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Research report

# Aripiprazole augmentation to antidepressant therapy in Japanese patients with major depressive disorder: A randomized, double-blind, placebo-controlled study (ADMIRE study)☆☆

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ABSTRACT

*Objective:* This randomized, placebo-controlled study evaluated the efficacy and safety of a fixed dose (3 mg/day) and flexible dose (3–15 mg/day) schedule of aripiprazole as augmentation therapy in Japanese patients with inadequate response to antidepressant therapy (ADT).

*Method:* During an 8-week prospective treatment phase, patients experiencing a major depressive episode received clinicians' choice of ADT. Subjects with inadequate response to ADT were randomized to receive adjunctive treatment with placebo ($n=195$), fixed dose aripiprazole ($n=197$) or flexible dose aripiprazole ($n=194$) for 6 weeks. The primary efficacy endpoint was mean change in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score from the end of prospective treatment (baseline) to the end of randomized treatment.

*Results:* More than 90% of patients in all treatment groups completed the 6-week double-blind treatment phase. Mean MADRS total score was improved to a significantly greater extent with fixed dose aripiprazole and flexible dose aripiprazole (−10.5 and −9.6, respectively) than with placebo (−7.4). Aripiprazole was well tolerated. The incidence of akathisia observed in the flexible dose group may relate to a higher prevalence of the CYP2D6*10 allele in Asian populations.

*Limitations:* Six weeks of adjunctive treatment is insufficient to draw conclusions about the long-term benefits of aripiprazole. Exclusion of patients with established medical comorbidities does not reflect real-world practice.

*Conclusions:* Aripiprazole augmentation at a fixed or flexible dose was superior to ADT alone and was reasonably well tolerated in Japanese patients with inadequate response to ADT.

*Clinical trials registration:* ClinicalTrials.gov identifier NCT00876343.



## 1. Introduction

Approximately 60% patients with major depressive disorder (MDD) do not achieve a sufficient response to standard antidepressant therapy (ADT) and about two-thirds of patients receiving initial ADT do not achieve timely remission (Fava, 2003; Rush et al., 2006). An augmentation strategy using atypical antipsychotics for treatment-resistant depression (TRD) is a widely used and promising approach in this clinical situation, and is supported by the results of a meta-analysis (Nelson and Papakostas, 2009) and major treatment guidelines, including those of the Canadian Network for Mood and Anxiety Treatments (Lam et al., 2009) and the American Psychiatric Association (2010).

Aripiprazole was the first atypical antipsychotic approved by the United States (US) Food and Drug Administration (FDA) for adjunctive treatment of MDD in patients showing inadequate response to ADT. Starting doses of aripiprazole are 2–5 mg/day and the recommended

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therapeutic doses range from 5 to 10 mg/day. The maximum dose is 15 mg/day based on results of two large, multicenter, randomized, double-blinded, placebo-controlled studies conducted in the US (Berman et al., 2007; Marcus et al., 2008).

Aripiprazole is approved for use in some Asian countries (e.g. South Korea and Taiwan), although approval was granted based on studies conducted in predominantly Caucasian populations (Berman et al., 2007, 2009; Marcus et al., 2008). To date, no adequately controlled clinical studies have investigated the efficacy and tolerability of aripiprazole specifically in Asian patients with MDD. As genetic/racial variations can cause differences in the metabolism of antipsychotic medications (Malhotra et al., 2004), which in turn may impact on treatment response and adverse event risk, it is important to study new treatment options in specific populations.

A lower prevalence of MDD (1–7%) has been reported in Asian countries such as Japan, Korea, and Taiwan relative to western countries (Kawakami et al., 2005, Cho et al., 2012), yet suicide rates in Japan and Korea are among the highest in the world (Värnik, 2012). MDD is an important risk factor for suicide and more than 50% of suicides met the diagnostic criteria for MDD according to a psychological autopsy study (McGirr et al., 2006).

The Aripiprazole Depression Multicenter Efficacy (ADMIRE) study was designed to evaluate the efficacy and safety of aripiprazole augmentation in Japanese patients with MDD. Considerable variability is known to exist among individuals in terms of their response to antidepressants; optimal doses may differ per patient and dosages may require frequent adjustments to strike a balance between efficacy and tolerability. In the current study, a flexible dose of 3–15 mg/day was set to assess the efficacy of augmentation therapy in conditions more closely simulating usual clinical practice. A fixed dose of aripiprazole 3 mg/day was also set to assess whether this starting dose was effective. Results of the trial were intended for regulatory submission of aripiprazole augmentation for treatment of MDD in Japan.

