A Randomized Controlled Trial Investigating the Safety and Efficacy of Aripiprazole in the Long-Term Maintenance Treatment of Pediatric Patients With Irritability Associated With Autistic Disorder

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ABSTRACT

Objective: To evaluate the efficacy and safety of aripiprazole versus placebo in preventing relapse of irritability symptoms associated with autistic disorder in pediatric patients.

Method: This multicenter, double-blind, randomized, placebo-controlled, relapse-prevention trial enrolled patients (6–17 years) who met the current *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DMS-IV-TR*) criteria for autistic disorder and who also had serious behavioral problems (ie, tantrums, aggression, self-injurious behavior, or a combination of these behavioral problems) between March 2011 and June 2012. In phase 1, single-blind aripiprazole was flexibly dosed (2–15 mg/d) for 13–26 weeks. Patients with a stable response (≥ 25% decrease in Aberrant Behavior Checklist-irritability subscale score and a rating of "much improved" or "very much improved" on the Clinical Global Impressions-Improvement scale) for 12 consecutive weeks were randomized into phase 2 to continue aripiprazole or switch to placebo. Treatment was continued until relapse or up to 16 weeks. The primary end point was time from randomization to relapse.

Results: Eighty-five patients were randomized in phase 2. The difference in time to relapse between aripiprazole and placebo was not statistically significant ($P = .097$). Kaplan-Meier relapse rates at week 16 were 35% for aripiprazole and 52% for placebo (hazard ratio [HR] = 0.57; number needed to treat [NNT] = 6). The most common adverse events during phase 1 were weight increase (25.2%), somnolence (14.8%), and vomiting (14.2%); and, during phase 2 (aripiprazole vs placebo), they were upper respiratory tract infection (10.3% vs 2.3%), constipation (5.1% vs 0%), and movement disorder (5.1% vs 0%).

Conclusions: In this study, there was no statistically significant difference between aripiprazole and placebo in time to relapse during maintenance therapy. However, the HR and NNT suggest some patients will benefit from maintenance treatment. Patients receiving aripiprazole should be periodically reassessed to determine the continued need for treatment.

Trial Registration: ClinicalTrials.gov identifier: NCT01227668

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Autistic disorder is characterized by impairments in social interactions and communication of varying severity, and is accompanied by repetitive, restricted, and stereotyped patterns of behavior. Patients may also display aggression, impulsivity, and irritability that can exacerbate problems with social interactions and place a considerable strain on both patients and their caregivers.[1,2]

The exact etiology of autistic disorder is unknown but most likely involves both genetic and environmental components, and the development of pharmacologic treatments that directly address the core symptoms of impaired social interaction, impaired language, and restricted and repetitive behaviors has been largely unsuccessful to date. Current pharmacologic therapies are instead directed at the associated behavioral issues. There are only 2 drugs approved by the US Food and Drug Administration in this regard: risperidone and aripiprazole.[3,4] Both are approved for the treatment of the associated symptoms of irritability, including such behaviors as aggression, tantrums, self-injury, and rapidly changing moods.

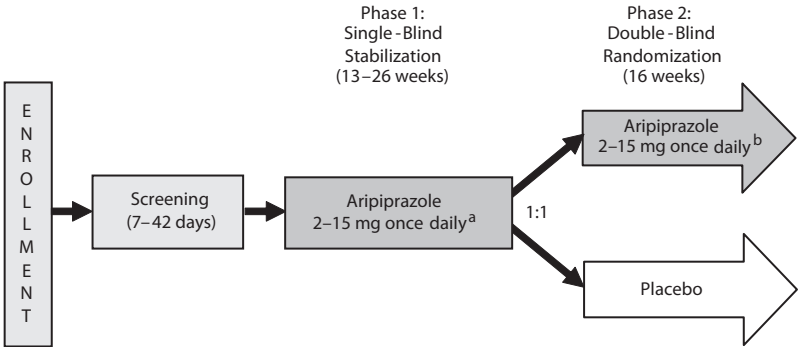
Aripiprazole acts as a partial agonist at D_2 and 5-HT_{1A} receptors, and as a 5-HT_{2A} antagonist.[3,5] The mean elimination half-life of aripiprazole is ~ 75 hours, and the active metabolite, dehydroaripiprazole, has a mean elimination half-life of ~ 94 hours; pharmacokinetic parameters in children and adolescents are similar to those seen in adults after adjusting for weight.[3,5,6] Therefore, aripiprazole is recommended to be administered once daily, and dose adjustments for the treatment of irritability associated with autistic disorder should occur at intervals of 1 week or more.[3,5,6]

Pivotal trials of aripiprazole for autistic disorder in pediatric patients (6–17 years) include 2 randomized, double-blind, short-term (8-week) trials and 1 open-label, long-term (52-week) extension.[7–10] Of the 2 short-term studies, 1 was a fixed-dose study[7] in which patients were randomized to receive aripiprazole (5, 10, or 15 mg/d) or placebo, and the other was a flexible-dose study[8] in which patients were randomized to receive aripiprazole (2–15 mg/d, titrated to optimal clinical effect, with dose options of 5, 10, or 15 mg/d) or placebo. In both short-term studies,[7,8] aripiprazole, at all doses tested, resulted in greater improvements compared with placebo in the Aberrant Behavior Checklist-irritability subscale (ABC-I)[11] scores. In the open-label

Clinical Points

- No statistically significant difference between aripiprazole and placebo in time to relapse was observed in pediatric patients with autistic disorder during maintenance treatment.
- The benefit of maintenance therapy with aripiprazole was seen for some patients, and the aripiprazole treatment arm statistically significantly differed from the placebo arm on some secondary efficacy measures.
- Aripiprazole was generally well tolerated, and most adverse events related to aripiprazole were mild in severity.
- It is recommended that patients receiving aripiprazole should be periodically reassessed to determine the continued need for treatment.

