DEPARTMENT OF HEALTH AND HUMAN SERVICES
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA #/Serial #:** | 21-436 /S_27 |
| **DRUG NAME**: | Aripiprazole (Abilify) |
| **INDICATION:** | Treatment of Irritability Associated with Autistic Disorder |
| **APPLICANT:** | Otsuka |
| **DATE OF RECEIPT:** | 01/21/2009 |
| **REVIEW PRIORITY:** | Standard |
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**KEY WORDS:** MMRM, Autistic Disorder

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# 1 EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

The sponsor's Aripiprazole autistic disorder program consisted of 2 placebo-controlled studies of identical design except that fixed dosing was used for one (CN138179) and flexible dosing for the other (CN138178).

In the flexible-dose study (CN138178), Aripiprazole demonstrated statistically significant efficacy relative to placebo in treating irritability in children and adolescents (ages 6-17 years) with a diagnosis of autistic disorder, as assessed by the mean change from baseline on the ABC Irritability Subscale at Week 8 of the treatment phase. Aripiprazole also produced statistically significant improvements over placebo on the key secondary efficacy measure, the change in CGI-I score at Week 8.

The fixed-dose study CN138179 evaluated target Aripiprazole doses of 5, 10 and 15 mg/day. All 3 dose groups demonstrated statistically significantly greater efficacy than placebo in treating irritability in children and adolescents (ages 6-17 years) with a diagnosis of autistic disorder, as measured by the mean change from baseline to Week 8 on the ABC Irritability Subscale.

## 1.2 Brief Overview of Clinical Studies

The Aripiprazole autistic disorder program consisted of 2 placebo-controlled studies of identical design except that fixed dosing was used for one (CN1381794) and flexible dosing for the other (CN1381785).

In CN138178, Aripiprazole was flexibly dosed at 2- 15 mg/day. All patients randomized to treatment with Aripiprazole started the study at the 2-mg dose for Week 1; the dose could be increased to 5 mg at Week 2, to 10 mg at Week 3, and to 15 mg at Week 4. No dose increases could occur after Week 6. If the dose was intolerable, the dose could be decreased at any time. There were 164 patients enrolled at 19 study centers in the United States from June 15, 2006 through February 18, 2008.

In CN138179, patients were randomized to either placebo or a target dose 5, 10, or 15 mg/day Aripiprazole. All Aripiprazole-treated patients started the study at 2 mg for Week 1. The 5-mg Aripiprazole group reached the randomized dose at Week 2, the 10-mg Aripiprazole group at Week 3, and the 15-mg Aripiprazole group at Week 4. If the dose was intolerable, patients were discontinued from the study. There were 368 patients enrolled at 33 study centers in the United States from June 15, 2006 through March 19, 2008.

The primary efficacy endpoint of both studies was the mean change from baseline to endpoint (Week 8, last observation carried forward [LOCF]) in the ABC Irritability Subscale score.

### 1.3 Statistical Issues and Findings

Both studies were positive on the primary endpoint. In study CN138178, the efficacy of Aripiprazole flexible doses (2 to 15 mg/day) versus placebo in the adjusted (by the ANCOVA model) mean change from baseline on the ABC Irritability Subscale at the endpoint visit (Week 8 LOCF) was demonstrated. In addition, Aripiprazole flexible dose also demonstrated statistically significant improvement compared with placebo on the key secondary efficacy endpoint, the clinician rated CGI-I score at the endpoint visit (Week 8 LOCF). In study CN138179, the efficacy of Aripiprazole at 5-, 10-, and 15-mg/day doses versus placebo in the adjusted mean change from baseline on the ABC Irritability Subscale starting at the endpoint visit (Week 8 LOCF) was demonstrated with three statistically significant p-values.

## 2 INTRODUCTION

### 2.1 Overview

This review provides a statistical evaluation of Aripiprazole as a treatment of irritability associated with autistic disorder in children and adolescents of ages 6 to 17 years.

Autistic disorder is a neurodevelopmental disorder characterized by abnormalities in social interaction, communication, and the presence of restricted and repetitive behaviors. Although not strictly part of the diagnostic criteria, there are many secondary behavioral features that are commonly associated with autism. These include irritability and tantrums, attention and/or hyperactivity disorders, self-injury, odd responses to sensory stimuli, lack of fear or excessive fearfulness, and many others. Many of these can profoundly impair functioning and cause substantial individual and family burden. Reducing symptom burden as much as possible is a commonly accepted therapeutic goal but few studies are available to guide clinicians on how to treat problematic symptoms.

ABILIFY (Aripiprazole) is approved for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder in adults in the United States (US, the European Union (EU), and several other countries. ABILIFY is also approved in the US as adjunctive treatment in adult patients with major depressive disorder. In pediatric patients, ABILIFY is approved in the US for the treatment of schizophrenia in adolescents (ages 13-17) and in children and adolescents (ages 10-17) with bipolar I disorder. Although Risperdal is the only drug approved for treating pediatric patients with irritability associated with autistic disorder, alternative treatment options would be beneficial in this setting where there remains a high unmet medical need.

This Aripiprazole autistic disorder program consisted of 2 placebo-controlled studies of identical design except that fixed dosing was used for one and flexible dosing for the other. Sponsor attempted to use these two studies to demonstrate Aripiprazole can be used as an alternative treatment option for treating irritability in children and adolescents (ages 6 - 17 years) with a diagnosis of autistic disorder.

### 2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\fdswa150\NONECTD\N21436\S_027\2009-01-21\crt\datasets

## 3 STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

The following description is based on the sponsor's clinical study report. Any discrepancy between the study report and study protocol will be discussed in the section of statistical reviewer's comments.

#### 3.1.1 STUDY CN138178

The objective of this study was to compare the efficacy of flexibly dosed Aripiprazole with that of placebo in reducing serious behavioral problems, specifically irritability, agitation, and self-injurious behavior, in children and adolescents with a diagnosis of Autistic Disorder, as measured by change from baseline to the endpoint visit on the Irritability Subscale of the Aberrant Behavior Checklist (ABC). In addition, as a key secondary objective, this study was also interested to compare the efficacy of Aripiprazole with placebo as measured by the clinician-rated Clinical Global Impression of Improvement (CGI-I).

##### 3.1.1.1 Study Design

This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter 8-week study designed to assess the efficacy, safety, and tolerability of Aripiprazole flexibly dosed in children and adolescents with a diagnosis of autistic disorder with serious behavioral problems characterized by irritability, agitation, and self-injurious behavior. This study consisted a screening phase of up to 42 days followed by an 8-week treatment phase.

Patients were randomized to treatment with either Aripiprazole (2 to 15 mg/day) or placebo in a 1:1 ratio. All patients randomized to Aripiprazole started the study at the 2-mg dose for week 1; the dose could be increased to 5 mg at week 2, to 10 mg at week 3, and to 15 mg at week 4. No dose increase could occur after week 6. If the dose was intolerable, the dose could be decreased at any time. The mean daily dose of Aripiprazole for all patients in the safety sample at endpoint was 8.5 mg/day, see Figure 1. Patients who completed the 8-week treatment were eligible for an open-label long term study. There were 164 patients enrolled at 19 study centers in the United States from June 15, 2006 through February 18, 2008.

**Figure 1 Number and Percentages of Patients Receiving Study Medication and Mean and Range of Mean Daily Double-Blind Dose**

| | Placebo Mean Daily Dose per Week (mg/day) (b) | | | | Aripiprazole Mean Daily Dose per Week (mg/day) | | | |
|---|---|---|---|---|---|---|---|---|
| Days | N (%) | Mean | Min | Max | N (%) | Mean | Min | Max |
| Day 1 - 7 | 50 (100.0) | 2.1 | 2 | 3 | 47 (100.0) | 2.1 | 1 | 3 |
| Day 8 - 14 | 50 (100.0) | 4.4 | 2 | 9 | 45 (95.7) | 4.0 | 2 | 6 |
| Day 15 - 21 | 46 (92.0) | 7.8 | 1 | 15 | 42 (89.4) | 6.2 | 0 | 11 |
| Day 22 - 28 | 42 (84.0) | 10.7 | 2 | 15 | 42 (89.4) | 7.5 | 0 | 15 |
| Day 29 - 35 | 40 (80.0) | 11.9 | 2 | 15 | 41 (87.2) | 9.1 | 0 | 15 |
| Day 36 - 42 | 38 (76.0) | 11.9 | 2 | 15 | 40 (85.1) | 9.0 | 2 | 15 |
| Day 43 - 49 | 38 (76.0) | 12.5 | 2 | 15 | 39 (83.0) | 8.6 | 2 | 15 |
| Day 50 - 56 | 36 (72.0) | 12.8 | 2 | 15 | 39 (83.0) | 8.9 | 2 | 15 |
| Day >56 | 14 (28.0) | 13.6 | 5 | 15 | 13 (27.7) | 10.0 | 5 | 15 |
| Endpoint (a) | 50 (100.0) | 11.4 | 2 | 15 | 47 (100.0) | 8.5 | 1 | 15 |

[Source: Sponsor's CSR Table 6.1]

### 3.1.1.2 Efficacy Measures

The primary efficacy measure was the mean change from baseline to endpoint (Week 8) in the ABC Irritability Subscale score. The key secondary efficacy outcome measure was the mean CGI-I score.

