CLINICAL REVIEW

Application Type	sNDA
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Priority or Standard	S
Submit Date(s)	21 January 2009
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Division / Office	DPP/ONE1
Reviewer Name(s)	Jing Zhang, MD., PhD.
Review Completion Date	October 30, 2009
Established Name	Aripiprazole
(Proposed) Trade Name	Abilify®
Therapeutic Class	Atypical Antipsychotic
Applicant	Otsuka Pharmaceutical Co, Ltd
Formulation(s)	2, 5, 10, & 15 mg tablets
Dosing Regimen	2 to 15 mg
Indication(s)	Irritability Associated with Autistic Disorder
Intended Population(s)	6 to 17 year old

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Otsuka submitted this sNDA intended to seek for a new indication of aripiprazole in the treatment of irritability associated with autistic disorder. Based on the available data submitted to this supplemental NDA, mainly obtained from two 8-week, double-blind, placebo-controlled studies, it is recommended that this NDA be granted an approval status.

Several labeling recommendations have been made. Please refer to section 9.2 Labeling Recommendations for detailed recommendations. Final approval is contingent on satisfactory response to the agency's recommendations and mutual agreement on labeling as well as the conclusions of the CMC, pharmacology/toxicology, and clinical pharmacology reviewers.

1.2 Risk Benefit Assessment

Autistic disorder is a neurodevelopmental disorder characterized by abnormalities in social interaction, communication, and the presence of restricted and repetitive behaviors. 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. Risperdal is an only approved medication for treating pediatric patients with irritability associated with autistic disorder. Alternative treatment options would be necessary.

The efficacy of aripiprazole in improving symptoms of irritability in children and adolescents with autistic disorder was demonstrated by positive results obtained from two 8-week, randomized, multicenter, double-blind, placebo-controlled studies (CN138178 and CN138179). The safety evaluation demonstrated that the safety profile of aripiprazole in autistic population is similar to that obtained from pediatric schizophrenic and bipolar populations. Aripiprazole was generally safe and well tolerated in this population.

Given irritability associated with autistic disorder is a serious psychiatric condition, and Risperdal is the only drug approved in the USA for this condition, it is believed that the benefit of having aripiprazole available for this psychiatric condition justifies the risk of potential adverse events with aripiprazole treatment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The safety profile of aripiprazole in pediatric autistic population is comparable to that obtained from pediatric schizophrenic and bipolar population. No specific safety concern had been identified from this submission. Risk Evaluation and Mitigation Strategies are not required at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The division requested BMS/Otsuka conduct a long-term maintenance study as a Post-market Commitment to assess the long-term efficacy and safety of aripiprazole in autistic patients ages 6 to 16 with a history of irritability. BMS/Otsuka had committed to conduct this study. The protocol for this study will be submitted 6 months post approval and initiated 1 year post approval. Study completion is anticipated 3 years after study start with a clinical study report submission 1 year after the study is completed.

2 Introduction and Regulatory Background

2.1 Product Information

Aripiprazole is a dopamine presynaptic D_2 auto-receptor partial agonist and belongs to atypical antipsychotic family. Same as other atypical antipsychotics, aripiprazole also acts as an antagonist at serotonin 5-HT_{1A} receptor.

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.

2.2 Tables of Currently Available Treatments for Proposed Indications

Risperdal is the only medication that has been approved in the USA for the indication of irritability associated with autistic disorder.

2.3 Availability of Proposed Active Ingredient in the United States

Aripiprazole is an approved drug in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Aripiprazole is an atypical antipsychotic. However, aripipirazole has a unique dopamine D_2 receptor partial agonist property. As a member of atypical antipsychotics, aripiprazole labeling carries same class warnings and precautions as other atypical antipsychotics. No important issues with pharmacologically related products were identified from this submission.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

07-Dec-2004	EOP2 meeting to discuss the registrational plan for treatment of serious behavior problems associated with autism
08-Apr-2005	Initial IND (IND 71,501) submission
08-Jun-2005	FDA letter in response to BMS request for special protocol assessment (CN138-178, -179, and -180)
25-Jul-2005	FDA statistical comments on CN138-178, and -179
17-Jan-2007	Met with FDA for a guidance meeting for autistic disorder program
08-Feb-2008	Statistical Analysis Plan for CN138-178 submitted
06-May-2008	Statistical Plan Updates for CN138-178 and -179 submitted
08-Aug-2008	Background Document for pre-sNDA meeting submitted
09-Sep-2008	Pre-sNDA meeting cancelled

2.6 Other Relevant Background Information

Aripiprazole has not been withdrawn from the market worldwide for any reason.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

During the course of the review, no problems with respect to data quality or integrity were identified.

The division of scientific investigation inspected 4 study sites: Dr. Melmed (Phoenix, AZ); Dr.Attala (Smyrna, GA); Dr. Hardan (Stanford, CA); and Dr. Rugino (Toms River, NJ). Anthony Orencia, MD., is the primary medical officer for this submission. Please refer to his clinical inspection summary of detailed pertinent information. The inspection did not find significant discrepancies with the data listings provided in the NDA and source documents at the clinical sites and concluded that the data generated by these sites appear reliable in support of the application.

3.2 Compliance with Good Clinical Practices

Study CN138-178 and CN138-179 were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

3.3 Financial Disclosures

(b) (6) who has participated in study (b) (6), received significant payments of other sorts made on or after February 2, 1999 from the sponsor such as a grant to found ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria. (b) (6) site has enrolled (b) (6) patients and (b) (6) of them were randomized.

(b) (6) who has participated in study (b) (6) might have received less than $25,000 from (b) (6) for giving speeches. (b) (6) site has enrolled (b) (6) patients and (b) (6) of them were randomized.

Both studies are multi-center, double-blinded studies. Thus, it is less likely that aforementioned arrangements have biased the study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There is no new CMC information provided in this submission. The Sponsor has requested a categorical exclusion from the preparation of an environmental assessment, under 21 CFR 25.31 (a), based on an estimate that the concentration of the active moiety in the environment will remain at less than 1 ppb, regardless of the potential increase in use, due to the additional indication. The CMC reviewer, Julia C.

Pinto, PhD, has no objection to the sponsor's exclusion request. No environmental assessment is required for this submission.

4.2 Clinical Microbiology

No clinical microbiology study was deemed necessary.

4.3 Preclinical Pharmacology/Toxicology

No preclinical pharmacology/toxicology study was submitted to this sNDA.

4.4 Clinical Pharmacology

No PK/PD or drug-drug interaction studies was submitted to this sNDA.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 summarizes the aripiprazole autistic disorder clinical program.

Table 1 Aripiprazole Autistic Disorder Clinical Program

Study Number	Number of Study Centers/ Location/ Study Dates	Design	Study Objective	Study Drugs	Randomized/ Treated	Gender/ Mean Age (Range)	Endpoints
Short-term Placebo-controlled Studies							
CN138178	18 US centers[a] / 6/06 - 4/08	Phase 3: Randomized, double-blind study comparing flexibly-dosed aripiprazole with placebo for 8 weeks	Efficacy and Safety	Aripiprazole flexibly dosed (2 - 15mg) Placebo	47/47 51/50	86 Males 12 Females 9.3 years (6-17)	Primary Efficacy: Mean change from baseline to endpoint (Week 8) in ABC Irritability Subscale Score. Key Secondary Efficacy: mean CGI-Improvement Score Safety: AEs, EPS-related AEs, Simpson-Angus Scale, Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, laboratory tests, vital sign measurements, 12-lead ECGs
CN138179	31 US centers[a] / 6/06 - 6/08	Phase 3: Randomized, double-blind study comparing fixed-dose aripiprazole with placebo for 8 weeks	Efficacy and Safety	Aripiprazole 5 mg Aripiprazole 10 mg Aripiprazole 15 mg Placebo	53/52 59/59 54/54 52/51	195 Males 23 Females 9.7 years (6-17)	Primary Efficacy: Mean change from baseline to endpoint (Week 8) in ABC Irritability Subscale Score. Safety: AEs, EPS-related AEs, Simpson-Angus Scale, Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, laboratory tests, vital sign measurements, 12-lead ECGs
Long-term Open-label Study							
CN138180	49 US centers/ 6/06 - ongoing	Phase 3: Open-label study with flexibly-dosed aripiprazole for 52 weeks	Safety	Aripiprazole flexibly dosed (2-15mg)	347/313	274 Males 39 Females 9.8 years (6-17)	Safety: AEs, EPS-related AEs, Simpson-Angus Scale, Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, laboratory tests, vital sign measurements, 12-lead ECGs

5.2 Review Strategy

Material reviewed in this review cycle includes Clinical Study Reports from CN138-178 and CN138-179, Clinical Summaries, Clinical Overview, Safety Update, and the proposed labeling. The efficacy review was performed in consultation with the statistical reviewer, Steven Bai, PhD. Please refer to his review for more detailed pertinent efficacy information.

5.3 Discussion of Individual Studies/Clinical Trials

The 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). Both studies are positive studies—aripiprazole demonstrated superiority over placebo in the treatment of irritability in children and adolescents (aged 6 - 17 years) with autistic disorder. Aripiprazole was generally safe and well tolerated in this population. In addition, there is an open-label uncontrolled safety study (CN138180) currently ongoing.

6 Review of Efficacy

A. Studies for the Indication of Irritability Associated with Autism Disorder

a. Rationale for Selection of Studies for Review

The autism program consisted of two 8-week, multi-center, double-blind, randomized, placebo-controlled efficacy studies of nearly identical design with the main exception that flexible dosing (5 to 15 mg) was used for one (CN138178) and fixed dosing (5, 10 and 15 mg) for the other (CN138179). For both studies, the primary endpoint is the mean change from baseline to Week 8 in the Aberrant Behavior Checklist (ABC) Irritability Subscale. There was a key secondary endpoint, the mean change from baseline to endpoint in Clinical Global Impressions Improvement (CGI-I) score in study CN138178. There was no key secondary endpoint in study CN138179. Both studies were positive studies and were reviewed in detail in this clinical review.

The ABC is an informant-based symptom checklist for assessing the classifying problem behaviors of children and adolescents with mental retardation. The 58 items are rated on a 4-point scale (0 = not at all a problem to 3 = the problem is severe in

degree), and resolve into 5 subscales: (1) irritability, agitation; (2) lethargy, social withdrawal; (3) stereotypic behavior; (4) hyperactivity, noncompliance; and (5) inappropriate speech. The ABC-Irritability Subscale consists of 15 items, each rated on a scale from 0 to 3, with a maximum score of 45. As a primary endpoint, ABC Irritability Subscale was used in Risperdal pediatric trials for the indication of irritability associated with autistic disorder. ABC Irritability Subscale had been accepted by the division as a valid measurement for irritability symptomatology in autistic patients.

The Clinical Global Impressions (CGI) Scale is a standardized assessment tool. Its goal is to allow the clinician to rate the severity of illness, change over time, and efficacy of medication, taking into account the patient's clinical condition and the severity of side effects. The CGI Scale is widely used in clinical psychopharmacology trials as an outcome measure. The measure had been accepted by the division as a reasonable secondary endpoint for many clinical trials.

b. Study Summaries

Study CN138178

i. *Method/Study Design/Analysis Plan*

Study CN138178 was conducted from 15 June 2006 to 28 April 2008 at 19 centers in the United States. A complete list of investigators, their staff, study centers, and number of patients enrolled per center are listed in Appendix 1.5 in the original sDNA submission.

