An open-label extension long-term study of the safety and efficacy of aripiprazole for irritability in children and adolescents with autistic disorder in Japan

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Aim: The purpose of this study was to evaluate the long-term safety and efficacy of aripiprazole in treating irritability in pediatric patients (6–17 years) with autistic disorder (AD) in Japan.

Methods: In this open-label extension study, patients who had completed a previous randomized, double-blind, placebo-controlled 8-week study were enrolled and were flexibly dosed with aripiprazole (1–15 mg/day) until the new indication of irritability in pediatric autism spectrum disorder was approved in Japan.

Results: Seventy (81%) out of 86 enrolled patients completed week-48 assessments. The mean duration of treatment was 694.9 days. The mean daily dose of aripiprazole over the treatment period was 7.2 mg and the mean of the final dose was 8.5 mg. The most common treatment-emergent adverse events (TEAE; ≥20%) included nasopharyngitis, somnolence, influenza, and increased weight. The majority of these TEAE were mild or moderate in severity, and there were no deaths, and no clinically relevant findings in laboratory values except prolactin decrease, vital signs, height, or ECG parameters. At week 48 (observed case), the mean change from baseline in the Irritability subscale score for the Aberrant Behavior Checklist Japanese Version was −6.3 in prior placebo patients and −2.6 in prior aripiprazole patients.

Conclusion: Aripiprazole was generally safe, well tolerated, and effective in the long-term treatment of irritability associated with AD in Japanese pediatric patients.

Key words: aripiprazole, autism spectrum disorder, children and adolescents, irritability, long-term.

BEFORE 2013, autism spectrum disorder (ASD) represented pervasive developmental disorders of variable severity, defined as autistic disorder (AD), Asperger’s disorder, and pervasive developmental disorder – not otherwise specified (PDD-NOS) in the American Psychiatric Association’s DSM-IV-TR. The diagnostic criteria for ASD changed significantly after the release of the DSM-5 in 2013. Autistic disorder, Asperger’s disorder, and PDD-NOS were combined into a single diagnosis of ASD – a single diagnosis with considerable diagnostic variability. ASD is characterized by impaired social communication and restricted and repetitive behaviors. Additionally, a range of behavioral
difficulties can be observed in ASD, including aggression, self-injury, tantrums, hyperactivity, obsessive–compulsive phenomena, and stereotypes. Understandably, these symptoms can have a substantial impact on affected individuals and their families. Pharmacologic interventions for behavioral difficulties may increase the ability of patients with ASD to profit from educational and other interventions and to remain in less restrictive environments through the management of severe and challenging behaviors. Risperidone and aripiprazole are approved in the USA and Japan for the treatment of pediatric patients with irritability associated with ASD, including symptoms of aggression toward others, deliberate self-injury, temper tantrums, and quickly changing moods.

Aripiprazole is an atypical antipsychotic with a partial agonism at dopamine D2 receptors and serotonin 5-HT1A receptors and an antagonism at 5-HT2A receptors. Aripiprazole may have a more favorable side-effect profile than other antipsychotics in child and adolescent patients with mental health disorders because of its unique mechanism of action. Aripiprazole was shown to be efficacious while generally safe and well tolerated for the treatment of children and adolescents (aged 6–17 years) with irritability associated with AD in two 8-week, double-blind, randomized, placebo-controlled studies and in a 52-week open-label flexible-dose study in the USA. Recently, results from an 8-week, multicenter, randomized double-blind, placebo-controlled study have demonstrated that aripiprazole is efficacious and generally safe and well tolerated for the treatment of Japanese pediatric patients aged 6–17 years with irritability associated with AD.

Although the short-term trial provided important safety and tolerability information regarding aripiprazole in this patient population, there is a need for additional long-term safety data. The primary aim of this study was to assess the longer-term safety, tolerability, and maintenance of efficacy of irritability associated with AD in Japan. The interim results of data through the cut-off date of 25 June 2015 have already been reported.

