CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	021436 S-036 (tablets) 021713 S-028 (oral solution) 021729 S-020 (orally disintegrating tablet) 021866 S-021 (IM injection)
Priority or Standard	Standard
Submit Date(s)	05/24/2013
Received Date(s)	05/24/2013
PDUFA Goal Date	03/24/2014
Division / Office	Division of Psychiatry Products Office of New Drugs 1
Reviewer Name(s)	Cara Alfaro, Pharm.D.
Review Completion Date	02/26/2014
Established Name	Aripiprazole
Trade Name	Abilify
Therapeutic Class	Antipsychotic
Applicant	Otsuka Pharmaceutical Company
Formulation(s)	2, 5, 10, and 15 mg tablets
Dosing Regimen	2 to 15 mg daily
Indication(s)	Irritability Associated with Autistic Disorder (maintenance)
Intended Population(s)	Pediatric (6 to 17 years)

Table of Contents

Tables

Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

(b) (4)

Abilify is currently approved for the treatment of irritability associated with autism in patients 6 to 17 years of age as demonstrated in two 8-week clinical trials.

The Sponsor has proposed language in labeling to describe this negative clinical trial. Proposed language is generally acceptable with some suggested modifications. No new safety findings were noted in this clinical trial that are not in currently approved product labeling.

This submission does fulfill the PREA Postmarketing Commitment 1570-1 under NDA 021436 for a maintenance treatment study to obtain long-term efficacy and safety data in patients ages 6 – 16 years.

1.2 Risk Benefit Assessment

The efficacy of aripiprazole was not established in this maintenance study. There was no evidence of clinical worsening in subjects receiving aripiprazole compared to those receiving placebo. It is not recommended that the sponsor conduct another maintenance study in this population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for a Postmarket Risk Evaluation and Mitigation Strategy at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommendations for Postmarket Requirements or Commitments.

2 Introduction and Regulatory Background

2.1 Product Information

ABILIFY (aripiprazole) was initially approved on November 15, 2002 for the treatment of schizophrenia in adults. ABILIFY is also approved for the following indications:

- treatment of acute manic or mixed episodes associated with bipolar I disorder (adults and children/adolescents [10-17 years]
- treatment of schizophrenia in adolescents [13-17 years]
- adjunctive treatment in major depressive disorder (adults)
- treatment of irritability associated with autistic disorder in pediatric patients [6-17 years]

The injection dosage form of ABILIFY is approved for the acute treatment of agitation associated with schizophrenia or bipolar I disorder.

2.2 Tables of Currently Available Treatments for Proposed Indications

Risperdal (risperidone) is the only medication that has been approved in the United States for the treatment of irritability associated with autistic disorder. Risperdal labeling (Section 14.4) includes a description of clinical trial data from short-term trials and one maintenance trial (double-blind withdrawal study).

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 and, as such, carries the same class warnings and precautions specific to this class of medications. Current labeling for most atypical antipsychotics, including aripiprazole, include the following warnings and precautions: elderly patients with dementia-related psychosis (increased risk of death and cerebrovascular adverse events), suicidality, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes (hyperglycemia, dyslipidemia, weight gain), orthostatic hypotension, leukopenia/neutropenia/agranulocytosis, seizures, potential for cognitive and motor impairment.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

11/19/2009 Aripiprazole was approved for the treatment of irritability associated with autistic disorder in pediatric patients [6-17 years]. A deferred study under PREA was outlined in the approval letter:

> 1570-1 A deferred pediatric study under PREA for a maintenance treatment study to obtain long-term efficacy and safety data in patients ages 6 – 16 years.

11/16/2010 Sponsor submitted protocol CN138603 to IND 071501. No comments regarding study design were communicated to the sponsor. Biometrics conveyed comments to the sponsor. There were significant discussions regarding the sponsor's plan to conduct an interim analysis after 20 relapses had occurred and a final analysis when 30 relapses have occurred (or 84 subjects had completed the study). Biometrics discouraged the interim analysis.

7/28/2011 Amendment 1 to protocol CN138603. This amendment removed reference to an interim analysis.

2.6 Other Relevant Background Information

No other relevant background information was identified.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

During the course of this review, no issues or concerns were noted with respect to data quality of integrity. The sponsor indicated that no audits were conducted for this study.

The sponsor submitted a negative study and no indications were being sought. Therefore, the Office of Scientific Investigations was not consulted to inspect any of the clinical sites.

3.2 Compliance with Good Clinical Practices

The sponsor indicated that Study CN138603 was performed in accordance with Good Clinical Practice, as defined by the International Conference n Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50.

3.3 Financial Disclosures

Per request, the sponsor submitted financial disclosure information for all clinical investigators on 7/23/2013. The sponsor indicated that no debarred persons were involved with the submitted application. There were over 40 sites that participated in this study, 34 that enrolled subjects.

The following is in accordance with the Clinical Investigator Financial Disclosure Review Template:

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 43 Principal Investigators and 277 subinvestigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 7		
Is an attachment provided with the reason	Yes X	No ☐ (Request explanation from applicant)

The sponsor identified 2 investigators with disclosable interests. (b) (6) principal investigator Site (b) (6), had a disclosable financial interest that included

speaking fees (promotional speaker). (b) (6)., subinvestigator Site (b) (6), had a disclosable financial interest that included speaking fees (promotional speaker). Few subjects were enrolled in these two clinical sites and only 1 subject from one of the sites was eligible for randomization – therefore, it is unlikely that inclusion of these subjects would have biased any study results.

Financial disclosure information was unable to be obtained from 6 subinvestigators from 6 clinical sites and the sponsor provided evidence of due diligence. Two of these clinical sites did not enroll any subjects into the clinical trial.

Due to the large number of clinical sites in this study (> 40), it is unlikely that the disclosable financial interests or the missing financial disclosure information for 6 subinvestigators influenced study results. This clinical trial was considered a negative study as efficacy was not established for aripiprazole.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC information was submitted.

4.2 Clinical Microbiology

No clinical microbiology studies were deemed necessary.

4.3 Preclinical Pharmacology/Toxicology

No preclinical pharmacology/toxicology studies were submitted.

4.4 Clinical Pharmacology

No clinical pharmacology studies/data were submitted.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This submission included results from a single clinical trial: CN138603 "Safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric subjects with irritability associated with autistic disorder"

5.2 Review Strategy

Material reviewed included the abbreviated clinical study report for CN138603, case report forms, clinical trial datasets (JMP) and proposed labeling. When the NDA was submitted, the sponsor had not provided datasets. Per request, these datasets were submitted on 8/30/2013 and 9/13/2013. The efficacy review was performed in consultation with the statistical reviewer, Andrejus Parfionovas, Ph.D.. Please refer to his review for a more detailed statistical review of efficacy.

5.3 Discussion of Individual Studies/Clinical Trials

This submission included results from one clinical trial, as noted in section 5.1.

6 Review of Efficacy

Efficacy Summary

Study CN138603 was a randomized withdrawal study to evaluate the long-term maintenance treatment of pediatric subjects (6 to 17 years of age) with irritability associated with autistic disorder. Subjects participated in a 13 to 26 week open-label stabilization phase and received aripiprazole 2 to 15 mg/day. Subjects who met criteria for clinical stability for 12 weeks were randomized to receive aripiprazole (2 – 15 mg/day) or placebo for 16 weeks. The protocol-specified primary efficacy endpoint was the time from randomization to relapse. There was no statistically significant difference between aripiprazole and placebo for the primary endpoint ($p = 0.097$). The Kaplan-Meier relapse rates at week 16 were 32% (13/41) for aripiprazole and 50% (22/44) for placebo (hazard ratio 0.57; 95% CI: 0.28, 1.12).

6.1 Indication – Treatment of Irritability Associated with Autistic Disorder

Clinical trial CN138603 "Safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric subjects with irritability associated with autistic disorder"
This study was initiated on March 7, 2011 and completed on June 20, 2012.