Overall Study Design

Study CN138178 was a 8 week, multicenter, flexible-dose, double-blind, randomized, placebo-controlled, parallel-group study designed to assess the efficacy, safety, and tolerability of aripiprazole in children and adolescents with a DSM-IV diagnosis of autistic disorder with serious behavioral problems characterized by irritability, agitation, and self-injurious behavior.

This study had 2 phases: a screening phase of up to 42 days followed by an 8-week treatment phase. Eligible patients were randomized to treatment with either aripiprazole (2 to 15 mg/day) or placebo in a 1:1 ratio. Patients visited the clinic at the end of treatment Weeks 1, 2, 3, 4, 5, 6, and 8, at which time efficacy and safety measures were collected. To assess patient well-being and medication tolerability between visits in the latter half of the double-blind treatment phase, a telephone contact occurred at Week 7. End of study assessments were performed at the end of Week 8 or at the time

of early termination. Patients who completed the 8-week, double-blind treatment phase were eligible for an open-label long-term study.

Approximately 100 patients were planned to be randomly assigned to receive aripiprazole (2 to 15 mg) or placebo. A total of 164 patients were enrolled with 98 randomized (51 in the placebo group and 47 in the aripiprazole group).

Dose and Administration

A flexible dosing regimen was used for each patient. For all patients randomized to receive aripiprazole, the starting dose was 2 mg. Doses can be increased to 5, 10 or 15 mg based on clinical response and tolerability. The maximum possible dose was 15 mg. No dose increases were to occur after Visit 8 (Week 6). Ideally, the dose should remain stable during the final 2 weeks of treatment. If, at any time, the patient experienced intolerance to the current dose taken, the dosage could be adjusted downward.

Study medication was administered once daily beginning on Day 1. Doses were to be taken at approximately the same time each day without regard to meals.

Selection of Study Population

Key Inclusion Criteria:

- Male or female children or adolescents 6 to 17 years of age, inclusive, met current DSM-IV-TR diagnostic criteria for autistic disorder and also demonstrated behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems. Diagnosis was confirmed by the Autism Diagnostic Interview—Revised.

- The patient had a CGI-S score ≥ 4 and an ABC Irritability Subscale score ≥ 18 at screening and baseline

- The patient and/or the designated guardian(s) or caregiver(s) were able to comprehend and satisfactorily comply with the protocol requirements, in the opinion of the investigator

- The patient had a documented mental age of at least 18 months

- Women of childbearing potential (WOCBP) had to use an adequate method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the study. WOCBP must have had a negative serum or urine pregnancy test.

Key Exclusion Criteria:

- The patient had a current diagnosis of bipolar disorder, psychosis, schizophrenia, or major depression

- The patient was currently diagnosed with another disorder on the autism spectrum including PDD-NOS, Asperger's Disorder, Rett's Disorder, Fragile-X Syndrome or Childhood Disintegrative Disorder

- The patient had a significant risk of committing suicide based on history or routine psychiatric status examination

- The patient had a history or current evidence of any unstable medical conditions (eg, history of congenital heart disease or arrhythmia, or cancer) that, in the judgment of the investigator, would expose him or her to undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial

- The patient was considered treatment resistant to neuroleptic medication, in the opinion of the investigator, based on lack of therapeutic response to 2 different neuroleptics after treatment of at least 3 weeks each

- The patient was considered treatment resistant to aripiprazole, in the opinion of the investigator, based on lack of therapeutic response to an adequate dose and duration of aripiprazole treatment

- Women who were pregnant or breastfeeding

- The following laboratory test results, vital sign and electrocardiogram (ECG) findings were exclusionary:

  - QTc > 475 msec
  - Platelets ≤ 75,000/mm3
  - Hemoglobin ≤ 9g/dL
  - Neutrophils ≤ 1.0 x E3/mm3 (or equivalent)
  - Aspartate transaminase (AST) [serum glutamic-oxaloacetic transaminase (SGOT)] or alanine transaminase (ALT) [serum glutamic-pyruvic transaminase (SGPT)] > 3x upper limit of normal
  - Creatinine ≥ 2 mg/dL

- The patient weighed < 15 kg

- The patient had a known allergy or hypersensitivity to aripiprazole or other dihydrocarbostyrils (eg, carteolol, vesnarinone, and cilostazol)

The Primary and Secondary Efficacy Endpoints

The primary efficacy outcome 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. Other secondary efficacy outcome measures included the mean change from baseline to endpoint in the other ABC subscale scores, response rate (response defined as a ≥ 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 endpoint in the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Compulsion Scale only).

Statistical Methods

The sample size of 90 evaluable patients (45 per treatment group) was estimated to provide 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 was 7.0. This assumed a standard deviation of 9.42 and a 2-sided test at the 0.05 level of significance.

The Randomized Sample included all patients who were randomized to double-blind treatment. The Safety Sample comprised all patients in the Randomized Sample who took at least 1 dose of study medication during the double-blind Treatment Phase, as identified on the dosing record. The Efficacy Sample comprised all patients who were in the Safety Sample and had at least 1 post-randomization efficacy evaluation and corresponding baseline value. The last observation carried forward (LOCF) data set included data recorded at a given timepoint or, if no observation was recorded at that timepoint, data carried forward from the previous timepoint with available data. Baseline data were not carried forward or averaged with the on-treatment data to impute missing values for the LOCF data set. The observed cases (OC) data set consisted of the actual observations at each timepoint.

For continuous measurements, such as the ABC Irritability Subscale score, change scores were evaluated by analysis of covariance (ANCOVA). The ANCOVA models for LOCF data sets included the baseline measure as a covariate and baseline body weight (2 categories: ≥ 40 kg and < 40 kg), study center, and treatment as main effects.

Categorical measures such as response were analyzed within the framework of the generalized Cochran-Mantel Haenszel (CMH) procedure. The analyses of the LOCF data set controlled for study center.

P-values were 2-tailed tests of significance rounded to 3 decimal places. All analyses were performed at the 5% significance level. 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. Thus, the CGI-I would be tested only if the aripiprazole treatment group was significantly different versus placebo from the primary efficacy endpoint analysis.

Safety and tolerability of study medication were evaluated by reports of AEs including clinically significant changes in ECGs, vital signs, physical examinations, and clinical laboratory tests. The incidence of AEs was tabulated by treatment, according to severity, and drug-attributability.

In addition, weight and body mass index (BMI) were also evaluated in terms of change from baseline. The analytical approaches described for the efficacy analyses were applied to the safety rating scales and weight/BMI evaluations.

All safety analyses were performed on the Safety Sample. For safety analyses, patients were analyzed by treatment received.

ii. Results

Demographics

Demographic characteristics for the Randomized Sample are presented 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%) which were consistent with the prevalence of autistic disorder (4-5 times more common in male than in female) and roughly consistent with the race distribution in the general population in the United States.

Table 2 Demographic Characteristics, Randomized Sample, Study CN138178

		Placebo (n=51)	Aripiprazole (n=47)	Total (n=98)
Age (years)	Mean	8.8	9.7	9.3
6-12	N (%)	46 (90.2)	37 (78.7)	83 (84.7)
13-17	N (%)	5 (9.8)	10 (21.3)	15 (15.3)
Gender				
Male	N (%)	44 (86.3)	42 (89.4)	86 (87.8)
Female	N (%)	7 (13.7)	5 (10.6)	12 (12.2)
Race				
White	N (%)	41 (80.4)	32 (68.1)	73 (74.5)
Black/African American	N (%)	7 (13.7)	11 (23.4)	18 (18.4)
Asian	N (%)	0	2 (4.3)	2 (2.0)
Other	N (%)	3 (5.9)	2 (4.3)	5 (5.1)

		Placebo (n=51)	Aripiprazole (n=47)	Total (n=98)
Weight (kg)	Mean	40.6	43.9	42.2
< 40 kg	N (%)	32 (62.7)	26 (55.3)	58 (59.2)
≥ 40 kg	N (%)	19 (37.3)	21 (44.7)	40 (40.8)
Height (cm)	Mean	138.6	140.9	139.7
BMI (kg/m^2)	Mean	19.96	21.08	20.50

Baseline Disease Characteristics

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

Table 3 Baseline Disease Characteristics, Randomized Sample, Study CN138178

Scale	Placebo N=51	Aripiprazole N=47	Total N=98
ABC, mean (SD)			
Irritability	30.2 (6.52)	29.6 (6.37)	29.9 (6.42)
Hyperactivity	35.3 (8.86)	34.0 (8.64)	34.7 (8.73)
Stereotypy	11.2 (5.79)	11.8 (6.13)	11.5 (5.93)
Social Withdrawal	18.8 (9.62)	19.9 (11.26)	19.3 (10.40)
Inappropriate Speech	6.8 (3.98)	6.9 (3.78)	6.8 (3.87)
CGI-Severity, mean (SD)	4.9 (0.63)	4.9 (0.71)	4.9 (0.67)
CY-BOCS, mean (SD)			
Compulsion	14.2 (3.39)	12.9 (4.94)	13.6 (4.24)

Patient Disposition

A total of 164 patients were enrolled in the study. Of these, 98 patients were randomized to receive treatment: 51 patients to the placebo group and 47 patients to aripiprazole. A total of 75 (76.5%) of the 98 randomized patients completed the double-blind phase of the study, 36 (70.6%) in the placebo group and 39 (83.0%) in the aripiprazole group. Placebo treatment was associated with higher discontinuation rate. The most frequent reasons for discontinuation in the placebo group were lack of efficacy, 6 (11.8%) patients, and for the aripiprazole group was adverse events (AE), 5 (10.6%) patients.

The disposition of randomized patients is presented in Table 4.

Table 4 Disposition of Patients, Study CN138178

Patient Status	Placebo	Aripiprazole	Total
Randomized, n	51	47	98
Completed, n (%)	36 (70.6)	39 (83.0)	75 (76.5)
Discontinued, n (%)	15 (29.4)	8 (17.0)	23 (23.5)
Lack of efficacy	6 (11.8)	1 (2.1)	7 (7.1)
Adverse event	3 (5.9)	5 (10.6)	8 (8.2)
Subject withdrew consent	2 (3.9)	1 (2.1)	3 (3.1)
Lost to follow-up	4 (7.8)	1 (2.1)	5 (5.1)

All randomized patients were included in the Safety Sample except for 1 patient in the placebo group who was lost to follow-up (CN138178-1-78148). One additional patient in each treatment group was not included in the Efficacy Sample (placebo: CN138178-3-78001 withdrew consent to participate; aripiprazole: CN138178-13-78058 had an AE of severe vomiting that started Day 1, he discontinued from the study on Day 2).

Concomitant Medication Use

The most commonly used CNS concomitant medications during this study for placebo-treated and aripiprazole-treated patients were “other analgesics and antipyretics” (placebo 22.0%, aripiprazole 19.1%). Only a few of patients used other concomitant CNS medications during this study, such hypnotic & sedative (placebo 6 (12%); aripiprazole 1 (2.1%)), and anxiolytic (placebo 2 (4%); aripiprazole 4 (8.5%)). It is unlikely that the concomitant medication use during this study had affected the final efficacy outcome.

Protocol Deviations

Clinical relevant protocol deviations were identified during the study and were summarized in Table 5. No patient was excluded from the analyses because of a relevant protocol deviation.