**METHODS**

This open-label extension (OLE) study was conducted at 50 sites in Japan between August 2012 and October 2016 in accordance with ethical principles originating from the Declaration of Helsinki and in compliance with International Conference on Harmonization Good Clinical Practice guideline. The institutional review board at each site approved the protocol. All parents/guardians provided written informed consent to participate in the study, and patients provided written informed assent when possible. The study was registered at ClinicalTrials.gov (identifier: NCT01617460).

**Patients**

Patients who had previously completed the antecedent 8-week double-blind, randomized, placebo-controlled study were eligible for inclusion. Eligible patients were children and adolescents aged 6–17 years with a diagnosis of AD defined by the DSM-IV-TR. The pervasive developmental disorders Autism Society Japan Rating Scale (PARS) was used as a preliminary assessment for all the patients who were enrolled in this trial. PARS is an evaluation method developed by the Autism Society Japan as a rating scale that is applicable to all ASD, including patients with high-functioning autism or Asperger’s syndrome, and has sufficient reliability and validity. The scores of the PARS showed correlation with that of the Autism Diagnostic Interview-Revised.

Patients who had complications or histories of schizophrenia, other psychosis, and mood disorders, including bipolar disorder and major depression, according to the DSM-IV-TR criteria were excluded. Other exclusion criteria included a diagnosis of Rett disorder, childhood disintegrative disorder, Asperger’s disorder, or PDD-NOS, according to the DSM-IV-TR, or a diagnosis of fragile X syndrome.

**Study design**

All patients who had received placebo/aripiprazole in the antecedent study started therapy with aripiprazole at 1 mg/day, with a target dosage of 1, 3, 6, 9, 12, or 15 mg/day. Patients received aripiprazole until the approval of the new indication of irritability in pediatric ASD in Japan. Dose increases occurred at intervals of at least 1 week, and dosage could be adjusted downward based on tolerability, at the clinician’s discretion.

Concomitant medications, such as antipsychotics, antiparkinson drugs (except biperiden and trihexyphenidyl), beta-blockers, adrenaline, clonidine,
guanabenz, methyldopa, and carbamazepine were prohibited during the trial.

**Assessments**

Patients had study visits at the end of weeks 1, 2, 4, 6, and 8 (±3 days), and 12, 16, 20, and 24 (±7 days), and thereafter at an interval of 8 weeks (±14 days), and at the time of termination (±7 days). Monitoring for presence and the severity of treatment-emergent adverse events (TEAE) was performed at any time during the trial. Monitoring for vital signs, extrapyramidal symptoms (EPS)-related TEAE using the Drug-Induced Extrapyramidal Symptoms Scale, the Barnes Akathisia Rating Scale, and the Columbia Suicide Severity Rating Scale, was performed at baseline and each visit. Monitoring for bodyweight was performed at baseline and weeks 4, 8, and all visits thereafter. Monitoring for height was performed at baseline and intervals of 8 weeks. Twelve-lead electrocardiograms (ECG) and laboratory tests were conducted at baseline and weeks 8, 24, 48, and thereafter at intervals of 48 weeks.

Efficacy was evaluated using the caregiver-rated Aberrant Behavior Checklist Japanese Version (ABC-J) score, which has five subscales designated as Irritability (15 items), Lethargy/Social Withdrawal (16 items), Stereotypic Behavior (seven items), Hyperactivity (16 items), and Inappropriate Speech (four items). Each individual item on the ABC-J is scored on a Likert scale from 0 (not at all a problem) to 3 (the problem is severe in degree). In initial examinations of the utility of the measure, the ABC-J was shown to have sound psychometric properties with high internal consistency among subscales (0.85–0.95), high test–retest reliability (0.84–0.90), and acceptable inter-rater reliability (0.58–0.78). Participants were also assessed on the clinician-rated Clinical Global Impression (CGI)–Improvement (CGI-I) score, the CGI–Severity of Illness scale (CGI-S) score, the Children’s Yale-Brown Obsessive–Compulsive Scale (CY-BOCS, Compulsion scale only) score, and the Children’s Global Assessment Scale (CGAS) score. CGAS is a 100-point rating scale measuring psychological, social, and school functioning for children. Increase in scores of CGAS reflects improvement in symptoms. ABC-J and CGI-S ratings were obtained at baseline and all study visits. CGI-I was assessed at all study visits except at baseline. CY-BOCS and CGAS were evaluated at baseline and intervals of 24 weeks.