## 2. Methods

### 2.1. Patients

Patients eligible for enrollment in the screening phase were required to be 20–65 years of age who met DSM-IV-TR criteria for MDD as a primary diagnosis and who had a score of $\geq 18$ on the 17-item Hamilton Depression Rating Scale (HAM-D17; Hamilton, 1960). Patients were also required to have had a major depressive episode that had lasted $\geq 8$ weeks prior to inclusion without adequate response to 1–3 antidepressant trials of at least 6-weeks' duration.

Patients were excluded if they had a current Axis I diagnosis of delirium, dementia, amnestic or other cognitive disorders, schizophrenia or other psychotic disorders, bipolar disorders, eating disorders, obsessive–compulsive disorder, panic disorder, posttraumatic stress disorder, or substance use disorders; or, a current Axis II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorders. Patients experiencing hallucinations, delusions, or any psychotic symptomatology in the current depressive episode were also excluded. Patients were excluded if they had an Item suicide (No. 11) score in HAM-D17 of $\geq 3$ and posed a suicidal risk.

In addition, patients were excluded if they had received electroconvulsive therapy; treatment with aripiprazole in past years; adjunctive antipsychotic (except sulpiride at a dose $\leq 300$ mg/day) or psychostimulant during the current episode; treatment with monoamine oxidase inhibitor within 2 weeks prior to the prospective treatment phase, and with benzodiazepines (except short-acting benzodiazepines) within 1 week prior to the prospective treatment phase; participated in a clinical trial with aripiprazole in past years and with other investigational product within the past month; had a history of neuroleptic malignant syndrome, serotonin syndrome, and seizure disorder; had required hospitalization in the current episode during the screening phase.

### 2.2. Study design

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 169 sites in Japan between April 2009 and January 2012, in accordance with the Declaration of Helsinki. Prior to study entry, all patients provided written informed consent after receiving explanation of the study procedure and potential risks.

The study consisted of 3 phases. Patients first entered a 1–28 day screening phase in which prohibited psychotropic medications (ADTs, benzodiazepines, and most hypnotic agents) were discontinued. Those patients experiencing a major depressive episode, which was defined as a total score of $\geq 18$ on HAM-D17 at the end of the screening phase, qualified for an 8-week, single-blind, prospective treatment phase. This phase was designed to establish that patients had an inadequate response to standard ADT before being randomized to adjunctive aripiprazole or placebo. During this phase, all patients received single-blind ADT (investigators, but not patients, knew of the treatment assignment), and adjunctive placebo, so that patients were unaware of transition into the randomization phase. All patients received ADT in accordance with current product labeling, based on the investigator's judgment from the subject's clinical response and tolerability.

Patients meeting the criteria for inadequate response ($< 50\%$ reduction in the HAM-D17 total score from baseline to the end of the prospective treatment phase; a HAM-D17 total score of $\geq 14$; or a Clinical Global Impression-Improvement (CGI-I; Guy, 1976a) score of $\geq 3$ were eligible to enter a 6-week, randomized, double-blind phase (actual study visits, weeks 8–14), in which participants were randomly assigned in a 1:1:1 ratio to continue the same ADT (no dose adjustment was permitted) plus either adjunctive placebo, adjunctive aripiprazole at a fixed dose (3 mg/day), or adjunctive aripiprazole at a flexible dose (3–15 mg/day).

### 2.3. Dosing schedule for double-blind treatment

Patients randomized to the aripiprazole flexible dose group started with a dose of 3 mg/day; investigators could increase the dose by 3 mg/day once per week to a maximum of 15 mg/day if well tolerated. Patients assigned to the aripiprazole fixed dose group also started with a dose of 3 mg/day. If patients did not respond, investigators could increase placebo tablets once per week to a maximum of 5 tablets, equivalent to 15 mg/day. Similarly, patients assigned to the placebo group started with one placebo tablet and, if patients did not respond, investigators could increase placebo tablets once per week to a maximum of 5 tablets, equivalent to 15 mg/day. Dose reduction for tolerability reasons was permitted at any visit. No dose increase was permitted in the last week of the study.

### 2.4. Assessments

The primary efficacy endpoint was mean change in the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) total score from the end of the prospective treatment phase (week 8 visit) to the end of the randomized, double-blind treatment phase (week 14, last observation carried forward [LOCF]). A key secondary endpoint was mean change in the Sheehan Disability Scale (SDS; Leon et al., 1992) score during the randomized, double-blind phase. The SDS evaluates the extent to which depression interferes with work, family and social life; each aspect is scored on a scale from 0 (not at all) to 10 (extreme),

and a mean score of 0–10 is generated from the individual items. Other secondary efficacy measures included mean change in the MADRS total score by week, the CGI-I and CGI Severity of Illness (CGI-S; Guy, 1976a), and the HAM-D17 total score. Furthermore, MADRS response and remission rates were assessed. Response was defined as a reduction in the MADRS total score of at least 50% relative to the end of the prospective treatment phase. Remission was defined as a response plus an absolute MADRS total score of $\leq 10$. CGI-I response was defined as the proportion of patients with CGI-I scores of 1 and 2.

