MRTU 960* aripiprazole 2-month ready-to-use 960 mg, *BP-I* bipolar I disorder, *ET* early termination, *R* randomization

2 Methods

2.1 Trial Design and Population

This was an open-label, multiple-dose, randomized, parallel-arm, multicenter trial in adults with schizophrenia or BP-I (ClinicalTrials.gov identifier: NCT04030143). The study started on 1 August 2019 and was completed on 8 July 2020. Participants were enrolled into the study at 16 clinical trial sites in the United States (US).

Key inclusion criteria were: age 18–64 years, current diagnosis of schizophrenia or BP-I (as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-5] criteria) [1], body mass index of 18–35 kg/m^2, good physical health, clinical stability on an atypical antipsychotic medication (except for clozapine, which was not allowed) for ≥2 months prior to screening (participants with BP-I were also allowed to continue concomitant mood stabilizer and antidepressant treatment), and prior history of tolerating oral aripiprazole and/or AOM 400 (according to the investigator's judgment). Participants without a history of tolerating aripiprazole received three single oral aripiprazole doses of 10 mg on 3 consecutive days (30 mg in total, in addition to their current oral antipsychotic) during the screening period to establish tolerability.

Key exclusion criteria were substance use disorder (as defined by DSM-5 criteria) [1] within the past 180 days or a positive test for drugs of abuse (excluding nicotine, alcohol, and marijuana if sufficient rationale was provided, which must have included rationale/indication for use, review of patterns and frequency of use, and justification to support compliance with the protocol for the intended duration of treatment); use of any cytochrome P450 (CYP) 2D6 and CYP3A4 inhibitors or CYP3A4 inducers within 14 days (fluoxetine or fluoxetine/olanzapine within 28 days) prior to dosing, for the duration of the trial, and 30 days after the last study drug dose; current acute relapse of schizophrenia; current DSM-5 diagnosis other than schizophrenia or BP-I [1]; a significant risk of committing suicide (based on history, routine psychiatric status examination, investigator's judgment, or a 'yes' answer to questions 4 or 5 [current or over the last 6 months] on the baseline Columbia Suicide Severity Rating Scale [C-SSRS] questionnaire); treatment resistance to an atypical antipsychotic medication; and history of neuroleptic malignant syndrome or clinically significant tardive dyskinesia (as assessed by the investigator).

The study design is shown in Fig. 1.

Participants were randomized (1:1) to the two treatment arms (Ari 2MRTU 960 and AOM 400). Randomization was stratified by disease type (schizophrenia or BP-I) and pharmacokinetic (PK) blood sampling schedule (robust or sparse, with the robust sampling schedule providing more frequent PK sampling timepoints [blood sampling schedules are presented in electronic supplementary Table 1]). A block size of 2 was used to generate the randomization sequence. As this was an open-label study, randomization sequence was not concealed internally. An Interactive Response System was used for participant randomization, and treatment assignments were based on a computer-generated code provided by Otsuka Pharmaceutical Development & Commercialization Inc. Access to the assignment codes was restricted.

All study treatments were administered by the investigators at the clinical trial sites. For participants stabilized on oral antipsychotic treatment, overlapping oral antipsychotic

treatment was administered for 7 days after the first administration of Ari 2MRTU 960 or for 14 days after the first administration of AOM 400; there was no oral overlap for participants stabilized on AOM 400 (Fig. 1). Participants enrolled to a sparse sampling schedule could have been stabilized on oral aripiprazole, a non-aripiprazole oral antipsychotic, or AOM 400. For those stabilized on oral aripiprazole, they continued to receive oral aripiprazole for Days 1–7 (if randomized to Ari 2MRTU 960) or Days 1–14 (if randomized to AOM 400). For those stabilized on a non-aripiprazole oral antipsychotic, they continued to receive their current oral antipsychotic for Days 1–7 (if randomized to Ari 2MRTU 960) or Days 1–14 (if randomized to AOM 400). For those stabilized on AOM 400, no overlapping oral antipsychotic treatment was administered.

To be enrolled to the robust sampling schedule, participants must have been stabilized on a non-aripiprazole oral antipsychotic and must have demonstrated prior tolerability to aripiprazole. Participants enrolled to a robust sampling schedule discontinued their current oral antipsychotic and switched to 10–20 mg oral aripiprazole per day for the period of overlapping oral antipsychotic treatment with the first administration of study drug (overlap was 7 or 14 days depending on treatment group, with dose determined by the investigator).

In case of safety and tolerability issues, a one-time dose reduction was allowed for Ari 2MRTU 960 (to 660 mg) and AOM 400 (to 300 mg), with one-time subsequent increase back to 960 mg for Ari 2MRTU 960 or to 400 mg for AOM 400 allowed.

Participants enrolled to the robust sampling schedule and randomized to Ari 2MRTU 960 were housed in a trial site clinic for 21 days after the first and fourth doses of Ari 2MRTU 960. Participants enrolled to the robust sampling schedule and randomized to AOM 400 stayed in a trial site clinic for 21 days after the administration of the first, seventh, and eighth doses of AOM 400. Participants enrolled to the sparse sampling schedule were outpatients for the administration of all study drug doses but could be housed in the trial clinic for up to 21 days after the administration of the first study drug dose at the discretion of the investigator.

2.2 Endpoints

Primary safety and tolerability endpoints were evaluated throughout the 32 weeks of study duration and included reported adverse events (AEs); investigator's assessment of the most recent injection site for symptoms of pain, swelling, redness, and induration; Visual Analog Scale (VAS) [29] scores for participant-reported rating of pain at the most recent injection site (range 0 [no pain] to 100 [extreme pain]); extrapyramidal symptoms (EPS), assessed by the Simpson–Angus Scale (SAS) [30], Abnormal Involuntary Movement Scale (AIMS) [31], and Barnes Akathisia Rating Scale (BARS) [32]; vital signs; electrocardiograms (ECGs); clinical laboratory monitoring (serum chemistry, hematology, and urinalysis); physical examinations; and suicidality (assessed by the C-SSRS) [33]. A schedule of safety and tolerability assessments is presented in electronic supplementary Table 2.

