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Supplementary Material

Article Title: Safety and Efficacy of Aripiprazole 2-Month Ready-to-Use 960 mg: Secondary Analysis of Outcomes in Adult Patients With Schizophrenia in a Randomized, Open-label, Parallel-Arm, Pivotal Study

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Supplementary Figure 1 Study design

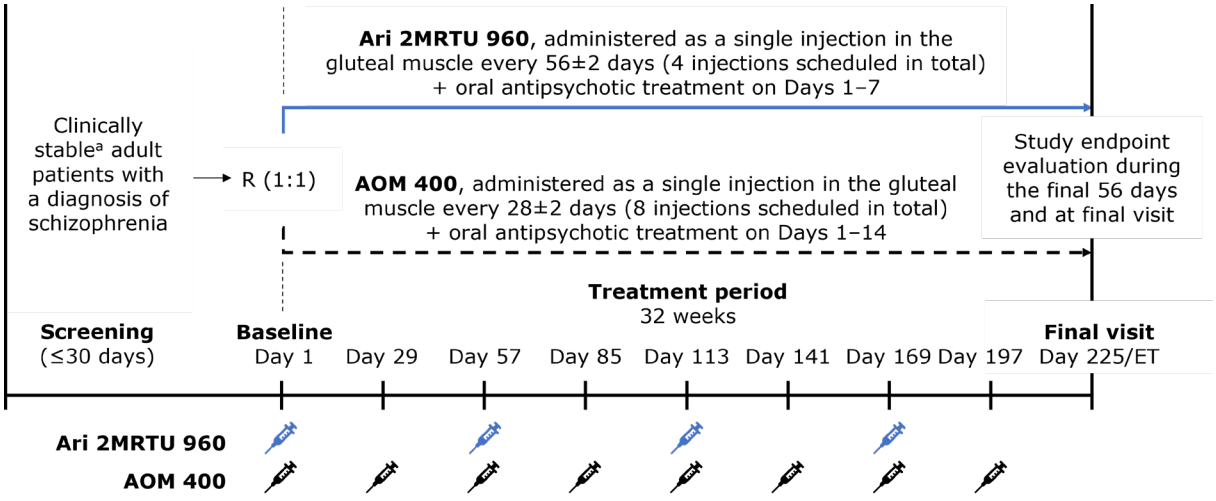

Figure adapted from Harlin et al. (2023).[1]

Patients received overlapping oral antipsychotic treatment (on Days 1 to 7 in the Ari 2MRTU 960 group and on Days 1 to 14 in the AOM 400 group) to transition from their current oral antipsychotic treatment to the study drug. Patients stabilized on a non-aripiprazole oral antipsychotic who were enrolled to the sparse (less frequent) pharmacokinetic sampling schedule continued their medication, while those enrolled to the robust (more frequent) sampling schedule switched to 10–20 mg/day oral aripiprazole. Patients stabilized on oral aripiprazole received 10 mg/day with the first dose of the study drug if their previous dose was 10–20 mg/day, or 15 mg/day if their previous dose was >20–30 mg/day. No overlapping oral antipsychotic treatment was given to patients stabilized on AOM 400.

[a]Based on investigator judgment, patient/caregiver report, and/or documentation.

Abbreviations: AOM 400=aripiprazole once-monthly 400 mg; Ari 2MRTU 960=aripiprazole 2-month ready-to-use 960 mg; ET=early termination; R=randomization.

Supplementary Table 1 Overview of the scales used for the evaluation of efficacy endpoints

CGI-I Scale	The CGI-I scale is a 7-point scale requiring the clinician to compare patient's overall clinical condition to the one-week period just prior to the initiation of the medication the patient is currently receiving, ranging from 1 (very much improved since the initiation of treatment) to 7 (very much worse since the initiation of treatment).[3]
CGI-S Scale	The CGI-S is a 7-point scale requiring the clinician to rate the severity of the patient's illness at the time of assessment relative to the clinician's past experience of patients with this particular patient population, ranging from 1 (normal, not at all ill) to 7 (extremely ill).[2] The rating is based on observed and reported symptoms, behavior, and function in the last seven days.[3]
PANSS Scale	The PANSS was developed to evaluate the representation of positive and negative symptoms experienced by patients with schizophrenia, and assess their relationship to one another and the overall psychopathology present.[4] The scale consists of 30 items with a 7-point symptom rating system ranging from 1 (absent) to 7 (extreme), with higher scores representing increasing levels of psychopathology.[4]
SWN-S Scale	The SWN-S is a self-report instrument for patients with schizophrenia used to evaluate their subjective well-being under neuroleptic treatment.[5] Constructed following an item analysis based on SWN data from 212 patients with schizophrenia receiving antipsychotic treatment, the SWN-S is comprised of five subscales: mental functioning, social integration, emotional regulation, physical functioning, and self-control.[5] Each subscale has four items (thus, 20 items in total), to be rated on a 6-point Likert scale, and the scores from each subscale are combined to provide an SWN-S Total score.[5] Items refer to the last seven days and are formulated to be clear and easy to understand, so that the questionnaire can be completed within 10–15 minutes.[5] Total scores range from 20 to 120 points, with higher scores indicative of greater well-being.[6]

Abbreviations: CGI-I=Clinical Global Impression – Improvement; CGI-S=Clinical Global Impression – Severity; PANSS=Positive and Negative Syndrome Scale; SWN=Subjective Well-being under Neuroleptic Treatment; SWN-S=Subjective Well-being under Neuroleptic Treatment – Short Form.