Figure 1. Study Design



[a]Aripiprazole was titrated from an initial dose of 2 mg/d at the beginning of the stabilization phase and adjusted within the range of 2–15 mg/d based on efficacy and tolerability.
[b]Patients continued at the dose prescribed at the end of the single-blind stabilization phase; the dose could be increased or decreased (within the range of 2–15 mg/d) based on clinical effects.

study,[9,10] aripiprazole was flexibly dosed (2–15 mg/d), and patients who had received aripiprazole in the prior studies maintained symptom improvement already achieved with aripiprazole. Patients who had not received prior aripiprazole treatment (ie, enrolled in the placebo arm of a prior study or enrolled directly into the extension study) demonstrated improvements in the ABC-I versus baseline.[9,10]

This current study was designed to expand on these previous trials of aripiprazole by providing placebo-controlled data evaluating maintenance treatment. The objective of this study was to determine if patients with irritability associated with autistic disorder who had become stable on aripiprazole should be maintained on treatment long term.

METHOD

Design Overview

This was a multicenter, double-blind, randomized, placebo-controlled study with 2 parallel treatment groups designed to assess the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. The study was conducted between March 2011 and June 2012 in the United States and was registered on ClinicalTrials.gov (identifier: NCT01227668). This study was conducted in accordance with the Declaration of Helsinki,[12] and the ethics committee for each site approved the protocol. Each site had the option to use a central institutional review board (IRB) if allowed by the site's guidelines, and 70% of the enrolling sites utilized this central IRB. The IRB (either the central or site-specific) approved the study, and written, informed consent was obtained from a legally authorized representative (eg, guardian or caregiver); patient assent was also obtained where applicable.

The study included 2 phases (Figure 1). Phase 1 (stabilization phase) comprised 13–26 weeks of single-blind aripiprazole treatment, and phase 2 (randomization phase) comprised up to 16 weeks of double-blind treatment with aripiprazole or placebo. Phase 1 was conducted as a single-blind phase in which the patient and caregiver did not know if the patient was receiving active treatment. The intent of this design was to minimize rater bias for the caregiver-rated ABC-I from a perceived, potential change in medication. In phase 1, aripiprazole was flexibly dosed and taken once daily at the same time each day without regard to meals until the patient was stabilized. All patients were to have aripiprazole titrated from an initial dose of 2 mg/d at the beginning of this phase and adjusted within the dose range based upon the investigator's assessment of efficacy and tolerability. The allowable dose range was between 2–15 mg/d (ie, 2, 5, 10, or 15 mg/d), with the expected target dose being 5, 10, or 15 mg/d. All dose increases were incremental from the current dose level to the next and occurred no more often than every 4 days.

Patients whose symptoms of irritability demonstrated a stable response to aripiprazole therapy for 12 consecutive weeks in phase 1 were eligible for randomization (1:1) into phase 2. Response was defined as follows: ≥25% decrease from baseline in the caregiver-rated ABC-I *and* a rating of 1 or 2 ("very much improved" or "much improved") on the clinician-rated Clinical Global Impressions-Improvement scale (CGI-I).[13] After patients had achieved response, to meet the criteria for maintenance of response, they must have demonstrated continued response as described above over a 12-week period (inclusive), with no more than 1 excursion of response criteria (ie, either a decrease in score of < 25% from baseline on the ABC-I or a CGI-I rating of ≥ 3 occurring at any 1 clinic visit). Patients were discontinued if they no longer had the opportunity to achieve 12 weeks of response over the maximum 26 weeks of participation in this phase.

Those patients randomized to aripiprazole continued at the dose prescribed at the end of phase 1 (ie, 2, 5, 10, or 15 mg/d). Investigators increased or decreased the dose (within the range of 2–15 mg/d) in phase 2 at their discretion based

on clinical effects, and adjustments were made similarly as in the stabilization phase. Randomization was performed via a centralized call-in system. Patients randomized to placebo were not titrated downward (because of the long half-life of aripiprazole) but were switched directly to placebo. Double-blind aripiprazole or matching placebo was taken once daily at the same time each day without regard to meals for up to 16 weeks or until relapse.

Study Population

The study population included male or female children or adolescents between the ages of 6 and 17 years who met the current *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DMS-IV-TR*)[1] criteria for autistic disorder and who also had serious behavioral problems (ie, tantrums, aggression, self-injurious behavior, or a combination of these behavioral problems). Diagnosis of autistic disorder was confirmed by the Autism Diagnostic Interview-Revised (ADI-R),[14] which was administered by an experienced interviewer, who had been previously trained and approved as "research reliable" on the ADI-R or who had successfully completed a 2-day rater training course conducted by an ADI-R certified trainer. Patients also had to have demonstrated an ABC-I score ≥ 18 and a Clinical Global Impressions-Severity of Illness scale (CGI-S)[13] score ≥4 at the screening and baseline visits.