All AEs were coded by system organ class and the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. A serious AE included any event that resulted in death; was life-threatening (i.e. the participant was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); resulted in persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions; required hospitalization or prolonged hospitalization; resulted in congenital anomaly or birth defect; or resulted in any other medically significant events that, based on appropriate medical judgment, may jeopardize the participant and require medical or surgical intervention to prevent one of the previously listed outcomes. A treatment-emergent AE (TEAE) was defined as an AE that started after the first dose of study drug or an AE that continued from baseline and was serious, related to the study drug, or resulted in death, discontinuation, interruption, or reduction of the study drug dose.

Primary PK endpoints were plasma concentration of aripiprazole 56 days after the fourth dose of Ari 2MRTU 960 (C_{56}) and 28 days after the eighth dose of AOM 400 (C_{28}), calculated based on PK data from participants enrolled to the sparse and robust sampling schedules; and area under the concentration–time curve (AUC) from Day 0 to 56 postdose ($AUC_{0–56}$) after the fourth dose of Ari 2MRTU 960, or AUC from Day 0 to 28 ($AUC_{0–28}$) after the seventh and eighth doses of AOM 400, calculated based on PK data from participants enrolled to the robust sampling schedule.

Secondary PK endpoints included maximum (peak) plasma concentration of aripiprazole (C_{max}) and time to maximum (peak) plasma concentration (T_{max}) after the fourth dose of Ari 2MRTU 960, and after the seventh and eighth doses of AOM 400 (in participants enrolled to the robust sampling schedule only) and $AUC_{0–28}$ and AUC from Day 29 to 56 ($AUC_{29–56}$) after the fourth dose of Ari 2MRTU 960 (in participants enrolled to the robust sampling schedule only). Peak-to-trough percentage fluctuation (PTF%) after the fourth dose of Ari 2MRTU 960 and after the eighth dose of AOM 400 were also evaluated (in participants enrolled to the robust sampling schedule only).

Secondary endpoints pertaining to efficacy were assessed by the Positive and Negative Syndrome Scale (PANSS) [34] and Clinical Global Impression—Severity (CGI-S) [31] for participants with schizophrenia, and by the Young Mania Rating Scale (YMRS) [35], Montgomery–Åsberg

Depression Rating Scale (MADRS) [36] and Clinical Global Impression—Bipolar Version (CGI-BP) [37] for participants with BP-I. All participants were also evaluated using the Clinical Global Impression—Improvement (CGI-I) [31] and Subjective Well-being under Neuroleptic Treatment—Short Form (SWN-S) [38]. Efficacy outcomes were evaluated on Days 1, 29, 57, 113, 169, 197 and 225 or upon early termination of the study.

2.3 Statistical Analysis

Standard non-compartmental methods were applied to calculate the PK parameter values. The 90% confidence interval (CI) of the geometric means ratio (GMR) of C_{56} of aripiprazole after the fourth injection of Ari 2MRTU 960 (test) to C_{28} after the eighth injection of AOM 400 (reference) was calculated for all participants. Similarly, the 90% CI of the GMR of $AUC_{0–56}$ of aripiprazole after the fourth injection of Ari 2MRTU 960 (test) to the sum of $AUC_{0–28}$ after the seventh and eighth injections of AOM 400 (reference) was calculated for participants with robust PK sampling schedules. The GMRs and corresponding 90% CIs were derived from an analysis of variance (ANOVA) including treatment formulation and disease population as fixed effects for AUC and including treatment formulation, PK sampling and disease population as fixed effects for C_{56}/C_{28}. One-sided *t*-tests of treatment formulation within the specified ANOVA were performed to test the null hypothesis of the ratio of PK parameters for Ari 2MRTU 960 compared with the PK parameters for AOM 400 being ≤ 0.8.

It was estimated that a total of ≥ 100 participants (i.e., ≥ 50 per group) completing the trial would have ≥80% power to ensure that the lower limit of the 90% CI of the GMR of C_{56} after the fourth dose of Ari 2MRTU 960 (test) to C_{28} after the eighth dose of AOM 400 (reference) would be >0.80, assuming that the actual GMR of concentrations was 1.0. Among these 100 participants, at least 30 completers enrolled to the robust sampling schedule would provide ≥80% power to ensure that the lower limit of the 90% CI of the GMR of $AUC_{0–56}$ of Ari 2MRTU 960 (test) to the sum of $AUC_{0–28}$ values of AOM 400 (reference) after the seventh and eighth doses was > 0.80, assuming the actual GMR of concentrations was 1.15. Assuming a dropout rate of 34%, at least 152 enrolled participants were required to ensure at least 100 completers.

No data imputation was done for missing data in the PK analysis. The last observation carried forward (LOCF) method was used to impute missing data of efficacy assessment scales at post-baseline visits.

All randomized participants who received at least one study drug injection dose, regardless of any protocol violation, were included in the safety analysis. Time and dose of each study drug administration was recorded for each participant, along with information regarding any inappropriately administered dose. Treatment non-adherence criteria were defined as having a period of < 54 days between injections for Ari 2MRTU 960 and a period of < 26 days between injections for AOM 400.

The PK sample consisted of all dosed participants who had at least one evaluable aripiprazole PK parameter. For the primary PK endpoint analysis, only the completers with available values of the primary endpoints after the last scheduled injection were included.

All randomized participants who received at least one study drug dose and had at least one efficacy assessment were included in the efficacy analysis.

3 Results

3.1 Participants

Of the 394 adults who were screened, 266 were enrolled and randomized to receive Ari 2MRTU 960 ($n = 132$) or AOM 400 ($n = 134$). Of the 266 enrolled participants, 84 were allocated to the robust PK sampling group and 182 were allocated to the sparse PK sampling group. Participant disposition is shown in Fig. 2.

The study completion rate was 77.3% (102/132 participants) in the Ari 2MRTU 960 group and 68.7% (92/134 participants) in the AOM 400 group. Treatment adherence was achieved in 98.5% of participants (130/132) receiving Ari 2MRTU 960 and in 88.1% of participants (118/134) receiving AOM 400.