Table 5 Protocol Deviations of Clinical Relevance, Study CN138178

Deviation	Number of Patients N=98[a]
Randomized patients with missing vital signs at screening or baseline	22
Randomized patients with missing or exclusionary ECG result at screening or baseline	1
Randomized patients with concomitant prohibited or restricted medications	2
Treated patients with study medication not administered per protocol	3

Efficacy Findings

Primary Efficacy Endpoint

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 LOCF in the ABC Irritability Subscale score (placebo -5.0, aripiprazole -12.9, difference -7.9, 95% CI (-11.7, -4.1), p<0.001) (Table 6). These results were corroborated by the OC data set (Table 7). Differences between treatment groups on this measure were statistically significant consistently from Week 1 onward.

Table 6 Adjusted Mean Change from Baseline in ABC Irritability Subscale Score, Study CN138178, LOCF, Efficacy Sample

Visit	Placebo		Aripiprazole		Arip. vs. PLA
	n	Mean (SE)	n	Mean (SE)	p-value
Baseline	49	30.8 (1.00)	46	29.6 (1.01)	0.372
Week 1	46	-2.7 (1.02)	45	-5.5 (1.01)	0.039
Week 2	49	-3.6 (1.13)	46	-8.5 (1.13)	0.002
Week 3	49	-4.6 (1.18)	46	-10.4 (1.19)	<0.001
Week 4	49	-6.6 (1.23)	46	-11.8 (1.24)	0.002
Week 5	49	-5.7 (1.35)	46	-12.0 (1.36)	<0.001
Week 6	49	-6.2 (1.43)	46	-13.2 (1.44)	<0.001
Week 8	49	-5.0 (1.43)	46	-12.9 (1.44)	<0.001
Week 8: Treatment difference vs. placebo and corresponding 95% CI					-7.9 (-11.7, -4.1)

Table 7 Adjusted Mean Change from Baseline in ABC Irritability Subscale Score, Study CN138178, OC, Efficacy Sample

Visit	Placebo		Aripiprazole		Arip. vs. PLA
	n	Mean (SE)	n	Mean (SE)	p-value
Baseline	49	30.6 (0.94)	46	29.6 (0.95)	0.435
Week 1	46	-2.5 (0.93)	45	-5.1 (0.92)	0.044
Week 2	46	-3.4 (1.01)	42	-8.8 (1.04)	<0.001
Week 3	43	-4.5 (1.10)	40	-10.8 (1.12)	<0.001
Week 4	39	-6.0 (1.19)	40	-12.0 (1.16)	<0.001
Week 5	40	-5.8 (1.30)	39	-12.9 (1.31)	<0.001
Week 6	38	-7.0 (1.47)	38	-14.6 (1.46)	<0.001
Week 8	34	-5.2 (1.49)	38	-14.5 (1.41)	<0.001
Week 8: Treatment difference vs. placebo and corresponding 95% CI					-9.2 (-13.3, -5.2)

iii. Conclusions

In study CN138178, aripiprazole at dose of 2 to 15 mg/d demonstrated clinically relevant and statistically significant improvement compared with placebo on the primary efficacy endpoint, the adjusted mean change from baseline on the ABC Irritability Subscale, starting at Week 1 and continuing through endpoint (Week 8 LOCF).

The statistical reviewer, Steve Bai PhD., reanalyzed the date using both LOCF and MMRM analyses and confirmed the efficacy findings.

Study CN138179

i. Method/Study Design/Analysis Plan

Study CN138179 was conducted from 15 June 2006 to 03 June 2008 at 37 centers in the United States. A complete list of investigators, their staff, study centers, and number of patients enrolled per center are listed in Appendix 1.5 in the original DNA submission.

Overall Study Design

The study design of CN138179 was identical to that of study CN 138178 except study CN138179 was a fixed-dose study and CN138178 was a flexible-dose study.

Study CN138179 was a fixed-dose (5, 10 or 15 mg/d), double-blind, randomized, placebo-controlled, parallel-group, multicenter 8-week study designed to assess the efficacy, safety, and tolerability of aripiprazole in children and adolescents with a DSM-IV diagnosis of autistic disorder with serious behavioral problems characterized by irritability, agitation, and self-injurious behavior.

The study had 2 phases: a screening phase of up to 42 days followed by an 8-week treatment phase. Eligible 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 visited the clinic at the end of treatment Weeks 1, 2, 3, 4, 5, 6, and 8, at which time efficacy and safety measures were collected. To assess patient well-being and medication tolerability between visits in the latter half of the double-blind treatment phase, a telephone contact occurred at Week 7. End of study assessments were performed at the end of Week 8 or at the time of early termination. Patients who completed the 8-week, double-blind treatment phase were eligible for an open-label, flexible-dosed, long-term study.

Approximately 220 patients were planned to be randomly assigned to receive aripiprazole (2, 5 or 15 mg/d) or placebo. A total of 368 patients were enrolled with 218 patients randomized to receive treatment: 52 received placebo; 53, 59, and 54 received aripiprazole 5, 10 and 15 mg respectively.

Dose and Administration

A fixed dosing regimen was used for each patient. For all patients randomized to receive aripiprazole, the starting dose was 2 mg for the first week. All patients were titrated to their randomized dose at weekly increments in a blinded fashion. For example, a patient randomized to 15 mg took 2 mg the 1st week, 5 mg the 2nd week, 10 mg the 3rd week, 15 mg the 4th week, and continued on 15 mg for the remainder of the study. Patients unable to tolerate a dose to which they were randomized were discontinued from the study.

Study medication was administered once daily beginning on Day 1. Doses were to be taken at approximately the same time each day without regard to meals.

Selection of Study Population

Key inclusion and exclusion criteria in study CN138179 were same as that in study CN138178. Please refer to section *6 Review of Efficacy/Study CN138178/Selection of Study Population* for detailed key inclusion and exclusion criteria.

The Primary and Secondary Efficacy Endpoints

The primary efficacy outcome measure was the mean change from baseline to endpoint (Week 8) in the ABC Irritability Subscale score. Secondary efficacy outcome measures included the mean change from baseline to endpoint in the CGI-I, the other ABC subscale scores, response rate (response defined as a ≥ 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 endpoint in the CY-BOCS (Compulsion Scale only). No key secondary endpoint was pre-specified.

Statistical Methods

The planned sample size of 240 evaluable patients (51 per treatment group) was estimated to provide 92% power to differentiate between placebo and at least 1 or 2 higher dosage aripiprazole treatment groups (10 or 15 mg/d) when the true difference in the mean changes from baseline in the ABC Irritability Subscale score was 7.0. This assumed a standard deviation of 9.42 and a 2-sided test at the 0.05 level of significance.

The rest of the statistical plan was same as that in study CN138178. Please refer to section *6 Review of Efficacy/Study CN138178/Statistical Methods* for detailed statistical methods.

ii. Results

Demographics

Demographic characteristics for the Randomized Sample are presented in Table 8. The mean age of the randomized patients was 9.7 years. Patients were predominantly male (89.4%) and white (71.1%) which were consistent with the prevalence of autistic disorder (4-5 times more common in male than in female) and the race distribution in the general population in the United States.

Table 8 Demographic Characteristics, Study CN138179, Randomized Sample

		Placebo (n=52)	Aripiprazole 5 mg (n=53)	Aripiprazole 10 mg (n=59)	Aripiprazole 15 mg (n=54)	Total (n=218)
Age (years)	Mean	10.2	9.0	10.0	9.5	9.7
6-12	N (%)	35 (67.3)	44 (83.0)	45 (76.3)	42 (77.8)	166 (76.1)
13-17	N (%)	17 (32.7)	9 (17.0)	14 (23.7)	12 (22.2)	52 (23.9)
Gender						
Male	N (%)	48 (92.3)	47 (88.7)	50 (84.7)	50 (92.6)	195 (89.4)
Female	N (%)	4 (7.7)	6 (11.3)	9 (15.3)	4 (7.4)	23 (10.6)
Race						
White	N (%)	35 (67.3)	37 (69.8)	41 (69.5)	42 (77.8)	155 (71.1)
Black/African American	N (%)	13 (25.0)	13 (24.5)	15 (25.4)	9 (16.7)	50 (22.9)
Asian	N (%)	3 (5.8)	1 (1.9)	2 (3.4)	0	6 (2.8)
Other	N (%)	1 (1.9)	2 (3.8)	1 (1.7)	3 (5.6)	7 (3.2)
Weight (kg)	Mean	45.6	38.9	44.8	42.2	42.9
< 40 kg	N (%)	24 (46.2)	35 (66.0)	33 (55.9)	34 (63.0)	126 (57.8)
≥ 40 kg	N (%)	28 (53.8)	18 (34.0)	26 (44.1)	20 (37.0)	92 (42.2)
Height (cm)	Mean	144.9	136.5	142.3	139.3	140.8
BMI (kg/m^2)	Mean	20.49	19.91	21.06	20.14	20.41

Baseline Disease Characteristics

The ABC, CGI-S, and CY-BOCS ratings from the end of baseline are presented in Table 9. Mean baseline ratings were similar between treatment groups.

Table 9 Baseline Disease Characteristics, Randomized Sample, Study CN138179

Scale	Placebo N=52	Aripiprazole 5 mg N=53	Aripiprazole 10 mg N=59	Aripiprazole 15 mg N=4	Total N=218
ABC, mean (SD)					
Irritability	28.0 (6.89)	28.6 (7.56)	28.2 (7.36)	28.9 (6.41)	28.4 (7.04)
Hyperactivity	32.7 (11.0)	33.7 (9.99)	34.7 (10.17)	33.2 (8.56)	33.6 (9.93)
Stereotypy	10.7 (6.25)	11.1 (5.70)	11.5 (5.65)	11.6 (4.56)	11.2 (5.4)
Social Withdrawal	18.8 (11.15)	17.2 (9.96)	17.0 (9.17)	18.9 (8.65)	17.9 (9.72)
Inappropriate Speech	6.4 (3.74)	6.0 (3.85)	7.0 (4.10)	6.4 (3.87)	6.5 (3.89)

Scale	Placebo N=52	Aripiprazole 5 mg N=53	Aripiprazole 10 mg N=59	Aripiprazole 15 mg N=4	Total N=218
CGI-Severity, mean (SD)	4.9 (0.76)	5.1 (0.84)	4.9 (0.71)	5.1 (0.77)	5.0 (0.77)
CY-BOCS, mean (SD)					
Compulsion	13.8 (3.09)	13.7 (4.38)	13.3 (4.58)	13.9 (4.68)	13.7 (4.23)

Patient Disposition

A total of 368 patients were enrolled in the study. Of these, 218 patients were randomized to receive treatment: 52 in placebo, 53 in aripiprazole 5 mg, 59 in aripiprazole 10 mg, and 54 in aripiprazole 15 mg group. A total of 178 (81.7%) of the 218 randomized patients completed the double-blind phase of the study, 38 (73.1%) in the placebo group, 44 (83.0%) in the 5-mg aripiprazole group, 49 (83.1%) in the 10-mg group, and 47 (87.0%) in the 15-mg group. The most frequent reason for discontinuation in all treatment groups was due to AEs: 4 (7.7%) in placebo, 5 (9.4%) in aripiprazole 5 mg, 8 (13.6%) in aripiprazole 10 mg, and 4 (7.4%) in aripiprazole 15 mg group.

Placebo treatment was associated with higher discontinuation rate (26.9%) and higher rate of discontinuation due to lack of efficacy (5.8%) compared with aripiprazole treated groups (13 to 17%, and 0% respectively).