Safety was evaluated by monitoring adverse events (AEs), body weight, vital signs, laboratory parameters, and 12-lead electrocardiography. In addition, evaluations of extrapyramidal symptoms included changes in the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS; Inada, 2009), the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976b), and the Barnes Akathisia Clinical Assessment (BARS; Barnes, 1989).

### 2.5. Statistical analyses

The randomized sample comprised all patients who were randomized in the double-blind treatment phase. The efficacy sample included all patients who had received at least one dose of double-blind study medication and for whom at least one post-randomization efficacy evaluation had been obtained. The safety sample included randomized patients who had received at least one dose of double-blind study medication and for whom at least one safety evaluation had been obtained. Analyses were conducted using LOCF data.

The primary efficacy outcome measure, mean change in the MADRS total score from end of the prospective treatment phase to end of the double-blind treatment phase, was assessed by analysis of covariance (ANCOVA) with the score at the end of the prospective treatment phase as a covariate and treatment as a factor. CGI-S scores, SDS scores and HAM-D17 total scores were evaluated using ANCOVA, with the score at the end of prospective treatment phase as a covariate and treatment as a factor. MADRS response and remission rates, and CGI-I response between the treatment and placebo groups were compared using Chi-square tests. The results of all statistical tests were interpreted at the 5% significance level.

## 3. Results

### 3.1. Patient disposition

In total, 1388 patients were screened, of whom 1115 were eligible to enter the prospective treatment phase; 869 patients completed this treatment phase (Fig. 1). Of these, 283 patients met the criteria for response during prospective ADT treatment (HAM-D17 improvement $\geq 50\%$, HAM-D17 $< 14$, or CGI-I $< 3$) and did not proceed to the double-blind treatment phase. Of 586 patients randomized in the double-blind treatment phase, 195 received adjunctive placebo, 197 received adjunctive fixed dose (3 mg/day) of aripiprazole and 194 received adjunctive flexible dose (3–15 mg/dy) of aripiprazole. The randomized, double-blind treatment phase was completed by 91–93% of patients in all treatment groups. Reasons for treatment discontinuation are provided in Fig. 1.

Treatment groups were well balanced with respect to baseline demographics and disease characteristics (Table 1). All participants were Japanese. At the time of randomization to double-blind treatment, the overall distribution of specific ADTs was as follows: sertraline, 38.4%; fluvoxamine, 20.0%; paroxetine, 19.3%; milnacipran, 12.8%; and duloxetine, 9.6%. The distribution was representative of ADTs selected during the initial prospective treatment phase and was similar among placebo and aripiprazole treatment arms (data not shown).

The mean dose of adjunctive aripiprazole in the flexible group at endpoint was 9.8 mg/day. The distribution of adjunctive aripiprazole dose at endpoint was as follows: 3 mg/day, 16.5%; 6 mg/day, 20.6%; 9 mg/day, 14.4%; 12 mg/day, 16.0% and 15 mg/day, 32.5%. For patients in the fixed dose group and placebo group, mean dose equivalents (based on number of tablets) were 10.1 mg/day and 12.3 mg/day, respectively.