Patients were excluded if they were considered by the investigator to be treatment resistant to antipsychotic medication (lack of therapeutic response to 2 different antipsychotics with treatment of ≥ 3 weeks each) or if they had been previously treated with an adequate daily dose of aripiprazole for ≥ 3 weeks without a clinically meaningful response. Patients with a lifetime diagnosis of bipolar disorder, psychosis, or schizophrenia or a current diagnosis of major depressive disorder, pervasive developmental disorder-not otherwise specified, Asperger syndrome, Rett syndrome, childhood disintegrative disorder, or fragile X syndrome were excluded. Other exclusion criteria included a history of neuroleptic malignant syndrome, a history of seizures within the past year or of severe head trauma or stroke, a history or current unstable medical conditions (eg, congenital heart disease or cancer), a history of low white blood cell count, or abnormal laboratory test results that, in the investigator's judgment, were medically significant. Patients were not to have taken any investigational agent within 1 month of the screening visit. Prohibited medications during the study included antipsychotics other than aripiprazole, antidepressants, benzodiazepines (allowed for procedures only), stimulants, α–agonists, mood stabilizers, and atomoxetine. Diphenhydramine for sleep or serious behavior problems, nonbenzodiazepine sleep aids (eg, zolpidem, zaleplon, zopiclone, eszopiclone) for insomnia, and melatonin for insomnia were permitted, but doses could be adjusted during phase 1 only; patients were not permitted to start or make changes to their sleep aid treatment during phase 2.

Study Assessments

The primary efficacy end point was the time from randomization to relapse. Relapse was defined in 1 of 4 ways: (1) ABC-I score increase of ≥ 25% compared to the end of phase 1 score and CGI-I rating of "much worse" or "very much worse" relative to the end of phase 1 for 2 consecutive visits, (2) ABC-I and CGI-I scores as per definition 1 at one visit plus "lost to follow-up" at the next visit, (3) ABC-I and CGI-I scores as per definition 1 at one visit plus initiation of a prohibited drug to treat worsening symptoms of irritability associated with autistic disorder at the next visit, or (4) the patient discontinued due to a hospitalization for worsening symptoms of irritability associated with autistic disorder (eg, self-injurious behavior) or due to lack of efficacy based upon the investigator's assessment.

The CGI-I and ABC-I were assessed every 2 weeks in the double-blind phase. Additional assessments included other ABC subscales and CGI-S, the Pediatric Quality of Life Inventory (PedsQL),[15] and the Caregiver Strain Questionnaire[16] evaluations. The PedsQL is a health-related quality-of-life instrument developed and validated for use with children and adolescents, and items on the PedsQL are reverse scored and linearly transformed to a 0–100 scale so that higher scores indicate better health-related quality of life. The Caregiver Strain Questionnaire is a 21-item self-report instrument assessing the impact that caring for children and adolescents with serious emotional, mental, and behavioral disturbances has on families. The PedsQL and Caregiver Strain Questionnaire were administered every 4 weeks in the double-blind phase. Safety was assessed by the frequency and severity of adverse events and serious adverse events; extrapyramidal symptom (EPS) measures; changes in vital signs, routine laboratory tests, and electrocardiograms; and the mean change from baseline in weight and body mass index (BMI). Safety assessments were made every 2 weeks in the double-blind phase.

Extrapyramidal syndrome-related side effects were evaluated by the Abnormal Involuntary Movement Scale (AIMS),[17] Simpson-Angus Scale,[18] and Barnes Akathisia Rating Scale (BARS).[19] The AIMS is a valid and reliable method of screening for tardive dyskinesia and consists of 10 items rated on a 4-point scale of severity, with 0 being none and 4 being severe. The Simpson-Angus Scale is a 10-item scale that rates gait, arm dropping, shoulder shaking, elbow and wrist rigidity, head rotation, glabella tap reflex, tremor, salivation, and akathisia on a 5-point scale ranging from 1 (normal) to 5 (extreme symptoms). The BARS is used to measure drug-induced akathisia that incorporates diagnostic criteria for pseudoakathisia and mild, moderate, and severe akathisia. The scale comprises items for rating the observable, restless movements that characterize the condition, the subjective awareness of restlessness, and any distress associated with the akathisia (each on a 0- to 3-point scale from normal to severe), and there is a global severity item for akathisia rated on a 0- to 5-point scale (absent to severe akathisia).

Statistical Methods

A total of 35 relapses (13 aripiprazole and 22 placebo) provided 86% power to detect a significant difference in time to relapse between the 2 treatment arms using the log rank test. This calculation assumed a relapse rate of 25% in the aripiprazole arm, a relapse rate of 55% in the placebo arm, and a 2-sided α level of .05. This assumption was based on the results of the 2 short-term studies[7,8] of aripiprazole and the maintenance study[20] of risperidone in pediatric patients with irritability associated with autistic disorder. The hazard ratio (HR) for these assumed relapse rates was 0.36.

The last observation carried forward (LOCF) data set was the primary data set and included data recorded at a given visit or, if no observation was recorded at that visit, data were carried forward from the previous visit. The observed case data set consisted of the actual observation at each visit and was considered secondary to corroborate the LOCF data set.

The primary efficacy outcome measure was evaluated by a survival analysis using the randomized sample. The survivorship function and estimated survivorship curves were obtained from Kaplan-Meier estimates. Survival distributions of the 2 treatment groups were compared using the log rank test, stratified by baseline body weight (2 categories: ≥ 40 kg and < 40 kg). Patients who did not relapse, including those patients who discontinued early for reasons other than relapse, were censored on their date of last efficacy evaluation or their last dose of study medication, whichever was later. Any randomized patients who were never treated and did not experience an event were censored on their randomization date. The estimated HR and 95% confidence interval (CI) were obtained from the Cox regression model, with baseline body weight (2 categories: ≥ 40 kg and < 40 kg) as a stratification factor and treatment group as a covariate.