**Statistical analyses**

The safety dataset included all patients who had received at least one dose of aripiprazole and who had had at least one post-baseline safety evaluation. The efficacy dataset included all patients who had received at least one dose of aripiprazole and who had had at least one post-baseline efficacy evaluation and corresponding baseline value (if applicable).

Two patient groups based on previous treatment were defined for the purpose of the analyses presented herein: (i) prior aripiprazole patients; and (ii) prior placebo patients. For the purpose of analysis, all baseline values were derived from the last evaluation during double-blind treatment for prior aripiprazole/placebo patients. TEAE with onset/worsening during OLE treatment were included in the summary tables; TEAE with onset during double-blind treatment that continued into OLE treatment were not included. For the safety and efficacy evaluations, descriptive statistics were calculated for the mean change from baseline, or for mean score in the case of CGI-I. As this was an OLE, with no placebo or active control group, no prior formal statistical testing was planned; all results are reported as descriptive statistics. Values are expressed by mean and SD. Of note, the baseline measurements were taken at the last evaluation during double-blind treatment after having received study medications for 8 weeks. As such, mean changes in efficacy scores and prolactin levels in the prior aripiprazole group were expected to be small over the course of long-term treatment and would merely indicate that previous symptom control and an effect were maintained.

**RESULTS**

**Patient disposition and demographics**

All enrolled patients (n = 86) were included in the safety and efficacy datasets. Baseline demographic characteristics of patients are shown in Table 1. The mean (± SD) time on study therapy for the entire population was 694.9 ± 390.7 days (prior placebo patients, 636.3 ± 402.1 days; prior aripiprazole patients, 748.3 ± 376.6 days). Patient disposition is shown in Figure 1. Of the 86 patients entering OLE...
enrolled in this long-term study.

Table 1. Baseline demographics and clinical characteristics

|                      | Prior placebo (n = 41) | Prior aripiprazole (n = 45) | Total (n = 86) |
|----------------------|------------------------|-----------------------------|---------------|
| Sex                  |                        |                             |               |
| Male                 | 32 (78.0)              | 37 (82.2)                   | 69 (80.2)     |
| Female               | 9 (22.0)               | 8 (17.8)                    | 17 (19.8)     |
| Age (years)†         | 9.7 (2.9)              | 10.4 (3.1)                  | 10.0 (3.0)    |
| 6–12                 | 35 (85.4)              | 32 (71.1)                   | 67 (77.9)     |
| 13–17                | 6 (14.6)               | 13 (28.9)                   | 19 (22.1)     |
| Height (cm)†         | 136.4 (17.0)           | 141.2 (19.0)                | 138.9 (18.1)  |
| Weight (kg)†         | 35.4 (14.5)            | 40.1 (17.7)                 | 37.8 (16.3)   |
| <40 kg               | 28 (68.3)              | 24 (53.3)                   | 52 (60.5)     |
| ≥40 kg               | 13 (31.7)              | 21 (46.7)                   | 34 (39.5)     |
| BMI (kg/m²)†         | 18.2 (3.8)             | 19.1 (4.1)                  | 18.7 (4.0)    |
| ABC-J Irritability subscale score† | 19.9 (9.5) | 15.5 (10.0) | 17.6 (10.0) |
| CGI-S                | 4.1 (1.2)              | 3.5 (0.9)                   | 3.8 (1.1)     |

Data are expressed as n (%) or †mean (SD).
Baseline demographics were obtained at the last evaluation of the double-blind treatment period after having received study medications for 8 weeks.
ABC-J, Aberrant Behavior Checklist Japanese Version; BMI, body mass index; CGI-S, Clinical Global Impressions–Severity of Illness scale.