Demographic characteristics and baseline disease characteristics were generally well balanced between groups (Table 1). Most (66.2%) participants were men, over two-thirds (72.9%) were Black or African American, and the overall mean age was 47.3 years. In the Ari 2MRTU 960 group, 34.1% of participants (45/132) had been treated with oral aripiprazole prior to the start of the study treatment phase compared with 26.1% of participants (35/134) in the AOM 400 group. Most participants (91.0%) took at least one concomitant medication during the trial, with similar rates of use between the two treatment groups. Concomitant medications used by ≥ 10% of participants are presented in Table 1.

3.2 Safety and Tolerability

All 266 randomized participants received at least one study drug dose and were included in the safety analyses. Most participants (99.2% [131/132] in the Ari 2MRTU 960 group and 98.5% [132/134] in the AOM 400 group) did not require dose adjustment during the trial.

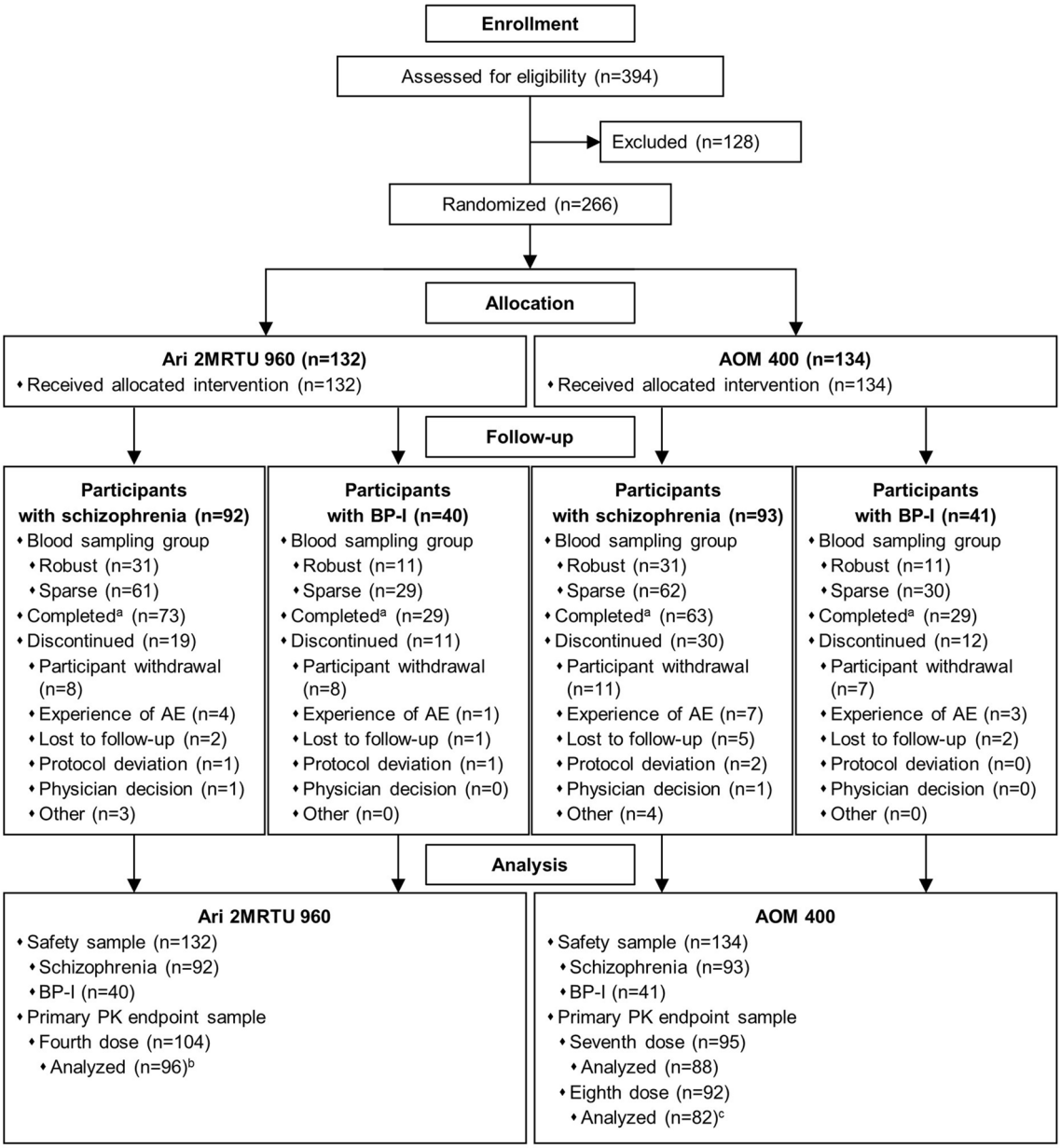

Fig. 2 Participant disposition. [a] Completed visit on Day 225. [b] Of the 104 participants receiving four doses of Ari 2MRTU 960, 2 participants were excluded from analysis due to dose administration outside of the permitted 2-day window, and 6 participants were excluded from analysis due to C_{56} being outside of the collection window, or due to insufficient PK profile. [c] Of the 92 participants receiving the eighth dose of AOM 400, 1 participant was excluded from analysis due to having missed a dose, and 9 participants were excluded from analysis due to C_{28} being outside of the collection window or due to insufficient PK profile. *AE* adverse event, *AOM 400* aripiprazole once-monthly 400 mg, *Ari 2MRTU 960* aripiprazole 2-month ready-to-use 960 mg, *BP-I* bipolar I disorder, C_{28} plasma concentration of aripiprazole 28 days after AOM 400 administration, C_{56} plasma concentration of aripiprazole 56 days after Ari 2MRTU 960 administration, *PK* pharmacokinetic

Overall, 71.1% of participants (189/266) experienced TEAEs (71.2% [94/132] in the Ari 2MRTU 960 and 70.9% [95/134] in the AOM 400 group). The incidence of serious TEAEs was similar between the two treatment groups: 4.5% (6/132) in the Ari 2MRTU 960 group and 6.0% (8/134) in the AOM 400 group. Most TEAEs were mild or moderate in severity. A summary of TEAEs and serious TEAEs is presented in Table 2, stratified by disease type.