The disposition of randomized patients is presented in Table 10.

Table 10 Disposition of Patients, Study CN138179 (Double-Blind Phase), Ramdomized Sample

Patient Status	Placebo	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg	Total
Randomized, n	52	53	59	54	218
Completed, n (%)	38 (73.1)	44 (83.0)	49 (83.1)	47 (87.0)	178 (81.7)
Discontinued, n (%)	14 (26.9)	9 (17.0)	10 (16.9)	7 (13.0)	40 (18.3)
Lack of efficacy	3 (5.8)	0	0	0	3 (1.4)
Adverse event	4 (7.7)	5 (9.4)	8 (13.6)	4 (7.4)	21 (9.6)
Subject withdrew consent	2 (3.8)	2 (3.8)	1 (1.7)	0	5 (2.3)
Lost to follow-up	3 (5.8)	1 (1.9)	0	1 (1.9)	5 (2.3)
Poor/non-compliance	1 (1.9)	1 (1.9)	1 (1.7)	1 (1.9)	4 (1.8)
Other	1 (1.9)	0	0	1 (1.9)	2 (0.9)

All randomized patients were included in the Safety Sample except for 2 patients, 1 in the placebo group who no longer met study criteria and 1 in the aripiprazole 5-mg group who withdrew consent to participate. Three patients were not included in the Efficacy Sample (2 in the placebo group: one was lost to follow up and one withdrew consent to participate; and 1 in the aripiprazole 15-mg group: due to elevated potassium level.

Concomitant Medication Use

The most commonly used CNS concomitant medications during this study for all treatment groups were “other analgesics and antipyretics’ (placebo, 17.6%; aripiprazole 5 mg, 23.1%; 10 mg, 20.3%; and 15 mg, 22.2%). One (2.0%) placebo-treated patient and 10 (6.1%) aripiprazole-treated patients (5 mg, 4 [7.7%]; 10 mg, 1 [1.7%]; 15 mg, 5 [9.3%]) took a concomitant medication for potential treatment of EPS. Only a few patients used anxiolytic (3 [5.9%] in placebo, and 1-2 [1.7 to 3.8%] in aripiprazole treatment groups) and hypnotic & sedative (2 [3.9%] in placebo, and 1-2 [1.7 to 3.8%] in aripiprazole treatment group) during the study. It is unlikely that the concomitant medication use during this study had affected the final efficacy outcome.

Protocol Deviations

Clinical relevant protocol deviations were identified during the study and were summarized in Table 11. No patient was excluded from the analyses because of a relevant protocol deviation.

Table 11 Protocol Deviations of Clinical Relevance, Study CN138179

Deviation	Number of Patients N = 218[a]
Treated WOCBP patients with missing or positive pregnancy test within 3 Days prior to start of study medication	1
Randomized Patients with exclusionary ABC Irritability Subscale score	2
Randomized patients with missing vital signs at screening or baseline	44
Treated patients given wrong study medication	4
Randomized patients with concomitant prohibited or restricted medications	13
Treated patients with study medication not administered per protocol	16

Efficacy Findings

Primary Efficacy Endpoint

The primary endpoint was the mean change from baseline to Week 8 LOCF in the ABC Irritability Subscale score. All 3 doses of aripiprazole demonstrated statistically significant improvement compared with placebo on the primary efficacy endpoint—the mean change from baseline to Week 8 LOCF in the ABC Irritability Subscale score (placebo: -8.4; arip. 5 mg: -12.4, difference = 4.0, p = 0.032; arip. 10 mg: -13.2, difference = -4.8, p = 0.008; arip. 15 mg: -14.4, difference -6.0, p = 0.001) (see

Table 12). Statistically significant results were corroborated by the OC data set for the 10- and 15-mg groups (see Table 13).

The repeated measures analysis corroborated the results for the primary endpoint with a statistically significant treatment difference versus placebo from Week 1 onward for the 15-mg group and from Week 2 onward for the 5- and 10-mg groups (LOCF).

Table 12 Adjusted Mean Change from Baseline in ABC Irritability Subscale Score, Study CN138179, LOCF, Efficacy Sample

	Placebo		Arip. 5 mg		Arip. 10 mg		Arip. 15 mg		Arip. Vs. Placebo p-value		
Visit	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	5 mg	10 mg	15 mg
Baseline	49	26.9 (1.04)	52	28.3 (1.03)	59	27.6 (0.94)	49	28.3 (0.99)	0.309	0.598	0.308
Week 1	47	-5.6 (1.35)	51	-7.0 (1.30)	59	-7.2 (1.18)	53	-9.2 (1.30)	0.424	0.352	0.049
Week 2	49	-6.4 (1.36)	52	-11.8 (1.34)	59	-11.8 (1.23)	53	-10.8 (1.29)	0.004	0.002	0.015
Week 3	49	-6.4 (1.34)	52	-11.6 (1.31)	59	-13.0 (1.21)	53	-11.2 (1.27)	0.004	<0.001	0.008
Week 4	49	-8.0 (1.38)	52	-12.1 (1.36)	59	-13.2 (1.25)	53	-13.5 (1.31)	0.026	0.004	0.003
Week 5	49	-8.3 (1.38)	52	-14.4 (1.36)	59	-13.5 (1.25)	53	-14.1 (1.31)	0.001	0.004	0.002
Week 6	49	-7.8 (1.41)	52	-13.4 (1.38)	59	-14.4 (1.27)	53	-15.3 (1.34)	0.004	<0.001	<0.001
Week 8	49	-8.4 (1.39)	52	-12.4 (1.36)	59	-13.2 (1.25)	53	-14.4 (1.31)	0.032	0.008	0.001
Week 8: Treatment difference vs. placebo and corresponding 95% CI											
			-4.0 (-7.7, -0.4)		-4.8 (-8.4, -1.3)		-6.0 (-9.6, -2.3)				

Table 13 Adjusted Mean Change from Baseline in ABC Irritability Subscale Score, Study CN138179, OC, Efficacy Sample

	Placebo		Arip. 5 mg		Arip. 10 mg		Arip. 15 mg		Arip. Vs. Placebo p-value		
Visit	n	Mean	n	Mean	n	Mean	n	Mean	5 mg	10 mg	15 mg
Baseline	49	27.8	52	28.8	59	28.2	53	28.9	0.476	0.768	0.439
Week 1	47	-5.2	51	-6.6	59	-6.7	49	-9.0	0.427	0.375	0.032
Week 2	45	-6.6	48	-12.6	56	-11.9	49	-10.7	0.001	0.003	0.025
Week 3	39	-6.8	46	-11.9	53	-13.1	46	-11.2	0.012	0.001	0.029
Week 4	42	-8.3	45	-12.4	52	-13.4	46	-14.2	0.039	0.008	0.003
Week 5	37	-8.9	44	-15.2	51	-13.8	45	-14.7	0.003	0.016	0.006
Week 6	38	-9.0	44	-13.6	49	-15.3	47	-15.8	0.029	0.002	0.001
Week 8	38	-9.2	44	-12.4	49	-13.8	45	-14.4	0.124	0.022	0.013
Week 8: Treatment difference vs. placebo and corresponding 95% CI											
			-3.2 (-7.2, -0.9)		-4.5 (-8.4, -0.6)		-5.1 (-9.2, -1.1)				

iii. Conclusions

In study CN138179, all 3 doses of aripiprazole at doses of 5, 10 and 15 mg, demonstrated clinically relevant and statistically significant improvement compared with placebo on the primary efficacy endpoint at Week 8 (LOCF), the adjusted mean change from baseline on the ABC Irritability Subscale score.

The statistical reviewer, Steve Bai PhD., reanalyzed the data using LOCF analysis and confirmed the primary efficacy findings. He also performed an analysis on the treatment effect over time based on an MMRM method and found that the treatment effects were consistent with the primary efficacy results.

c. Crosscutting Issues

i. Subgroup Analyses

For the population subset analyses (age, gender, and race) of the ABC Irritability Subscale score, results from both studies were consistently in favor of aripiprazole across all subsets and none of the treatment-by-subgroup interaction terms were statistically significant. An additional analysis using different age groupings (6 to 11 and 12 to 17 years) was conducted and showed no statistically significant interaction.

ii. Dose Response

Study CN138178 is a flexible-dose study. No dose response relationship can be identified from this study. Study CN138179 is a fixed-dose study and consists of 3 aripiprazole treatment arms, 5, 10, and 15 mg. Even though all three aripiprazole doses showed significant efficacy compared with placebo at week 8, no dose-response relationship was found in this study. The higher aripiprazole dose groups (10 and 15 mg) did slightly better than the 5 mg group in reduction of ABC irritability subscale score at week 8 (placebo adjusted mean change: -4.0, -4.8, and -6.0 in arip. 5, 10, and 15 mg respectively). But, clearly the differences were small and there was no dose-response relationship identified.

iii. Key Secondary Endpoints

In CN138178, the mean CGI-Improvement score was the key secondary efficacy measure; in CN138179, it was a secondary efficacy measure but was not considered a key secondary measure.

In CN138178, the treatment difference of the mean CGI-Improvement score achieved statistically significant improvement for aripiprazole compared with placebo at Week 8

(-1.4, p < 0.001, LOCF). The treatment differences were also statistically significant in favor of aripiprazole for all dose groups in CN138179 (5 mg: -0.7, p = 0.003; 10 mg: -0.8, p < 0.001; and 15 mg: -0.8, p < 0.001). These findings were confirmed by our statistical reviewer.

iv. Effect Size

The acute efficacy of aripiprazole in treatment of irritability associated with autistic disorder were demonstrated in two 8 weeks, double-blind, placebo-controlled studies: CN138178, a flexible-dose study (2 to 15 mg) and CN138179, a fixed-dose study (5, 10, and 15 mg).

The only drug that has been approved for the same indication in the USA is risperidone (NDA 20-272/S036). The acute efficacy of risperidone in reducing irritability-like symptomatology in autistic patients aged 5 to 16 was demonstrated in two 8-week, flexible-dose, double-blind, placebo-controlled studies, CAN-23 (n=80) and USA-150/Part I (n=101). The risperidone doses ranging from 0.02 to 0.06 mg/kg in CAN-23, and ranging from 0.25mg to 2.5mg (for weight between 20kg and 45kg) or 0.5mg to 3.5 mg/day (for 45kg and over).

A primary efficacy measure in all 4 studies (2 aripiprazole and 2 risperidone studies) was the ABC Irritability subscale.

The mean changes from baseline to week 8 (LOCF) in the ABC Irritability subscale in the 4 clinical trials (CN138178, CN138179, CAN-23 and USA-150/Part I) are displayed in Table 14. The mean decreases from baseline are also represented as fractions (%) of the baseline values.