The key secondary efficacy outcome measure was the mean CGI-I score at endpoint (week 8 LOCF).

Other secondary efficacy outcome measures will include the following:

- Mean change from baseline to Weeks 1, 2, 3, 4, 5, and 6 (LOCF and OC), as well as Week 8 (OC) in the ABC Irritability Subscale score
- Mean CGI-I score at Weeks 1, 2, 3, 4, 5 and 6 (LOCF and OC), as well as at Week 8 (OC)
- Mean change from baseline to Weeks 1, 2, 3, 4, 5, 6 and 8 (LOCF and OC) in the following ABC Subscales: Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech
- Response rate at Weeks 1, 2, 3, 4, 5, 6 and 8 (LOCF and OC) defined as $\geq$ 25% reduction from baseline in the ABC Irritability Subscale score AND a CGI-I score of 1 or 2
- Mean change from baseline to Week 8 in the CY-BOCS (LOCF and OC)
- Mean change from baseline to Week 8 in the CGI-S (LOCF and OC)

### 3.1.1.3 Statistical Analysis Plan

The hypothesis of this study is to demonstrate that Aripiprazole flexibly dosed (2-15 mg/day) is more effective than placebo in decreasing serious behavioral problems in children and adolescents with a diagnosis of Autistic Disorder, as measured by the Irritability Subscale of the ABC. The primary analysis will occur at the end of the study after all patients have completed the study. No interim analyses are planned.

It is expected that 100 patients will have to be randomized to obtain 90 evaluable patients (45 per treatment group). This sample size will yield 93% power to differentiate between placebo and the Aripiprazole treatment group when the true difference in the mean changes from baseline in the ABC Irritability Subscale score is 7.0. This assumes a standard deviation of 9.42 and a two sided test at the 0.05 level of significance.

For the purpose of analysis, four different study cohorts have been defined: Enrolled Sample, Randomized Sample, Safety Sample, and Efficacy Sample. The Safety Sample comprises all patients in the Randomized Sample who take at least one dose of study medication during the double-blind Treatment Phase, as identified on the dosing record. The efficacy sample comprises all patients who are in the safety sample and have at least one post-randomization efficacy evaluation and corresponding baseline value.

Furthermore, two different datasets have been defined: LOCF and OC dataset. The LOCF data set includes data recorded at a given time point or, if no observation is recorded at that time point, data carried forward from the previous time point with available data. Baseline data will not be carried forward or averaged with the on treatment data to impute missing values for the LOCF data set. The LOCF data set was the primary data set.

For continuous measurements, such as the ABC Irritability Subscale score, data were evaluated by ANCOVA with treatment, baseline body weight (two categories: ≥ 40 kg and < 40 kg), study center as main effects and baseline score as a covariate for the LOCF data set. Categorical measures such as response will be analyzed with the Cochran-Mantel Haenszel (CMH) procedure. For the analysis of the key secondary efficacy endpoint, a hierarchical testing procedure was used in order to protect the overall experiment-wise type I error rate at 0.05. CGI-I would be tested only if the primary efficacy endpoint was statistically significant.

### 3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

A total of 164 subjects enrolled into the study. Of these, 98 subjects were randomized to receive treatment: 51 patients to the placebo and 47 patients to Aripiprazole. The disposition of these 98 patients is listed in Table 1.

**Table 1 Reasons for Discontinuation**

| | **Treatment** | |
|---|---|---|
| | Aripiprazole (N=47) n (%) | Placebo (N=51) n (%) |
| Completed study | 39 (83.0) | 36 (70.6) |
| Terminated due to: | | |
| Adverse event | 5 (10.6) | 3 (5.9) |
| Lost to follow up | 1 (2.1) | 4 (7.8) |
| Lack of efficacy | 1 (2.1) | 6 (11.8) |
| Subject withdrew consent | 1 (2.1) | 2 (3.9) |

[Source: Reviewer's results and Sponsor's Table 5.1 of CSR]

**Demographic characteristics for the Randomized Sample are presented by randomized group in**

Table 2. The mean age of the randomized patients was 9.3 years (range 6 - 17 years). Patients were predominantly male (87.8%) and white (74.5%).

**Table 2 Demographic Characteristics**

| Parameter | Category | Statistic | Treatment | |
|---|---|---|---|---|
| | | | Placebo | Aripiprazole |
| **Age (years)** | | Mean (sd)<br>Median<br>Min - Max | 8.8 (2.57)<br>8.0<br>6-17 | 9.7 (3.20)<br>9.0<br>6 – 17 |
| **Gender** | Male<br>Female | n (%)<br>n (%) | 44 (86.3)<br>7 (13.7) | 42 (89.4)<br>5 (10.6) |
| **Race** | White<br>Black<br>Asian<br>Other | n (%)<br>n (%)<br>n (%)<br>n (%) | 41 (80.4)<br>7 (13.7)<br>0 (0.00)<br>3 (5.9) | 32 (68.1)<br>11 (23.4)<br>2 (4.3)<br>2 (4.2) |

[Source: Sponsor's Table 5.3.1 of CSR]

The ABC, CGI-S, and CY-BOCS ratings from the end of baseline are presented in Table 3. Mean baseline rates were similar between treatment groups.

**Table 3 End of Baseline Ratings for Randomized Sample**

| Scale | | Placebo (N=51) | Aripiprazole (N=47) | Total (N=98) |
|---|---|---|---|---|
| ABC (Irritability) | N | 51 | 47 | 98 |
| | Mean | 30.2 | 29.6 | 29.9 |
| | SD | 6.52 | 6.37 | 6.42 |
| | Median | 30.0 | 30.0 | 30.0 |
| | (Min, Max) | (19, 44) | (18, 45) | (18, 45) |
| ABC (Hyperactivity) | N | 51 | 47 | 98 |
| | Mean | 35.3 | 34.0 | 34.7 |
| | SD | 8.86 | 8.64 | 8.73 |
| | Median | 36.0 | 35.0 | 36.0 |
| | (Min, Max) | (9, 48) | (14, 48) | (9, 48) |
| ABC (Stereotypy) | N | 51 | 47 | 98 |
| | Mean | 11.2 | 11.8 | 11.5 |
| | SD | 5.79 | 6.13 | 5.93 |
| | Median | 10.0 | 12.0 | 11.5 |
| | (Min, Max) | (1, 21) | (0, 21) | (0, 21) |
| ABC (Social Withdrawal) | N | 51 | 47 | 98 |
| | Mean | 18.8 | 19.9 | 19.3 |
| | SD | 9.62 | 11.26 | 10.40 |
| | Median | 20.0 | 20.0 | 20.0 |
| | (Min, Max) | (0, 41) | (0, 48) | (0, 48) |
| ABC (Inappropriate Speech) | N | 51 | 47 | 98 |
| | Mean | 6.8 | 6.9 | 6.8 |
| | SD | 3.98 | 3.78 | 3.87 |
| | Median | 8.0 | 8.0 | 8.0 |
| | (Min, Max) | (0, 12) | (0, 12) | (0, 12) |

| Scale | | Placebo (N=51) | Aripiprazole (N=47) | Total (N=98) |
|---|---|---|---|---|
| CGI-Severity | N | 51 | 47 | 98 |
| | Mean | 4.9 | 4.9 | 4.9 |
| | SD | 0.63 | 0.71 | 0.67 |
| | Median | 5.0 | 5.0 | 5.0 |
| | (Min, Max) | (4, 6) | (4, 6) | (4, 6) |
| CY-BOCS (Compulsion) | N | 51 | 47 | 98 |
| | Mean | 14.2 | 12.9 | 13.6 |
| | SD | 3.39 | 4.94 | 4.24 |
| | Median | 15.0 | 14.0 | 14.5 |
| | (Min, Max) | (4, 20) | (0, 20) | (0, 20) |

[Source: sponsor's table 5.3.2 of CSR]

### 3.1.1.5 Sponsor's Key Efficacy Results

The primary endpoint was the mean change from baseline to Week 8 LOCF in the ABC Irritability Subscale score. There was a statistically significant difference between the treatment groups in favor of Aripiprazole in the adjusted mean change from baseline to Week 8 in ABC Irritability Subscale score, see Table 4.