The mean change from baseline in the irritability subscale score was evaluated using an analysis of covariance (ANCOVA) model that included the end of phase 1 irritability score as a covariate, and treatment and baseline body weight (2 categories: ≥ 40 kg and < 40 kg) as main effects. The mean CGI-I score was evaluated using an ANCOVA model, with CGI-S end of phase 1 score as a covariate and treatment and baseline body weight (2 categories: ≥ 40 kg and < 40 kg) as main effects. For the analysis of the secondary outcome measures, a hierarchical testing procedure was used in order for the overall experiment-wise type I error rate to be kept at ≤ .05.

The secondary efficacy outcome measures were evaluated using ANCOVA. These measures were the remaining ABC subscales (hyperactivity, stereotypy, inappropriate speech, social withdrawal), the Caregiver Strain Questionnaire, and the PedsQL. The ANCOVA model included the corresponding end of phase 1 score as a covariate (the end of phase 1 CGI-S score for the CGI-I analysis) and treatment and baseline body weight (2 categories: ≥ 40 kg and < 40 kg) as main effects. For the ANCOVA analyses on the secondary efficacy measures, model-based mean changes from end of phase 1 (mean values for CGI-I analysis) and 95% CIs for the treatment difference were displayed. Descriptive statistics were used for the safety and tolerability end points. All analyses were performed using SAS statistical software V8.2 or higher (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Patient Population

A total of 215 patients were enrolled in the study (Figure 2), and 157 patients entered the single-blind phase 1. Eighty-five (41 aripiprazole, 44 placebo) patients were randomized in phase 2. Overall, 19 patients in the aripiprazole arm discontinued during phase 2, compared with 25 in the placebo arm. Lack of efficacy was the most common reason for discontinuation in both the aripiprazole (n = 13) and placebo (n = 23) arms.

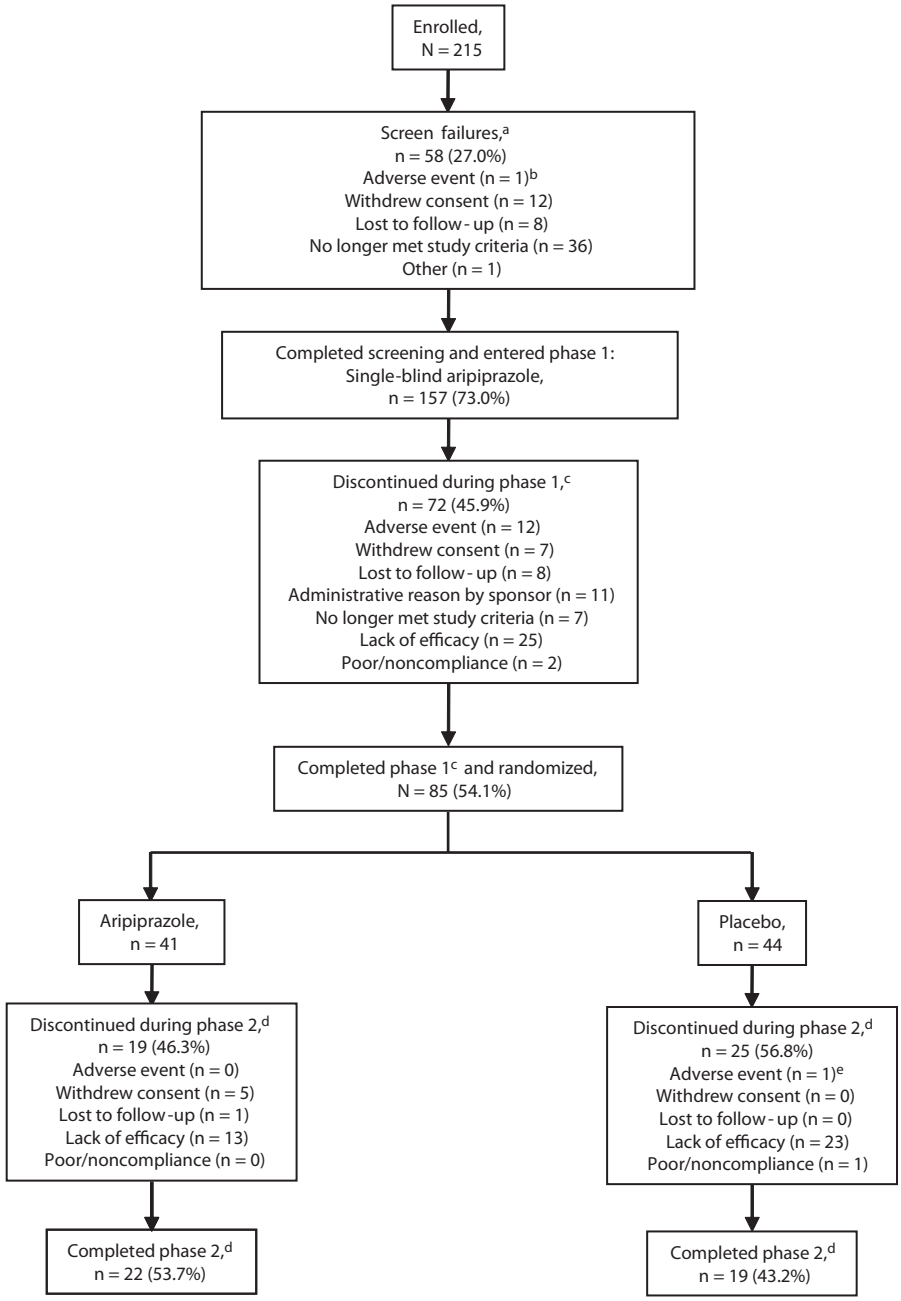
Demographics of the randomized sample were generally similar between the 2 groups (Table 1). Most patients were ≤ 12 years old (76.5%), male (80.0%), and white (69.4%). The mean (SD) ending doses of aripiprazole during phase 1 in patients who were randomized in phase 2 to aripiprazole or placebo were 9.0 (4.5) mg/d aripiprazole and 9.5 (4.2) mg/d aripiprazole, respectively. Among aripiprazole-treated patients who completed phase 2 (week 16), the mean (SD) dose was 9.7 (4.9) mg/d aripiprazole and in the placebo arm, the mean ending dose was 10.0 (4.2) mg/d placebo.