Figure 1. Patient disposition.
Patients who completed the 8-week randomized double-blind placebo-controlled trial with aripiprazole at 1–15 mg/day were enrolled in this long-term study.

treatment, 40 (47%) discontinued, and 70 (81%), 39 (45%), 22 (26%), and eight (9%) completed weeks 48, 96, 144, and 192 assessment, respectively. Common reasons for discontinuation were adverse events (n = 7 [8.1%]) and worsening of primary disease (n = 3 [3.5%]). Additional reasons for discontinuation, generally unrelated to study medication, included withdrawal of consent (n = 9 [10.5%]), receiving prohibited drugs (n = 4 [4.7%]), inadequate compliance (n = 1 [1.2%]), and other (n = 16 [18.6%]). Reasons for discontinuation until 48-week assessments were adverse events (n = 4 [4.7%]), worsening of primary disease (n = 2 [2.3%]), withdrawal of consent (n = 5 [5.8%]), receiving prohibited drugs (n = 1 [1.2%]), and other (n = 4 [4.7%]).
Dosing

The mean (± SD) daily dose of aripiprazole over the treatment period was 7.2 ± 4.0 mg and the mean of the final dose was 8.5 ± 4.7 mg. The proportion of patients receiving each aripiprazole dose (1, 3, 6, 9, 12, or 15 mg/day) at the final dose was as follows: 1 mg, \( n = 4 \) (4.7%); 3 mg, \( n = 17 \) (19.8%); 6 mg, \( n = 22 \) (25.6%); 9 mg, \( n = 12 \) (14.0%); 12 mg, \( n = 10 \) (11.6%); and 15 mg, \( n = 21 \) (24.4%).

Overall, 62.8% of patients received concomitant central nervous system (CNS) medications during the study. The most commonly used CNS concomitant medications were analgesics-antipyretics (50.0%), general cold drug (15.1%), and anxiolytics (11.6%).

Safety

Of the 86 patients who were included in the safety dataset, 84 (97.7%) experienced a TEAE. TEAE occurring in ≥5% of patients in any group are presented in Table 2. The most common TEAE (≥20% of patients) included nasopharyngitis, somnolence, influenza, and increased weight. The majority of those TEAE were mild or moderate in severity. There were no deaths. Serious TEAE were reported in 10 patients. Reported serious TEAE were: worsening of primary disease (\( n = 2 \)), adenoid hypertrophy (\( n = 2 \)), malaise (\( n = 1 \)), purulent cervical lymphadenitis (\( n = 1 \)), hand fracture (\( n = 1 \)), blue nevus (\( n = 1 \)), hyperexcitability (\( n = 1 \)), acute glomerulonephritis (\( n = 1 \)), status asthmaticus (\( n = 1 \)), enlarged tonsil (\( n = 1 \)), and sexual abuse (\( n = 1 \)). Ten patients (11.6%) discontinued due to TEAE. The most frequent TEAE leading to discontinuation in >2% of patients were increased weight (\( n = 3 \) [3.5%]), worsening of primary disease (\( n = 3 \) [3.5%]), and increased appetite (\( n = 2 \) [2.3%]) in the overall population.

EPS-related TEAE occurred in 11 (12.8%) patients in this study. The most frequently reported EPS-related TEAE (>2% of patients) were salivary hypersecretion (\( n = 6 \) [7.0%]) and akathisia (\( n = 4 \) [4.7%]). The severity of all observed EPS-related TEAE were judged to be mild in severity.

The mean change from baseline in metabolic laboratory measurements and prolactin levels, height, weight, and body mass index (BMI) at week 48 (observed case [OC]) and end-point (last observation carried forward [LOCF]) are shown in Table 3. In the total population, there were no clinically relevant findings in laboratory values except prolactin decrease, vital signs, weight, height, BMI or ECG parameters.

The occurrence of suicidal ideation or behavior, as recorded on the Columbia Suicide Severity Rating Scale, was low. One patient who had suicidal ideation at baseline reported worsening of it. A different patient reported occurrence and worsening of suicidal ideation. There was no occurrence of suicidal behavior.