Serious TEAEs occurring in more than one participant were auditory hallucination (two people in the Ari 2MRTU 960 group), psychotic disorder (one person in each treatment group) and akathisia (one person in each treatment group) (Table 2). There was one death (cardiac arrest) in a

Table 1 Demographics and baseline disease characteristics

	Ari 2MRTU 960			AOM 400		
	Participants with schizophrenia [$n = 92$]	Participants with BP-I [$n = 40$]	All participants [$n = 132$]	Participants with schizophrenia [$n = 93$]	Participants with BP-I [$n = 41$]	All participants [$n = 134$]
Demographic characteristics						
Age, years	48.1 (10.4)	47.2 (11.8)	47.8 (10.8)	47.7 (11.8)	44.8 (11.3)	46.8 (11.7)
≥45 [*n* (%)]	65 (70.7)	26 (65.0)	91 (68.9)	63 (67.7)	25 (61.0)	88 (65.7)
Age at diagnosis, years	27.5 (10.4)	31.3 (13.6)	28.6 (11.5)	25.8 (9.7)	32.3 (13.3)	27.8 (11.3)
Female [*n* (%)]	27 (29.3)	15 (37.5)	42 (31.8)	26 (28.0)	22 (53.7)	48 (35.8)
BMI, kg/m^2	28.2 (4.4)	28.1 (4.1)	28.2 (4.3)	29.1 (4.2)	27.2 (4.9)	28.6 (4.5)
Race [*n* (%)]						
Black or African American	80 (87.0)	19 (47.5)	99 (75.0)	77 (82.8)	18 (43.9)	95 (70.9)
White	11 (12.0)	18 (45.0)	29 (22.0)	12 (12.9)	21 (51.2)	33 (24.6)
Other	1 (1.1)	3 (7.5)	4 (3.0)	4 (4.3)	2 (4.9)	6 (4.5)
Prior aripiprazole treatment						
Oral aripiprazole	28 (30.4)	17 (42.5)	45 (34.1)	22 (23.7)	13 (31.7)	35 (26.1)
AOM 400	5 (5.4)	1 (2.5)	6 (4.5)	3 (3.2)	0 (0.0)	3 (2.2)
Took ≥1 concomitant medication [*n* (%)]	83 (90.2)	38 (95.0)	121 (91.7)	80 (86.0)	41 (100.0)	121 (90.3)
Concomitant medication taken by ≥10% of participants [*n* (%)]						
Lorazepam	38 (41.3)	17 (42.5)	55 (41.7)	29 (31.2)	20 (48.8)	49 (36.6)
Ibuprofen	22 (23.9)	7 (17.5)	29 (22.0)	22 (23.7)	13 (31.7)	35 (26.1)
Paracetamol	19 (20.7)	10 (25.0)	29 (22.0)	15 (16.1)	15 (36.6)	30 (22.4)
Quetiapine fumarate	16 (17.4)	10 (25.0)	26 (19.7)	16 (17.2)	10 (24.4)	26 (19.4)
Zolpidem tartrate	17 (18.5)	4 (10.0)	21 (15.9)	18 (19.4)	4 (9.8)	22 (16.4)
Risperidone	17 (18.5)	6 (15.0)	23 (17.4)	10 (10.8)	4 (9.8)	14 (10.4)
Zolpidem	11 (12.0)	6 (15.0)	17 (12.9)	6 (6.5)	7 (17.1)	13 (9.7)
Lisinopril	8 (8.7)	4 (10.0)	12 (9.1)	12 (12.9)	4 (9.8)	16 (11.9)
Olanzapine	8 (8.7)	3 (7.5)	11 (8.3)	12 (12.9)	4 (9.8)	16 (11.9)
Baseline disease characteristics						
PANSS Total score	62.0 (13.5)	NA	NA	61.8 (13.5)	NA	NA
CGI-S score	3.3 (0.9)	NA	NA	3.1 (0.9)	NA	NA
YMRS Total score	NA	6.7 (7.3)	NA	NA	9.4 (8.2)	NA
MADRS Total score	NA	10.9 (9.4)	NA	NA	13.5 (9.7)	NA
CGI-BP severity score (overall illness)	NA	2.4 (1.1)	NA	NA	2.8 (1.2)	NA
SWN-S Total score	94.3 (16.4)	92.1 (17.2)[a]	93.7 (16.6)[b]	95.6 (15.6)	88.6 (18.6)[c]	93.6 (16.8)[d]

Data are expressed as mean (SD), unless stated otherwise

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, *CGI-S* Clinical Global Impression—Severity, *MADRS* Montgomery–Åsberg Depression Rating Scale, *NA* not applicable, *PANSS* Positive and Negative Syndrome Scale, *SD* standard deviation, *SWN-S* Subjective Well-being under Neuroleptic Treatment— Short Form, *YMRS* Young Mania Rating Scale

[a] $n = 37$

[b] $n = 129$

[c] $n = 38$

[d] $n = 131$

Table 2 Summary of TEAEs and serious TEAEs

	Ari 2MRTU 960			AOM 400		
	Participants with schizophrenia [*n* = 92]	Participants with BP-I [*n* = 40]	All participants [*n* = 132]	Participants with schizophrenia [*n* = 93]	Participants with BP-I [*n* = 41]	All participants [*n* = 134]
Participants with TEAEs[a]	61 (66.3)	33 (82.5)	94 (71.2)	59 (63.4)	36 (87.8)	95 (70.9)
Participants with serious TEAEs[a]	5 (5.4)	1 (2.5)	6 (4.5)	5 (5.4)	3 (7.3)	8 (6.0)
Participants discontinuing due to TEAEs	3 (3.3)	1 (2.5)	4 (3.0)	7 (7.5)	3 (7.3)	10 (7.5)
TEAEs occurring in ≥5% of participants in either treatment group						
Weight increased	20 (21.7)	10 (25.0)	30 (22.7)	17 (18.3)	11 (26.8)	28 (20.9)
Injection-site pain	14 (15.2)	10 (25.0)	24 (18.2)	9 (9.7)	3 (7.3)	12 (9.0)
Akathisia	8 (8.7)	5 (12.5)	13 (9.8)	7 (7.5)	5 (12.2)	12 (9.0)
Anxiety	6 (6.5)	5 (12.5)	11 (8.3)	5 (5.4)	5 (12.2)	10 (7.5)
Insomnia	8 (8.7)	2 (5.0)	10 (7.6)	8 (8.6)	3 (7.3)	11 (8.2)
Headache	6 (6.5)	4 (10.0)	10 (7.6)	2 (2.2)	3 (7.3)	5 (3.7)
Constipation	4 (4.3)	4 (10.0)	8 (6.1)	5 (5.4)	3 (7.3)	8 (6.0)
Toothache	0 (0.0)	2 (5.0)	2 (1.5)	4 (4.3)	6 (14.6)	10 (7.5)
Serious TEAEs						
Auditory hallucination	1 (1.1)	1 (2.5)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Akathisia	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	1 (2.4)	1 (0.7)
Psychotic disorder	1 (1.1)	0 (0.0)	1 (0.8)	1 (1.1)	0 (0.0)	1 (0.7)
Adenocarcinoma of colon	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Cardiac arrest	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Cellulitis	1 (1.1)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis acute	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.7)
Depressive symptom	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.7)
Schizophrenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.7)