**Table 4 Adjusted Mean Change from Baseline in ABC Irritability Subscale Score**

| Statistics | Placebo | Aripiprazole |
|---|---|---|
| N | 49 | 46 |
| Mean Baseline (SD) | 30.3 (6.6) | 29.5 (6.3) |
| Mean change from Baseline (SE) | -5.0 (1.4) | -12.9 (1.4) |
| Difference from Placebo | -7.9 | |
| 95% CI | (-11.7, -4.1) | |
| p-value | <.0001 | |

[Source: Reviewer's results]

### 3.1.1.6 Sponsor's Other Efficacy Results

As a sensitivity analysis, the results in Table 4 were repeated for the OC data set. The results corroborated with the primary findings, and Aripiprazole showed a statistically significantly improvement over placebo, see Table 5.

**Table 5 Sensitivity Analysis: Change from Baseline to Week 8 in the ABC Score**

| | **Placebo** | **Aripiprazole** |
|---|---|---|
| Sample Size at Week 8 | 34 | 38 |
| Mean change from Baseline (SE) | -5.2 (1.5) | -14.5 (1.4) |
| Difference from Placebo | -9.2 | |
| 95% CI | (-13.3, -5.2) | |
| p-value | <.0001 | |

[Source: Reviewer's results]

For the key secondary efficacy endpoint, the adjusted mean CGI-I score, the difference between the treatment groups in the adjusted mean at Week 8 LOCF was statistically significant in favor of Aripiprazole, see Table 6.

**Table 6 Adjusted Mean CGI-Improvement Score, LOCF Data set**

| Statistics | Placebo | Aripiprazole |
|---|---|---|
| N | 49 | 46 |
| Mean (SE) | 3.6 (.18) | 2.2 (.18) |
| Treatment difference | -1.4 | |
| 95% CI | (-1.9, -1.0) | |
| p-value | <.0001 | |

[Source: Reviewer's results]

The other secondary endpoints listed in section 3.1.1.2 were also analyzed by the sponsor, but none was pre-specified as key secondary endpoints and no multiple testing procedures was

applied to control the overall study wise Type I error rate. This review only included their means and standard errors as exploratory findings, see Table 7 and Table 8.

**Table 7 Mean Change from Baseline in ABC Irritability Subscale Score, LOCF and OC Data Sets, by Each Visit Week**

| Visit | LOCF | | | |
|---|---|---|---|---|
| | Placebo | | Aripiprazole | |
| | N | Mean (SE) | N | Mean (SE) |
| Week 1 | 46 | -2.7 (1.02) | 45 | -5.5 (1.01) |
| Week 2 | 49 | -3.6 (1.13) | 46 | -8.5 (1.13) |
| Week 3 | 49 | -4.6 (1.18) | 46 | -10.4 (1.19) |
| Week 4 | 49 | -6.6 (1.23) | 46 | -11.8 (1.24) |
| Week 5 | 49 | -5.7 (1.35) | 46 | -12.0 (1.36) |
| Week 6 | 49 | -6.2 (1.43) | 46 | -13.2 (1.44) |
| Visit | OC Set | | | |
| | Placebo | | Aripiprazole | |
| | N | Mean (SE) | N | Mean (SE) |
| Week 1 | 46 | -2.5 (0.93) | 45 | -5.1 (0.92) |
| Week 2 | 46 | -3.4 (1.01) | 42 | -8.8 (1.04) |
| Week 3 | 43 | -4.5 (1.10) | 40 | -10.8 (1.12) |
| Week 4 | 39 | -6.0 (1.19) | 40 | -12.0 (1.16) |
| Week 5 | 39 | -5.8 (1.30) | 39 | -12.9 (1.31) |
| Week 6 | 38 | -7.0 (1.47) | 38 | -14.6 (1.46) |
| Week 8 | 34 | -5.2 (1.49) | 38 | -14.5 (1.41) |

[Source: Reviewer's results]

**Table 8 Adjusted Mean CGI-Improvement Score, LOCF and OC Data Sets**

| Visit | LOCF Set | | | |
|---|---|---|---|---|
| | Placebo | | Aripiprazole | |
| | N | Mean (SE) | N | Mean (SE) |
| Week 1 | 46 | 3.9 (0.14) | 45 | 3.2 (0.13) |
| Week 2 | 49 | 3.6 (0.15) | 46 | 2.8 (0.16) |
| Week 3 | 49 | 3.5 (0.15) | 46 | 2.7 (0.15) |
| Week 4 | 49 | 3.5 (0.18) | 46 | 2.4 (0.18) |
| Week 5 | 49 | 3.6 (0.17) | 46 | 2.4 (0.18) |
| Week 6 | 49 | 3.5 (0.18) | 46 | 2.3 (0.18) |
| Visit | OC Set | | | |
| | Placebo | | Aripiprazole | |
| | N | Mean (SE) | N | Mean (SE) |
| Week 1 | 46 | 4.0 (0.12) | 45 | 3.2 (0.12) |
| Week 2 | 46 | 3.6 (0.13) | 43 | 2.8 (0.14) |
| Week 3 | 43 | 3.4 (0.12) | 40 | 2.7 (0.12) |
| Week 4 | 39 | 3.4 (0.16) | 40 | 2.3 (0.15) |

| | | | | |
|---|---|---|---|---|
| Week 5 | 39 | 3.4 (0.16) | 39 | 2.4 (0.17) |
| Week 6 | 38 | 3.3 (0.17) | 38 | 2.2 (0.17) |
| Week 8 | 34 | 3.4 (0.17) | 38 | 2.2 (0.16) |

[Source: Reviewer's results]

Aripiprazole also showed numerical improvement over placebo in most of the other ABC subscale scores. Table 9 displayed the mean changes from baseline to Week 8 LOCF for four of those subscale scores.

**Table 9 Mean Change (SE) from Baseline in Other ABC Scores (LOCF)**

| | **Placebo** | **Aripiprazole** |
|---|---|---|
| Hyperactivity | -2.8 (1.5) | -12.7 (1.52) |
| Stereotype | -2.0 (0.62) | -4.8 (0.63) |
| Social Withdraw | -6.2 (1.1) | -7.9 (1.2) |
| Inappropriate Speech | -0.4 (0.4) | -2.5 (0.40) |

[Source: Reviewer's results]

Furthermore, Aripiprazole also performed numerically better than placebo in a response rate, which is defined as a reduction ≥ 25% in ABC Irritability Subscale score compared to baseline and a score of 1 or 2 in the CGI-scale. The response rates are 14.3% vs. 52.2% for placebo and Aripiprazole, respectively.

Finally, the differences between treatment groups in the mean change from baseline to Week 8 LOCF in the CY-BOCS and CGI-S scores were also numerically in favor of Aripiprazole, see Table 10.

**Table 10 Mean Change (SE) from Baseline in CY-BOCS and CGI-S scores**

| | **Placebo** | **Aripiprazole** |
|---|---|---|
| CY-BOCS | -0.8 (0.52) | -3.8 (0.50) |
| CGI-S | -0.4 (0.15) | -1.2 (0.14) |

[Source: Reviewer's results]

### 3.1.1.7 Reviewer's Results and Comments

This reviewer confirms the findings based on the primary efficacy variable as presented in Table 4. Aripiprazole demonstrated statistically significant improvement compared with placebo on the adjusted mean change from baseline on the ABC Irritability Subscale at Week the endpoint visit (Week 8 LOCF).

Furthermore, the findings based on the key secondary efficacy variable were also confirmed as presented in Table 6. Aripiprazole demonstrated statistically significant improvement compared with placebo on the clinician rated CGI-I score at the endpoint visit (Week 8 LOCF).

This reviewer performed an analysis on the treatment effect over time based on an MMRM analysis. The treatment effects appeared to be consistent with the primary efficacy results, see Table 11.