Table 14 Effect Size Comparison between Aripiprazole and Risperidone Clinical Trials

	Aripiprazole Studies (LOCF)						Risperidone Studies (LOCF)			
	CN138178		CN138179				CAN-23		USA-150/Part I	
	PLA	Arip.	PLA	Arip. 5 mg	Arip. 10 mg	Arip. 15 mg	PLA	Risp.	PLA	Risp.
Baseline	30.8	29.6	26.9	28.3	27.6	28.3	21.6	20.6	25.0	26.1
Week 8	-5.0	-12.9	-8.4	-12.4	-13.2	-14.4	-7.5	-13.5	-3.5	-14.9
% Reduction	-16	-44	-31	-44	-48	-51	-35	-66	-14	-57
Difference from placebo		-7.9		-4.0	-4.8	-6.0		-6.0		-11.4

The effect sizes in aripiprazole studies were comparable with that seen in study CAN-23 and smaller than that obtained from study USA-150/Part I. This comparison is only a rough comparison because the nature of the studies (where, when, testing medications, dose, sample size, study population) was different. It is hard to perform the direct comparison without bias. However, in both aripiprazole trials, the mean decreases in the

Irritability subscale score were ≥ 44% of the baseline value of the aripirazole treated groups. Changes of such magnitude are likely to be clinically significant.

v. Long-term Efficacy

No long-term study for the indication of irritability associated with autistic disorder was conducted by the sponsor. A long-term efficacy and safety study for this indication is required by the division as a phase 4 commitment.

vi. Pediatric Development

These two aripiprazole studies were conducted in children aged 6 to 17. No more short term pediatric study will be required. A long-term efficacy and safety study for the maintenance treatment indication is requested by the division as a post-marketing commitment.

d. Efficacy Conclusion Regarding the Indication of Irritability Associated with Autism Disorder

Individual analyses of the 2 placebo-controlled studies in patients with autistic disorder showed that treatment with aripiprazole is efficacious in improving the symptoms of irritability in children and adolescents with autism, as demonstrated by results on the primary endpoint, ABC Irritability Subscale.

In both studies, aripiprazole showed clinically meaningful and statistically significant improvement compared with placebo within 1 to 2 weeks that continued throughout the study to endpoint (Week 8) on the primary efficacy measures.

In both studies, the treatment difference of the mean CGI-Improvement score (a key secondary endpoint of study CN138178) achieved statistically significant improvement for all aripiprazole treated groups compared with placebo at Week 8.

There was no dose-response pattern with respect to efficacy for the primary endpoint.

None of the treatment-by-subgroup interaction terms (age, gender and race) were statistically significant.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

There are two datasets were used in the integrated safety review:

Placebo-controlled Studies in Autistic Disorder: Data from patients in the 2 completed pivotal studies (CN138178, and CN138179) have been pooled for presentation.

All Pediatric Aripiprazole Dataset: Cumulative data on all pediatric patients exposed to aripiprazole in all Phase 2/3 studies includes studies 31-03-238,31-03-239, 31-03-240, 31-03-241, 31-05-243, CN138014 and the 3 autistic disorder studies (CN138178, CN138179, CN138180).

During this sNDA review, a 120-Day Safety Update were submitted on May 21, 2009, which presents a review of the safety of the oral-tablet formulation in the clinical trials database as of the cutoff date of 15-Nov-2008. A summarization of post-marketing safety information, including a review of Periodic Safety Update Reports (PSURs) as of 16-Jul-2008, is also presented.

7.1.2 Categorization of Adverse Events

An AE was defined as any new untoward medical occurrence or worsening of a preexisting medical condition regardless of causal relationship with treatment. An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product.

A SAE was any untoward medical occurrence at any dose that:

- results in death
- is life-threatening (defined as an event in which the subject or patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a cancer

- is a congenital anomaly/birth defect
- results in the development of drug dependency or drug abuse
- is an important medical event (including pregnancy or overdose)

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Data from patients in the two completed pivotal studies (CN138178, CN138179) have been pooled for presentation because of similarity of study design.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 362 pediatric patients received aripiprazole in the autistic disorder clinical trial program; 920 pediatric patients received aripiprazole across all Phase 1/2/3 studies. Overall, patient exposure years (PEY) total 517.3, with 170.7 years for patients with autistic disorder. Table 15 presents a summary of the number of patients who received aripiprazole in the safety sample of these studies.

Table 15 Summary of Patients Who Received Aripirazole in the Safety Sample

Pools by Indication and Study Design	Enumeration of Patients by Treatment Group: Placebo	Aripiprazole
Autistic Disorder		
8-Week Placebo-Controlled	101	212
Ongoing, Uncontrolled/Open-Label		313
		(163) (a)
Total Autistic Disorder	101	362
Schizophrenia		
Short-Term Placebo-Controlled	100	202
Ongoing, Uncontrolled/Open-Label		240
		(160) (a)
Total Schizophrenia	100	282
Bipolar Disorder		
Short-Term Placebo-Controlled	97	197
Uncontrolled/Open-Label		98
		(50) (a)
Total Bipolar Disorder	97	245
Other Indications		
Conduct Disorder		23
Other		8
Total Other Indications		31
Total Phase 1/2/3 Exposure	298	920

(a) The number of patients also counted under Aripiprazole in the Placebo-Controlled row.

There were 212 patients who received aripiprazole during the randomization phase of the placebo-controlled studies in autistic disorder and 85.4% of these patients received between 50 - 56 days of study drug. There were 52.8% of patients who received overall mean doses of aripiprazole of > 7.5 mg - ≤ 12.5 mg, 41.0% who received > 3.5 mg - ≤ 7.5 mg, and 6.1% who received ≤ 3.5 mg. No patient had an overall mean dose of > 12.5 mg/day during the 8-week placebo-controlled phase.

In the 120-Day Safety Update (SU) submitted on 21 May 2009, the sponsor reported that the extent of exposure of patients in all pediatric disorder patients was similar to that reported in the original submission.

7.2.2 Explorations for Dose Response

Study CN138-189 is a fixed-dose study. The safety data from each dose group were analyzed separately. The Cochran-Armitage Exact test was conducted to assess the dose-response relationship of AEs (ie, increased incidence of AEs with increased dose) and was analyzed including and excluding placebo.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or In Vitro testing was deemed necessary.

7.2.4 Routine Clinical Testing

Routine clinical testing includes deaths, adverse events (serious AEs and common AEs), safety laboratory tests (hematology, clinical chemistry and urinalysis), vital signs, body weight, ECG and plasma prolactin levels.

7.2.5 Metabolic, Clearance, and Interaction Workup

Atypical antipsychotics as a class are associated with metabolic syndrome. To explore metabolic effects of aripiprazole, mean changes from baseline values and clinically significant changes for blood glucose, lipids, body weight, and BMI over time were studied.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Atypical antipsychotics are associated with increased prolactin levels, EPS, and metabolic syndrome. Plasma prolactin, glucose, and lipid (cholesterol, triglycerides, LDL and HDL) levels were tested during the study. Body weight, BMI, and EPS were assessed over time during the study.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths among 362 pediatric patients exposed to aripiprazole in all autistic disorder studies.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events (SAEs) were reported in 2 (0.9%) aripiprazole-treated patients during the autistic disorder studies: 1 event of presyncope that was mild and considered possibly related to treatment and 1 event of aggression that was severe/very severe and considered not likely related to treatment.

7.3.3 Dropouts and/or Discontinuations

A total of 10.4% aripiprazole-treated and 7.9% placebo-treated patients discontinued from the placebo-controlled studies in autistic disorder (see Table 16). The most frequently reported reason for discontinuation in the aripiprazole group was sedation (3.3%); in the placebo group it was mania (2.0%).

Table 16 Summary of Discontinuation Due to Adverse Events, CN138178 & CN138179, Safety Sample

System Organ Class/ Preferred Term (b)	Number (%) of Patients (a)	
	Placebo	Aripiprazole
# Pts in Safety Sample	101	212
# Male Pts in Safety Sample	91	188
# Female Pts in Safety Sample	10	24
Any AE Leading to Discontinuation	8 (7.9)	22 (10.4)
Nervous System Disorders	4 (4.0)	14 (6.6)
Sedation	0	7 (3.3)
Drooling	0	4 (1.9)
Tremor	0	4 (1.9)
Akathisia	1 (1.0)	2 (0.9)
Extrapyramidal Disorder	0	3 (1.4)
Psychomotor Hyperactivity	1 (1.0)	1 (0.5)
Convulsion	1 (1.0)	0
Dyskinesia	0	1 (0.5)
Hyperkinesia	1 (1.0)	0
Lethargy	0	1 (0.5)
Presyncope	0	1 (0.5)
Psychiatric Disorders	4 (4.0)	5 (2.4)
Aggression	1 (1.0)	1 (0.5)
Mania	2 (2.0)	0
Agitation	0	1 (0.5)
Flat Affect	0	1 (0.5)
Impulsive Behaviour	1 (1.0)	0
Insomnia	1 (1.0)	0
Intentional Self-Injury	0	1 (0.5)
Intermittent Explosive Disorder	0	1 (0.5)
Negativism	1 (1.0)	0
Social Avoidant Behaviour	0	1 (0.5)
General Disorders And Administration Site Conditions	1 (1.0)	3 (1.4)
Irritability	1 (1.0)	1 (0.5)
Fatigue	0	1 (0.5)
Gait Disturbance	0	1 (0.5)
Gastrointestinal Disorders	0	3 (1.4)
Vomiting	0	3 (1.4)

System Organ Class/ Preferred Term (b)	Number (%) of Patients (a)	
	Placebo	Aripiprazole
Eye Disorders	0	2 (0.9)
Conjunctivitis	0	1 (0.5)
Eye Rolling	0	1 (0.5)
Investigations	1 (1.0)	1 (0.5)
Alanine Aminotransferase Increased	1 (1.0)	0
Weight Increased	0	1 (0.5)
Metabolism And Nutrition Disorders	0	2 (0.9)
Decreased Appetite	0	1 (0.5)
Increased Appetite	0	1 (0.5)
Cardiac Disorders	0	1 (0.5)
Tachycardia	0	1 (0.5)
Injury, Poisoning And Procedural Complications	1 (1.0)	0
Laceration	1 (1.0)	0
Musculoskeletal And Connective Tissue Disorders	0	1 (0.5)
Musculoskeletal Stiffness	0	1 (0.5)
Renal And Urinary Disorders	0	1 (0.5)
Urinary Incontinence	0	1 (0.5)
Vascular Disorders	0	1 (0.5)
Hypertension	0	1 (0.5)

In All Pediatric Aripiprazole Dataset, the overall incidence of treatment-emergent AEs that led to discontinuation of study therapy was similar across all indications.

7.3.4 Significant Adverse Events

Neuroleptic Malignant Syndrome (NMS)

A comprehensive search of the AE database for all Phase 1/2/3 pediatric studies was completed to identify aripiprazole-treated patients who had NMS reported as an AE. Of the 920 pediatric patients exposed to aripiprazole, 1 pediatric schizophrenia patient had an AE of NMS. This case was previously reported in the schizophrenia/bipolar mania combined submission. No autistic disorder patients reported NMS.

Seizures

A comprehensive search of the AE database for all Phase 1/2/3 pediatric studies was conducted to identify patients with a seizure-related AE using the following terms: seizure, convulsion, grand mal, petit mal, epilepsy, fits, electroencephalogram, EEG,

and lobe. There were no seizure-related AEs in aripiprazole-treated patients in the placebo controlled studies in autistic disorder.

Suicide-Related Events

AEs related to suicidality were identified in the AE database based on the following search criteria:

- Any AE text term or MedDRA preferred term (PT) with the text string 'suici'
- Any AE with a MedDRA PT of 1 of the following: completed suicide, intentional overdose, intentional self-injury, multiple drug overdose intentional, poisoning deliberate, self injurious behavior, self mutilation, suicide attempt, intentional misuse, depression suicidal, self-injurious ideation, suicidal ideation

The reported events were grouped into 3 categories for presentation purposes, and were defined as follows:

- Completed Suicide: completed suicide
- Suicide Attempt: intentional overdose, intentional self-injury, multiple drug overdose intentional, poisoning deliberate, self injurious behaviour, self mutilation, suicide attempt, intentional misuse
- Suicidal Ideation: depression suicidal; self-injurious ideation; suicidal ideation

In the placebo-controlled studies in autistic disorder, the incidence of suicide-related AEs was 0.5% in the aripiprazole group and 4.0% in the placebo group (Table 17). No aripiprazole-treated patient completed suicide during these studies.