Efficacy Assessment

The Kaplan-Meier relapse rates at week 16 were 35% for aripiprazole and 52% for placebo, for an HR (aripiprazole/placebo) of 0.57 (95% CI, 0.28 to 1.12). The mean time until 25% of patients treated with aripiprazole relapsed was 56 days (95% CI, 31 to undefined), and, for placebo, it was 29 days (95% CI, 25 to 45). For the primary end point of time from randomization to relapse (Figure 3), the difference between aripiprazole and placebo was not statistically significant ($P = .097$). Reasons for relapse in the aripiprazole arm were an increase in ABC-I score of at least 25% *and* a rating of "much worse" or "very much worse" on the CGI-I at 2 consecutive visits (n = 7) and investigator assessment of lack of efficacy (n = 6). For the placebo arm, reasons for relapse were an increase in ABC-I score *and* CGI-I rating at 2 consecutive visits (n = 11), investigator assessment of lack of efficacy (n = 11), and both (n = 1). A post hoc analysis demonstrated a number needed to treat (NNT) of 6 (95% CI, 2.58 to not approached) to prevent 1 additional relapse.

As part of the prespecified statistical analysis, a treatment-by-race interaction was explored, and a statistically significant treatment-by-race interaction was observed ($P = .034$). Among white patients (n = 59), aripiprazole treatment resulted in a statistically significantly lower relapse rate than placebo (25.8% vs 60.7%, respectively), with an HR of 0.33 (95% CI, 0.14 to 0.78; $P = .011$), whereas among nonwhite patients (n = 26), the 2 treatment arms did not significantly differ (50.0% vs 31.3%, respectively), with an HR of 1.68 (95% CI, 0.49 to 5.83; $P = .410$). An age interaction test found no statistically significant age interaction ($P = .243$).

Figure 2. Patient Disposition



[a]Percentages are based on the number of patients enrolled.
[b]One subject had a serious adverse event (severe worsening of aggression and severe delusions) that occurred before study drug was administered.
[c]Percentages are based on the number of patients who completed screening phase and entered phase 1 (stabilization phase).
[d]Percentages are based on the number of patients randomized.
[e]The adverse event began in phase 1, and the patient was randomized in error and did not receive treatment in phase 2.

For the secondary end point, ABC-I (Figure 4), the mean increase from end of phase 1 to week 16 of phase 2 (LOCF) was 5.2 points among patients receiving aripiprazole and 9.6 points among patients receiving placebo, for a treatment difference of –4.40 (95% CI, –8.82 to 0.02; $P = .051$). As seen in Figure 5, the mean CGI-I score at week 16 (LOCF) was 4.2 for aripiprazole and 4.8 for placebo, for a treatment difference of –0.62 (95% CI, –1.35 to 0.10; $P = .090$).

In addition, differences between aripiprazole and placebo in mean change at week 16 were seen in the following ABC subscales (LOCF): ABC-hyperactivity (5.0 vs 10.3; difference = –5.2 [95% CI, –10.2 to –0.2]; $P = .041$), ABC-stereotypy (0.8 vs 2.8; difference = –2.0 [95% CI, –3.7 to –0.4]; $P = .018$), and ABC-inappropriate speech (0.6 vs 2.1; difference = –1.5 [95% CI, –2.6 to –0.3]; $P = .013$). A difference was not seen in the ABC-social withdrawal

subscale (0 vs 1.5; difference = –1.6 [95% CI, –4.0 to 0.9]; $P = .205$).

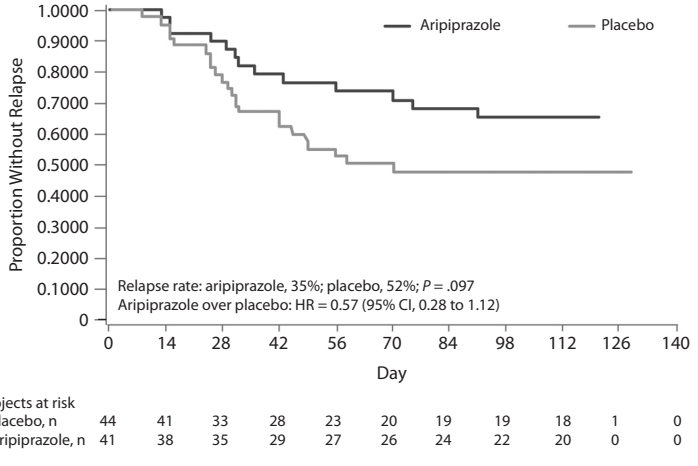
The week 16 mean treatment difference in the Caregiver Strain Questionnaire global score was more beneficial for aripiprazole, with a treatment difference of –1.2 (95% CI, –2.0 to –0.3). Results from the objective strain, subjective externalized strain, and subjective internalized strain subscales similarly favored aripiprazole. However, the mean treatment difference at week 16 of 6.3 points (95% CI, –0.63 to 13.22) on the PedsQL was similar for aripiprazole and placebo. Differences between aripiprazole and placebo for the combined PedsQL scale within individual age groups, and on the emotional, social, and cognitive functioning subscales were also not statistically significant.