Efficacy

The mean ABC-J Irritability subscale scores over time are shown in Figure 2. For prior placebo patients, at weeks 2, 4, and 6 (OC), the mean (SD) change from baseline ABC-J Irritability scores was -4.5 (5.9), -5.3 (6.6), and -6.0 (6.4), respectively. This improvement was maintained to study end-point. For prior aripiprazole patients, at weeks 2, 4, and 6 (OC), the mean (SD) change from baseline ABC-J Irritability scores was 0.6 (6.2), 0.7 (5.2), and -1.0 (4.5), respectively. This score remained constant over the course of long-term treatment, indicating that prior improvement experienced with aripiprazole treatment during the randomized treatment period was maintained during the OLE study. Table 4 presents the mean changes from baseline in efficacy outcomes for the ABC-J Irritability, Lethargy/Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech subscales, and CGI-S, CGAS, and CY-BOCS at week 48 (OC) and end-point (LOCF). Total population and prior placebo patients showed mean improvements from baseline in these efficacy scores at week 48 (OC) and end-point (LOCF). Prior aripiprazole patients showed a mean improvement in all ABC-J subscales and CGI-S scores at week 48 for patients who remained on treatment (OC). The mean (SD) CGI-I scores at week 48 (OC) and end-point (LOCF) were 2.5 (1.0; \( n = 30 \)) and 2.5 (1.1; \( n = 41 \)) for prior placebo patients, 3.1 (1.3; \( n = 40 \)) and 3.2 (1.4; \( n = 45 \)) for prior aripiprazole patients, and 2.8 (1.2; \( n = 70 \)) and 2.9 (1.3; \( n = 86 \)) for total patients, respectively.

DISCUSSION

The antecedent short-term study in Japan showed that aripiprazole was effective and generally safe and
well tolerated in the treatment of irritability associated with AD in Japanese children and adolescents. This study showed that aripiprazole was safe, well-tolerated, and effective for the longer-term treatment of irritability in Japanese children and adolescents aged 6–17 years with AD. In the antecedent short-term study in Japan, aripiprazole showed a very high completion rate (100%). In this OLE study, most of these patients were included. The continuation rate until week-48 assessments with aripiprazole in the current study was 81%. This rate is higher than that reported in the open-label 26-week study of risperidone (71%) and the open-label 52-week study of aripiprazole in the USA (60.3%). In the risperidone study, the most common reasons for discontinuation were insufficient response (9%) and adverse