Table 17 Incidence of Treatment-Emergent Suicide-Related AEs, CN138178 & CN138179, Safety Sample

	Number (%) of Patients (a)	
System Organ Class/ Preferred Term (b)	Placebo N=101	Aripiprazole N=212
Any Suicide-Related AE	4 (4.0)	1 (0.5)
Suicide Attempt	3 (3.0)	1 (0.5)
Self Injurious Behaviour	3 (3.0)	0
Intentional Self-Injury	0	1 (0.5)
Suicidal Ideation	1 (1.0)	0
Self-Injurious Ideation	1 (1.0)	0

In All Pediatric Aripiprazole Dataset, the overall incidence of suicide-related AEs was similar across the indications.

Extrapyramidal Symptoms (EPS)

Incidence of Treatment-Emergent EPS-Related AEs

Overall, 20.8% of aripiprazole-treated and 9.9% of placebo-treated patients reported EPS-related AEs in the placebo-controlled studies in autistic disorder (see Table 18). The incidence of non-akathisia EPS-related AEs was 17.9% in aripiprazole-treated patients and 2.0% in placebo-treated patients, and the incidence of akathisia events was 3.3% in the aripiprazole group and 8.9% in the placebo group. The most frequently reported events in aripiprazole-treated patients were tremor (9.9% aripiprazole; 0% placebo) and extrapyramidal disorder (6.1% aripiprazole; 0% placebo).

Table 18 Incidence of Treatment-Emergent EPS-Related AEs, CN138178 & CN138179, Safety Sample

	Number (%) of Patients (a)	
EPS Category/ Preferred Term (b)	Placebo N=101	Aripiprazole N=212
Any EPS-Related AE	10 (9.9)	44 (20.8)
Non-Akathisia Events	2 (2.0)	38 (17.9)
Akathisia Events	9 (8.9)	7 (3.3)
Parkinsonism Events	0	35 (16.5)
Tremor	0	21 (9.9)
Extrapyramidal Disorder	0	13 (6.1)
Hypokinesia	0	2 (0.9)
Bradykinesia	0	1 (0.5)
Cogwheel Rigidity	0	1 (0.5)
Akathisia Events	9 (8.9)	7 (3.3)
Psychomotor Hyperactivity	4 (4.0)	4 (1.9)
Akathisia	4 (4.0)	3 (1.4)
Hyperkinesia	1 (1.0)	0
Dyskinetic Events	1 (1.0)	3 (1.4)
Dyskinesia	1 (1.0)	3 (1.4)
Dystonic Events	1 (1.0)	1 (0.5)
Muscle Rigidity	0	1 (0.5)
Muscle Spasms	1 (1.0)	0

In the fixed-dose study (CN138179), the events of tremor and extrapyramidal disorder (patient reported 2 or more EPS AEs simultaneously) showed an increased incidence with increasing aripiprazole dose level (see Table 19).

Table 19 Incidence of Treatment-Emergent EPS-Related AEs, CN138179, Safety Sample

	Number (%) of Patients (a)			
		Aripiprazole		
EPS Category/ Preferred Term (b)	Placebo N=51	5 mg N=52	10 mg N=59	15 mg N=54
Any EPS-Related AE	6 (11.8)	12 (23.1)	13 (22.0)	12 (22.2)
Parkinsonism Events	0	6 (11.5)	11 (18.6)	12 (22.2)
Tremor	0	4 (7.7)	7 (11.9)	6 (11.1)
Extrapyramidal Disorder	0	2 (3.8)	4 (6.8)	6 (11.1)
Bradykinesia	0	0	0	1 (1.9)
Cogwheel Rigidity	0	0	0	1 (1.9)
Hypokinesia	0	1 (1.9)	0	0
Akathisia Events	5 (9.8)	4 (7.7)	2 (3.4)	0
Akathisia	3 (5.9)	1 (1.9)	2 (3.4)	0
Psychomotor Hyperactivity	2 (3.9)	3 (5.8)	0	0
Dyskinetic Events	1 (2.0)	2 (3.8)	1 (1.7)	0
Dyskinesia	1 (2.0)	2 (3.8)	1 (1.7)	0

Discontinuation due to EPS-related AEs occurred at a similar rate in the aripiprazole group (4.2%) and in the placebo group (3.0%). The most common EPS-related AE that led to discontinuation of study therapy in the aripiprazole group was tremor.

EPS Scales

Results of mean change from baseline to endpoint and highest score in EPS scales are presented in Table 20.

There were statistically significant differences between the groups on the mean change from baseline to endpoint (LOCF) in the SAS Total Score. There was no change from baseline in the aripiprazole group while the placebo group showed improvement.

There was also a statistically significant difference between the groups on the mean change from baseline to endpoint (LOCF) in the AIMS Total Score. The aripiprazole group showed improvement and there was no change in the placebo group.

There were no differences at endpoint between the treatment groups in the Barnes Akathisia Clinical Global Assessment score.

Table 20 Adjusted Mean Change from Baseline to Endpoint and Highest Score of SAS, AIMS Total Score and Barnes Akathisia Global Clinical Assessment (LOCF), CN138178 & CN138179, Safety Sample

EPS Scale (a)	Placebo	Aripiprazole	Aripiprazole vs Placebo p-value (b)
SAS Total Score	N=92	N=203	
Mean Baseline (SE)	11.2 (0.24)	10.9 (0.15)	
Change from Baseline at Endpoint (SE)	-0.4 (0.20)	0.1 (0.15)	0.030
Change from Baseline at Highest Score (SE)	0.4 (0.27)	1.2 (0.21)	0.012
AIMS Total Score	N=98	N=209	
Mean Baseline (SE)	0.7 (0.23)	0.7 (0.15)	
Change from Baseline at Endpoint (SE)	-0.0 (0.11)	-0.4 (0.09)	0.005
Change from Baseline at Highest Score (SE)	0.6 (0.18)	0.2 (0.14)	0.096
Barnes Akathisia	N=95	N=209	
Mean Baseline (SE)	0.3 (0.07)	0.1 (0.03)	
Change from Baseline at Endpoint (SE)	0.1 (0.06)	-0.0 (0.04)	0.106
Change from Baseline at Highest Score (SE)	0.3 (0.07)	0.2 (0.05)	0.055

Metabolic and Glucose Assessment

Weight Gain

The AE of weight gain associated with aripiprazole treatment seemed more prominent in this submission. At the end of the 8-week treatment, aripiprazole treated patients gained average 1.6 kg compared with 0.4 kg in placebo treated patient and 26.3% of aripiprazole treated patients compared with 7.1% of placebo-treated patients gained ≥ 7% of their body weight from baseline. There was a wilder age range (6-17years old) in this autistic program. Normal growth/development should be taken consideration while analyzing the weight data.

Placebo-Controlled Studies

On the adjusted mean change from baseline to endpoint (LOCF) in body weight, there were statistically significant differences between the treatment groups in the placebo-controlled autistic disorder studies. The adjusted mean change in body weight was higher in the aripiprazole group than the placebo group (1.6 kg vs. 0.4 kg, respectively, $p<0.001$), and 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 (0.12 standard deviations vs. -0.01 standard deviations, respectively, $p < 0.001$).

On potentially clinically relevant weight gain (an increase of at least ≥ 7% from baseline), there was a statistically significantly greater number of aripiprazole-treated patients (26.3%) than placebo-treated patients (7.1%) who demonstrated weight gain at endpoint (LOCF). However, there was no statistically significant difference ($p = 0.849$) between aripiprazole and placebo groups in the percentage of patients with clinically

relevant weight, as defined by Z-scores in the 95th percentile or higher. One aripiprazole-treated patient discontinued from the studies because of weight increase.

In order to further explore the weight again associated with aripiprazole treatment in these studies and to identify potential risk factors, the statistical reviewer, Steven Bai PhD, had conducted additional analyses on the weight data requested from the sponsor during this review cycle. The following are some of his findings.

Aripiprazole and placebo treated patients had average baseline weight Z-score of 0.762 and 0.928 respectively, which correspond to the 77.7th and the 82.3th percentiles of their respective populations. This suggests that patients in these two studies were heavier than age-matched general population at the baseline, and the patients in placebo arm were heavier compared with aripiprazole group. Aripiprazole patients increased their mean body weight Z-score by 0.105 standard deviations at the end of 8 weeks, which corresponds to a ~3% upward shift (77.7% to 80.7%) in the population body weight percentiles. The placebo group, on the other hand, reduced by 0.015 standard deviations in Z-score, which corresponds to a 0.4% decrease (82.3% to 81.9%) of the population body weight percentiles.

Dr. Bai also preformed additional analyses on the baseline body weight Z-score, age and gender. Please refer to his review for detailed analysis result. He found that with aripiprazole treatment the heavier (baseline z-score > 75%) and younger (6 to 12 years old) subjects tended to gain more weight ($p < 0.0001$ in both occasions). It is also noted that younger patients had a larger mean baseline weight Z-score (heavier) compared with the other age group (0.835 versus 0.74, corresponding to the 79.8th and 77th percentiles). 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 in body weight Z-score.

All Pediatric Database

The incidence of potentially clinically relevant weight increase (≥7% increases from baseline) in aripiprazole-treated pediatric patients by treatment indication is listed in Table 21. More aripiprazole-treated patients (62%) in autistic disorder studies gained clinically significant weight (≥ 7% baseline weight) compared with patients in other indication studies (43% in bipolar studies and 37% in schizophrenia studies). The autistic program included younger children: 79% (249/316) of the patients were 12 or younger. It is possible that younger children are more vulnerable to aripiprazole induced weight gain. Dr. Bai's analyses on weight data obtained from the controlled dataset showed that heavier (baseline Z-score > 75% of population body weight percentiles) and younger (6 to 12 years old) children tended to gain more weight during the controlled, autistic studies. The rates of clinically relevant weight gain over time in autistic disorder studies are presented in Table 22. Table 23 summaries the baseline

body weight, the weight change over time, the corresponding z-scores, and the weight change in percent of population body weight percentiles over time.

Interpretation of these findings is complicated by lack of a placebo control group and the fact that they do not take into account normal weight gain during development. However, Z-score analysis, which does take into account weight gain during development, demonstrated that there was an increase in weight relative to normal growth up to the period of 3-6 months, but then remained stable (6-9 months) or decreased (> 9 months).