Supplementary Table 2 Schedule of safety and efficacy assessments for patients with schizophrenia

	Screening	Day 1	Day ±2											
	Day -30 to -1	Day 1	8, 15, 22	29	36[a] 43[a] 50[a]	57	85	113	141	169	176[b] 183[b] 190[b]	197	204 211 218	225 /ET
Safety assessments														
12-lead ECG	X	X	X (Day 15)	X		X		X						X
Assess and record AEs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X[d]	X	X	X	X	X	X	X	X[d]	X	X[d]	X
Hematology, clinical chemistry and urinalysis	X	X		X										X
Investigator assessment of injection site		X		X[e]		X	X[e]	X	X[e]	X		X[e]		
Motoric assessments (SAS, AIMS, BARS)	X	X	X	X		X	X	X	X	X		X		X
Physical examination	X	X	X (Day 15)	X				X						X
VAS (perceived pain at injection site)		X		X[e]		X	X[e]	X	X[e]	X		X[e]		
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X		X		X	X	X	X	X		X		X
Efficacy assessments														
PANSS	X	X		X		X		X		X		X		X
CGI-S	X	X		X		X		X		X		X		X
SWN-S	X	X		X		X		X		X		X		X
CGI-I						X								X

[a]Patients receiving Ari 2MRTU 960 only.

[b]In patients randomized to the sparse (less frequent) sampling group, evaluations of AEs, C-SSRS and vital signs on Days 176, 183, and 190 were carried out only in patients receiving Ari 2MRTU 960.

[c]In patients randomized to the robust (more frequent) sampling group, AEs were also assessed and recorded on Days 2, 3, 5, 10, 13, 18, 170, 171, 173, 178, 181, and 186, with patients receiving AOM 400 also having AEs assessed and recorded on Days 198, 199, 201, 206, 209, and 214.

[d]In patients randomized to the robust (more frequent) sampling schedule, C-SSRS was not evaluated on Days 8, 15, 176 and 183. On Days 204 and 211, C-SSRS was evaluated only in patients receiving Ari 2MRTU 960.

[e]Patients receiving AOM 400 only.

[f]Assessment of vital signs included systolic and diastolic blood pressure, heart rate, and body temperature. Vital signs were obtained prior to pharmacokinetic blood draws according to the sparse (less frequent) or robust (more frequent) sampling schedule, and prior to ECGs at the nominal time points, where applicable. In patients from either treatment group randomized to the robust sampling group, vital signs were also assessed on Days 2, 3, 5, 10, 13, 18, 170, 171, 173, 178, 181, and 186, with patients receiving AOM 400 also having vital signs evaluated on Days 198, 199, 201, 206, 209, and 214. At each time point, blood pressure (systolic and diastolic) and heart rate were taken after patients had been in the supine position for at least 5 minutes and again after subjects had been standing for 2 minutes, but not more than 3 minutes. Body temperature was taken with the patient in the supine position (i.e., only once).

Abbreviations: AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; AOM 400=aripiprazole once-monthly 400 mg; Ari 2MRTU 960=aripiprazole 2-month ready to use 960 mg; BARS=Barnes Akathisia Rating Scale; CGI-I=Clinical Global Impression – Improvement; CGI-S=Clinical Global Impression – Severity; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; PANSS=Positive and Negative Syndrome Scale; SAS=Simpson–Angus Scale; SWN-S=Subjective Well-being under Neuroleptic Treatment – Short Form; VAS=Visual Analog Scale.

Supplementary Table 3 ECG results reported for the patient with schizophrenia who experienced cardiac arrest with a fatal outcome on Day 211 of the study

Day	Overall interpretation	Findings
-20	Abnormal[a]	ST segment, T wave, and U wave: depressed Atrioventricular conduction: first degree AV block ST segment, T wave, and U wave: inverted
1	Abnormal	Atrioventricular conduction: first degree AV block ST segment, T wave, and U wave: inverted ST segment, T wave, and U wave: prolonged QTc
15	Abnormal	ST segment, T wave, and U wave: depressed ST segment, T wave, and U wave: inverted
29	Abnormal	ST segment, T wave, and U wave: depressed ST segment, T wave, and U wave: inverted
57	Abnormal	ST segment, T wave, and U wave: depressed Atrioventricular conduction: first degree AV block ST segment, T wave, and U wave: inverted
113	Abnormal	ST segment, T wave, and U wave: inverted

[a]The ECG abnormalities identified at screening were assessed as not clinically significant or exclusionary for participation by the investigator.

Abbreviations: AV=atrioventricular; ECG=electrocardiogram.

Supplementary Table 4 Motoric scale scores at baseline and change from baseline at Week 32 in patients with schizophrenia (LOCF)[a]

	Ari 2MRTU 960		AOM 400	
	n	**Mean (SD)**	**n**	**Mean (SD)**
SAS Total Score				
Baseline[b]	92	0.2 (0.5)	93	0.1 (0.4)
Change from baseline at Week 32	92	0.1 (0.6)	92	0.1 (0.6)
AIMS Movement Score				
Baseline[b]	92	0.1 (0.4)	93	0.2 (0.8)
Change from baseline at Week 32	92	0.0 (0.4)	92	-0.1 (0.7)
BARS Global Score				
Baseline[b]	92	0.0 (0.3)	93	0.0 (0.3)
Change from baseline at Week 32	92	0.2 (0.6)	92	0.0 (0.2)

[a]Data are for the safety sample.

[b]Baseline values are scores recorded at the last predose evaluation.

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; AOM 400=aripiprazole once-monthly 400 mg; Ari 2MRTU 960=aripiprazole 2-month ready-to-use 960 mg; BARS=Barnes Akathisia Rating Scale; LOCF=last observation carried forward; SAS=Simpson-Angus Scale; SD=standard deviation.

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