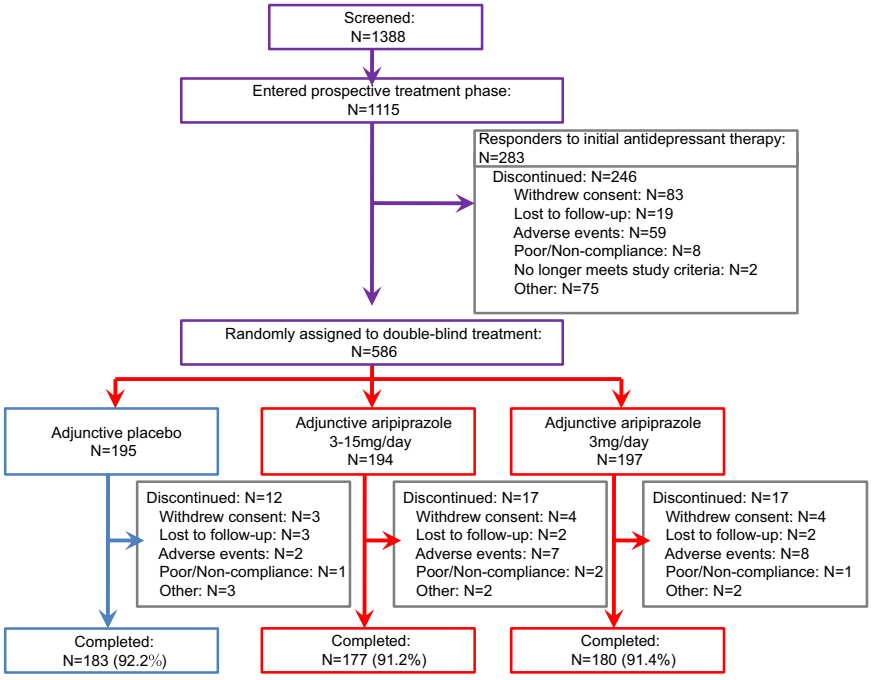


**Fig. 1.** Patient disposition.

**Table 1**
Baseline demographic and clinical characteristics of randomized patients.

| Characteristics | Aripiprazole | | placebo ($n=195$) |
|---|---|---|---|
| | 3–15 mg/day ($n=194$) | 3 mg/day ($n=197$) | |
| Gender, male, *n* (%) | 101 (52.1) | 124 (62.9) | 115 (59.0) |
| Age, mean (SD), years | 38.1 (9.6) | 39.2 (9.1) | 38.7 (9.2) |
| Weight, mean (SD), kg | 62.5 (14.1) | 65.1 (14.7) | 63.7 (14.2) |
| Duration of the current episode (mons) | 17.5 (26.1) | 15.7 (21.6) | 15.6 (16.4) |
| No. of adequate antidepressant trials in the current episode, *n* (%) | | | |
| 1 trial | 119 (61.3) | 130 (66.0) | 124 (63.6) |
| 2 trials | 54 (27.8) | 53 (26.9) | 49 (25.1) |
| 3 trials | 21 (10.8) | 14 (7.1) | 22 (11.3) |
| 4 trials or more | 0 (0) | 0 (0) | 0 (0) |
| Depressive episode, *n* (%) | | | |
| Single | 102 (52.6) | 122 (61.9) | 113 (57.9) |
| Recurrent | 92 (47.4) | 75 (38.1) | 82 (42.1) |
| MADRS total score, mean (SD) | 25.3 (7.3) | 25.2 (7.2) | 25.5(7.4) |

*Abbreviations*: SD=standard deviation, MADRS=Montgomery–Åsberg Depression Rating Scale, CGI-S= =Clinical Global Impressions-Severity of Illness, HAMD-17=17-item Hamilton Depression Rating Scale for Depression.

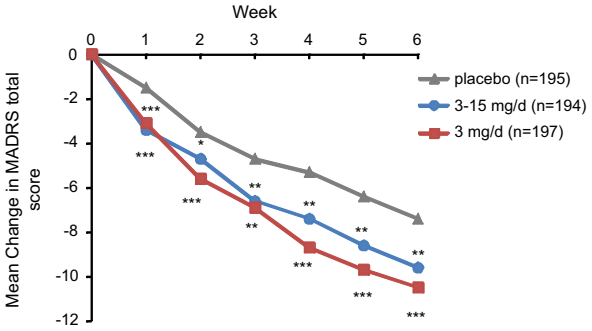


**Fig. 2.** Mean change in Montgomery–Åsberg Depression Rating Scale (MADRS) total score from baseline in the randomized, double-blind treatment phase (LOCF). * $p<0.05$; ** $p<0.01$; *** $p<0.001$ vs adjunctive placebo (ANCOVA). Mean baseline MADRS total scores: aripiprazole 3–15 mg/day 25.3; 3 mg/day 25.2; placebo 25.5.

### 3.2. Efficacy

Patients who received either the adjunctive fixed dose or flexible dose of aripiprazole experienced significantly greater improvement in their mean MADRS total score (−10.5 and −9.6, respectively) at study endpoint than patients treated with adjunctive placebo (MADRS total score, −7.4) (Fig. 2). MADRS response rates at week 6 were significantly higher in the adjunctive aripiprazole groups (39.2% for flexible dose; 42.1% for fixed dose) than in the adjunctive placebo group (28.2%) (Fig. 3A). Remission rates were also significantly higher in the adjunctive aripiprazole groups (30.4% for flexible dose; 32.5% for fixed dose) than in the adjunctive placebo group (20.5%) at week 6 (Fig. 3B).