Table 21 Incidence of Weight Gain ≥7% from Baseline by Indication, Overall, Safety Sample

	Number (%) of Aripiprazole Patients			
Variable	Autistic Disorder N=361	Bipolar Disorder N=239	Schizophrenia N=276	All Aripiprazole (a) N=906
Weight (b)				
Weight Increase	224 (62.0)	103 (43.1)	103 (37.3)	447 (49.3)

Table 22 Incidence of Weight Gain ≥7% from Baseline in Autistic Studies by Time, Overall, Safety Sample

	Number (%) of Aripiprazole Patients (a)			
Variable	<=3 months N=361	3-6 months N=238	6-9 months N=165	>9 months N=85
Weight (b)				
Weight Increase	133 (36.8)	153 (64.3)	108 (65.5)	46 (54.1)

Table 23 Summary of weight change over time in autistic disorder program, overall, safety sample

	Study Months			
	≤ 3 months	3-6 months	6-9 months	> 9 months
	Mean, n=354	Mean, n=220	Mean, n=141	Mean, n=61
Body Weight (kg):				
Baseline	43.22	43.99	45.7	48.58
Δ from Baseline	1.32	4.45	6.12	7.31
Body Weight Z-Score:				
Baseline	0.727	0.727	0.772	0.796
Δ from Baseline	0.102	0.259	0.253	0.207
Δ of population body weight percentile (increase)	3%	7%	7%	6%

Lipids and Glucose Assessment

The incidence of treatment emergent metabolic and glucose laboratory measurements of potential clinical relevance (total cholesterol, HDL, LDL, triglycerides, and glucose) during the placebo-controlled studies in autistic disorder was similar between the treatment groups. The limited sample size and study design preclude meaningful interpretation of the results.

There were no hyperglycemia-related AEs reported during the placebo-controlled studies in autistic disorder.

Prolactin

There was a statistically significant mean decrease in prolactin at endpoint in the aripiprazole group (-5.41 ng/mL) compared with the placebo group (1.21 ng/mL) (Table 24). There was no apparent dose-response relationship between prolactin and aripiprazole dose (Table 25).

Table 24 Analysis of Prolactin Levels, CN138178 & CN138179, Safety Sample

	Prolactin Level (a)		
	Placebo	Aripiprazole	P-value
Sample Size (b)	74	170	
Mean Baseline	6.84	7.96	0.214
Mean Change at Endpoint	1.21	-5.41	<0.001

Table 25 Analysis of Prolactin Levels by Dose, CN138179, Safety Sample

	Prolactin Level			
		Aripiprazole		
	Placebo	5 mg	10 mg	15 mg
Sample Size (a)	36	43	50	41
Mean Baseline	6.92	7.19	6.54	6.67
Mean Change at Endpoint	0.79	-5.73	-4.99	-5.68

7.3.5 Submission Specific Primary Safety Concerns

No submission specific primary safety concerns were identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The criteria currently used to determine common AEs are those AEs that occurred at an incidence of ≥ 5% (including numbers that equaled 5% after rounding) and twice the rate of placebo. For the placebo-controlled studies in autistic disorder, events of sedation, fatigue, somnolence, tremor, drooling, pyrexia, extrapyramidal disorder, decreased appetite, and salivary hypersecretion, vomiting, and lethargy met these criteria. Table 26 summarizes the overall incidence of treatment-emergent adverse events (TEAEs) occurred ≥ 2% in aripiprazole treated group in placebo-controlled dataset.

Table 26 Incidence of Treatment-Emergent AEs Occurred ≥2% in Aripiprazole Group, CN138178 & CN138179, Safety Sample

System Organ Class/ Preferred Term (b)	Placebo		Aripiprazole	
# Pts in Safety Sample	101		212	
# Male Pts in Safety Sample	91		188	
# Female Pts in Safety Sample	10		24	
Any AE	75	(74.3)	189	(89.2)
Nervous System Disorders	27	(26.7)	114	(53.8)
Headache	10	(9.9)	16	(7.5)
Somnolence	4	(4.0)	22	(10.4)
Extrapyramidal Disorder	0		13	(6.1)
Sedation	4	(4.0)	44	(20.8)
Akathisia	4	(4.0)	3	(1.4)
Tremor	0		21	(9.9)
Dizziness	0		0	
Drooling	0		19	(9.0)
Lethargy	0		10	(4.7)
Dystonia	0		0	
Hypersomnia	0		5	(2.4)
Gastrointestinal Disorders	21	(20.8)	71	(33.5)
Vomiting	7	(6.9)	29	(13.7)
Nausea	3	(3.0)	8	(3.8)
Diarrhoea	9	(8.9)	16	(7.5)
Abdominal Pain Upper	2	(2.0)	8	(3.8)
Salivary Hypersecretion	1	(1.0)	12	(5.7)
Constipation	4	(4.0)	11	(5.2)
Stomach Discomfort	0		1	(0.5)
Dry Mouth	0		3	(1.4)
Dyspepsia	0		1	(0.5)

System Organ Class/ Preferred Term (b)	Placebo		Aripiprazole	
# Pts in Safety Sample	101		212	
# Male Pts in Safety Sample	91		188	
# Female Pts in Safety Sample	10		24	
Psychiatric Disorders	26	(25.7)	44	(20.8)
Insomnia	11	(10.9)	11	(5.2)
Aggression	7	(6.9)	6	(2.8)
Agitation	2	(2.0)	5	(2.4)
Anxiety	0		2	(0.9)
Restlessness	3	(3.0)	5	(2.4)
Schizophrenia	0		0	
General Disorders And Administration Site Conditions	7	(6.9)	59	(27.8)
Fatigue	2	(2.0)	35	(16.5)
Pyrexia	1	(1.0)	19	(9.0)
Asthenia	0		0	
Thirst	1	(1.0)	5	(2.4)
Infections And Infestations	18	(17.8)	43	(20.3)
Nasopharyngitis	5	(5.0)	18	(8.5)
Upper Respiratory Tract Infection	5	(5.0)	6	(2.8)
Gastroenteritis Viral	2	(2.0)	6	(2.8)
Respiratory, Thoracic And Mediastinal Disorders	16	(15.8)	46	(21.7)
Cough	5	(5.0)	13	(6.1)
Nasal Congestion	2	(2.0)	9	(4.2)
Rhinorrhoea	2	(2.0)	8	(3.8)
Epistaxis	0		7	(3.3)
Metabolism And Nutrition Disorders	10	(9.9)	41	(19.3)
Increased Appetite	7	(6.9)	27	(12.7)
Decreased Appetite	2	(2.0)	14	(6.6)
Musculoskeletal And Connective Tissue Disorders	5	(5.0)	11	(5.2)
Arthralgia	1	(1.0)	3	(1.4)
Back Pain	0		0	
Musculoskeletal Stiffness	0		5	(2.4)
Investigations	4	(4.0)	12	(5.7)
Weight Increased	3	(3.0)	8	(3.8)
Skin And Subcutaneous Tissue Disorders	4	(4.0)	12	(5.7)
Rash	2	(2.0)	5	(2.4)
Eye Disorders	5	(5.0)	3	(1.4)
Vision Blurred	0		0	
Renal And Urinary Disorders	5	(5.0)	14	(6.6)
Enuresis	5	(5.0)	7	(3.3)
Reproductive System And Breast Disorders	0		3	(1.4)
Dysmenorrhoea*	0		0	

The incidence of TEAEs that occurred in ≥5% in different aripiprazole dosing groups and placebo group in study CN138-179 is presented in Table 27. Sedation, tremor, drooling, extrapyramidal disorder, salivary hypersecretion, fatigue and pyrexia are reported in higher frequency in higher aripiporazole dose groups and showed a dose response trend, but they are not statistically significant when placebo was included in the analysis. Fatigue is the only AE which showed a statistically significant dose-response relationship.

Table 27 Incidence of Treatment-Emergent Adverse Events that Occurred in ≥5% of Patients by Treatment Group, CN138-179, Safety Sample

System Organ Class Preferred Term (b)	Number (%) of Patients (a) Placebo	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg
# Pts in Safety Sample	51	52	59	54
# Male Pts in Safety Sample	47	46	50	50
# Female Pts in Safety Sample	4	6	9	4
Any Adverse Event	37 (72.5)	46 (88.5)	53 (89.8)	46 (85.2)
Nervous System Disorders	13 (25.5)	24 (46.2)	39 (66.1)	28 (51.9)
Sedation	3 (5.9)	9 (17.3)	17 (28.8)	13 (24.1)
Tremor	0	4 (7.7)	7 (11.9)	6 (11.1)
Somnolence	2 (3.9)	4 (7.7)	5 (8.5)	5 (9.3)
Drooling	0	2 (3.8)	8 (13.6)	5 (9.3)
Headache	2 (3.9)	3 (5.8)	5 (8.5)	5 (9.3)
Extrapyramidal Disorder	0	2 (3.8)	4 (6.8)	6 (11.1)
Lethargy	0	4 (7.7)	3 (5.1)	3 (5.6)
Akathisia	3 (5.9)	1 (1.9)	2 (3.4)	0
Hypersomnia	0	3 (5.8)	0	2 (3.7)
Psychomotor Hyperactivity	2 (3.9)	3 (5.8)	0	0
Gastrointestinal Disorders	9 (17.6)	11 (21.2)	22 (37.3)	24 (44.4)
Vomiting	4 (7.8)	5 (9.6)	12 (20.3)	5 (9.3)
Diarrhoea	4 (7.8)	2 (3.8)	5 (8.5)	5 (9.3)
Constipation	3 (5.9)	2 (3.8)	6 (10.2)	3 (5.6)
Salivary Hypersecretion	1 (2.0)	1 (1.9)	4 (6.8)	6 (11.1)
Nausea	1 (2.0)	1 (1.9)	3 (5.1)	4 (7.4)
Abdominal Pain Upper	1 (2.0)	2 (3.8)	1 (1.7)	4 (7.4)
Psychiatric Disorders	13 (25.5)	12 (23.1)	13 (22.0)	9 (16.7)
Insomnia	6 (11.8)	1 (1.9)	5 (8.5)	2 (3.7)
Aggression	3 (5.9)	2 (3.8)	3 (5.1)	0
General Disorders And Administration Site Conditions	1 (2.0)	9 (17.3)	20 (33.9)	16 (29.6)
Fatigue	0	2 (3.8)	13 (22.0)	10 (18.5)
Pyrexia	0	3 (5.8)	7 (11.9)	5 (9.3)
Thirst	1 (2.0)	3 (5.8)	1 (1.7)	1 (1.9)

System Organ Class Preferred Term (b)	Number (%) of Patients (a) Placebo	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg
Respiratory, Thoracic And Mediastinal Disorders	7 (13.7)	13 (25.0)	16 (27.1)	9 (16.7)
Cough	2 (3.9)	8 (15.4)	4 (6.8)	0
Rhinorrhoea	1 (2.0)	2 (3.8)	5 (8.5)	1 (1.9)
Nasal Congestion	1 (2.0)	1 (1.9)	1 (1.7)	4 (7.4)
Pharyngolaryngeal Pain	3 (5.9)	1 (1.9)	1 (1.7)	1 (1.9)
Epistaxis	0	0	4 (6.8)	1 (1.9)
Infections And Infestations	6 (11.8)	13 (25.0)	9 (15.3)	13 (24.1)
Nasopharyngitis	2 (3.9)	6 (11.5)	5 (8.5)	5 (9.3)
Gastroenteritis Viral	0	1 (1.9)	3 (5.1)	1 (1.9)
Upper Respiratory Tract Infection	0	2 (3.8)	0	3 (5.6)
Metabolism And Nutrition Disorders	4 (7.8)	14 (26.9)	8 (13.6)	11 (20.4)
Increased Appetite	2 (3.9)	10 (19.2)	3 (5.1)	7 (13.0)
Decreased Appetite	1 (2.0)	5 (9.6)	5 (8.5)	3 (5.6)
Skin And Subcutaneous Tissue Disorders	3 (5.9)	3 (5.8)	4 (6.8)	3 (5.6)
Rash	1 (2.0)	0	3 (5.1)	1 (1.9)
Investigations	1 (2.0)	4 (7.7)	3 (5.1)	3 (5.6)
Weight Increased	1 (2.0)	4 (7.7)	1 (1.7)	2 (3.7)
Renal And Urinary Disorders	1 (2.0)	2 (3.8)	1 (1.7)	7 (13.0)
Enuresis	1 (2.0)	0	1 (1.7)	3 (5.6)
Immune System Disorders	5 (9.8)	1 (1.9)	0	1 (1.9)
Seasonal Allergy	4 (7.8)	0	0	1 (1.9)

7.4.2 Laboratory Findings

In the placebo-controlled studies in autistic disorder, the incidences of treatment-emergent serum chemistry laboratory abnormalities of potential clinical relevance and serum electrolyte measurements were similar between treatment groups. No patient had elevated ALT, AST, or total bilirubin. No aripiprazole-treated patient discontinued from the studies because of a laboratory abnormality. There were no clinically meaningful serum chemistry findings by age, gender, or race.