Thirty four clinical sites in the United States enrolled subjects (Appendix 9.4).

6.1.1 Methods/Study Design/Analysis Plan

The primary objective of this study was to evaluate the efficacy of aripiprazole compared to placebo in pediatric subjects (6 to 17 years of age) as measured by the time from randomization to relapse.

Methods/Study Design
This was a multicenter, double-blind, randomized, placebo-controlled study in male or female subjects 6 to 17 years of age with a DSM IV-TR diagnosis of autistic disorder and demonstrating behaviors such as tantrums, aggression, self-injurious behavior or a combination of these symptoms (see inclusion criteria). Following a 7 to 42 day screening phase, subjects continued into an open-label stabilization phase (Phase 1) followed by the double-blind randomization phase (Phase 2):

- Phase 1 was the stabilization phase – 13 to 26 weeks of single-blind aripiprazole treatment (2 to 15 mg/day, administered once daily). Aripiprazole was initiated at 2 mg/day and adjusted based on tolerability and efficacy. During this phase, study visits occurred every 2 weeks. Phone visits were staggered with office visits – though investigators could substitute an office visit for a phone visit when the subject was potentially eligible for randomization.

- Phase 2 was the randomization phase – 16 weeks of double-blind treatment with aripiprazole (2 to 15 mg/day) or placebo administered once daily. Subjects randomized (1:1) to aripiprazole were to continue at the dose prescribed at the end of Phase 1. During Phase 2, the dose of study medication could be increased or decreased within the dose range. During this phase, study visits occurred at weeks 1, 2, 3, 4, 6, 8, 10, 12, 14 and 16 with interim visits to be scheduled as needed to assess criteria for relapse.

Definition of Response during Phase 1: Subjects in Phase 1 who demonstrated a stable response for 12 weeks with regard to symptoms of irritability were eligible for randomization into Phase 2. Response was defined as a $\geq$ 25% decrease from baseline in the Aberrant Behavior Checklist-Irritability subscale (ABC-I) and a rating of "much improved" or "very much improved" on the Clinical Global Impressions-Improvement (CGI-I) scale. Response must have been demonstrated over a 12-week period (inclusive) with no more than 1 excursion of response criteria (ABC-I < 25% decrease from baseline or a CGI-I rating $\geq$ 3 occurring at any 1 clinic visit). Subjects who experience a second excursion continued in Phase 1 until they achieved response criteria again and could maintain the response for 12 weeks. If insufficient time remained in Phase 1 to achieve response for 12 weeks, those subjects were discontinued.

Definition of Relapse during Phase 2: There were five different definitions of relapse in this study

1. The subject meets the following criteria for 2 consecutive visits: ABC-I score ≥ 25% increase compared to the end of Phase 1 score and CGI-I rating of "much worse" or "very much worse" relative to the end of Phase 1. After relapse criteria are met at one visit, the second visit should occur in approximately one week to repeat the assessments. The date of relapse is the first of the 2 clinic visits at which the subject had elevated scores.

2. The subject discontinues for reason of Lost to Follow-up following a study visit in which the subject had an ABC-I score ≥ 25% increase compared to the end of Phase 1 score and CGI-I rating of "much worse" or "very much worse" relative to the end of Phase 1

3. The subject initiates a prohibited drug to treat worsening symptoms of irritability associated with autistic disorder following a visit in which the subject had an ABC-I score ≥ 25% increase compared to the end of Phase 1 score and CGI-I rating of "much worse" or "very much worse" relative to the end of Phase 1

4. The subject discontinues the study due to a hospitalization for worsening symptoms of irritability associated with autistic disorder (e.g. self-injurious behavior)

5. The subject discontinues the study due to lack of efficacy based upon the investigator's assessment

Inclusion/exclusion criteria
Key inclusion and exclusion criteria are summarized in this section. A complete list of criteria are in Appendix 9.6.
Included in this study were generally healthy male or female subjects, 6 to 17 years of age (inclusive), DSM-IV-TR diagnosis for Autistic disorder with behaviors such as tantrums, aggression, self-injurious behavior or a combination of these symptoms. The diagnosis of autistic disorder was confirmed by the Autism Diagnostic Interview-Revised (ADI-R). Subjects had to have a mental age of at least 24 months as assessed by the investigator. Subjects had to have an ABC-Irritability subscale score ≥ 18 and a CGI-S score ≥ 4 (moderately ill) at screening and baseline visits.

Excluded from this study were subjects considered treatment resistant to antipsychotic medication based on lack of therapeutic response to 2 different antipsychotics after treatment of at least 3 weeks each and those subjects previously treated with aripiprazole (≥ 3 weeks/adequate dose) and did not demonstrate a clinically meaningful response. Also excluded were subjects with a lifetime diagnosis of bipolar disorder, psychosis or schizophrenia or a current diagnosis of major depressive disorder. Subjects with diagnoses of Pervasive Developmental Disorder Not Otherwise Specified,

Asperger's Syndrome, Rett's Syndrome, Childhood Disintegrative Disorder or Fragile X Syndrome were excluded. Subjects with a significant risk of committing suicide (based on history or psychiatric examination) were also excluded.

Concomitant medications
The following concomitant medications were not allowed during either Phase 1 or Phase 2: antipsychotics, antidepressants, stimulants, alpha agonists (e.g. clonidine, guanfacine), mood stabilizers/anticonvulsants, atomoxetine, CYP3A4 or CYP2D6 inducers, and nutritional supplements/herbal supplements with CNS effects. Allowable concomitant medications included benzodiazepines (for procedures only), non-benzodiazepines (e.g. zolpidem etc.) for insomnia, benztropine for treatment of EPS, propranolol for treatment of akathisia/tremor, and diphenhydramine or hydroxyzine for sleep or serious behavior problems.

Assessments
For a complete list of assessments/procedures and frequency, refer to the Schedule of Events in Appendix 9.5.

Efficacy assessments included the following rating scales: Aberrant Behavior Checklist, Clinical Global Impression-Improvement, Clinical Global Impression-Severity, Caregiver Strain Questionnaire, Pediatric Quality of Life Inventory.

Safety assessments included physical examination, weight, height, ECG, vital signs (supine/standing), adverse events, routine laboratory tests. Rating scales for the assessment of extrapyramidal adverse events included the Simpson Angus Scale, Barnes Akathisia Scale and Abnormal Involuntary Movement Scale. The Tanner Staging was also included in the protocol.

Analysis Plan
Refer to the Biometrics review for a more comprehensive description of the statistical analysis plan for this study. A brief review of the statistical approach for the primary efficacy analysis only is included here.

The primary efficacy outcome measure was the time from randomization to relapse. Per the sponsor, a total of 30 relapses provided 80% power to detect a significant difference in time to relapse between the placebo and aripiprazole groups using the log-rank test. The sponsor assumed a relapse rate of 25% in the aripiprazole group, a relapse rate of 55% in the placebo group and a 2-sided alpha level of 0.05. The hazard ratio for the assumed relapse rates was 0.36. The sponsor assumed a 20% dropout rate (for reasons other than relapse) so that approximately 42 randomized subjects per arm would yield 30 relapses. It was estimated that 200 subjects would need to enter Phase 1 in order to obtain 84 randomized subjects (42/arm). The study was to be terminated when a total of 30 relapses had occurred or a total of 84 subjects had been randomized and had completed the study, whichever was first.

The primary efficacy outcome measure was evaluated by a survival analysis using the randomized sample. Survivorship function and estimated survivorship curves were obtained from Kaplan-Meier estimates. Survivor distributions of the placebo and aripiprazole groups were compared using the log-rank test, stratified by baseline body weight (≥ 40 kg and < 40 kg). Subjects who did not experience a relapse, including those that discontinued early for any other reason, were censored on their date of last efficacy evaluation or their last dose of study medication (whichever was later). The estimated hazard ratio and 95% confidence interval was obtained from the Cox regression model with baseline body weight (≥ 40 kg and < 40 kg) as a stratification factor and with treatment group as a covariate. Relapses that occurred more than 3 days after the last dosing date of double-blind medication were excluded from the analysis.