Table 1. Baseline Demographics, Randomized Population

Variable	Aripiprazole (n = 41)	Placebo (n = 44)	Total (n = 85)
Age, mean (SD), y [a]	10.1 (2.8)	10.8 (2.8)	10.4 (2.8)
Age group, n (%)			
≤ 12 y	32 (78.0)	33 (75.0)	65 (76.5)
> 12 y	9 (22.0)	11 (25.0)	20 (23.5)
Gender, n (%)			
Male	30 (73.2)	38 (86.4)	68 (80.0)
Female	11 (26.8)	6 (13.6)	17 (20.0)
Race, n (%)			
White	31 (75.6)	28 (63.6)	59 (69.4)
Black/African American	8 (19.5)	11 (25.0)	19 (22.4)
Asian	0	3 (6.8)	3 (3.5)
American Indian/ Alaska Native	0	1 (2.3)	1 (1.2)
Other	2 (4.9)	1 (2.3)	13 (3.5)
Ethnicity, n (%)			
Hispanic/Latino	10 (24.4)	9 (20.5)	19 (22.4)
Not Hispanic/Latino	29 (70.7)	34 (77.3)	63 (74.1)
Weight, mean (SD), kg [b]	51.7 (24.4)	50.6 (21.9)	51.1 (23.0)
Weight group, n (%)			
< 40 kg	17 (41.5)	15 (34.1)	32 (37.6)
≥ 40 kg	24 (58.5)	29 (65.9)	53 (62.4)
Body mass index (kg/m^2), mean (SD) [b]	24.0 (7.4)	21.9 (5.2)	22.9 (6.4)

[a] Age assessed at date of first dose of single-blind study medication.
[b] Weight and body mass index assessed at last measurement on or before first day of double-blind dosing in phase 2.

Figure 3. Time From Randomization to Relapse



Safety Assessment

In the single-blind phase, 80% of patients reported a treatment-emergent adverse event, of which the majority were mild in intensity (Table 2). The most common adverse events were weight increase (25.2%), somnolence (14.8%), and vomiting (14.2%). The only serious adverse event was aggression (n = 1), which was not considered related to aripiprazole by the investigator. The only adverse events that led to discontinuation reported in more than 1 patient were aggression and weight increase (2 patients each). In this phase, 27 subjects (17.4%) had treatment-emergent, EPS-related adverse events; but the only treatment-emergent, EPS-related adverse event reported in ≥ 5% of subjects was tremor (6.5%).

In the randomized phase, 56.4% of patients receiving aripiprazole and 32.6% of patients receiving placebo reported a treatment-emergent adverse event (Table 2). Commonly observed adverse events (incidence ≥ 5% and at least twice the rate of placebo) in this phase with aripiprazole were upper respiratory tract infection (10.3% vs 2.3% for placebo), constipation (5.1% vs 0% for placebo), and movement disorder (5.1% vs 0% for placebo). Extrapyramidal symptom–related adverse events were observed in 7.7% (n = 3; movement disorder in 2 subjects, akathisia, extrapyramidal disorder, and tremor in 1 subject each) of patients in the aripiprazole group and 7.0% (n = 3; akathisia, muscle twitching, and tremor in 1 subject each) of placebo recipients. As in phase 1, the majority of events were mild in intensity. No patients reported a serious adverse event, and no patients discontinued due to adverse events in this phase. There were no deaths in the study.

Mean baseline weight for the population was 46.2 kg, and, at the end of phase 1, the mean change in weight *z* score (LOCF) was 0.2. Patients had a mean increase in weight of 3.2 kg (LOCF) and 2.6 kg (observed case). Phase 2 baseline weights were 52.0 kg for the aripiprazole group and 50.5 kg for the placebo group. The adjusted mean change from phase 2 baseline to week 16 in weight *z* score was statistically significantly greater in the aripiprazole group (0.1 kg, LOCF; 0.2 kg, observed case) than in the placebo group (–0.0 kg, LOCF; –0.1 kg, observed case), for a treatment difference (LOCF) of 0.15 SDs (95% CI, 0.06 to 0.24; $P = .001$). Two aripiprazole-treated patients (5.1%) and 1 placebo recipient (2.3%) experienced a ≥ 0.5 *z* score change. At week 16 of phase 2, aripiprazole-treated patients gained a mean of 2.2 kg (LOCF; 2.9 kg, observed case) and placebo recipients gained 0.6 kg (LOCF; 0.8 kg, observed case).

Median changes in fasting metabolic parameters during phase 1 were minimal: –6.0 mg/dL total cholesterol, –3.0 mg/dL low-density lipoprotein (LDL) cholesterol, –1.0 mg/dL high-density lipoprotein (HDL) cholesterol, 0 mg/dL glucose, and 4.0 mg/dL triglycerides. In phase 2, fasting metabolic changes from baseline did not differ between the 2 arms. Mean

Figure 4. Mean Change From Phase 2 Baseline in Aberrant Behavior Checklist-Irritability Subscale (ABC-I) Score (last observation carried forward) During Phase 2

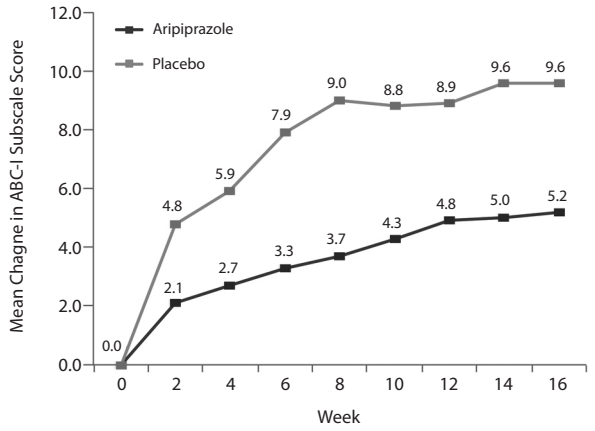


Figure 5. Adjusted Mean Clinical Global Impressions-Improvement Scale (CGI-I) Score (last observation carried forward) During Phase 2