7.4.3 Vital Signs

The incidences of potentially clinically relevant vital sign measurements for the placebo-controlled studies in autistic disorder were generally similar between treatment groups. One aripiprazole-treated patient discontinued from the study because of hypertension. There were no clinically meaningful vital sign findings by age, gender, or race.

7.4.4 Electrocardiograms (ECGs)

In the placebo-controlled studies in autistic disorder, the incidence of potentially clinically relevant ECG abnormalities was low for aripiprazole-treated patients and comparable to that of placebo-treated patients except for the measurement of sinus tachycardia and the non-specific category of other abnormalities. The incidence of sinus tachycardia was higher in aripiprazole-treated patients (2.6%) than placebo-treated patients (0%), and 1 aripiprazole-treated patient discontinued from the study because of tachycardia.

The data from all aripiprazole Phase 1/2/3 studies are presented as the mean change from baseline to study endpoint and mean change from baseline to maximum on-treatment QTcE (fractional exponent correction method). No clinically meaningful differences were observed between treatment groups in the mean change from baseline to endpoint and at maximum reading in QTcE measurements. No aripiprazole-treated patient demonstrated a QTcE greater than 500 msec or > 60 msec change in QTcE interval. There were no clinically meaningful differences between the treatment groups by gender, age, or race.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this indication.

7.4.6 Immunogenicity

No immunogenicity study was deemed necessary.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Cochran-Armitage Exact test was conducted by the sponsor to assess the dose-response relationship of AEs (ie, increased incidence of AEs with increased dose) and was analyzed including and excluding placebo. When placebo was included in the analysis, the AEs of sedation, tremor, drooling, extrapyramidal disorder, salivary hypersecretion, fatigue, and pyrexia showed a statistically significant ($p < 0.05$) dose-response relationship. When placebo was excluded from the analysis, only the AE of fatigue showed a statistically significant dose-response relationship.

7.5.2 Time Dependency for Adverse Events

The time dependency for adverse events was not studied in this submission.

7.5.3 Drug-Demographic Interactions

The overall incidences of treatment-emergent AEs were similar across age groups for aripiprazole-treated and placebo-treated patients. There was a statistically significant difference between the age groups for the event of salivary hypersecretion (ages 6 - 12: 6.6% aripiprazole; 0% placebo; ages 13 - 17: 2.2% aripiprazole; 4.5% placebo), indicating that this event was more prominent in younger children than older children with autistic disorder. Tremor occurred more frequent in children aged 6 to 12 with aripiprazole treatment (11.4%, vs. 0% in PLA) compared with in children aged 13 to 17 with aripiprazole treatment (4.4%, vs. 0% in PLA).

There was no clinically meaningful difference in the AE profile (aripiprazole versus placebo) between males and females. However, the limited number of females precluded meaningful interpretation of AEs relative to gender across groups.

In general, there was no difference in the AE profile among racial groups. However, the limited number of patients in racial groups other than white and black precluded meaningful interpretation of AEs relative to race across all groups.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied in this submission.

7.5.5 Drug-Drug Interactions

Aripiprazole is a marketed drug in the USA for many years. Drug-drug interaction profile had been well established and has been addressed in current approved aripiprazole

labeling. No drug-drug interaction studies were deemed necessary in the aripiprazole autistic disorder clinical program.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity study was deemed necessary.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported in this autistic disorder program.

7.6.3 Pediatrics and Assessment of Effects on Growth

This submission included two 8-week, short-term studies. Significant weight gain associated with aripiprazole treatment was observed in both studies. Please refer to section *7.3.5 Submission Specific Primary Safety Concerns* for more discussion regarding the weight gain issue. Height change was not assessed during these two trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

A comprehensive review of aripiprazole-treated patients participating in autistic disorder studies was conducted to identify cases of overdose. No cases of overdose were identified in aripiprazole-treated patients in autistic disorder studies.

A comprehensive review of aripiprazole-treated patients participating in autistic disorder studies was conducted to identify AEs that might indicate possible abuse of aripiprazole. No cases of drug abuse were identified in the pediatric autistic disorder population.

No studies were conducted in patients with autistic disorder to assess withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

A 120-Day Safety Update (SU) was submitted on May 21, 2009 presented a review of the safety of the oral-tablet formulation based on data available in the clinical trials database as of the cutoff date of 15-Nov-2008.

Newly-reported data since the cutoff date for the autistic disorder clinical summary of safety (CSS) were reviewed for deaths, SAEs, and discontinuations due to AEs, and are

presented in this SU. The cut-off date for the autistic disorder CSS was 1-Jun-2008 for all ongoing studies.

The extent of exposure of patients in all pediatric autistic disorder patients for this SU was similar to that reported in the autistic disorder CSS. A total of 367 pediatric autistic disorder patients have been treated with aripiprazole in Phase 3 studies. Of these, 243 (66.2%) patients were treated with aripiprazole for 180 days or longer.

Data in this SU on the aripiprazole tablet formulation in pediatric patients were reviewed for discontinuations due to AE, SAEs, and deaths. The safety and tolerability of aripiprazole as demonstrated in this SU (data cutoff 15-Nov-2008) indicate a safety profile consistent with that reported in other pediatric indications. Results are consistent with what has been seen throughout the development and marketing of oral-tablet aripiprazole. No new safety concerns were identified.

8 Postmarket Experience

Aripiprazole was first approved for the treatment of schizophrenia in adults on 17-Jul-2002 (International Birth Date) in Mexico and subsequently in the United States on 15-Nov-2002 and the European Union on 4-Jun-2004. Aripiprazole was approved for use in adolescent schizophrenia in the United States on 29-Oct-2007 and the application is currently under review in the European Union. In addition, aripiprazole was approved for acute manic or mixed episodes associated with Bipolar I Disorder in adults in the United States on 29-Sep-2004, and in pediatric patients on 27-Feb-2008. It is also approved for acute mania in adults in the EU, Switzerland, Turkey, Brazil, Indonesia, Korea, Mexico, Venezuela, Chile, Colombia, Egypt, Hong Kong, Peru, and Russia.

An estimate of the number of treated patients was derived from sales figures received from IMS for the period from 1-Oct-2002 to 31-Mar-2008 inclusive. Based on the information available to Otsuka/BMS, (b) (4) milligrams (mg) were sold during the period referenced above. The total number of patients exposed during the period referenced above is estimated to be (b) (4).

Review of the aripiprazole worldwide AE data received from spontaneous postmarketing reports and from clinical trials, as presented in the PSURs, PADERs, indicated an overall benefit risk profile similar to and consistent with the previously established clinical trial experience as described in the Company Core Safety Information (CCSI) and in the existing USPI for Abilify.

9 Appendices

9.1 Literature Review/References

A worldwide literature search for published articles pertaining to the safety and efficacy of aripiprazole was conducted. The literature search timeframe includes published articles from June 1, 2007 through a cut-off date of June 30, 2008.

This literature search encompassed databases searched from 01June2007 through 30June2008. Search terms included the keywords: aripiprazole, abilitat, abilify, opc()14597 or opc14597, opc()31 or opc31.

Databases searched via Dialog from 31January 2008 through 30June 2008 included the following:

- MEDLINE(R) 1990-2008/Aug 04
- Biosis Previews(R) 1993-2008/Aug W1
- EMBASE 1993-2008/Aug 05
- EMBASE Alert 2008/Aug 06
- Derwent Drug File 1983-2008/Jun W4
- SciSearch(R) Cited Ref Sci 1990-2008/Jul W4
- CA SEARCH(R) 1967-2008/UD=14905
- ToxFile 1965-2008/Jul W4
- Int.Pharm.Abs 1970-2008/May B2
- Adis Clinical Trials Insight 1990-2008/Jul W4

Databases searched via STN prior to 31January2008 included the following:

- MEDLINE
- BIOSIS/Biological Abstracts
- EMBASE/EMBASE ALERTS
- DRUGU/Derwent Drug File
- SCISEARCH/Science Citation Index
- CAPLUS/Chemical Abstracts
- TOXCENTER
- LIFESCI/Life Sciences Collection
- IPA/International Pharmaceutical Abstracts
- ADISCTI: Adis Clinical Trials Insight.

Following the review, it has been determined that the literature contains no findings that would adversely affect conclusions about the safety and efficacy of aripirazole contained in supplemental submission to NDA 21-436.

9.2 Labeling Recommendations

The following are the sponsor proposed changes and the reviewer's recommendations. Changes are shown as ~~strikethroughs~~ for deletion and underline for addition.

In section 6.1 Overall Adverse Reactions Profile/Weight Gain, the sponsor proposed following addition:

(b) (4)

In section 14.4, the sponsor proposed following addition:

14.4 Irritability Associated with Autistic Disorder

Pediatric Patients

The efficacy of ABILIFY (aripiprazole) in the treatment of irritability associated with Autistic Disorder was established in two 8-week, placebo-controlled trials in pediatric patients (6 to 17 years of age) who met the DSM-IV criteria for Autistic Disorder and demonstrated behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems. Over 75% of these subjects were under 13 years of age.

Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Improvement (CGI-I) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured the emotional and behavioral symptoms of irritability in Autistic Disorder, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. The results of these trials are as follows:

1. In one of the 8-week, placebo-controlled trials, children and adolescents with Autistic Disorder (n=98), aged 6 to 17 years, received daily doses of placebo or ABILIFY 2 mg/day to 15 mg/day. ABILIFY, starting at 2 mg/day andincreasing up to 15 mg/d base on clinical response and tolerability, significantly improved scores on the ABC-I subscale and on the CGI-I scale compared with placebo. The mean daily dose of aripiprazole at the end of 8 weeks was 8.6 mg/day.

2. In the other 8-week, placebo-controlled trial in children and adolescents with Autistic Disorder (n=218), aged 6 to 17 years, three fixed doses of ABILIFY (5 mg/day, 10 mg/day, or 15 mg/day) were compared to placebo. ABILIFY dosing started at 2 mg/day and was increased to 5 mg/day after one week. After a second week, it was increased to 10 mg/day for patients in the 10 mg and 15 mg dose arms, and after a third week, it was increased to 15 mg/day in the 15 mg/day treatment arm. All three doses of ABILIFY significantly improved scores on the ABC-I subscale compared with placebo.

The reviewer has reviewed all other proposed clinical related labeling changes. The changes are acceptable.

9.3 Advisory Committee Meeting

No advisory committee meeting is planed for this submission.

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

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

/s/

JING ZHANG
10/30/2009