The clinical protocol originally included plans for an interim analysis. Based on comments from biometrics, the sponsor decided to forego an interim analysis and this was removed from the protocol by amendment.

6.1.2 Results

The following populations were analyzed

	Placebo	Aripiprazole
Phase 1 Safety Population	-	155
Phase 1 Efficacy Population	-	152
Randomized Population	44	41
Phase 2 Safety Population	43	39
Phase 2 Efficacy Population	43	39

Phase 1 was the 13 to 26-week open-label stabilization phase. Phase 2 was the 16-week double-blind randomization phase. The mean (median) time for subjects in Phase 1 was 135 (129) days in the aripiprazole group and 125.3 (125.5) days in the placebo group.

Demographics

Demographics for Phase 1 (open-label) and Phase 2 (double-blind) are in Table 1. For the randomized group, the two populations were similar with regard to demographic characteristics. More males were enrolled into the clinical trial compared to females which is consistent with the distribution of autistic disorder in the population.

Table 1. Demographic Characteristics

	Phase 1	Phase 2	
	Aripiprazole 2-15 mg/day N = 155	Placebo N = 44	Aripiprazole 2-15 mg/day N = 41
Age (years)			
Mean (SD)	10 (2.8)	10.8 (2.8)	10.1 (2.8)
Median	10	11	10
Minimum	6	6	6
Maximum	17	17	16
Age group (years), n (%)			
6 – 12 years old	126 (81.3)	33 (75)	32 (78)
13 – 17 years old	29 (18.7)	11 (25)	9 (22)
Gender, n (%)			
Male	123 (79.4)	38 (86.4)	30 (78)
Female	32 (20.6)	6 (13.6)	11 (26.8)
Race, n (%)			
White	107 (69)	28 (63.6)	31 (75.6)
Black/African American	36 (23.2)	11 (25)	8 (19.5)
Asian	6 (3.9)	3 (6.8)	0
American Indian or Alaska Native	2 (1.3)	1 (2.3)	0
Other	4 (2.6)	1 (2.3)	2 (4.9)
Ethnic group, n (%)			
Hispanic or Latino	27 (17.4)	9 (20.5)	10 (24.4)
Not Hispanic or Latino	124 (80)	34 (77.3)	29 (70.7)
Weight (kg)			
Mean (SD)	46.2 (22.5)	50.6 (21.9)	51.7 (24.4)
Median	39	44.2	43.6
Minimum	20	19	21
Maximum	141	110	117
BMI (kg/m2)			
Mean (SD)	21.5 (6.1)	21.9 (5.2)	24 (7.4)
Median	19.7	20.7	22.6
Minimum	14	14	15
Maximum	42	38	43

Source: Tables S.3.2 and 4.3.1 CSR.

Baseline Disease Characteristics

The sponsor provided a summary of baseline disease characteristics which consisted primarily of baseline scores on rating scales to assess disease severity (Table 2). As expected, baseline scores for Phase 1 (open-label) were much higher than for Phase 2 (double-blind) since subjects must have achieved clinical response criteria to enter into Phase 2. The mean ABC subscale scores and CGI-S scores in Phase 2 were similar between the two treatment groups, though slightly higher in the aripiprazole group.

Table 2. Baseline* Disease Characteristics

	Phase 1	Phase 2	
	Aripiprazole 2-15 mg/day N = 155	Placebo N = 44	Aripiprazole 2-15 mg/day N = 41
ABC Irritability subscale			
Mean (SD)	29.6 (6.6)	8.2 (6.2)	9.5 (5.8)
Median	30	8	9
Minimum	18	0	0
Maximum	44	22	22
ABC Hyperactivity subscale			
Mean (SD)	31.8 (10.3)	10.1 (9.4)	10.9 (7.2)
Median	34	8	10
Minimum	4	0	0
Maximum	48	36	25
ABC Stereotypy subscale			
Mean (SD)	10 (5.1)	3.9 (3.7)	4.3 (3.4)
Median	10	3	5
Minimum	0	0	0
Maximum	21	13	11
ABC Social withdrawal			
Mean (SD)	16.9 (9)	5.8 (6.6)	7.5 (6)
Median	16	3	7
Minimum	1	0	0
Maximum	43	25	20
ABC Inappropriate speech subscale			
Mean (SD)	6.5 (3.6)	2.1 (2.5)	2.7 (3)
Median	7	1	2
Minimum	0	0	0
Maximum	12	9	12
CGI-Severity			
Mean (SD)	5 (0.8)	2.9 (1.1)	3 (0.9)
Median	5	3	3
Minimum	4	1	1
Maximum	7	6	5

*Baseline Phase 1 = scores assessed at last measurement on or before first day of single-blind dosing in Phase 1; Phase 2 = scores assessed at last measurement on or before first day of double-blind dosing in Phase 2
Source: Tables S.3.3, S.3.4,

Though not summarized, the sponsor did provide medical and psychiatric histories for the subjects. Not unexpectedly, the medical histories for these subjects were extensive. The psychiatric histories included primarily ADHD, irritability, aggression, insomnia and anxiety. The most common psychiatric history was ADHD which was reported in 27% (12/44) of subjects in the placebo group and 7.3% (3/41) of subjects in the aripiprazole group. No subjects were taking concomitant medications for ADHD in either Phase 1 or Phase 2 (see section 6.1.2.4 of the review).

The Sponsor also provided a by-patient listing of “cognitive evaluation” which was an evaluation of the subject’s mental development by assessing school performance. The categories reported were average/above average IQ, borderline IQ, mild/moderate retardation, and severe retardation. The distribution per category was similar between

the placebo and aripiprazole groups with ~32-36% of subjects having average/above average IQ, 25-32% having borderline IQ, 36% having mild/moderate retardation and 2% (n = 1, placebo group) having severe retardation.

Subject Disposition

A total of 215 subjects were enrolled in the study, 157 (73%) entered Phase 1. Eighty-five subjects completed Phase 1 and were randomized into Phase 2 (n = 41 aripiprazole, n = 44 placebo).

In Phase 1, the reasons for discontinuation were lack of efficacy (n = 25, 15.9%), adverse event (n = 12, 7.6%), administrative reason by Sponsor (n = 11, 7.0%), withdrew consent (n = 7, 4.5%), lost to follow-up (n = 8, 5.1%), no longer meets study criteria (n = 7, 4.5%) and non-compliance (n = 2, 1.3%). Upon query, the sponsor clarified that the discontinuations due to administrative reasons was because the target number of randomizations for the clinical trial (84 subjects) had been reached (10/31/13 submission to NDA).

Discontinuations due to adverse events in Phase 2 would be expected to be low since subjects had already been receiving aripiprazole for a significant period of time during Phase 1. Most of the subjects discontinuing due to "lack of efficacy" had met criteria for relapse, the primary efficacy endpoint for the study.

Table 3. Subject Disposition in Phase 2 (double-blind)

	Number (%) of Patients	
	Placebo	Aripiprazole 2-15 mg/day
Patients Randomized to Phase 2	44	41
Completed Phase 2	19 (43.2)	22 (53.7)
Discontinued during Phase 2	25 (56.8)	19 (46.3)
Adverse event	1 (2.3)	0
Lack of efficacy	23 (52.3)	13 (31.7)
Withdrawal of consent*	0	5 (12.2)
Lost to follow-up	0	1 (2.4)
Non-compliance	1 (2.3)	0

*Individual subjects reviewed, most withdrawal of consents due to subject unavailability (e.g. not due to lack of efficacy).
Source: Table 4.2.1 of CSR

Concomitant Medication Use

In Phase 1, 58% (90/155) of subjects took concomitant medications. In Phase 2, 51% (22/43) of subjects in the placebo group and 54% (21/39) of subjects in the aripiprazole group took concomitant medications. The Sponsor provided a summary of concomitant

medications by category and a listing of specific concomitant medications by patient. Table 4 lists concomitant medication categories taken by ≥ 2% of subjects in Phase 1 and > 5 % of subjects in Phase 2.