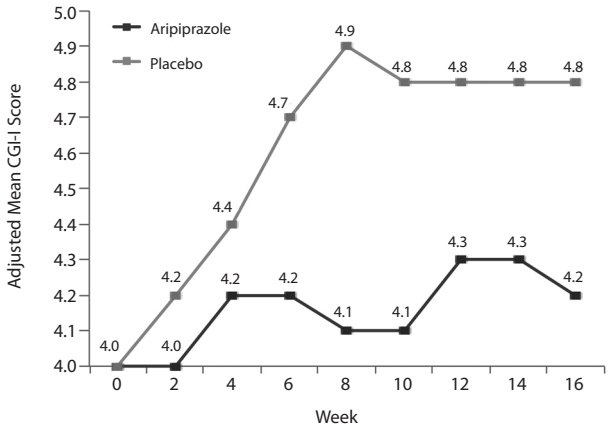


Table 2. Adverse Events for Phase 1 (≥ 5%) and Phase 2 (≥ 5% in either group)

Adverse Event	Aripiprazole (n = 155), n (%)	
Phase 1: single-blind phase		
Any adverse event	124 (80.0)	
Weight increase	39 (25.2)	
Somnolence	23 (14.8)	
Vomiting	22 (14.2)	
Increased appetite	20 (12.9)	
Upper respiratory tract infection	16 (10.3)	
Fatigue	13 (8.4)	
Insomnia	13 (8.4)	
Diarrhea	11 (7.1)	
Tremor	10 (6.5)	
Aggression	9 (5.8)	
Nasopharyngitis	9 (5.8)	
Headache	8 (5.2)	
Lethargy	8 (5.2)	
Pyrexia	8 (5.2)	
Phase 2: randomized phase	Aripiprazole (n = 39), n (%)	Placebo (n = 43), n (%)
Any adverse event	22 (56.4)	14 (32.6)
Upper respiratory tract infection	4 (10.3)	1 (2.3)
Constipation	2 (5.1)	0
Vomiting	2 (5.1)	2 (4.7)
Movement disorder	2 (5.1)	0

changes for aripiprazole and placebo, respectively, were 1.0 mg/dL and 0 for total cholesterol ($P = .885$); –2.0 mg/dL and 1.0 mg/dL for LDL cholesterol ($P = .901$); –1.0 mg/dL and –2.0 mg/dL for HDL cholesterol ($P = .950$); –1.0 mg/dL and –5.0 mg/dL for glucose ($P = .220$); and –2.0 mg/dL and 3.0 mg/dL for triglycerides ($P = .950$). The adjusted mean (standard error [SE]) change from baseline in serum prolactin during phase 1 was –4.7 ng/mL (0.65). During phase 2, the mean change in prolactin (week 16 LOCF) was –0.2 ng/mL and 4.6 ng/mL in the aripiprazole and placebo groups, respectively, for a treatment difference of –4.8 (95% CI, –6.8 to –2.9).

During phase 2, no differences in sexual maturation were observed between aripiprazole- and placebo-treated patients, and patients matured as expected when compared with published norms.[21–23] The number of patients who advanced a Tanner stage for pubic hair was 3 and 4 in the aripiprazole and placebo groups, respectively. The number of patients who advanced a Tanner stage for breast/genitals was 5 and 4 in the aripiprazole and placebo groups, respectively.

In the phase 1 safety sample, the unadjusted mean change from baseline in the AIMS total score to week 26 (LOCF) was –0.4. The unadjusted mean change from baseline in AIMS score items 8 (severity of abnormal movements overall), 9 (incapacitation due to abnormal movements), and 10 (patient awareness of abnormal movements) to week 26 (LOCF) was –0.1, –0.1, and –0.0, respectively. In phase 2, the adjusted mean change from baseline in AIMS total score to week 16 (LOCF) was –0.1 in the aripiprazole group and 0.1 in the placebo group, for a treatment difference of –0.15 (95% CI, –0.50 to 0.19; $P = .38$). In phase 1, the unadjusted mean change from baseline in Simpson-Angus Scale score from baseline to week 26 (LOCF) was –0.4, and, during phase 2, the adjusted mean change from baseline in Simpson-Angus Scale score to week 16 (LOCF) was larger in the aripiprazole group (–0.3) than in the placebo group (0.0), with a treatment difference of –0.37 (95% CI, –0.73 to –0.00; $P = .05$). In the phase 1 safety sample, the unadjusted mean change (SE) from baseline in BARS score to week 26 (LOCF) was –0.1 (0.04). In phase 2, the adjusted mean change from baseline in BARS score to week 16 (LOCF) was similar in the aripiprazole group (–0.1) and the placebo group (0.0) for a treatment difference of –0.10 (95% CI, –0.23 to –0.03; $P = .14$).