Significantly greater improvement in the mean SDS score was noted with adjunctive aripiprazole (−1.03 for flexible dose; −0.96 for fixed dose) compared with adjunctive placebo (−0.46) at endpoint ($p<0.01$, Table 2). Significant improvements over adjunctive placebo were observed with both fixed dose and flexible dose adjunctive aripiprazole in all sub-score items (work/school, $p<0.01$; social life, $p<0.01$; family, $p<0.01$). Both adjunctive aripiprazole regimens also produced significantly greater improvements in CGI-S scores ($p<0.05$), CGI-I response rate ($p<0.05$), and HAM-D17 total score ($p<0.01$) than adjunctive placebo (Table 2).

### 3.3. Safety and tolerability

#### 3.3.1. Adverse events

During the double-blind phase, 117 (60.0%) patients in the placebo group, 141 (71.6%) patients in the aripiprazole fixed dose group, and 151 (77.8%) patients in the aripiprazole flexible dose group experienced at least 1 AE. AEs experienced at an incidence of ≥5% in either aripiprazole group and at least twice that of the placebo group are shown in Table 3. The most common AEs in the aripiprazole groups were akathisia and tremor, and the incidence was higher in the flexible dose vs fixed dose group (Table 3). The majority of AEs were mild (aripiprazole flexible dose 59.3%, fixed dose 54.8%, placebo 48.7%) or moderate (17.0%, 15.7%, 10.8%) in severity. Serious AEs occurred in 3 patients (1.5%) in the placebo

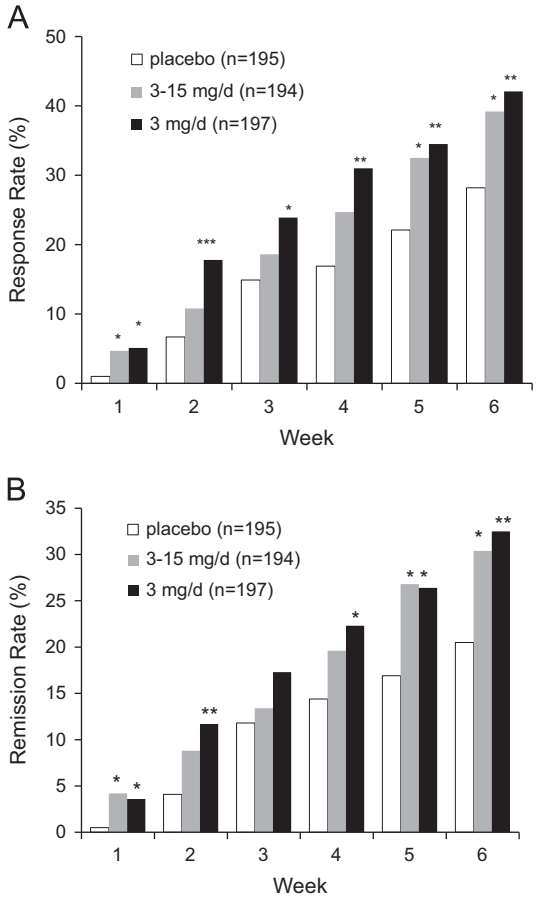


**Fig. 3.** Response rates (A) and remission rates (B) with adjunctive placebo or adjunctive aripiprazole during the double-blind treatment phase (LOCF). * $p<0.05$; ** $p<0.01$; *** $p<0.001$ vs adjunctive placebo group ($\chi^2$ test).

group, 2 patients (1.0%) in the adjunctive aripiprazole fixed dose group, and 3 patients (1.5%) in the adjunctive aripiprazole flexible dose group; no deaths were reported.

Discontinuation due to AEs in the double-blind treatment phase occurred in 2 patients (1.0%) in the placebo group, 5 patients (2.5%) in the aripiprazole fixed dose group, and 5 patients (2.6%) in the aripiprazole flexible dose group. Patients who experienced AEs leading to dose reduction were 6 (3.1%) in the placebo group, 17 (8.6%) in the aripiprazole fixed dose group and 33 (17.0%) in the aripiprazole flexible dose group.

### 3.3.2. Extrapyramidal symptoms

Akathisia and AEs related to extrapyramidal symptoms during the double-blind phase were examined with AIMS, BARS, and DIEPSS. Mean changes in AIMS total scores did not differ significantly between aripiprazole and placebo groups, and only minimal but significant changes from end of the prospective treatment phase to study endpoint were noted in BARS Global Clinical Assessment of Akathisia scores (aripiprazole flexible dose group $0.3 \pm 0.0$ vs placebo group $0.0 \pm 0.0$; $p < 0.001$). A significant difference in the DIEPSS total score at endpoint (LOCF) was found between placebo group ($0.1 \pm 0.1$) and both aripiprazole groups (flexible dose, $0.7 \pm 0.1$, $p < 0.001$; fixed dose, $0.3 \pm 0.1$, $p = 0.042$).