Table 4. Concomitant Medications in > 2% of Subjects in Phase 1 (Open-label)

	Phase 1
	Aripiprazole 2-15 mg/day N = 155
Antihistamine for systemic use	28 (18.1)
Analgesic/antipyretic	27 (17.4)
"All other therapeutic product"*	19 (12.3)
Multivitamin	11 (7.1)
Anxiolytic	8 (5.2)
Treatment of peptic ulcer	7 (4.5)
Macrolide/lincosamide	7 (4.5)
Other respiratory system product	7 (4.5)
Penicillin	6 (3.9)
Anti-asthmatic inhalant, other	5 (3.2)
Corticosteroid	4 (2.6)
Adrenergic, inhalant	4 (2.6)
Nasal decongestant for systemic use	4 (2.6)
Anticholinergic	4 (2.6)
Other nutrient	4 (2.6)

*Other therapeutic products included melatonin, other nebulizers, prune juice, turmeric, Miralax, and Echinacea (JMP dataset)
Source: Appendix 4.4 CSR

Table 5. Concomitant Medications in > 5% of Subjects in Phase 2 (Double-blind)

	Phase 2	
	Placebo N = 44	Aripiprazole 2-15 mg/day N = 41
Antihistamine for systemic use	6 (14)	5 (12.8)
Cough/cold preparation	0	5 (12.8)
Analgesic/antipyretic	3 (7)	4 (10.3)
Multivitamin	3 (7)	3 (7.7)
Macrolide/lincosamide	1 (2.3)	3 (7.7)
Anti-asthmatic for systemic use, other	3 (7)	2 (5.1)
Anticholinergic	4 (9.3)	2 (5.1)
Antiemetic	0	2 (5.1)
Expectorant	0	2 (5.1)
Nasal decongestant	1 (2.3)	2 (5.1)
Other beta-lactam antibacterial	0	2 (5.1)
Other nutrient	1 (2.3)	2 (5.1)
Other respiratory system product	2 (4.7)	2 (5.1)
"All other therapeutic product"*	5 (11.6)	1 (2.6)
Anti-asthmatic, inhalant, other	3 (7)	0

*Other therapeutic products included melatonin, other nebulizers, prune juice, turmeric, Miralax, and Echinacea (JMP dataset)
Source: Appendix 4.3 CSR

Most of the concomitant use of anxiolytics was in Phase 1 and was predominantly benzodiazepines for procedural sedation. The category "antihistamine for systemic use" included the antihistamines diphenhydramine and hydroxyzine – antihistamines usually prescribed for agitation, insomnia, or adverse events. A review of the JMP dataset (CMED) found that 6 subjects required diphenydramine or hydroxyzine during Phase 1 for the following reasons: adverse event, serious behavioral problem or "other". Only one subject (placebo group) required these specific antihistamines during Phase 2.

The frequency of concomitant medication use was low and involved medications that were unlikely to confound clinical trial results.

Analysis of Primary Endpoint(s)

The primary endpoint was the time from randomization to relapse. There was no statistically significant difference between aripiprazole and placebo for the primary endpoint (p = 0.097). The Kaplan-Meier relapse rates at Week 16 were 32% (13/41) for aripiprazole and 50% (22/44) for placebo (hazard ratio 0.57; 95% CI: 0.28, 1.12).

The Kaplan-Meier survival data is depicted in Figure 1 (Sponsor's figure). The Cox proportional hazards model used Phase 2 baseline weight category (≥ 40 kg, < 40 kg) as a stratification factor and treatment group as a covariate.

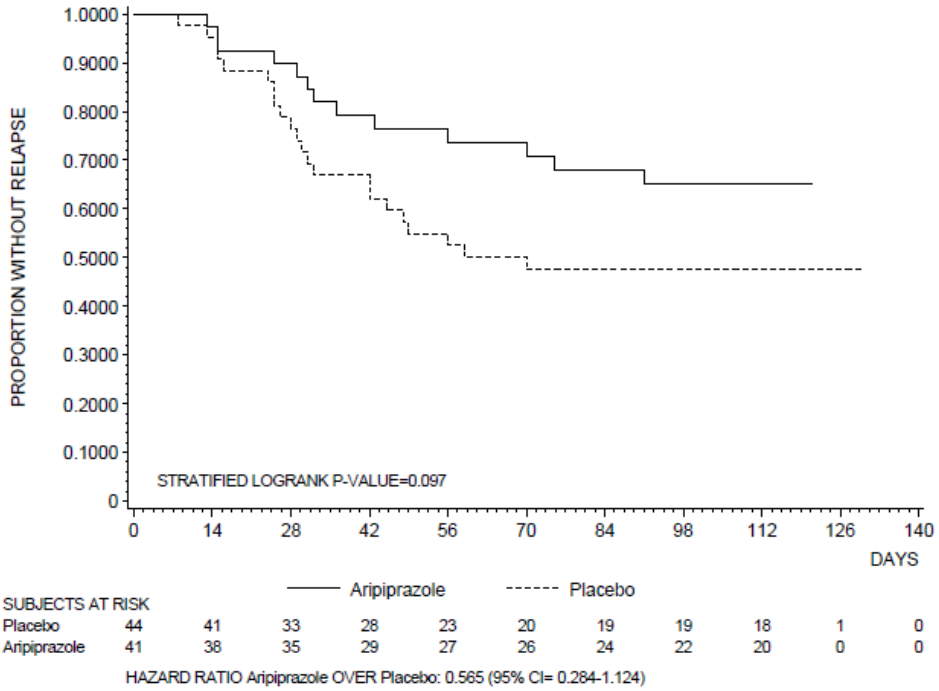

Figure 1. Sponsor's Figure: Time from Randomization to Relapse.
Source: Figure 6.1 from CSR

The results were similar using the unadjusted model (without stratification by weight), log-rank test p-value = 0.085, hazard ratio (0.55, CI: 0.28, 1.10). The results were also similar when evaluating subjects ≤ 12 and > 12 years of age. The p-value for the treatment by age group interaction was 0.243. The hazard ratio and CI for the ≤ 12 year old group was 0.68, CI: 0.32, 1.43. The hazard ratio and CI for the > 12 year old group was 0.18, CI: 0.02, 1.51.

There were 5 different definitions for relapse in the protocol (see Study Design). A total of 35 subjects met relapse criteria during the study, 22 in the placebo group and 13 in the aripiprazole group. All of the subjects who relapsed met criteria 1 or 5 as indicated in Table 6. No subjects were hospitalized for worsening of irritability symptoms.

Table 6. Subjects Meeting Relapse Criteria

Relapse Criterion	Placebo N = 43	Aripiprazole N = 39
1. ABC-I ≥ 25% increase and CGI-I score "much worse" or "very much worse" at 2 consecutive visits*	12	7
2. Lost to follow up, last visit ABC-I ≥ 25% increase and CGI-I score "much worse" or "very much worse"	0	0
3. Prohibited medication to treat worsening symptoms of irritability, last visit ABC-I ≥ 25% increase and CGI-I score "much worse" or "very much worse"	0	0
4. Hospitalization for worsening irritability symptoms	0	0
5. Lack of efficacy	10*	6

One subject in the placebo group met criteria for both ABC-I/CGI-I for two consecutive weeks and lack of efficacy per investigator, counted only in the ABC-I/CGI-I category
*One additional subject in the placebo group met criteria for relapse due to lack of efficacy but was censored since the relapse occurred > 3 days after receiving the last dose of study medication.
Source: Appendix 5.1 from CSR

See Section 6.1.7 for a discussion of a similarly designed pivotal Risperdal (risperidone) clinical trial as well as comments on the primary analysis results for CN138603.