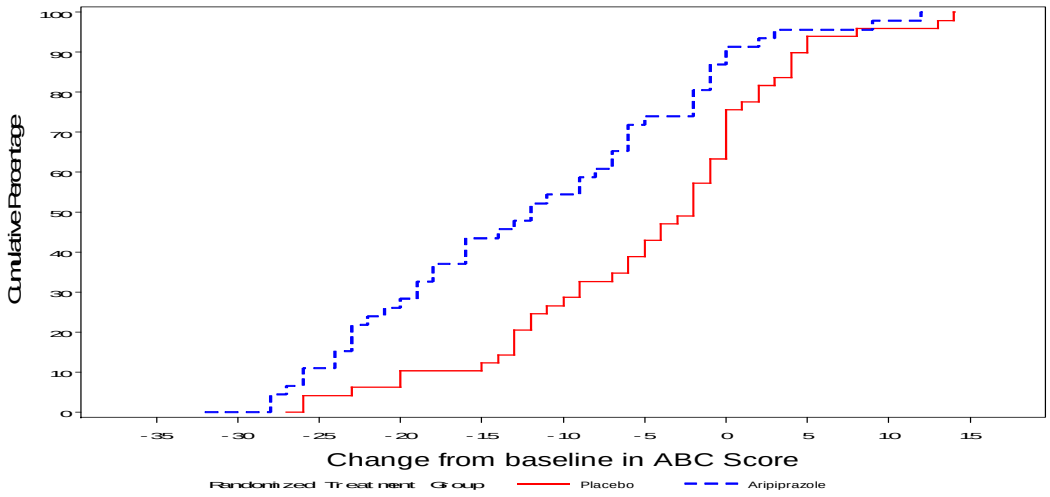
**Table 11 Change from Baseline in ABC Score (MMRM) over Weeks in the ITT sample**

| | Placebo | | Aripiprazole | | Aripiprazole-Pbo | |
|---|---|---|---|---|---|---|
| **Visit** | **N** | **Mean** | **N** | **Mean** | **LS Mean** | **P-value*** |
| Week 1 | 49 | -2.6 | 45 | -5.4 | -2.2 | 0.08 |
| Week 2 | 47 | -3.4 | 42 | -8.7 | -1.9 | 0.18 |
| Week 3 | 42 | -4.6 | 41 | -10.8 | -4.0 | 0.01 |
| Week 4 | 39 | -5.8 | 41 | -12.1 | -3.7 | 0.04 |
| Week 5 | 38 | -6.1 | 40 | -13.1 | -4.9 | 0.02 |
| Week 6 | 38 | -6.5 | 40 | -13.8 | -4.9 | 0.02 |
| Week 8 | 34 | -5.2 | 38 | -14.5 | -7.3 | 0.0009 |

[Source: Reviewer's results]

*p-values are not adjusted for multiplicity

**Figure 2 Cumulative Distribution Function of the Primary Endpoint by Treatment**




[Source: Reviewer's results]

Figure 2 displays the cumulative probability of these ABC Irritability Subscale score changes from baseline at Week 8 which were plotted across the range of observed values. The vertical axis indicates the proportion of patients whose score changes from baseline were less than or equal to a given number of score change (horizontal axis). For example, 50% of patients in the Aripiprazole group had reduced the score by up to approximately 12 and 50% of patients in the Placebo group had reduced the score only by up to approximately 2. The plots suggested a separation between Aripiprazole and placebo. The cumulative distribution function of Aripiprazole is entirely above of the distribution function of placebo, which is also consistent with the findings in Table 4. The raw means of each treatment group were generated from the LOCF data set, and were used to construct the curves in the Figure 2.

In summary, this study demonstrated the efficacy of Aripiprazole over placebo on the change from baseline to Week 8 in the ABC Irritability Subscale score. In addition, the improvement on the key secondary endpoint, the CGI-I scale, was statistically significantly greater for Aripiprazole versus placebo by the end of the treatment period (Week 8).

### 3.1.2 STUDY CN138179

The objective of this study was to compare the efficacy of Aripiprazole 5 mg, 10 mg, or 15 mg/day with placebo in reducing serious behavioral problems, specifically irritability, agitation, and self-injurious behavior, in children and adolescents with a diagnosis of autistic disorder, as measured by change from baseline to the endpoint visit on the Irritability Subscale of the Aberrant Behavior Checklist (ABC).

In addition, this study also has the following four efficacy secondary objectives:

- To compare the efficacy of Aripiprazole with placebo as measured by the clinician-rated Clinical Global Impression6 of Improvement (CGI-I)
- To compare the efficacy of Aripiprazole with that of placebo as measured by other subscales of the ABC (Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech)
- To compare the Response Rate of Aripiprazole with placebo (response defined as ≥ 25% reduction from baseline in the ABC Irritability Subscale score and a CGI-I score of 1 [much improved] or 2 [very much improved])
- To compare the effect of Aripiprazole with placebo on reduction in compulsive behavior as measured by the Children's Yale-Brown Obsessive Compulsive Scale7 (CY-BOCS Compulsion Scale only)

#### 3.1.2.1 Study Design

This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter 8-week study designed to assess the efficacy, safety, and tolerability of Aripiprazole flexibly dosed in children and adolescents with a diagnosis of autistic disorder with serious behavioral problems characterized by irritability, agitation, and self-injurious behavior. This study consisted of a screening phase of up to 42 days followed by an 8-week treatment phase.

Patients were randomized to treatment with Aripiprazole 5 mg, 10 mg, or 15 mg/day or placebo in a 1:1:1:1 ratio. Patients who completed the 8-week treatment were eligible for an open-label long term study. There were 368 patients enrolled at 33 study centers in the United States from June 15, 2006 through March 19, 2008.

#### 3.1.2.2 Efficacy Measures

The primary efficacy measure was the mean change from baseline to Week 8 in the ABC Irritability Subscale score.

The secondary efficacy outcome measures included the mean CGI-I score, response rate (defined as ≥ 25% reduction from baseline to endpoint in the ABC Irritability Subscale score AND a CGI-I score of 1 or 2 at endpoint), and mean change from baseline to Week 8 in the CY-BOCS.

#### 3.1.2.3 Statistical Analysis Plan

For continuous measurements, such as the ABC Irritability Subscale score, data were evaluated by ANCOVA with treatment, baseline body weight (2 categories: ≥ 40 kg and < 40 kg), study center as main effects and baseline value as a covariate for the LOCF data set. Only those

patients with both a baseline score and at least one post-baseline score will be included in the model. The models for OC data sets and subgroup analyses do not include study center.

Categorical measures such as response will be analyzed with the Cochran-Mantel Haenszel (CMH) procedure. The analyses of the LOCF data set controlled for study center and analyses of the OC data sets did not control for study center.

Except for the primary endpoint analysis, all other analyses were performed at the 5% significance level. For the primary efficacy analysis, and in order to protect the experiment-wise alpha level at 0.05 when comparing the three Aripiprazole doses versus placebo, the statistical testing will be carried out using the following sequential procedure. First the two higher Aripiprazole doses (10 mg, 15 mg) will be compared to placebo using the Hochberg procedure. Superiority to placebo will be claimed if both pairwise comparisons are significant at the 0.05 level, or one of the two is significant at the 0.025 level. Then, if both higher doses are declared statistically significant, the lower Aripiprazole dose (5 mg) will be compared to placebo and will be considered superior to placebo if the pairwise comparison is significant at the 0.05 level.

### 3.1.2.4 Patient Disposition, Demographic and Baseline Characteristics

A total of 368 subjects were enrolled into the study. Of these, 218 subjects were randomized to receive treatment. The disposition of these 218 patients is listed in Table 12.

**Table 12 Disposition of Patients**

| | **Treatment** | | | |
|---|---|---|---|---|
| | Aripiprazole | | | Placebo |
| | 5 mg (N=53) | 10 mg (N=59) | 15 mg (N=54) | (N=52) |
| Completed study | 44 (83.0%) | 49 (83.1%) | 47 (87.0) | 36 (70.6) |
| Terminated due to: | | | | |
| Adverse event | 5 (9.4%) | 8 (13.6%) | 4 (7.4%) | 4 (7.7%) |
| Lost to follow up | 1 (1.9%) | 0 | 1 (1.9%) | 3 (5.8%) |
| Lack of efficacy | 0 | 0 | 0 | 3 (5.8%) |
| Subject withdrew consent | 2 (3.8%) | 1 (1.7%) | 0 | 2 (3.8%) |
| Other | 1 (1.9%) | 1 (1.7%) | 2 (3.9%) | 2 (3.8%) |

[Source: Sponsor's Table 5.1 of CSR]

Demographic characteristics for the Randomized Sample are presented by randomized group in Table 13. The mean age of the randomized patients was 9.7 years (range 6 - 17 years). Patients were predominantly male (89.4%) and white (71.1%).

**Table 13 Demographic Characteristics**

| | Category | Statistic | Treatment | | | | Total N=218 |
|---|---|---|---|---|---|---|---|
| | | | Placebo | Aripiprazole 5 mg | Aripiprazole 10 mg | Aripiprazole 15 mg | |
| **Age (years)** | | Mean (sd)<br>Median<br>Min - Max | 10.2 (3.08)<br>9.0<br>6-16 | 9.0 (2.83)<br>8.0<br>6-17 | 10.0 (3.17)<br>10.0<br>6-17 | 9.5 (3.11)<br>8.0<br>6-17 | 9.7 (3.1)<br>9.0<br>6-17 |
| **Gender** | Male<br>Female | n (%)<br>n (%) | 48 (92.3)<br>4 (7.7) | 47 (88.7)<br>6 (11.3) | 50 (84.7)<br>9 (15.3) | 50 (92.6)<br>4 (7.4) | 195 (89.4)<br>23 (10.6) |
| **Race** | White<br>Black<br>Asian<br>Other | n (%)<br>n (%)<br>n (%)<br>n (%) | 35 (67.3)<br>13 (25.0)<br>3 (5.8)<br>0 | 37 (69.8)<br>13 (24.5)<br>1 (1.9)<br>0 | 41 (69.5)<br>15 (25.4)<br>2 (3.4)<br>0 | 42 (77.8)<br>9 (16.7)<br>0<br>1 (1.9) | 155 (71.1)<br>50 (22.9)<br>6 (2.8)<br>7 (3.2) |

[Source: Sponsor's Table 5.3.1 of CSR]

### 3.1.2.5 Sponsor's Efficacy Results for Primary Endpoint

The primary endpoint was the mean change from baseline to Week 8 LOCF in the ABC Irritability Subscale score. According to the statistical analysis plan, the superiorities to placebo of all three Aripiprazole doses were established with statistically significant differences in the adjusted mean change from baseline to Week 8 in ABC Irritability Subscale score, see Table 14.