The majority of patients with akathisia rated the severity as either mild (aripiprazole flexible dose 78.9%, fixed dose 75.0%, placebo 100.0%) or moderate (21.1%, 25.0%, 0.0%). For patients in the aripiprazole flexible dose group and fixed dose group in whom akathisia occurred, 29.6% and 10.7% received dose reduction, and 45.1% and 46.4% used an anti-Parkinsonian drug, respectively.

### 3.3.3. Weight gain and laboratory results

The mean weight change during the double-blind phase was significantly greater in the adjunctive aripiprazole groups (flexible dose, $1.63 \pm 0.13$ kg, $p < 0.001$; fixed dose, $1.68 \pm 0.13$ kg, $p < 0.001$) than in the adjunctive placebo group ($0.44 \pm 0.13$ kg) (LOCF). A statistically significant difference was also noted in the proportion of patients who showed clinically significant weight gain ($\geq 7\%$ from the double-blind baseline; LOCF) (placebo, 1.6%; aripiprazole fixed dose, 8.1%, $p = 0.003$; aripiprazole flexible dose, 10.4%, $p < 0.001$).

There were no clinically meaningful differences between aripiprazole groups and placebo group in vital signs, electrocardiographic findings or laboratory values. Mean change in blood glucose levels during the double-blind phase did not increased in the adjunctive aripiprazole groups (flexible dose −0.4 mg/dL; fixed dose −2.9 mg/dL) and adjunctive placebo group (−1.3 mg/dL). Mean serum prolactin levels for aripiprazole and placebo groups were within the normal range at baseline and at the end of the prospective phase. A small reduction in prolactin levels was noted in the adjunctive aripiprazole groups compared with no change in the adjunctive placebo group.

**Table 3**
Adverse events occurring during the double-blind phase.

| Adverse event | Aripiprazole | | | | Placebo | |
|---|---|---|---|---|---|---|
| | 3–15 mg/day ($n=194$) | | 3 mg/day ($n=197$) | | ($n=195$) | |
| | *n* | (%) | *n* | (%) | *n* | (%) |
| Akathisia | 71 | (36.6) | 28 | (14.2) | 8 | (4.1) |
| Tremor | 20 | (10.3) | 14 | (7.1) | 5 | (2.6) |
| Constipation | 15 | (7.7) | 7 | (3.6) | 4 | (2.1) |
| Dry mouth | 13 | (6.7) | 10 | (5.1) | 3 | (1.5) |
| Increased Alanine Aminotransferase | 13 | (6.7) | 14 | (7.1) | 3 | (1.5) |
| Weight gain | 12 | (6.2) | 8 | (4.1) | 1 | (0.5) |
| Insomnia | 10 | (5.2) | 8 | (4.1) | 3 | (1.5) |
| Increased Aspartate Aminotransferase | 8 | (4.1) | 10 | (5.1) | 1 | (0.5) |
| Increased blood creatine phosphokinase | 6 | (3.1) | 10 | (5.1) | 0 | (0.0) |

Occurring at an incidence of >5% in either group and at least twice that of the placebo group with aripiprazole.

**Table 2**
Mean change in secondary efficacy outcomes at the end of randomized, double-blind phase (LOCF).

| Rating Scale[a] | Aripiprazole | | | | Placebo |
|---|---|---|---|---|---|
| | 3–15 mg ($n=194$) | *p* value | 3 mg ($n=197$) | *p* value | ($n=195$) |
| SDS mean score , mean (SE) | | | | | |
| Double-blind baseline | 5.0 (0.1) | <0.001[c] | 5.0 (0.1) | 0.001[c] | 5.3 (0.1) |
| Change to Week 6 | −1.0 (0.1)[e] | | −1.0 (0.1) | | −0.5 (0.1)[e] |
| SDS Work/School score, mean (SE) | | | | | |
| Double-blind baseline | 5.4 (0.2) | <0.001[c] | 5.4 (0.2) | 0.003[c] | 5.6 (0.2) |
| Change to Week 6 | −1.0 (0.1)[e] | | −0.9 (0.1) | | −0.4 (0.1)[e] |
| SDS Social Life score, mean (SE) | | | | | |
| Double-blind baseline | 5.5 (0.2) | <0.001[c] | 5.2 (0.2) | 0.003[c] | 5.6 (0.2) |
| Change to Week 6 | −1.2 (0.1)[e] | | −1.1 (0.1) | | −0.6 (0.1)[e] |
| SDS Family score, mean (SE) | | | | | |
| Double-blind baseline | 4.3 (0.2) | 0.003[c] | 4.4 (0.2) | 0.003[c] | 4.7 (0.2) |
| Change to Week 6 | −0.9 (0.1)[e] | | −0.9 (0.1) | | −0.3 (0.1)[e] |
| CGI-I response rate[b] (%) | | | | | |
| At Week 6 | 50.5 % | 0.013[d] | 57.9 % | <0.001[d] | 37.9 % |
| CGI-S score, mean (SE) | | | | | |
| Double-blind baseline | 4.0 (0.0) | 0.033[c] | 4.1 (0.0) | <0.001[c] | 4.0 (0.0) |
| Change to Week 6 | −0.8 (0.1) | | −0.9 (0.1) | | −0.6 (0.1) |
| HAMD-17 total score, mean (SE) | | | | | |
| Double-blind baseline | 19.8 (0.3) | 0.004[c] | 20.0 (0.3) | <0.001[c] | 20.2 (0.3) |
| Change to Week 6 | −7.0 (0.4)[e] | | −7.6 (0.4) | | −5.3 (0.4)[e] |