Table 2. Summary of treatment-emergent adverse events

|                      | Prior placebo (n = 41) | Prior aripiprazole (n = 45) | Total (n = 86) |
|----------------------|------------------------|----------------------------|---------------|
| At least one TEAE    | 40 (97.6)              | 44 (97.8)                  | 84 (97.7)     |
| Serious TEAE         | 3 (7.3)                | 7 (15.6)                   | 10 (11.6)     |
| Severe TEAE          | 2 (4.9)                | 4 (8.9)                    | 6 (7.0)       |
| Discontinuation due to TEAE | 6 (14.6)             | 4 (8.9)                    | 10 (11.6)     |
| Incidence of TEAE reported by ≥5% patients in any group |
| Nasopharyngitis      | 25 (61.0)              | 28 (62.2)                  | 53 (61.6)     |
| Somnolence           | 18 (43.9)              | 10 (22.2)                  | 28 (32.6)     |
| Influenza            | 10 (24.4)              | 15 (33.3)                  | 25 (29.1)     |
| Increased weight     | 13 (31.7)              | 8 (17.8)                   | 21 (24.4)     |
| Vomiting             | 8 (19.5)               | 4 (8.9)                    | 12 (14.0)     |
| Gastroenteritis      | 1 (2.4)                | 9 (20.0)                   | 10 (11.6)     |
| Increased appetite   | 4 (9.8)                | 6 (13.3)                   | 10 (11.6)     |
| Rhinitis allergic    | 6 (14.6)               | 3 (6.7)                    | 9 (10.5)      |
| Upper respiratory tract inflammation | 3 (7.3)        | 6 (13.3)                   | 9 (10.5)      |
| Dental caries        | 2 (4.9)                | 6 (13.3)                   | 8 (9.3)       |
| Pyrexia              | 1 (2.4)                | 7 (15.6)                   | 8 (9.3)       |
| Upper respiratory tract infection | 5 (12.2)       | 3 (6.7)                    | 8 (9.3)       |
| Decreased appetite   | 2 (4.9)                | 5 (11.1)                   | 7 (8.1)       |
| Worsening of primary disease | 2 (4.9)              | 5 (11.1)                   | 7 (8.1)       |
| Nausea               | 2 (4.9)                | 4 (8.9)                    | 6 (7.0)       |
| Salivary hypersecretion | 6 (14.6)            | 0                          | 6 (7.0)       |
| Contusion            | 4 (9.8)                | 2 (4.4)                    | 6 (7.0)       |
| Eczema               | 3 (7.3)                | 3 (6.7)                    | 6 (7.0)       |
| Conjunctivitis allergic | 1 (2.4)             | 4 (8.9)                    | 5 (5.8)       |
| Diarrhea             | 2 (4.9)                | 3 (6.7)                    | 5 (5.8)       |
| Malaise              | 2 (4.9)                | 3 (6.7)                    | 5 (5.8)       |
| Bronchitis           | 3 (7.3)                | 2 (4.4)                    | 5 (5.8)       |
| Pharyngitis          | 1 (2.4)                | 4 (8.9)                    | 5 (5.8)       |
| Rhinitis             | 2 (4.9)                | 3 (6.7)                    | 5 (5.8)       |
| Arthropod bite       | 1 (2.4)                | 4 (8.9)                    | 5 (5.8)       |
| Headache             | 2 (4.9)                | 3 (6.7)                    | 5 (5.8)       |
| Stomatitis           | 0                      | 4 (8.9)                    | 4 (4.7)       |
| Impetigo             | 1 (2.4)                | 3 (6.7)                    | 4 (4.7)       |
| Otitis media         | 3 (7.3)                | 1 (2.2)                    | 4 (4.7)       |
| Dermatitis           | 3 (7.3)                | 1 (2.2)                    | 4 (4.7)       |
| Laceration           | 3 (7.3)                | 0                          | 3 (3.5)       |

Data are expressed as n (%). Baseline was at the last evaluation of the double-blind treatment period after having received study medications for 8 weeks. TEAE, treatment-emergent adverse event.
events (6%). Additional reasons for discontinuation, generally unrelated to study medication, included loss to follow-up (5%), patient choice (3%), non-compliance (4%), and other (3%). In the US aripiprazole study, the most common reasons for discontinuation were adverse events (10.6%) and lack of efficacy (6.1%). Additional reasons for discontinuation, generally unrelated to study medication, included loss to follow-up (9.4%), withdrawal of consent (8.2%), inadequate compliance (1.5%), administrative reasons (1.2%), and other (2.9%). In our study, there was no discontinuation due to loss to follow-up and only 2.3% of the patients discontinued due to worsening of primary disease. These low frequencies may contribute to the high continuation rate in our study. In this long-term study, the end-point of many patients was beyond 48 weeks, and end-points of 45% of patients were ≥96 weeks. The findings of this study are noteworthy due to the large patient population who remained on aripiprazole long term. In our study, somnolence was one of the commonly reported TEAE, and the frequency was higher than that in the US study (3.9%). Frequencies of insomnia and sedation as TEAE in this study were under 5% and lower than that in the US study respectively. It is unclear why these differences occurred between the Japanese and US studies.

In the antecedent 8-week study in Japan, the most common TEAE (≥5% of aripiprazole group) were somnolence, nasopharyngitis, decreased appetite, nausea, vomiting, and fatigue; however, weight gain was not reported as a TEAE and increased appetite was reported as a TEAE in less than 5% of patients. In this extension study, weight gain and increased appetite were common TEAE, and prior placebo patients’ mean weight and BMI z-score changes were 0.33 and 0.39 at the week-48
assessment, and these z-score changes at end-point were 0.21 and 0.24, respectively. These data suggest that weight and BMI are important parameters to monitor in this population. All pediatric patients receiving treatment with atypical antipsychotics should be monitored for weight gain.\textsuperscript{18}