Data are expressed as *n* (%). Data are shown for the safety sample

AOM 400 aripiprazole once-monthly 400 mg, *Ari 2MRTU 960* aripiprazole 2-month ready-to-use 960 mg, *BP-I* bipolar I disorder, *MedDRA* Medical Dictionary for Regulatory Activities, *TEAEs* treatment-emergent adverse events

[a]Multiple occurrences of a TEAE were counted once per MedDRA preferred term. Participants experiencing TEAEs from multiple different categories were only counted once towards the total

participant with schizophrenia in the Ari 2MRTU 960 group (41 days after the participant's last dose of study drug), which was assessed as unrelated to the study drug by both the investigator and the sponsor. The participant's relevant medical history (including hypertension, diabetes mellitus, tobacco consumption, postmenopausal status, and vitamin D deficiency) was considered a potential risk factor for the reported fatal event by the investigator and the sponsor; there were no significant changes to the participant's ECG findings during the study visits compared with their ECG findings during the screening period.

The most frequently reported TEAE was increased weight, experienced by 22.7% of participants (30/132) in the Ari 2MRTU 960 group and 20.9% of participants (28/134) in the AOM 400 group.

Injection-site pain was experienced by more participants in the Ari 2MRTU 960 group (18.2% [24/132]) than in the AOM 400 group (9.0% [12/134]). Most events coincided with the first injection and resolved within 5 days (two people in each treatment group had injection-site pain lasting longer than 5 days). Overall, mean VAS scores for pain were similar between the groups at the last injection: 0.8 predose and 1.4 postdose in the Ari 2MRTU 960 group; and 0.9 predose and 1.3 postdose in the AOM 400 group (VAS range 0–100, where 0 represents no pain and 100 the worst possible pain) [29]. In > 90% of participants, the investigator's assessment of the most recent injection site was rated as 'absent' for symptoms of pain, swelling, redness, and induration after the first and last injections. All events of

injection-site pain were rated by the investigators as 'mild' or 'moderate' in intensity.

No notable improvement or decline from baseline was observed in EPS rating scale scores in either treatment group (electronic supplementary Table 3). EPS-related TEAEs were reported in 18.2% of participants (24/132) in the Ari 2MRTU 960 group and 13.4% of participants (18/134) in the AOM 400 group (electronic supplementary Table 4). The most frequently observed EPS event was akathisia, appearing in 9.8% of participants (13/132) in the Ari 2MRTU 960 group and 9.0% of participants (12/134) in the AOM 400 group (electronic supplementary Table 4). In total, 11.4% of participants (15/132) in the Ari 2MRTU 960 group and 8.2% of participants (11/134) in the AOM 400 group received anticholinergic treatments for EPS-related TEAEs.

No notable differences between groups were observed in laboratory test results, vital signs, ECG results, or suicidality.

3.3 Pharmacokinetics

Aripiprazole plasma concentrations following the fourth administration of Ari 2MRTU 960 or the seventh and eighth administrations of AOM 400 are presented in Fig. 3. PK parameters of aripiprazole following the fourth administration of Ari 2MRTU 960 or the seventh and eighth administrations of AOM 400 are presented in Table 3. GMRs and 90% CIs of PK parameters following the fourth administration of Ari 2MRTU 960 and the seventh and eighth administrations of AOM 400 are presented in Table 4. Aripiprazole plasma concentrations on the last day of the dosing interval following the fourth dose of Ari 2MRTU 960 (C_{56}) or the eighth dose of AOM 400 (C_{28}) were equivalent (GMR 1.011, 90% CI 0.893–1.145; $p = 0.0011$) (see Tables 3 and 4).

Aripiprazole exposure over the 56-day dosing interval after the fourth injection of Ari 2MRTU 960 ($AUC_{0–56}$) and the sum of exposure over the respective 28-day dosing intervals after the seventh and eighth injections of AOM 400 ($AUC_{0–28}$) were equivalent (GMR 1.006, 90% CI 0.851–1.190; $p = 0.0129$) (Tables 3 and 4). Mean aripiprazole exposure after the fourth Ari 2MRTU 960 injection was similar for the period of 0–28 days postdose and 29–56 days postdose ($AUC_{0–28}$ 7190 day·ng/mL; $AUC_{29–56}$ 7500 day·ng/mL) [Table 3], indicating aripiprazole exposure remained consistent over the entire duration of the Ari 2MRTU 960 dosing interval, and comparable with aripiprazole exposure over two AOM 400 dosing intervals.

C_{max} and PTF% were comparable for both treatment groups (Table 3).