Analysis of Secondary Endpoints(s)

The Sponsor did not identify any secondary endpoints as key secondary endpoints. Secondary endpoints included mean change from baseline in the ABC-Irritability subscale score and CGI-Improvement score. The mean change from baseline to week 16 for the ABC-I subscale score approached significance favoring the aripiprazole group.

Table 7. Secondary Endpoints: Mean Change from Baseline (ABC-I) to Week 16, Mean Score at Week 16 (CGI-I) (LOCF)

	Placebo N = 43	Aripiprazole N = 39
ABC-I subscale score		
Mean Baseline (SE)	8.2 (0.9)	9.4 (0.95)
Mean Change (SE)	9.6 (1.6)	5.2 (1.6)
Difference from Placebo		-4.4
p-value (95% CI)		0.051 (-8.8, 0.0)
CGI-I score		
Mean Baseline (SE)	2.8 (0.15)	3.0 (0.16)
Mean CGI-I score at Week 16 (SE)	4.8 (0.26	4.2 (0.26)
Difference from Placebo		-0.6
p-value (95% CI)		0.090 (-1.3, 0.1)

Source: Table S.5.2 and S.5.30 from CSR

The completers analyses were consistent with the LOCF analyses. At week 16, the mean change from baseline in the ABC-I subscale was 3.6 in the placebo group (n = 18) and -1.0 in the aripiprazole group (n = 20); the difference from placebo was -4.55 (95% CI -8.62, -0.48; p=0.029). At week 16, the mean CGI-I score was 3.7 in the placebo group (n = 19) and 2.9 in the aripiprazole group (n = 20); the difference from placebo was -0.81 (95% CI -1.77, 0.15; p = 0.094).

6.1.3 Other Endpoints

The Sponsor also evaluated the mean change from baseline on other subscales of the ABC scale. For most of these subscales (hyperactivity, stereotypy, inappropriate speech subscales), the results statistically favored aripiprazole over placebo. There were no differences between aripiprazole and placebo on the ABC social withdrawal subscale score. The mean baseline CGI-S score was 2.8 in the placebo group and 3.0 in the aripiprazole group, mean changes at week 16 were 0.9 and 0.6 respectively (difference from placebo -0.3, 95% CI: -0.9, 0.3; p = 0.291).

6.1.4 Subpopulations

The Sponsor evaluated two subgroups, age (6-12, 13–17 years) and race (White, nonWhite). An analysis of gender subgroup was not performed, likely due to the few numbers of females enrolled in the clinical trial (n = 6 in the placebo group, n = 11 in the aripiprazole group). There was no treatment by age group interaction noted. A treatment by race subgroup interaction was found with the nonwhite subgroup having a lower relapse rate in the placebo group compared to the aripiprazole group. It is difficult to interpret this finding since the numbers of nonWhite subjects enrolled in this trial was fairly low.

Table 8. Time from Randomization to Relapse: Age Subgroups (6-12, 13–17 years)

	Placebo	Aripiprazole		
	Relapse Rate	Relapse Rate	Hazard Ratio	95% CI
6-12 years	48.5% (16/33)	37.5% (12/32)	0.68	0.32, 1.43
13-17 years	54.5% (6/11)	11.1% (1/9)	0.18	0.02, 1.51
	p-value for treatment by age group interaction			0.243

Source: Tables S.5.6 and S.5.7 from CSR

Table 9. Time from Randomization to Relapse: Race Subgroups (White/nonWhite)

	Placebo	Aripiprazole		
	Relapse Rate	Relapse Rate	Hazard Ratio	95% CI
White	60.7% (17/28)	25.8% (8/31)	0.33	0.14, 0.78
Non-White	31.3% (5/16)	50% (5/10)	1.68	0.49, 5.83
	p-value for treatment by race group interaction			0.034

6.1.5 Analysis of Clinical Information Relevant to Dosing Recommendations

Efficacy was not established in this clinical trial, dosing recommendations are not applicable.

6.1.6 Discussion of Persistence of Efficacy and/or Tolerance Effects

The design of a maintenance trial can also be perceived as an evaluation of persistence of efficacy. See Results, Analysis of Primary Endpoint.

6.1.7 Additional Efficacy Issues/Analyses

Risperidone (Risperdal) is the only other antipsychotic approved for the treatment of irritability associated with autistic disorder (10/6/2006 approval date). Product labeling includes a section describing efficacy in the long-term treatment of irritability associated with autistic disorder and describes a randomized withdrawal trial similar to the study design for CN138603.

In brief, following completion of an 8-week double-blind study, subjected entered an open-label extension study and received risperidone for 4 to 6 months. Subjects who maintained their positive response to risperidone (> 25% improvement on ABC-I subscale and a CGI-C rating of “much improved” or “very much improved”) during the open-label phase were randomized to receive risperidone or placebo during an 8-week, double-blind withdrawal study.

Interim analyses were planned to occur after completion of the first 16, 32 and 50 subjects. If the relapse rate on placebo versus risperidone reached significance (2-tailed p-value < 0.01), the study would be stopped. This stop criterion was met after 32 subjects and the study was terminated at that point.

There was some confusion regarding the definition of relapse for this protocol. The following definitions were included in the protocol: "having two consecutive weeks with a CGI-C rating of "much or very much worse" AND at least 25% worsening in the ABC-I subscale compared to baseline at entry of the randomized withdrawal phase". The protocol analysis section of the protocol defined relapse as 1) the changes of CGI-C ratings of much or very much worse for 2 weeks, 2) an increase of > 25% score from baseline in the ABC-I score or 3) any withdrawal not meeting criteria (1) or (2) relating to lack of efficacy.

Regardless, the primary efficacy analysis (Mantel-Haenszel) using the definition of relapse "having two consecutive weeks with a CGI-C rating of much or very much worse AND at least 25% worsening in the ABC-I subscale compared to baseline at entry of the randomized withdrawal phase" was statistically significant. Relapse rates were 68.8% (11/16) for placebo compared to 12.5% (2/16) for risperidone (OR 15.4; 95% CI 2.50, 95.05; p = 0.001). These results were also statistically significant in the secondary Kaplan-Meier analysis. An analysis conducted by the FDA statistician using the alternative criteria for relapse was not statistically significant (Mantel-Haenszel, p = 0.41).

There was much internal discussion about what constituted a clinically acceptable definition of relapse. It was decided that neither of those definitions were appropriate in this context. The primary issue was the use of the CGI in both of these definitions. The CGI rates the global condition of the patient and not the variable of primary interest, the irritability-related symptoms. One definition was felt to be too restrictive in that it required a decrement in the global condition of the patient in addition to deterioration in the irritability-like symptoms. The other definition was considered too broad in that worsening in the global condition itself is counted as a relapse independent of any change in the irritability rating.

It was felt that the change on the ABC-I scale alone would be the most appropriate primary variable. When the odds of relapse were analyzed using deterioration in the ABC-I subscale as the definition, the result was not significant (p = 0.20). The sponsor was asked to reanalyze the study using the Kaplan-Meier survival analysis and the definition of relapse based only on the ABC-I subscale change.

This reviewer had a difficult time trying to determine whether this additional analysis was ever performed. The current labeling for Risperdal states "Relapse was defined as > 25% worsening on the most recent assessment of the ABC-I subscale…". It appears that perhaps this analysis may have been performed since the CGI-C criterion is not mentioned in product labeling. The "most recent assessment" language indicates, to this reviewer, that the two consecutive week criterion was not used in this analysis.

Regardless of the thoughts on inclusion of the CGI as part of the relapse criteria, the primary analysis (ABC-I and CGI for 2 consecutive weeks) for the Risperdal clinical trial was similar to the relapse criteria used in the Abilify randomized withdrawal clinical trial. The interim analysis results for risperidone showed statistical differences between risperidone and placebo after 32 subjects had completed the study.