DISCUSSION

In this study, there was no statistically significant difference between aripiprazole and placebo in the primary outcome measure: time to relapse during maintenance therapy. The Kaplan-Meier relapse rates at week 16 of phase 2 were 35% for aripiprazole and 52% for placebo ($P = .097$), for an HR of 0.57. Although no significant difference was observed, it is worth noting that a post hoc analysis demonstrated

a clinically relevant[24,25] NNT of 6 to prevent 1 additional relapse. Similar to the primary end point, no statistically significant differences between aripiprazole and placebo were observed in the mean change from baseline (end of phase 1) to week 16 end point in ABC-I score ($P = .051$) and mean CGI-I score ($P = .090$) at week 16. In accordance with the established short-term efficacy of aripiprazole, few patients discontinued due to lack of efficacy in phase 1. Also, while half of the patients randomized to placebo in phase 2 did not relapse, half did, suggesting that maintenance treatment is beneficial for some patients.

The prespecified treatment-by-race interaction demonstrated a statistically significant treatment-by-race relationship ($P = .034$). Among white patients, aripiprazole treatment resulted in a statistically significantly lower relapse rate than placebo, but, among nonwhite patients, the 2 treatment arms did not significantly differ. These results were surprising, as previous studies in schizophrenia and depression did not demonstrate a difference in efficacy or safety of antipsychotic agents when stratified by race.[26–28] However, given that the study did not meet its primary end point and the number of patients in each race category was small, any conclusions about a possible treatment-by-race interaction are limited. The aripiprazole treatment arm statistically significantly differed from the placebo arm on some secondary efficacy measures. However, these results must be interpreted with caution and should be considered hypothesis generating, given that the 2 treatment arms did not statistically significantly differ on the primary end point.

Adverse events observed during phase 1 (single-blind aripiprazole) were consistent to what has been observed during the short-term and single-blind trials of aripiprazole for this indication.[7–10] The most common adverse events were weight increase, somnolence, and vomiting. Generally, modest weight gain was observed for some patients. This population was mostly antipsychotic-naive, which is a population at greater risk for antipsychotic-associated weight gain.[29] During phase 2, the overall incidence of treatment-emergent adverse events was higher in the aripiprazole group (56.4%) than the placebo group (32.6%). The majority of events were mild in intensity, and there were no serious adverse events or discontinuations due to adverse events during the randomized phase. Potentially, a portion of the adverse events observed in the placebo arm may stem from residual exposure to aripiprazole in phase 1, particularly given the long half-life of aripiprazole.

The incidence of clinically significant weight gain (defined as an increase in z score of ≥ 0.5 SDs[30,31]) was rare (2 aripiprazole patients and 1 placebo recipient) in the randomized phase; a z score change of < 0.5 SD is considered not clinically significant. However, other studies have shown that aripiprazole is associated with weight gain,[3] and, in the randomized phase of this study, aripiprazole patients gained an average of 1.6 kg more than placebo recipients. Therefore, careful monitoring of weight should be performed over the course of treatment. However, fasting metabolic changes in this long-term study were small, and there was no obvious trend across these measures in favor of either aripiprazole or placebo, which is consistent with other studies of aripiprazole in this population.[9]

As observed in the other trials of aripiprazole, EPS-related adverse events were observed in about a fifth of patients in phase 1, but there were few changes on mean objective score measures.[7,10] The equivalent proportion of patients in each arm who exhibited EPS, as well as the AIMS, Simpson-Angus Scale, and BARS scores during phase 2, suggests no incremental EPS-related burden with continued aripiprazole treatment compared with switching to placebo for maintenance therapy. As observed in previous trials using aripiprazole, and as would be expected with a dopamine receptor partial agonist, aripiprazole lowered mean serum prolactin concentrations compared with placebo; however, we know of no known clinical consequence of this magnitude change. In addition, Tanner staging results show no difference between the aripiprazole and placebo groups. Overall, these safety results demonstrate an acceptable safety and tolerability profile for continued aripiprazole treatment.

There were a number of limitations to this study. Although the HR and NNT suggest some clinical benefit with maintenance aripiprazole treatment, the effect size observed was smaller than what was used to power the study. The assumptions used to power this study were based on the 2 positive short-term studies[7,8] of aripiprazole in irritability associated with autistic disorder, and a maintenance study[20] of the atypical antipsychotic risperidone conducted by the Research Units on Pediatric Psychopharmacology Autism Network (RUPP). In addition to different treatments, the RUPP study design differed meaningfully from the design of the present study, and these variations may have contributed to the difference in results. The patients in the RUPP study may have been a highly enriched population of long-term risperidone responders because they had received risperidone treatment for 6 months prior to randomization as opposed to the 12 weeks in this study. Moreover, the study was conducted at just 5 clinical sites (versus the 34 sites of the present study), which could have resulted in reduced site-to-site variation.

In addition, patients in this study received slightly lower doses of aripiprazole than patients in the prior aripiprazole single-blind, long-term study, where the mean ending dose at 52 weeks was 10.6 mg/d and most patients were taking either 10 mg/d or 15 mg/d.[9,10] In the present study, which lasted up to 42 weeks, the mean dose of aripiprazole was slightly lower at 9.6 mg/d.

In any event, as with all pharmacologic interventions, especially the long-term treatment of children, clinicians must carefully consider the risks. Additionally, it is important to realize that the emergence of irritable behaviors on or off treatment can be driven by a number of factors, including disruptive changes in schedule, starting or discontinuing new medications, changes in the child's developmental status, development of new coping and other skills, and a

broad range of other related factors. Because these behaviors may stem from a number of contributors, clinicians need to consider treatment of these behaviors not just from a pharmacologic perspective but from a holistic perspective, using an approach that integrates the needs of the child and caregivers.

Drug names: aripiprazole (Abilify), atomoxetine (Strattera), eszopiclone (Lunesta and others), risperidone (Risperdal and others), zaleplon (Sonata and others), zolpidem (Ambien, Edluar, and others).

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Author contributions: All of the authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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