**Table 14 Mean Change from Baseline in ABC Irritability Score to Week 8 (LOCF)**

| Statistics | Placebo | Arip 5mg | Arip 10mg | Arip 15mg |
|---|---|---|---|---|
| N | 49 | 52 | 59 | 53 |
| Mean Baseline (SD) | 27.8 (6.5) | 28.7 (7.5) | 28.2 (7.4) | 28.8 (6.5) |
| Mean change from Baseline (SD) | -7.9 (8.8) | -12.6 (10.1) | -12.9 (9.6) | -14.5 (10.9) |
| Treatment Differences with Placebo and 95% CI | --<br>-- | -4.05<br>(-7.7, -0.35) | -4.82<br>(-8.4, -1.29) | -5.98<br>(-9.64, -2.32) |
| p-values* | -- | 0.0319 | 0.0078 | 0.0015 |

[Source: Reviewer's results]

*p-values are nominal p-values

### 3.1.2.6 Sponsor's Other Efficacy Results

The primary analysis model was repeated using the per-protocol population. The results are summarized in Table 15. This ANCOVA model did not include study center as one of the factor. Using the Hochberg method, both Aripiprazole 15 mg and 10 mg were statistically superior to placebo. However, the lower dose (5 mg) failed to achieve the statistical significance difference from placebo.

**Table 15 Change from baseline to Week 8 in ABC Score in the OC sample**

| Statistics | Placebo | Arip 5mg | Arip 10mg | Arip 15mg |
|---|---|---|---|---|
| N at week 8 | 38 | 44 | 49 | 45 |
| Mean change from Baseline (SE) | -9.2 (1.5) | -12.4 (1.4) | -13.8 (1.3 | -14.4 (1.4) |
| Treatment Differences with Placebo and 95% CI | -- -- | -3.2 (-7.2, 0.9) | -4.5 (-8.4, -0.6) | -5.1 (-9.2, -1.1) |
| p-values | -- | 0.124 | 0.022 | 0.013 |

[Source: Reviewer's results]

All the secondary analysis results can not be used to assess the statistical significances of their corresponding secondary endpoints. There is no pre-specified multiplicity adjustment to control the study-wise type I error. This reviewer verified Sponsor's results for the CGI-Improvement score, response rate, and mean change in CY-BOCS as shown in Table 16. All three Aripiprazole doses outperformed placebo numerically in all three endpoints.

**Table 16 Means and SEs for the secondary endpoints at Week 8 (LOCF)**

| **Statistics** | **Placebo** | **Arip 5mg** | **Arip 10mg** | **Arip 15mg** |
|---|---|---|---|---|
| **CGI-I Score** | 3.3 (.18) | 2.6 (.17) | 2.5 (.16) | 2.5 (.17) |
| **Response Rate (N)** | 49 | 52 | 59 | 53 |
| Number of Responders | 17 | 29 | 29 | 28 |
| Proportions | 34.7% | 55.8% | 49.2% | 52.8% |
| **CY-BOCS Score** | -1.8 (.6) | -2.8 (.6) | -2.3 (.5) | -3.4 (.5) |

[Source: Reviewer's results]

### 3.1.2.7 Reviewer's Results and Comments

Study CN138179 was designed to compare the efficacy of 3 fixed doses of Aripiprazole (5, 10 and 15 mg/day) with placebo in treating irritability in children and adolescents (ages 6-17 years) with a diagnosis of autistic disorder, as assessed by the mean change from baseline to endpoint (week 8) on the ABC Irritability Subscale. This reviewer confirms the findings based on the primary efficacy variable as presented in Table 6. Based on 213 evaluable subjects in the Efficacy Sample who were treated for up to 8 weeks, the mean change from baseline to Week 8 on the primary endpoint was statistically significantly greater for patients on all 3 doses of Aripiprazole versus placebo (5 mg: $p<0.05$, 10 mg: $p<0.01$, 15 mg: $p<0.001$).

This reviewer performed an analysis on the treatment effect over time based on an MMRM analysis. The treatment effects appeared to be consistent with the primary efficacy results, see Table 17.

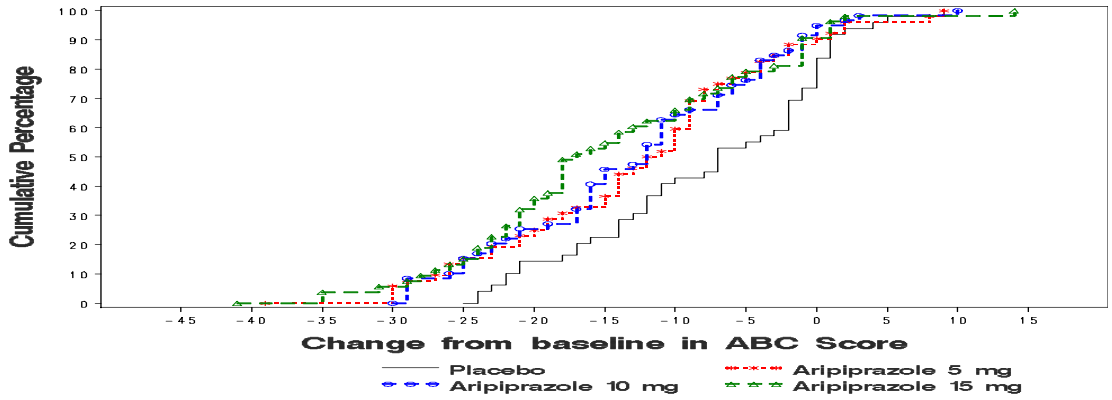
**Table 17 Change from Baseline in ABC score (MMRM) over Weeks in the ITT sample**

| Visit | Aripiprazole vs Placebo | | | | | |
|---|---|---|---|---|---|---|
| | 5 mg | | 10 mg | | 15 mg | |
| | Diff | p-value* | Diff | p-value* | Diff | p-value* |
| Week 1 | -2.65 | 0.1764 | -2.68 | 0.1566 | -5.62 | 0.0041 |
| Week 2 | -6.08 | 0.0049 | -6.34 | 0.0025 | -5.72 | 0.0075 |
| Week 3 | -5.25 | 0.0153 | -6.51 | 0.002 | -5.08 | 0.075 |
| Week 4 | -4.36 | 0.496 | -5.39 | 0.0124 | -6.84 | 0.002 |
| Week 5 | -5.98 | 0.008 | -5.15 | 0.0181 | -6.57 | 0.0032 |
| Week 6 | -4.51 | 0.059 | -6.69 | 0.0041 | -8.58 | 0.0003 |
| Week 8 | -4.24 | 0.06 | -5.17 | 0.0185 | -7.19 | 0.0015 |

[Source: Reviewer's results] *p-values are not adjusted for multiplicity

Figure 3 displays the cumulative probability of these ABC Irritability Subscale score changes from baseline at Week 8 which were plotted across the range of observed values. The vertical axis indicates the proportion of patients whose score changes from baseline were less than or equal to a given number of score change (horizontal axis). For example, 50% of patients in the Aripiprazole 5, 10 and 15 mg groups had reduced the scores by up to approximately 12, 13, and 17, respectively. And 50% of patients in the Placebo group had reduced the score only by up to approximately 7. The plots suggested a separation between all three Aripiprazole doses and placebo. The cumulative distribution functions of all three Aripiprazole doses are entirely above of the distribution function of placebo, which is also consistent with the findings in Table 117. The raw means of each treatment group were generated from the LOCF data set, and were used to construct the curves in the Figure 3.