It is unclear whether a larger sample size or a longer duration of the randomization phase would have resulted in statistically significant differences between aripiprazole and placebo. The duration of the randomization phase (16 weeks) was twice the duration of the randomization phase in the clinical trial with risperidone (8 weeks). To this reviewer's knowledge, there were no discussions regarding the appropriateness of the *a priori* definition of relapse in the aripiprazole clinical trial. Though the results for aripiprazole did not reach statistical significance, the Kaplan-Meier survival curve and overall relapse rates numerically favor aripiprazole. However, since statistical significance was not demonstrated, overall efficacy for aripiprazole in the maintenance treatment of irritability associated with autistic disorder was not demonstrated.

It is unlikely that the results from this clinical trial would significantly alter the clinical practice of prescribers. Patients would continue to be monitored and, if irritability symptoms continue to show improvement with aripiprazole, it is likely that aripiprazole would be continued in that individual patient. Although not impossible, it does not seem likely that a drug that shows benefit in the acute treatment phase would not be effective in the maintenance treatment of the disorder. There may have been other issues (statistical power, dose) that could have impacted these study results.

7 Review of Safety

Safety Summary

In general, it is difficult to interpret safety data from randomized withdrawal trials. This trial included a 13 to 26 week open-label stabilization phase (Phase 1) in which subjects received open-label aripiprazole 2 to 15 mg/day. Phase 1 was followed by a 16 week double-blind randomization phase in which eligible subjects were randomized to receive placebo or aripiprazole 2 to 15 mg/day (Phase 2). In Phase 1, subjects are not randomized and there is no comparison group to interpret study findings. In Phase 2, though randomized with a comparison group (placebo), these are subjects who were able to tolerate aripiprazole during Phase 1 so this might be considered an enriched sample. This reviewer did review all safety data generated from this clinical trial to evaluate overall safety but focused the review on significant safety signals (deaths, other serious adverse events, and discontinuations due to adverse events).

There were no deaths that occurred in this clinical trial. Serious adverse events occurred only during Phase 1 (open-label) in two subjects. One subject experienced severe aggression on study day 4 which resolved upon discontinuation of aripiprazole,

hospitalization and treatment. Another subject experienced severe aggression and delusions during the washout phase, she was discontinued from the trial before receiving aripiprazole. Discontinuations due to adverse events occurred only during Phase 1 (open-label) and occurred in 13 subjects. These adverse events included aggression, weight increased, abdominal pain, akathisia, anxiety, bruxism, cognitive disorder, dysphagia, gait disturbance, insomnia, restlessness, salivary hypersecretion, neutropenia, sedation, somnolence, tearfulness, toe walking, tongue disorder, tremor an vomiting (see review for more details).

The most common adverse events in Phase 1 (open-label) and Phase 2 (double-blind) are consistent with adverse events in current product labeling including those occurring in the 8-week clinical trials in subjects with autistic disorder.

The most significant finding for routine labs was an increase in triglycerides. Though difficult to interpret due to the study design, there did not appear to be a significant safety finding with regard to vital signs. Based on vital signs alone, orthostatic hypotension was infrequent. A mean increase in weight of 3.2 kg (week 26 LOCF) was noted in Phase 1 (open-label). In Phase 2 (double-blind) [week 16 LOCF], the mean change in weight in the placebo group was 0.6 kg compared to 2.2 kg in the aripiprazole group ($p < 0.001$).

In general, though difficult to interpret due to the study design, this reviewer did not note any new and significant safety findings that would merit addition to aripiprazole product labeling. Safety findings noted in this clinical trial are currently reflected in product labeling.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This submission included results from a single clinical trial: CN138603 “Safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric subjects with irritability associated with autistic disorder”

7.1.2 Categorization of Adverse Events

MedDRA version 15 was the coding dictionary used in this study. A review of the JMP adverse event database for Phase 1 and Phase 2 of the study did not note any discrepancies in the coding of verbatim terms to preferred terms.

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

Since this submission included data from only one clinical trial, there was no pooling of data across studies.

7.2 Adequacy of Safety Assessments

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

Aripiprazole is approved for the treatment of irritability associated with autistic disorder. Efficacy was established in two 8-week trials. Per labeling and as supported by the clinical trials, aripiprazole should be initiated at 2 mg/day with a target dose range of 5 to 15 mg/day.

Phase 1 of the study was a 13 to 26 week open-label stabilization phase – subjects demonstrating a stable response for 12 weeks were eligible for randomization into Phase 2 (16 week, double-blind). The mean (median) time for subjects in Phase 1 was 135 (129) days in the aripiprazole group and 125.3 (125.5) days in the placebo group. Of the 155 subjects in Phase 1, 80 (~50%) were exposed to aripiprazole for up to 119 days (17 weeks). The mean weekly daily dose of aripiprazole ranged from 2.1 mg/day (week 1) to 12.5 mg/day (week 25).

The mean weekly daily dose of aripiprazole in Phase 2 ranged from 8.9 to 10.5 mg/day; the mean daily dose ranged from 2 to 15 mg/day. Of the 39 subjects randomized to aripiprazole, 22 (56.4%) were exposed for up to 16 weeks.

7.2.2 Explorations for Dose Response

There were no explorations for dose response in this randomized withdrawal trial. Aripiprazole was flexibly dosed (2 to 15 mg/day) in Phase 1 (open-label) and Phase 2 (double-blind) of the trial.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal and/or in vitro testing in this submission.

7.2.4 Routine Clinical Testing

Routine clinical testing was included in the protocol as discussed in section 6.1.1. In general, it appears that clinical testing was adequate with the possible exception ECGs were performed during Phase 1 but not Phase 2.

7.2.5 Metabolic, Clearance, and Interaction Workup

No formal studies of drug metabolism or interactions were submitted with this supplement.

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

Significant adverse events included in the Warnings and Precautions section of product labeling for the atypical antipsychotics include suicidality (depending on approved indications), neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes (hyperglycemia, dyslipidemia, weight gain), orthostatic hypotension, leukopenia/neutropenia/agranulocytosis and seizures. Appropriate monitoring for these adverse events was included in the clinical trial.

The Columbia Suicide Severity Rating Scale (C-SSRS) was not included in this clinical trial due to the difficulties using this rating instrument in populations with autism. This assessment was based on reported adverse events. Class labeling regarding this risk has already been implemented for Abilify.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during this clinical trial.

7.3.2 Nonfatal Serious Adverse Events

Phase 1 (open-label). Two subjects experienced serious adverse events (SAEs) during Phase 1 of the clinical trial. A 15 YOBM experienced severe aggression that started on study day 4. Aripiprazole was discontinued. The subject was hospitalized and treated and the event resolved. A 9 YOWF experienced severe aggression and severe delusions beginning approximately 5 days after risperidone was discontinued during the washout phase of the study. She was discontinued from the study and did not receive aripiprazole.

Phase 2 (double-blind). No subjects experienced SAEs during Phase 2 of the clinical trial.

7.3.3 Dropouts and/or Discontinuations

Phase 1 (open-label). Thirteen subjects (8.4%) had adverse events that led to discontinuation during Phase 1 of the clinical trial. The following adverse events were experienced in 2 subjects (1.3%): aggression and weight increased. The following adverse events were experienced in 1 subject (0.6%): abdominal pain, akathisia, anxiety, bruxism, cognitive disorder, dysphagia, gait disturbance (verbatim term "shuffling gait"), insomnia, restlessness, salivary hypersecretion, neutropenia, sedation, somnolence, tearfulness, toe walking, tongue disorder, tremor and vomiting.

Most of these adverse events are consistent with the known side effect profile of aripiprazole – especially those adverse events related to extrapyramidal adverse events. The verbatim term for the adverse event "tongue disorder" was increased tongue movement (mild) and this subject also experienced toe walking (mild) and somnolence.