[a] SDS=Sheehan Disablity Scale; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-severity of illness; HAMD-17=17-item Hamilton Depression Rating Scale.
[b] CGI-I response is defined as proportion of patients with CGI-I scores of 1 and 2.
[c] ANCOVA, with the score at the end of prospective treatment phase as a covariate and treatment as a factor.
[d] Chi-square test.
[e] $n=193$.

## 4. Discussion

This multicenter, randomized, placebo-controlled study showed that a flexible dose (3–15 mg/day) and fixed dose (3 mg/day) schedule of aripiprazole as adjunctive therapy to ADT was more effective than adjunctive placebo and well tolerated in Japanese MDD patients. To our knowledge, this is the first report showing that aripiprazole as augmentation therapy was effective in Japanese patients with MDD. Adjunctive aripiprazole was significantly superior to adjunctive placebo in improving depressive symptoms at endpoint and the onset of activity was evident from Week 1. Furthermore, adjunctive aripiprazole significantly improved SDS total score and all 3 domains (Work/School, Social Activity, Family Life) compared with placebo. These findings are consistent with previous controlled studies of aripiprazole conducted in non-Asian populations in the US (Berman et al., 2007, 2009; Marcus et al., 2008), suggestive of no ethnic differences in the ability to respond to treatment. This reproducibility of results may provide support for wider use of aripiprazole augmentation therapy in general practice in Japan and confer a reliable treatment for patients with TRD.

Interestingly, the findings revealed comparable clinical benefits between the fixed dose (3 mg/day) and flexible dose (3–15 mg/day) schedule of aripiprazole in our patient population. This is contrary to what was expected but is supported by other successful clinical experiences of low-dose aripiprazole as an adjunctive agent for refractory depression in Asian populations (Chen et al., 2012; Lin et al., 2011; Terao, 2008) but not in Western populations (Fava et al., 2012; Mischoulon et al., 2012). The CYP2D6*10 allele, which decreases CYP2D6 enzyme activity, is known to be highly prevalent in Asian populations but rare in Caucasian populations (Ji et al., 2002); this may affect the pharmacokinetics of aripiprazole in Japanese patients (Suzuki et al., 2011) and impact on treatment response and risk of AEs.

Akathisia was the most common AE with adjunctive aripiprazole treatment. The incidence in the flexible dose group (36.6%) was somewhat higher than that reported in a pooled analysis of three randomized, controlled trials in predominantly Caucasian populations (22.7%) (Pae et al., 2011) and may be a factor of the abovementioned CYP2D6*10 allele. However, approximately 80% of patients in the flexible dose group rated their akathisia as mild in severity and only 1 patient (0.5%) discontinued treatment because of akathisia. The incidence of akathisia in the fixed dose group was low at 14.2%. In both aripiprazole groups, akathisia was managed successfully with the addition of an anti-Parkinsonian drug or by dose reduction.

Although the incidences of most AEs, including that for akathisia, were lower in the fixed dose group, it is too early to conclude that aripiprazole 3 mg/day is the optimal dose for clinical practice in Japan. It is necessary also to take into account the manner in which acute titration might affect the efficacy and tolerability of the adjunctive flexible dose. Further investigation into the clinical profile of aripiprazole at various dosage levels is required.