**Figure 3 Cumulative Distribution Function of the Primary Endpoint by Treatment**

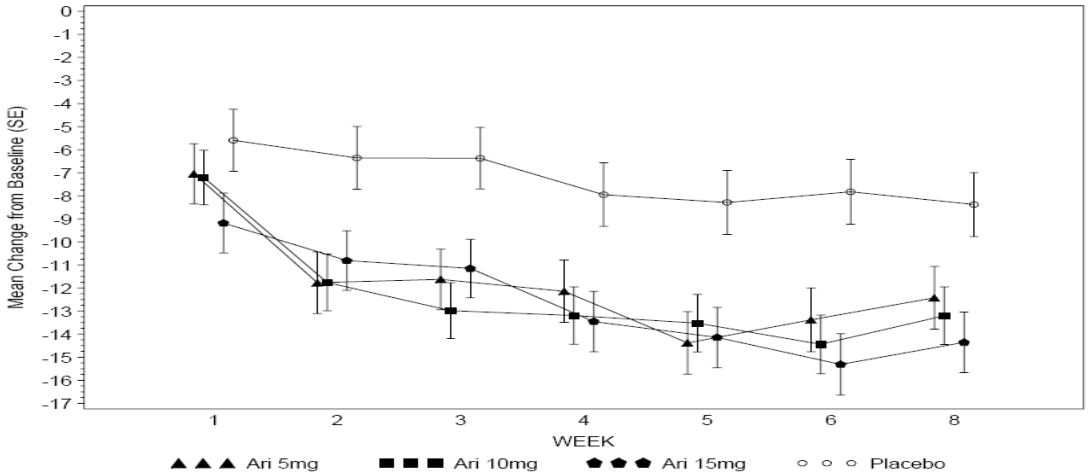



[Source: Reviewer's Results]

The adjusted mean change from baseline is also presented in Figure 4. Model based treatment differences versus placebo in the ABC Irritability Subscale score are presented in Figure 5. Both figures corroborated the findings in Table 14. The observed changes from baseline in primary scores on all three Aripiprazole doses were consistently lower than the scores on placebo throughout the entire course of the trial. However, there were never any significant separations among the three doses.

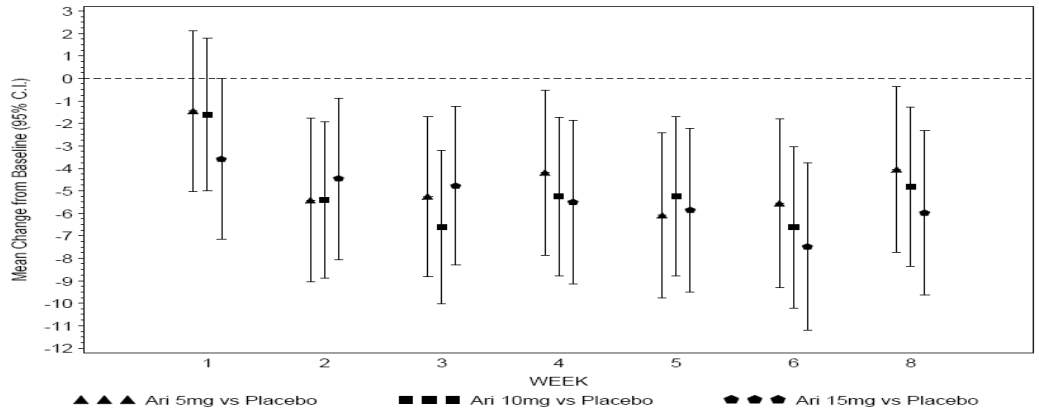
In summary, at 5-, 10-, and 15-mg/day doses, this study demonstrated the efficacy of Aripiprazole over placebo on the change from baseline to Week 8 in the ABC Irritability Subscale score.

**Figure 4 Adjusted Mean Change from Baseline in ABC Irritability Score, LOCF**




[Source: Sponsor's Figure 7.2A]

**Figure 5 Treatment Differences in ABC Irritability Subscale Score, LOCF**




[Source: Sponsor's Figure 7.2B]

The pairwise comparisons among the three Aripiprazole doses were drawn to explore whether the higher doses added additional benefit to the lower doses. Based on the results in Table 18, we noticed that each subsequent higher dose does add some benefit to the preceding lower doses. However, the standard error of each pairwise comparison is larger than the mean differences. Therefore, based on the results of Figure 4, Figure 5 and Table 18, the Aripiprazole 15 mg/day

group showed a numerically greatest benefit over the two lower doses; however, the difference did not appear to be statistically meaningful.

**Table 18 Pairwise Differences among the Aripiprazole Doses on Change from Baseline Scores to Week 8 (Based on Primary Statistical Model)**

| Treatments | Mean Differences | Standard Error |
|---|---|---|
| 5 mg vs. 10 mg | -0.77 | 1.77 |
| 5 mg vs. 15 mg | -1.93 | 1.82 |
| 10 mg vs. 15 mg | -1.16 | 1.76 |

[Reviewer's results]

## 3.2 Evaluation of Safety

Please refer to the clinical review for extensive safety evaluation and report. The following sections explore the effects of Aripiprazole on body weight and body mass. To explore the effects Aripiprazole on body weight, the sponsor carried out two exploratory analyses. The first analysis was on the change form baseline in body weight (in kg). The second analysis was on the change from baseline in BMI (in kg/m2). The results are summarized in Table 19 and Table 20 for both studies. Sponsor used ANCOVA model, controlling for treatment, study center, and baseline value, to obtain the treatment differences and corresponding p-values. It appears that Aripiprazole group had a significant increase in the adjustment mean change from baseline to Week 8 in patient body weight in both study. Note that the p-values are not adjusted for multiplicity. However, the differences in BMI are not as compelling as in body weight.

**Table 19 Adjusted Mean Change from Baseline in Weight and BMI, OC and LOCF, for Study CN138178**

| Variable | Visit | Placebo | Aripiprazole | Treatment Difference (p-value) |
|---|---|---|---|---|
| | | Mean (SE) | Mean (SE) | |
| Weight | Baseline | 39.4 (2.88) | 43.2 (3.01) | |
| | Change from baseline | | | |
| | Week 8 | 0.5 (0.38) | 1.9 (0.35) | 1.4 (0.009) |
| | Week 8 LOCF | 0.8 (0.29) | 2.0 (0.30) | 1.2 (0.004) |
| BMI | Baseline | 19.7(1.05) | 20.9 (1.01) | |
| | Change from Baseline | | | |
| | Week 8 | 0.1 (0.21) | 0.7 (0.19) | 0.6 (0.034) |
| | Week 8 LOCF | 0.3 (0.19) | 0.7 (0.18) | 0.4 (0.073) |

[Source: Sponsor's table 8.10.1A and 8.10.1D, confirmed by reviewer]

In the Summary of Clinical Safety, the sponsor pooled the two study, and reconfirmed the significant differences in adjusted mean change from baseline to endpoint (LOCF) in body weight between the pooled Aripiprazole group and the pooled placebo group (1.6 kg vs. 0.4 kg, respectively). Furthermore, sponsor also concluded that the adjusted mean change from baseline

to endpoint (LOCF) in body weight Z-score was higher in the Aripiprazole group compared with the placebo group. A Z-score for body weight were derived through the algorithm provided by the CDC, which is the number of standard deviations that one is from their gender/age standardized mean.

**Table 20 Adjusted Mean Change from Baseline in Weight and BMI, OC and LOCF, for Study CN138179**

| Variable | Visit | Placebo | Aripiprazole | | |
|---|---|---|---|---|---|
| | | | 5 mg | 10 mg | 15 mg |
| | | Mean (SE) | Mean (SE) | Mean (SE) | Mean (SE) |
| Weight | Baseline | 46.3 (3.21) | 39.0 (3.11) | 45.2 (2.90) | 42.3 (3.03) |
| | Change from Baseline | | | | |
| | Week 8 | 0.4 (0.37) | 1.5 (0.34) | 1.4 (0.33) | 1.6 (0.34) |
| | Week 8 LOCF | 0.3 (0.32) | 1.3 (0.31) | 1.3 (0.29) | 1.5 (0.30) |
| | Treatment difference with placebo (p-value) | | | | |
| | Week 8 | | 1.0 (0.044) | 1.0 (0.046) | 1.1 (0.023) |
| | Week 8 LOCF | | 1.0 (0.024) | 0.9 (0.027) | 1.2 (0.007) |
| BMI | Baseline | 21.0 (1.09) | 20.2 (1.04) | 21.1 (.095) | 20.8 (1.03) |
| | Change from Baseline | | | | |
| | Week 8 | 0.2 (0.18) | 0.5 (0.17) | 0.5 (0.16) | 0.7 (0.17) |
| | Week 8 LOCF | 0.2 (0.19) | 0.6 (0.18) | 0.6 (0.16) | 0.8 (0.18) |
| | Treatment difference with placebo (p-value) | | | | |
| | Week 8 | | 0.3 (0.233) | 0.3 (0.171) | 0.5 (0.041) |
| | Week 8 LOCF | | 0.4 (0.134) | 0.3 (0.189) | 0.6 (0.019) |