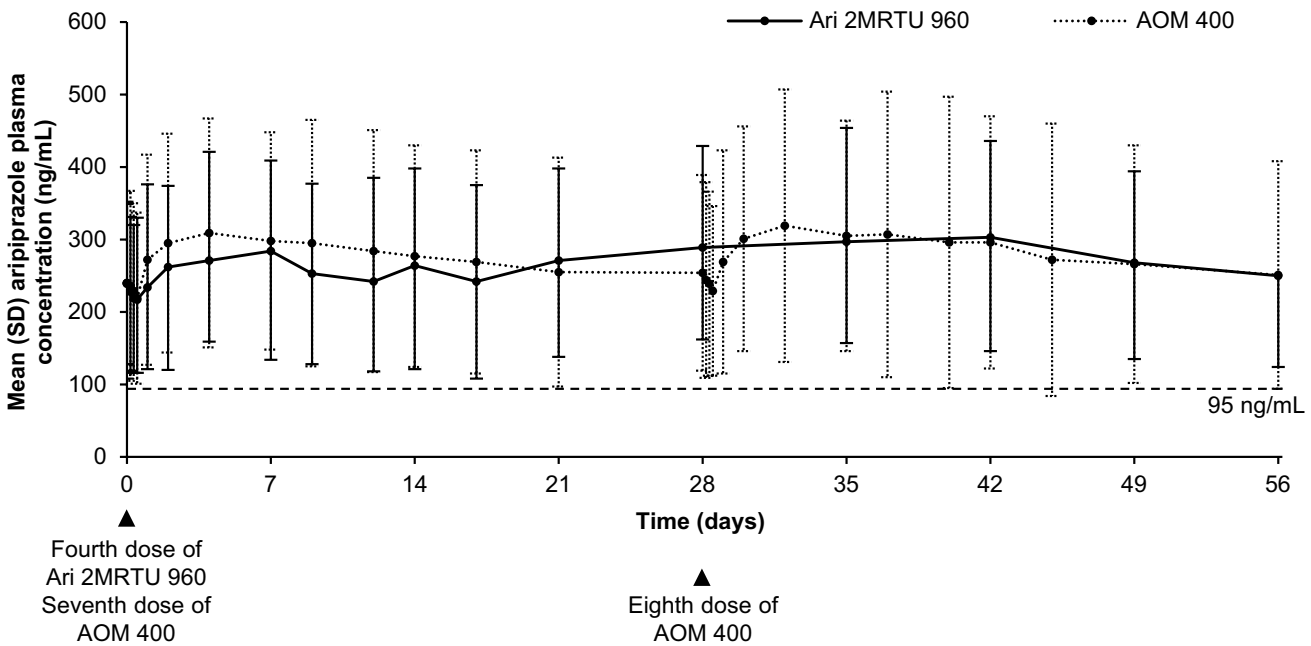

Fig. 3 Mean (SD) aripiprazole plasma concentrations after the fourth dose of Ari 2MRTU 960 versus the seventh and eighth doses of AOM 400 in adults with schizophrenia or BP-I. Ari 2MRTU 960 data are shown for 102 participants who received the fourth dose (sparse sampling schedule, $n = 67$; robust sampling schedule, $n = 35$). AOM 400 data are shown for 93 participants who received the seventh dose (sparse sampling schedule, $n = 60$; robust sampling schedule, $n = 33$), and for 91 participants who received the eighth dose (sparse sampling schedule, $n = 58$; robust sampling schedule, $n = 33$). Dotted line represents the estimated lower efficacy threshold of aripiprazole (95 ng/mL) [20]. *AOM 400* aripiprazole once-monthly 400 mg, *Ari 2MRTU 960* aripiprazole 2-month ready-to-use 960 mg, *BP-I* bipolar I disorder, *SD* standard deviation

Table 3 Aripiprazole PK parameters after the fourth dose of Ari 2MRTU 960 or the seventh and eighth doses of AOM 400 in adults with schizophrenia or BP-I

PK parameter	Ari 2MRTU 960	AOM 400	
	Fourth dose [$n = 96$]	Seventh dose [$n = 88$]	Eighth dose [$n = 82$]
C_{56}, ng/mL	250 (128)	ND	ND
C_{28}, ng/mL	ND	255 (137)	257 (162)
	[$n = 34$]	[$n = 33$]	[$n = 32$]
$AUC_{0–56,}$ day·ng/mL	14,700 (7460)	ND	ND
$AUC_{0–28,}$ day·ng/mL	7190 (3470)	7760 (4300)	7840 (5170)
$AUC_{29–56,}$ day·ng/mL	7500 (4200)	ND	ND
C_{max}, ng/mL	342 (157)	339 (168)	344 (212)
T_{max}, median days (min–max)	28.0 (0.93–49.0)	6.97 (1.05–28.0)	4.07 (0–28.0)
PTF%	63.4 (25.1)	ND	48.3 (19.0)

Data are expressed as mean (SD), unless stated otherwise

C_{56} and C_{28} values are based on data from participants randomized to the sparse and robust sampling schedules; AUC, C_{max}, T_{max}, and PTF% values are based on data from participants randomized to the robust sampling schedule only

AOM 400 aripiprazole once-monthly 400 mg, *Ari 2MRTU 960* aripiprazole 2-month ready-to-use 960 mg, *AUC* area under the concentration–time curve, $AUC_{0–28}$ AUC from Day 0 to Day 28 after study drug administration, $AUC_{0–56}$ AUC from Day 0 to Day 56 after Ari 2MRTU 960 administration, $AUC_{29–56}$ AUC from Day 29 to Day 56 after Ari 2MRTU 960 administration, *BP-I* bipolar I disorder, C_{28} plasma concentration of aripiprazole 28 days after AOM 400 administration, C_{56} plasma concentration of aripiprazole 56 days after Ari 2MRTU 960 administration, C_{max} maximum (peak) plasma concentration of the drug, *ND* not determined, *PK* pharmacokinetic, *PTF%* peak-to-trough percentage fluctuation, *SD* standard deviation, T_{max} time to maximum (peak) plasma concentration

Table 4 GMRs and 90% CIs for aripiprazole PK parameters following the fourth dose of Ari 2MRTU 960 versus the seventh and eighth doses of AOM 400

PK parameter	GMR[a]	90% CI	*p*-value[b]
AUC	1.006	(0.851–1.190)	0.0129
C_{56}/C_{28}[c]	1.011	(0.893–1.145)	0.0011
C_{max}[d]	1.071	(0.903–1.270)	0.0029

ANOVA analysis of variance, *AOM 400* aripiprazole once-monthly 400 mg, *Ari 2MRTU 960* aripiprazole 2-month ready-to-use 960 mg, *AUC* area under the concentration–time curve, C_{28} plasma concentration of aripiprazole 28 days after AOM 400 administration, C_{56} plasma concentration of aripiprazole 56 days after Ari 2MRTU 960 administration, *CI* confidence interval, C_{max} maximum (peak) plasma concentration of the drug, *GMR* geometric means ratio, *PK* pharmacokinetic