During this long-term study, 12.8\% of patients experienced EPS-related TEAE. However, these TEAE were mild in severity, and no patients discontinued treatment due to EPS-related TEAE. EPS-related TEAE with aripiprazole treatment were generally tolerable. Decreases in serum prolactin levels with aripiprazole treatment have previously been observed during the antecedent short-term treatment with aripiprazole in this population,\textsuperscript{11} and as in this short-term study, longer-term aripiprazole treatment was also associated with an overall mean decrease in serum prolactin levels in prior placebo patients. Although the clinical consequences of increased prolactin levels have been documented,\textsuperscript{19} the clinical consequences of decreased serum prolactin levels are unknown.

Results from this long-term study suggest that aripiprazole can reduce symptoms of irritability in Japanese children and adolescents with AD. Symptoms of irritability assessed using the caregiver-rated ABC-J Irritability subscale score were improved early in the course of treatment and these improvements were maintained during the study period in patients receiving aripiprazole for the first time during this study (prior placebo patients). The pattern of improvement seen in the first few weeks of aripiprazole treatment for prior placebo patients was similar to that observed with aripiprazole in the double-blind study: early symptom improvement within the first few weeks followed by further improvement up to week 8.\textsuperscript{11} For individuals who had previously received 8 weeks of aripiprazole treatment during the prior double-blind study, improvements in irritability symptoms were maintained during the OLE study period. In addition to the improvements in irritability observed in this long-term study, prior placebo patients also demonstrated improvements on the other ABC-J subscales and clinician-rated CGI-S score. Improvement in these measures was also seen in patients receiving aripiprazole during the short-term study,\textsuperscript{11} and this improvement was maintained during this study.

\begin{figure}
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\includegraphics[width=\textwidth]{figure2.png}
\caption{Mean (SD) Aberrant Behavior Checklist--Japanese Version (ABC-J) Irritability subscale scores over time (observed case dataset, also showing last observation carried forward [LOCF] end-point), efficacy sample. Prior placebo, patients randomly assigned to placebo during double-blind (DB) phase who continued into open-label extension (OLE) and received aripiprazole; Prior aripiprazole, patients randomly assigned to aripiprazole during DB phase who continued into OLE and received aripiprazole. Week 0: at the last evaluation of the double-blind treatment period after having received study medications for 8 weeks. End-point: the mean duration of treatment was 694.9 days. Patients received the treatment until the new indication of irritability in pediatric autism spectrum disorder was approved in Japan, October 2016 if not discontinued. (---) Prior aripiprazole and (---) prior placebo.}
\end{figure}
These safety and efficacy results in this study were similar to that in a previous long-term study in the USA, which showed that aripiprazole is an effective long-term treatment for controlling irritability associated with AD.9,10 To our knowledge, this is the first large open-label long-term trial to be conducted to evaluate the benefits of aripiprazole for the treatment of Japanese patients with AD. Thus, these findings have important implications for the long-term treatment of AD in this population. However, one of the limitations of the study is its open-label study design. It should be considered that this study was not specifically designed to assess maintenance of effect or the prevention of relapse. It should also be taken into account that this study included only patients with irritability associated with AD; the generalizability of these results to irritability in the context of other disorders cannot be determined from this study. Furthermore, all patients were titrated to aripiprazole at entry into open-label treatment, and this treatment decision may have had an impact on TEAE for patients who were previously receiving a stable dose of aripiprazole during the antecedent study. Conclusions regarding the relative safety and tolerability of aripiprazole compared with other antipsychotics in this population cannot be drawn from the data generated in this study.

In conclusion, aripiprazole was generally safe, well tolerated, and effective in the long-term treatment of irritability associated with AD in Japanese pediatric patients.

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AUTHOR CONTRIBUTIONS

H.I. advised the study design and interpretation of the data. H.O. designed the study, wrote the protocol, supervised the data acquisition, the monitoring activity, and contributed to interpretation of the data. M.H., A.Y., N.T., and T.O. acquired data. Y.T. drafted the manuscript. All authors contributed to and have approved the final manuscript.

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