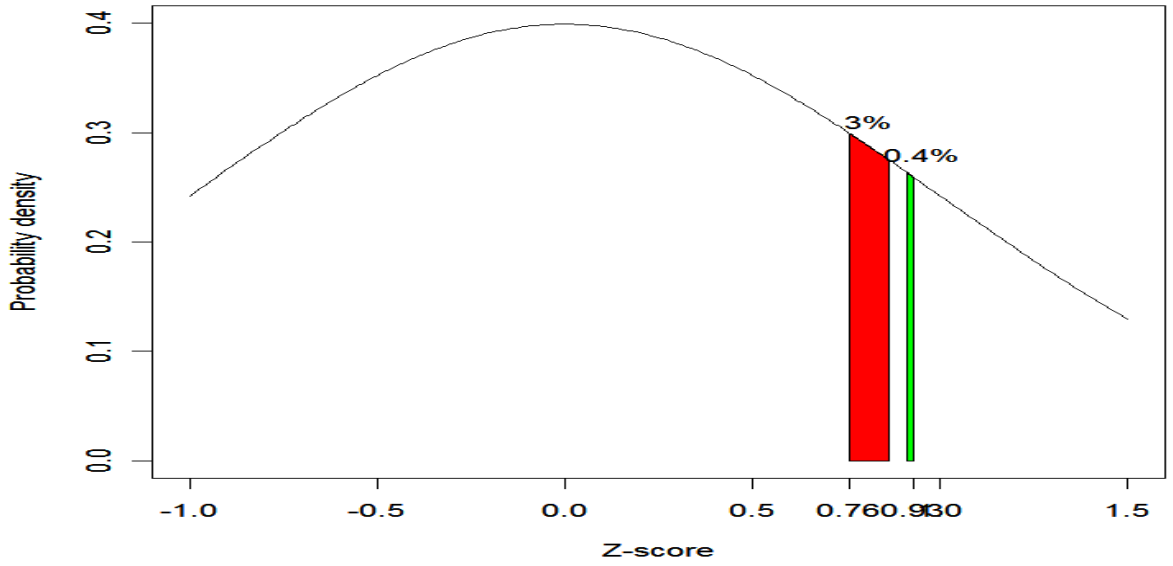
[Source: Sponsor's table 8.10.1A and 8.10.1D, confirmed by reviewer]

The agency's medical reviewer is interested in further exploring the adverse event of weight gain associated with aripiprazole treatment in pediatric autistic population and identifying potential risk factors in the pooled database. This reviewer conducted the following exploratory subgroup analyses on the mean change from baseline to the endpoint visit in body weight Z-score between the treatment groups by stratifying 1) the baseline body weight Z-score, 2) Age, and 3) Sex. The results are summarized in Table 21 and Table 22.

Overall, Aripiprazole patients and placebo patients had average baseline weight Z-score of 0.762 and 0.928 respectively, which correspond to the $77.7^{th}$ and the $82.3^{th}$ percentiles of their respective populations. This suggests that patients in these two studies had a heavier than normal average baseline weight. In addition, placebo patients were heavier at baseline than Aripiprazole patients. Whether the difference in baseline weight Z-score is of clinical relevancy is deferred to

the clinical review team. Aripiprazole patients increased their body weight Z-score by 0.105 standard deviations, which corresponds to an increase of the population body weight from the 77.7th percentile to the 80.7th percentile. However, the placebo group, on the other hand, reduced by 0.015 standard deviations in Z-score, which corresponds to a decrease of the population body weight from the 82.3th percentile to the 81.9th percentile. Therefore, a placebo patient on average shifted downward by 0.4%, but an Aripiprazole patient on average shifted upward by 3%, sees Figure 6. The difference appears statistically significant with a nominal p-value of 0.0001. However, whether the difference is of clinical relevancy is deferred to the clinical review team.

**Figure 6 Standard Normal Distribution Density Curve**




Based on the results in Table 21 and Table 22, Aripiprazole appears to have weight gain effect on the heavier and younger subjects. It is also noted that younger patients had a larger mean baseline weight Z-score compared with the other age group (0.835 versus 0.74, corresponding to the 79.8th and 77th percentiles in weight population). Upon further exploratory analysis, the pooled data seems to suggest that baseline weight Z-score and age group more or less contributed to the treatment differences in change from baseline at the endpoint visit in body weight Z-score. It is, however, uncertain whether the impact is clinical relevant.

**Table 21 Subgroup by Baseline Body Weight Z-score**

| Body Weight Z-score Percentile | Variable | Endpoint | Body Weight Z-score | | | | Treatment Comparison (a) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Placebo | | Aripiprazole | | | | |
| | | | N | Mean | N | Mean | Diff | 95% CI | P-value |
| Overall | Baseline | | 98 | 0.928 | 209 | 0.762 | -0.17 | -0.47, 0.14 | 0.29 |
| | Change from Baseline to Endpoint | OC | 71 | -0.027 | 176 | 0.116 | 0.143 | 0.07, 0.22 | 0.0001 |
| | | LOCF | 98 | -0.015 | 209 | 0.105 | 0.119 | 0.06, 0.145 | 0.0001 |
| < 25% | Change from Baseline to Endpoint | OC | 3 | 0.11 | 26 | 0.048 | -0.10 | -0.63, 0.42 | 0.693 |
| | | LOCF | 5 | 0.0235 | 31 | 0.0244 | -0.03 | -0.40, 0.34 | 0.872 |
| 25-50% | | OC | 13 | -0.079 | 20 | 0.178 | 0.29 | 0.07, 0.52 | 0.0129 |
| | | LOCF | 19 | -0.025 | 29 | 0.150 | 0.22 | 0.04, 0.41 | 0.0192 |
| 50-75% | | OC | 11 | 0.018 | 37 | 0.157 | 0.17 | -0.09, 0.44 | 0.196 |
| | | LOCF | 18 | 0.035 | 47 | 0.144 | 0.12 | -0.07, 0.31 | 0.214 |
| 75-100% | | OC | 43 | -0.03 | 85 | 0.11 | 0.16 | 0.09, 0.236 | <0.0001 |
| | | LOCF | 55 | -0.03 | 94 | 0.102 | 0.15 | 0.08, 0.219 | <0.0001 |
| < 40% | Change from Baseline to Endpoint | OC | 9 | -0.048 | 37 | 0.097 | 0.187 | -0.13, 0.51 | 0.242 |
| | | LOCF | 15 | -0.005 | 46 | 0.082 | 0.144 | -0.09, 0.378 | 0.225 |
| 40-60% | | OC | 9 | -0.04 | 25 | 0.17 | 0.196 | -0.045, 0.44 | 0.107 |
| | | LOCF | 13 | -0.013 | 35 | 0.144 | 0.155 | -0.03, 0.34 | 0.0967 |
| 60-90% | | OC | 24 | -0.022 | 50 | 0.145 | 0.22 | 0.062, 0.384 | 0.007 |
| | | LOCF | 32 | -0.028 | 58 | 0.133 | 0.12 | 0.068, 0.335 | 0.0035 |
| 90-100% | | OC | 28 | -0.023 | 56 | 0.088 | 0.12 | 0.048, 0.184 | 0.0011 |
| | | LOCF | 37 | -0.01 | 62 | 0.078 | 0.09 | 0.026, 0.155 | 0.0065 |
| < 50% | Change from Baseline to Endpoint | OC | 16 | -0.04 | 46 | 0.104 | 0.20 | -0.016, 0.42 | 0.0695 |
| | | LOCF | 24 | -0.015 | 60 | 0.085 | 0.16 | -0.01, 0.32 | 0.068 |
| ≥50% | | OC | 54 | -0.023 | 122 | 0.125 | 0.16 | 0.08, 0.245 | 0.0002 |
| | | LOCF | 73 | -0.016 | 141 | 0.116 | 0.14 | 0.07, 0.24 | 0.0001 |

[Source: Reviewer's Results] *p-values are not adjusted for multiplicity

(a) ANOCVA model, with treatment as a main effect, protocol as a stratification effect and Baseline weight Z-score as covariate. 95% confidence intervals for the differences and the p-values for pairwise comparisons are based on ANCOVA model.

**Table 22 Subgroup by Age and Sex**

| Age Subgroup | Variable | Population | Body Weight Z-score | | | | Treatment Comparison | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Placebo | | Aripiprazole | | | | |
| | | | N | Mean | N | Mean | Diff | 95% CI | P-value |
| 6-12 | Change | OC | 56 | -0.015 | 140 | 0.155 | 0.188 | 0.098, 0.278 | <0.0001 |
| | | LOCF | 77 | 0.005 | 165 | 0.140 | 0.154 | 0.076, 0.232 | <0.0001 |
| 13-17 | | OC | 15 | -0.069 | 36 | -0.036 | 0.041 | -0.11, 0.192 | 0.5855 |
| | | LOCF | 21 | -0.087 | 44 | -0.027 | 0.068 | -0.05, 0.188 | 0.2626 |
| Sex Subgroup | Variable | Population | Body Weight Z-score | | | | Treatment Comparison | | |
| | | | Placebo | | Aripiprazole | | | | |
| | | | N | Mean | N | Mean | Diff | 95% CI | P-value |
| Male | Change | OC | 63 | -0.023 | 156 | 0.117 | 0.159 | 0.073, 0.246 | 0.0004 |
| | | LOCF | 88 | -0.013 | 185 | 0.106 | 0.140 | 0.068, 0.213 | 0.0002 |
| Female | | OC | 8 | -0.059 | 20 | 0.113 | 0.205 | 0.013 0.398 | 0.038 |
| | | LOCF | 10 | -0.030 | 24 | 0.093 | 0.145 | -0.035, 0.325 | 0.1101 |

[Source: Reviewer's Analysis]

# 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

## 4.1 Gender, Age and Race group

### 4.1.1 STUDY CN138178

#### 4.1.1.1 Gender

There are 87.8% of all patients were males. Aripiprazole appeared to improve the ABC subscale for both males and females. There are no noticeable differences between two genders.