[a]GMR is derived from ANOVA for log-transformed PK parameters, including treatment formulation, PK sampling schedule (C_{56}/C_{28} only, AUC and C_{max} based on participants randomized to the robust sampling schedule only), and disease population as fixed effects

[b]*p*-value was derived from the one-sided *t*-test of treatment formulation within the specific ANOVA above to test the null hypothesis of the ratio of the PK parameter for Ari 2MRTU 960 to the PK parameter for AOM 400 ≤ 0.8

[c]GMR was calculated for C_{56} after the fourth injection of Ari 2MRTU 960 (test) to C_{28} after the eighth injection of AOM 400 (reference)

[d]GMR was calculated for C_{max} after the fourth injection of Ari 2MRTU 960 (test) to C_{max} after the eighth injection of AOM 400 (reference)

Overall, aripiprazole plasma concentrations were similar between the groups following multiple administrations of either Ari 2MRTU 960 or AOM 400 and, in most participants, trough aripiprazole plasma concentrations remained above the efficacy threshold of 95 ng/mL [20] during the entire study period, including after the first administration of either treatment (Fig. 4; electronic supplementary Table 5).

3.4 Efficacy

The trial population consisted of adults with schizophrenia or BP-I who were clinically stable at baseline. Assessments of efficacy at Week 32 showed that, on average, participants remained clinically stable throughout the treatment period of the study, with minimal change from baseline and minimal differences between treatment groups in participants with schizophrenia or BP-I (Table 5).

4 Discussion

In this study, Ari 2MRTU 960 was well tolerated, as evidenced by its discontinuation rate of 22.7% compared with 31.3% observed with AOM 400. This is similar to AOM discontinuation rates of approximately 25% observed in previous trials [25, 26].

The safety and tolerability profile of Ari 2MRTU 960 was consistent with that of AOM 400 observed in previous

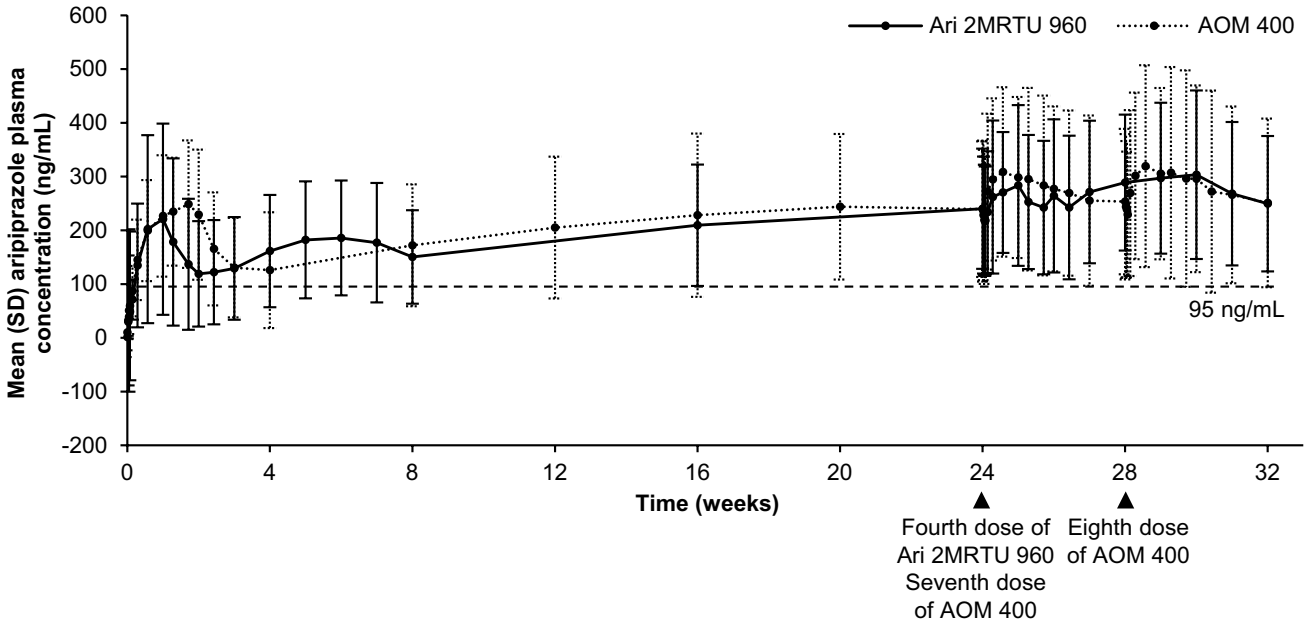

Fig. 4 Aripiprazole concentrations following the administration of four doses of Ari 2MRTU 960 or eight doses of AOM 400 over the course of 32 weeks in adults with schizophrenia or BP-I. Data for the first dose are for participants enrolled to the robust sampling schedule only (Ari 2MRTU 960, $n = 42$ [Day 0–56]; AOM 400, $n = 42$ [Day 0–28]). Data for all other timepoints are for participants enrolled to the sparse (Ari 2MRTU 960, $n = 90$; AOM 400, $n = 92$) and robust (Ari 2MRTU 960, $n = 42$; AOM 400, $n = 42$) sampling schedules. Dotted line represents the estimated lower efficacy threshold of aripiprazole (95 ng/mL) [20]. *AOM 400* aripiprazole once-monthly 400 mg, *Ari 2MRTU 960* aripiprazole 2-month ready-to-use 960 mg, *BP-I* bipolar I disorder, *SD* standard deviation

trials [25–28]. The overall incidence of TEAEs and serious TEAEs was comparable between the two treatment groups; most TEAEs were mild or moderate in severity.

While the incidence of injection-site pain with Ari 2MRTU 960 was approximately twice that of AOM 400 (18.2% vs. 9.0%), investigator and participant assessments showed that injections were associated with minimal reactions following administration. The incidence of injection-site pain following AOM 400 administration was similar to that reported for AOM 400 in previous trials (3.0–7.5%) [25, 26].