The subject who discontinued due to neutropenia was a 9 YOAM who had a baseline WBC of 5.86 x 10^3 c/μL (5.69 – 9.88) and ANC of 3.22 x 10^3 c/μL (2.77 – 6.34). On day 120, his WBC was 5.25 x 10^3 c/μL and ANC was 1 x 10^3 c/μL. No clinical labs were performed between baseline and day 120 and there are no further labs available. On day 125, the subject was reported to have a mild respiratory infection with no other clinical symptoms. On day 127, the investigator reported the adverse event of neutropenia and the study drug was discontinued. The subject's upper respiratory infection was reported resolved on day 127. The sponsor did not provide any further details or clinical labs.

Phase 2 (double-blind). No subjects discontinued due to AEs during Phase 2 of the clinical trial.

7.3.4 Significant Adverse Events

This reviewer did not identify significant adverse events occurring in this clinical trial that are not reflected in current product labeling for aripiprazole.

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

Common adverse events are noted in Table 10 for Phase 1 (open-label) and Table 11 for Phase 2 (double-blind). In general, the adverse events noted are consistent with the overall adverse event profile for aripiprazole as reflected in current product labeling.

Table 10. Adverse Events in ≥ 2% of Subjects – Phase 1 (open-label)

Adverse Event	Aripiprazole N = 155 Incidence (%)
Weight increased	39 (25.2)
Somnolence	23 (14.8)
Vomiting	22 (14.2)
Increased appetite	20 (12.9)
Upper respiratory tract infection	16 (10.3)
Fatigue	13 (8.4)
Insomnia	13 (8.4)
Diarrhea	11 (7.1)
Tremor	10 (6.5)
Aggression	9 (5.8)
Nasopharyngitis	9 (5.8)
Headache	8 (5.2)
Lethargy	8 (5.2)
Pyrexia	8 (5.2)
Nausea	7 (4.5)
Sedation	7 (4.5)
Akathisia	6 (3.9)
Musculoskeletal stiffness	6 (3.9)
Salivary hypersecretion	6 (3.9)
Decreased appetite	5 (3.2)
Drooling	5 (3.2)
Enuresis	5 (3.2)
Constipation	4 (2.6)
Cough	4 (2.6)
Fall	4 (2.6)
Glabellar reflex abnormal	4 (2.6)
Irritability	4 (2.6)
Joint stiffness	4 (2.6)
Nasal congestion	4 (2.6)
Restlessness	4 (2.6)
Rhinorrhea	4 (2.6)

Source: Table S.6.2 from CSR

Adverse events that are potentially associated with extrapyramidal adverse events are listed in Table 11. The frequency of extrapyramidal adverse events occurring in Phase 1 (open-label) are consistent with the frequencies noted in the 8-week clinical trials in

this population as reflected in current product labeling. See section 7.4.7 for assessment of extrapyramidal adverse events via rating scales.

Table 11. Extrapyramidal Adverse Events – Phase 1 (open-label)

Adverse Event	Aripiprazole N = 155 Incidence (%)
Tremor	10 (6.5)
Akathisia	6 (3.9)
Musculoskeletal stiffness	6 (3.9)
Glabellar reflex abnormal	4 (2.6)
Joint stiffness	4 (2.6)
Restlessness	4 (2.6)
Extrapyramidal disorder	3 (1.9)
Movement disorder	3 (1.9)
Tardive dyskinesia	2 (1.3)
Dyskinesia	1 (0.6)
Psychomotor retardation	1 (0.6)
Tongue disorder*	1 (0.6)

Source: Table S.6.2 from CSR
*verbatim term = increased tongue movement

A total of 14 (32.6%) subjects in the placebo group and 22 (56.4%) subjects in the aripiprazole group experienced adverse events during Phase 2 of the clinical study.

Table 12. Adverse Events in $\geq$ 5% of Subjects – Phase 2 (double-blind)

Adverse Event	Placebo N = 43 Incidence (%)	Aripiprazole N = 39 Incidence (%)
Upper respiratory tract infection	1 (2.3)	4 (10.3)
Constipation	0	2 (5.1)
Movement disorder	0	2 (5.1)
Vomiting	2 (4.7)	2 (5.1)

Source: Table S.6.3 from CSR

7.4.2 Laboratory Findings

For Phase 1 (open-label), the most significant finding was an increase in triglycerides. Laboratory data were available for ~ 110 subjects, approximately half of those subjects had fasting lab data.

Table 13. Clinical Laboratory: Median Change from Baseline - Phase 1 (open-label)

	Median Change from Baseline
	Aripiprazole N = 155
Chemistry	
ALT (U/L)	2
Alkaline phosphatase (U/L)	-5
AST (U/L)	-1
Bilirubin, total (mg/dL)	-0.1
BUN (mg/dL)	1
Calcium (mg/dL)	0.1
Chloride (mEq/L)	0
HDL [fasting] (mg/dL)	-1
HDL [non-fasting] (mg/dL)	-3
LDL [fasting] (mg/dL)	-3
LDL [non-fasting] (mg/dL)	3
Cholesterol, total [fasting] (mg/dL)	-6
Cholesterol, total [non-fasting] (mg/dL)	1
Creatine kinase (U/L)	4
Creatinine (mg/dL)	0
Glucose [fasting]	0
Glucose [non-fasting]	-4
Lactate dehydrogenase (U/L)	-7
Potassium (mEq/L)	0
Prolactin (ng/mL)	-3
Sodium (mEq/L)	0
Triglycerides [fasting] (mg/dL)	4
Triglycerides [non-fasting] (mg/dL)	11
Uric acid (mg/dL)	0.1
Hematology	
WBCs (x10*3 c/uL)	0.2
Eosinophils, relative (%)	-0.0
Neutrophils, relative (%)	2.1
Erythrocytes (x10*6 c/uL)	0.0
Hematocrit (%)	-0.5
Hemoglobin (g/dL)	-0.2
Platelets (x10*9 c/L)	12.5

Source: Table S.7.6 from CSR

Median change from baseline (end of Phase 1) in clinical laboratory parameters for Phase 2 (double-blind) are noted in Table 14. Assessments were available for most subjects, approximately half of the subjects had fasting labs for lipids and glucose. The only statistically significant differences between placebo and aripiprazole were for creatine kinase, prolactin, eosinophils and uric acid, most of these median changes from baseline were greater in the placebo group.

Table 14. Clinical Laboratory: Median Change from Baseline - Phase 2 (double-blind)

	Median Change from Baseline	
	Placebo N = 43	Aripiprazole N = 39
Chemistry		
ALT (U/L)	1	0.5
Alkaline phosphatase (U/L)	12	7
AST (U/L)	1	0
Bilirubin, total (mg/dL)	0	0
BUN (mg/dL)	0	0
Calcium (mg/dL)	0.1	0
Chloride (mEq/L)	0	-0.5
HDL [fasting] (mg/dL)	-2	-1
HDL [non-fasting] (mg/dL)	2	2.5
LDL [fasting] (mg/dL)	1	-2
LDL [non-fasting] (mg/dL)	6	5.5
Cholesterol, total [fasting] (mg/dL)	0	1
Cholesterol, total [non-fasting] (mg/dL)	7	6
Creatine kinase (U/L)	33	3.5
Creatinine (mg/dL)	0	0
Glucose [fasting]	-5	-1
Glucose [non-fasting]	-8	8.5
Lactate dehydrogenase (U/L)	12	3
Potassium (mEq/L)	0.1	0
Prolactin (ng/mL)	4	0
Sodium (mEq/L)	0	0
Triglycerides [fasting] (mg/dL)	3	-2
Triglycerides [non-fasting] (mg/dL)	-7	2
Uric acid (mg/dL)	0.1	0.5
Hematology		
WBCs (x10*3 c/uL)	0.1	-0.5
Eosinophils, relative (%)	0.5	-0.1
Neutrophils, relative (%)	-2.8	-2.2
Erythrocytes (x10*6 c/uL)	0	0
Hematocrit (%)	0.7	0.1
Hemoglobin (g/dL)	0	-0.1
Platelets (x10*9 c/L)	-11	-0.5

Source: Table S.7.5 from CSR

Potentially Clinically Significant Labs (PCS)
Definitions for PCS labs, as outlined in the clinical protocol, are in Appendix 9.7. Definitions for electrolytes and lipids were not included, so it is not known whether the sponsor evaluated any changes in electrolytes based on any PCS criteria.