A highly variable and often substantial placebo response rate in studies of depression has long been recognized (Walsh et al., 2002), and the list of potential contributing factors is wide and diverse (Fava et al., 2003). In clinical trials, a high placebo effect can reduce the likelihood of demonstrating statistical superiority of antidepressant treatment vs placebo (Dworkin et al., 2005). In the current study aripiprazole as augmentation therapy to ADT was shown to be significantly more effective than placebo in Japanese patients with MDD not responding adequately to ADT. The results replicate those of other large-scale placebo-controlled studies of aripriprazole in the adjunctive setting (Berman et al., 2007, 2009; Marcus et al., 2008), all of which have demonstrated superiority of aripiprazole over placebo.

Some methodological limitations of our study need to be considered. The 6-week implementation period of augmentation treatment does not allow conclusions to be drawn about long-term benefits of aripiprazole and the exclusion of patients with established medical comorbidities does not accurately reflect real-world practice. Although the manner of titration in the flexible dose group might be considered controversial, the parallel-group comparison of the study design has helped us to understand the efficacy and safety of augmentation therapy with aripiprazole and has overcome the limitations of the previous controlled studies.

In conclusion, our findings demonstrate that aripiprazole augmentation at a fixed dose of 3 mg/day and at a flexible dose of 3–15 mg/day had an efficacy superior to that of an antidepressant alone and was well tolerated in Japanese MDD patients who had inadequate response to antidepressant monotherapy.

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**Conflict of interest**

Dr. Kamijima has served as a consultant to Asahi Kasei Pharma and received speakers' honoraria from Pfizer, Glaxo SmithKline, Otsuka, Astellas, Eli Lilly, Shionogi, Dainihon Sumitomo, Yoshitomi, and Mochida. Dr. Higuchi has received research support or speakers' honoraria from, or has served as a consultant to, Abbot, Asahi Kasei Pharma, Bristol-Myers Squibb, Chugai, Dainippon Sumitomo, Eli Lilly, Glaxo SmithKline, Janssen, Kyowa-Hakko Kirin, Meiji Seika Pharma, Mochida, MSD, Otsuka, Pfizer, Shionogi, Taisho Toyama, and Tanabe Mitsubishi. Dr. Ishigooka has received research support or speakers' honoraria from, or has served as a consultant to, Yoshitomi, Pfizer, Astellas, Glaxo SmithKline, Meiji Seika Pharma, Eli Lilly, Novartis Pharma, Otsuka, Mochida, Chugai, Takeda, Shionogi, Dainippon Sumitomo, Tanabe Mitsubishi, and Kyowa-Hakko Kirin. Dr. Ohmori has received research support or speakers' honoraria from, or has served as a consultant to, Astellas, Chugai, Daiichi Sankyo, Dainippon Sumitomo, Ehzai, Eli Lilly, Glaxo SmithKline, Janssen, Meiji Seika Pharma, Mochida, MSD, Novartis, Ono, Otsuka, Pfizer, Shionogi, Takeda and Yoshitomi. Dr. N. Ozaki has received research support or speakers' honoraria from, or has served as a consultant to, Abbot, Asahi Kasei Pharma, Astellas, Dainippon Sumitomo, Eisai, Eli Lilly, Glaxo Smith Kline, Janssen, Meiji Seika Pharma, Mochida, MSD, Novartis Pharma, Ono, Otsuka, Pfizer, Shionogi, Takeda, Yoshitomi, Sanofi, and Tanabe Mitsubishi. Dr. Kanba received Grant/research supports from Pfizer, Ono, GlaxoSmithKline, Astellas, Janssen, Yoshitomiyakuhin, Eli Lilly Japan, Otsuka, Dainippon Sumitomo, Meiji Seika Pharma, Kyowa Hakko Kirin, Shionogi. SK received honoraria from Pfizer, Janssen, GlaxoSmithKline, Eli Lilly Japan, Eisai, Meiji Seika Pharma, Taisho Toyama, Astellas, Otsuka, Shionogi, Dainippon Sumitomo, Kyowa Hakko Kirin, Yoshitomiyakuhin, MSD, and Wyeth. Dr. Kinoshita has received research support or speakers' honoraria from, or has served as a consultant to, Asahi Kasei Pharma, Dainippon Sumitomo, Eli Lilly, Glaxo SmithKline, Janssen, Kyowa-Hakko Kirin, Meiji Seika Pharma, Mochida, MSD, Otsuka, Pfizer, Shionogi, and Tanabe Mitsubishi. Dr. Koyama has served as a consultant to Astellas, Eli Lilly Japan, Tanabe Mitsubishi, Chugai,, and Abott, and received speakers' honoraria from Otsuka, Meiji Seika Pharma, Astellas, Eli Lilly Japan, Janssen, Glaxo SmithKline, Kyowa Hakko Kirin, MSD, Pfizer, Shionogi, Taisho Toyama, and Asahi Kasei Pharma.

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