Minimal change from baseline was observed in EPS scores in both treatment groups. The most frequently observed EPS-related TEAE was akathisia, with incidence rates comparable between Ari 2MRTU 960 and AOM 400 (9.8% vs. 9.0%) and similar to the incidence rates of akathisia observed in previous AOM 400 trials (5.6–22.0%) [25, 26, 28].

Aripiprazole plasma concentrations on the last dosing interval day and aripiprazole plasma exposure over the entire dosing interval were equivalent for Ari 2MRTU 960 and AOM 400. The primary PK endpoints were thus met and the similarity of the PK profile of Ari 2MRTU 960 to that of AOM 400 was confirmed. Secondary PK parameters, including aripiprazole plasma concentration over the dosing interval following the first Ari 2MRTU 960 administration, were also comparable with those of AOM 400.

During the entirety of the individual 2-month dosing intervals following from Day 1 throughout the study period, mean aripiprazole plasma concentrations in the Ari 2MRTU 960 treatment group remained above the efficacy threshold of ≥ 95 ng/mL [20]. By maintaining aripiprazole plasma concentrations above this threshold, the risk of impending relapse is 4.41 times (95% CI 2.89–6.75) less likely compared with participants with schizophrenia with a minimum aripiprazole plasma concentration of <95 ng/mL [20]. Efficacy findings corroborated this conclusion, as participants in both treatment arms remained clinically stable after 32 weeks of treatment.

A limitation of this study is that it was conducted in the US only. In addition, the open-label design is associated with the potential of expectation bias [39]. Study strengths include the detailed evaluation of Ari 2MRTU 960 safety and tolerability parameters, detailed aripiprazole plasma concentration data collected throughout the dosing intervals of Ari 2MRTU 960 and AOM 400 due to the robust blood sampling schedule, and the large participant sample included in this phase 1b PK study.

Table 5 Efficacy outcomes at Week 32 in adults with schizophrenia or BP-I (LOCF)

	Ari 2MRTU 960		AOM 400	
	n	Mean (SD)	*n*	Mean (SD)
Schizophrenia				
SWN-S Total score				
Baseline	92	94.3 (16.4)	93	95.6 (15.6)
Change from baseline at Week 32	89	0.3 (14.8)	84	−0.8 (16.6)
PANSS Total score				
Baseline	92	62.0 (13.5)	93	61.8 (13.5)
Change from baseline at Week 32	89	− 2.6 (11.7)	85	− 1.7 (8.5)
CGI-S score				
Baseline	92	3.3 (0.9)	93	3.1 (0.9)
Change from baseline at Week 32	89	− 0.3 (0.6)	85	− 0.1 (0.7)
CGI-I score at Week 32	88	3.5 (1.0)	82	3.6 (0.9)
Bipolar I disorder				
SWN-S Total score				
Baseline	37	92.1 (17.2)	38	88.6 (18.6)
Change from baseline at Week 32	36	10.3 (16.1)	37	3.4 (21.4)
YMRS Total score				
Baseline	40	6.7 (7.3)	41	9.4 (8.2)
Change from baseline at Week 32	39	− 1.9 (7.1)	40	− 4.7 (7.7)
MADRS Total score				
Baseline	40	10.9 (9.4)	41	13.5 (9.7)
Change from baseline at Week 32	39	− 3.5 (9.1)	40	− 3.3 (12.5)
CGI-BP severity score (overall illness)				
Baseline	40	2.4 (1.1)	41	2.8 (1.2)
Change from baseline at Week 32	39	− 0.2 (1.0)	40	− 0.6 (1.2)
CGI-I score at Week 32	35	3.1 (1.2)	35	3.2 (1.5)

AOM 400 aripiprazole once-monthly 400 mg, *Ari 2MRTU 960* aripiprazole 2-month ready-to-use 960 mg, *BP-I* bipolar I disorder, *CGI-BP* Clinical Global Impression – Bipolar Version, *CGI-I* Clinical Global Impression – Improvement, *CGI-S* Clinical Global Impression – Severity, *LOCF* last observation carried forward, *MADRS* Montgomery–Åsberg Depression Rating Scale, *PANSS* Positive and Negative Syndrome Scale, *SD* standard deviation, *SWN-S* Subjective Well-being under Neuroleptic Treatment – Short Form, *YMRS* Young Mania Rating Scale

5 Conclusion

Multiple doses of Ari 2MRTU 960 were generally well tolerated in adults with schizophrenia or BP-I and did not show any new safety concerns compared with AOM 400.

The PK profile of Ari 2MRTU 960 is comparable with that of AOM 400, maintaining aripiprazole plasma concentrations above the 95 ng/mL efficacy threshold in most participants for the entire 2-month dosing interval. This finding was supported by the comparable efficacy outcomes for Ari 2MRTU 960 and AOM 400, with most participants in either treatment group remaining clinically stable throughout the treatment period of the study. In clinical practice, Ari 2MRTU 960 therefore offers an extended dosing interval compared with that of AOM 400, which may reduce burden on patients and clinicians, with the potential to improve adherence to antipsychotic treatment in adults with schizophrenia or BP-I.

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Declarations

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Conflicts of interest/disclosure Matthew Harlin, Jessica Madera-McDonough, Michael Jan, Na Jin, and Suzanne Watkin are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc. Murat Yildirim, Pedro Such, and Frank Larsen are full-time employees of H. Lundbeck A/S.

Author contributions Matthew Harlin and Frank Larsen participated in trial conception and design. All authors were involved in data collection and/or analysis; participated in the drafting or critical review of the article; gave final approval of the version to be published; and agree to be accountable for all aspects of this work.

Data availability statement To submit inquiries related to Otsuka clinical research, or to request access to individual participant data (IPD) associated with any Otsuka clinical trial, please visit https://clinicaltrials.otsuka.com/. For all approved IPD access requests, Otsuka will share anonymized IPD on a remotely accessible data-sharing platform.

Ethics approval The study was conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines and local regulatory requirements. The study protocol was approved by the governing Institutional Review Board or independent Ethics Committee for each investigational site.

Consent to participate All study participants provided written informed consent prior to the start of the study.

Consent for publication Not applicable.

Code availability Not applicable.

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