**Table 23 Subgroup Analysis for ABC Subscale Score by Gender**

| Subgroup | Aripiprazole | Placebo |
|---|---|---|
| **Male** | | |
| No. Subjects | 41 | 43 |
| Mean (SD) | -11.6 (11.1) | -4.6 (8.1) |
| **Female** | | |
| No. Subjects | 5 | 6 |
| Mean (SD) | -15.0 (4.4) | -6.2 (15.7) |

[Source: reviewer's result]

#### 4.1.1.2 Age

Age at entry was dichotomized to ≤ 12 versus > 12 years old. Aripiprazole appeared to improve the ABC subscale for both age groups. It also appeared to be more efficacious for the subjects under the age of 12 years. However, it should be noted that this age group accounted for more than 85% of the subjects. The results are summarized in Table 24.

**Table 24 Subgroup Analysis for ABC Subscale Score by Age**

| Subgroup | Aripiprazole | Placebo |
|---|---|---|
| **Age group (6-12)** | | |
| No. Subjects | 36 | 44 |
| Mean (SD) | -12.6 (11.0) | -4.4 (9.1) |
| **Age group (13-17)** | | |
| No. Subjects | 10 | 5 |
| Mean (SD) | -9.6 (8.9) | -7.8 (10.0) |

[Source: Reviewer's result]

#### 4.1.1.3 Race

Due to possible small sample sizes for certain ethnic groups, race was categorized into White, Black, and Other. Aripiprazole appeared to show numerical improvement in the primary endpoint in all three race groups, see Table 25. However, it should be noted that very few patients were in the Black and Other categories.

**Table 25 Subgroup Analysis for ABC Subscale Score by Race**

| Subgroup | Aripiprazole | Placebo |
|---|---|---|
| **Race = White** | | |
| No. Subjects | 32 | 39 |
| Mean (SD) | -12.3 (10.4) | -5.1 (9.2) |
| **Race = Black** | | |
| No. Subjects | 11 | 7 |
| Mean (SD) | -11.4 (11.8) | -1.7 (7.4) |
| **Race = Other** | | |
| No. Subjects | 3 | 3 |
| Mean (SD) | -10.7 (11.6) | -7.7 (13.9) |

[Source: Reviewer's results]

### 4.1.2 STUDY CN138179

#### 4.1.2.1 Gender

Table 26 shows the reviewer's subgroup analysis results on ABC subscale scores for gender. The number of patients by gender group is very comparable and the mean change from baseline stratified by gender appeared consistent with the primary result. All three Aripiprazole doses had numerical favorable results than placebo group in both gender, except the 15 mg/day female group. It could be explained by the very low enrollment in female subjects.

**Table 26 Subgroup Analysis for ABC Subscale Score by Gender**

| Subgroup | Arip 5 mg | Arip 10 mg | Arip 15 mg | Placebo |
|---|---|---|---|---|
| **Male** | | | | |
| No. Subjects | 46 | 50 | 49 | 45 |
| Mean (SD) | -12.7 (10.7) | -12.9 (9.6) | -15.0 (11.1) | -7.8 (9.0) |
| **Female** | | | | |
| No. Subjects | 6 | 9 | 4 | 4 |
| Mean (SD) | -12.3 (3.7) | -12.8(9.8) | -8.5 (7.9) | -8.8 (7.7) |

[Source: Reviewer's results]

#### 4.1.2.2 Age

Table 27 shows the reviewer's subgroup analysis results on ABC subscale scores for Age group. Age at entry was dichotomized to ≤ 12 versus > 12 years old. The number of patients by age group is very comparable and the mean change from baseline stratified by age appeared consistent with the primary result. All three Aripiprazole doses had numerical favorable results than placebo group in both age groups.

**Table 27 Subgroup Analysis for ABC Subscale Score by Age**

| Subgroup | Aripiprazole 5 mg | Aripiprazole 10 mg | Aripiprazole 15 mg | Placebo |
|---|---|---|---|---|
| **Age group (6-12)** | | | | |
| No. Subjects | 43 | 45 | 42 | 33 |
| Mean (SD) | -11.5 (10.2) | -11.8 (9.6) | -13.6 (10.4) | -7.5 (8.9) |
| **Age group (13-17)** | | | | |
| No. Subjects | 9 | 14 | 11 | 16 |
| Mean (SD) | -18.1 (8.0) | -16.5 (8.6) | -18.0 (12.8) | -8.5 (8.8) |

[Source: Reviewer's results]

### 4.1.2.3 Race

Table 28 shows the reviewer's subgroup analysis results on ABC subscale scores for Race group. Due to possible small sample sizes for certain ethnic groups, race was categorized into White, Black, and Other. The number of patients by race group is very comparable and the mean change from baseline stratified by race appeared consistent with the primary result. All three Aripiprazole doses had numerical favorable results than placebo group in White and Black patients. Aripiprazole 10 mg had poor performance in the Other group, it could be due to the lack of enrollment in this race group.

**Table 28 Subgroup Analysis for ABC Subscale Score by Race**

| Subgroup | Aripiprazole 5 mg | Aripiprazole 10 mg | Aripiprazole 15 mg | Placebo |
|---|---|---|---|---|
| **Race = White** | | | | |
| o. Subjects | 36 | 41 | 41 | 33 |
| Mean (SD) | -12.4 (11.3) | -13.5 (9.62) | -14.2 (11.2) | -7.4 (8.7) |
| **Race = Black** | | | | |
| No. Subjects | 13 | 15 | 9 | 12 |
| Mean (SD) | -12.5 (7.0) | -13.3 (9.5) | -15.9 (11.7) | -8.2 (9.1) |
| **Race = Other** | | | | |
| No. Subjects | 3 | 3 | 3 | 4 |
| Mean (SD) | -16.3 (7.8) | -2.7 (4.2) | -15.0 (6.2) | -10.5 (10.5) |

[Source: Reviewer's result]

## 4.2 Other Subgroup Populations

The entire patient population was enrolled within United States, so the comparison between U.S. and Non-U.S. sites can not be analyzed. Furthermore, no other subgroups were analyzed.

# 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

Both studies were positive on the primary endpoints. In study CN138178, the efficacy of Aripiprazole flexibly doses (2 to 15 mg/day) versus placebo in the adjusted mean change from baseline on the ABC Irritability Subscale at the endpoint visit (Week 8 LOCF) was demonstrated. In addition, Aripiprazole flexible dose also demonstrated statistically significant improvement compared with placebo on the key secondary efficacy endpoint, the clinician rated CGI-I score at the endpoint visit (Week 8 LOCF). In study CN138179, the efficacy of Aripiprazole at 5-, 10-, and 15-mg/day doses versus placebo in the adjusted mean change from baseline on the ABC Irritability Subscale at the endpoint visit (Week 8 LOCF) was demonstrated with three statistically significant p-values.

## 5.2 Conclusions and Recommendations

The sponsor's Aripiprazole autistic disorder program consisted of 2 placebo-controlled studies of identical design except that fixed dosing was used for one (CN138179) and flexible dosing for the other (CN138178).

In the flexible-dose study (CN138178), Aripiprazole demonstrated statistically significant efficacy relative to placebo in treating irritability in children and adolescents (ages 6-17 years) with a diagnosis of autistic disorder, as assessed by the mean change from baseline on the ABC Irritability Subscale at Week 8. Aripiprazole also produced statistically significant improvements over placebo on the key secondary efficacy measure, the CGI-I score, at Week 8.

The fixed-dose study CN138179 evaluated target Aripiprazole doses of 5, 10 and 15 mg/day. All 3 dose groups demonstrated significantly greater efficacy than placebo in treating irritability in children and adolescents (ages 6-17 years) with a diagnosis of autistic disorder, as measured by the mean change from baseline to Week 8 on the ABC Irritability Subscale.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-21436 | SUPPL-27 | OTSUKA PHARMACEUTICAL CO LTD | ABILIFY (ARIPIPRAZOLE) 10/15/20/30MG |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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