Many of the subjects with PCS changes during Phase 1 (open-label) exhibited the abnormal lab during the screening period. These PCS labs could have been a result of therapies received prior to baseline. Most of these PCS labs were in lipid parameters, mostly triglycerides.

Few subjects exhibited PCS laboratory parameters during Phase 2 (double-blind). Triglycerides were the only parameter for which more than 1 subject exhibited a PCS change. For fasting triglycerides, 1/18 (5.6%) in the placebo group compared to 3/19 (15.8%) in the aripiprazole group experienced a PCS change. The 3 subjects in the aripiprazole group with PCS changes in fasting triglycerides exhibited the following changes: 66 to 234 mg/dL, 129 to 164 mg/dL and 280 to 276 mg/dL. For nonfasting triglycerides, 6/20 (30%) in the placebo group compared to 10/17 (58.8%) in the aripiprazole group experienced a significant increase.

7.4.3 Vital Signs/Physical Examination

Per protocol, vital signs were taken in the supine position after subjects had rested for 5 minutes and then in the standing position after standing for 2 minutes. Sitting vital signs were allowed if standing measurements were not able to be obtained.
The majority of vital signs were obtained in the supine and standing positions, vital signs in the sitting position were obtained in fewer subjects (~20 in Phase 1 and ~5 in Phase 2).
Median changes in vital signs from baseline were small. For Phase 2 (double-blind), the median change from baseline for sitting heart rate was -12 in the aripiprazole group and 11.5 in the placebo group, but this is based on readings in ~5 subjects.

Table 15. Vital Signs: Median Change from Baseline - Phase 1 (open-label)

	Median Change from Baseline
	Aripiprazole N = 155
Supine SBP (mmHg)	0.5
Supine DBP (mmHg)	1.5
Supine Heart rate (bpm)	0
Sitting SBP (mmHg)	-1
Sitting DBP (mmHg)	0
Sitting Heart rate (bpm)	5
Standing SBP (mmHg)	0
Standing DBP (mmHg)	0
Standing Heart rate (bpm)	2

Source: Table S.7.17 from CSR

Table 16. Vital Signs: Median Change from Baseline - Phase 2 (double-blind)

	Median Change from Baseline	
	Placebo N = 43	Aripiprazole N = 39
Supine SBP (mmHg)	0.5	-2
Supine DBP (mmHg)	0	0.5
Supine Heart rate (bpm)	-0.5	2
Sitting SBP (mmHg)	3.5	1
Sitting DBP (mmHg)	2	7
Sitting Heart rate (bpm)	11.5	-12
Standing SBP (mmHg)	0	0
Standing DBP (mmHg)	0	2
Standing Heart rate (bpm)	2	2

Source: Table S.7.16 from CSR

PCS Changes in Vital Signs

The criteria in Table 17 were used by the sponsor to define potentially clinically significant vital signs. Subjects must meet *both* the criterion value and the change relative to baseline criterion to be considered potentially clinically significant.

Table 17. Vital Signs: Potentially Clinically Significant Definitions per Protocol

	Criterion Value	Criterion Value	Change Relative to Baseline
Systolic Blood Pressure	**7 to 12 years** ≥ 130 mmHg ≤ 117 mmHg	**13 to 17 years** ≥ 144 mmHg ≤ 120 mmHg	 Increase of ≥ 20 Decrease of ≥ 20
Diastolic Blood Pressure	**7 to 12 years** > 86 mmHg < 75 mmHg	**13 to 17 years** > 92 mmHg < 80 mmHg	 Increase of ≥ 15 Decrease of ≥ 15
Heart Rate	**5 to 14 years** > 140 bpm < 50 bpm	**15 to 17 years** > 120 bpm < 50 bpm	 Increase of ≥ 15 Decrease of ≥ 15

Source: Appendix 3 for Protocol CN138603

In Phase 1, more subjects met PCS criteria for decreases in systolic blood pressure and diastolic blood pressure compared to increases in these parameters. Since this phase does not include an active comparator, it is difficult to interpret these findings.

Table 18. Vital Signs: Potentially Clinically Significant Changes – Phase 1 (open-label)

	Incidence (%)
	Aripiprazole N = 155
Systolic Blood Pressure (mmHg)	
Standing Increase	9/147 (6.1)
Standing Decrease	30/147 (20.4)
Supine Increase	5/132 (3.8)
Supine Decrease	23/132 (17.4)
Sitting Increase	1/43 (2.3)
Sitting Decrease	20/43 (46.5)
Diastolic Blood Pressure (mmHg)	
Standing Increase	13/147 (8.8)
Standing Decrease	30/147 (20.4)
Supine Increase	9/132 (6.8)
Supine Decrease	23/132 (17.4)
Sitting Increase	5/43 (11.6)
Sitting Decrease	23/43 (53.5)
Heart Rate (bpm)	
Standing Increase	2/148 (1.4)
Standing Decrease	0/148
Supine Increase	1/132 (0.8)
Supine Decrease	0/132
Sitting Increase	0/44
Sitting Decrease	0/44

Source: Table S 7.13 from CSR

In Phase 2 (double-blind), the frequency of PCS changes was greater in the aripiprazole group for standing increase in DBP and sitting increase in DBP – though the latter is based on few subjects.

Table 19. Vital Signs: Potentially Clinically Significant Changes – Phase 2 (double-blind)

	Incidence (%)	
	Placebo N = 43	Aripiprazole N = 39
Systolic Blood Pressure (mmHg)		
Standing Increase	2/41 (4.9)	2/37 (5.4)
Standing Decrease	4/41 (9.8)	1/37 (2.7)
Supine Increase	1/36 (2.8)	1/32 (3.1)
Supine Decrease	4/36 (11.1)	2/32 (6.3)
Sitting Increase	0/9	0/5
Sitting Decrease	3/9 (33.3)	1/5 (20)
Diastolic Blood Pressure (mmHg)		
Standing Increase	2/41 (4.9)	4/37 (10.8)
Standing Decrease	5/41 (12.2)	5/37 (13.5)
Supine Increase	2/36 (5.6)	3/32 (9.4)
Supine Decrease	6/36 (16.7)	5/32 (15.6)
Sitting Increase	1/9 (11.1)	1/5 (20)
Sitting Decrease	3/9 (33.3)	0/5
Heart Rate (bpm)		
Standing Increase	0/41	0/37
Standing Decrease	0/41	0/37
Supine Increase	0/36	0/32
Supine Decrease	0/36	0/32
Sitting Increase	0/9	0/5
Sitting Decrease	0/9	0/5

Source: Table S.7.12 from CSR

The sponsor did not provide any data for vital sign changes for the evaluation of orthostatic hypotension. This reviewer evaluated the vital sign data in JMP to identify subjects with a change in supine blood pressure > 20 mmHg from supine to standing and a change in diastolic blood pressure > 10 mmHg from supine to standing. Two subjects in the aripiprazole group had a decrease in systolic blood pressure > 20 mmHg (-23 and 24 mmHg) from supine to standing positions, no subjects in the placebo group had a decrease in systolic blood pressure > 20 mmHg. Two subjects in the aripiprazole group had a decrease in diastolic blood pressure > 10 mmHg (-11 and -13 mmHg) from supine to standing positions and four subjects in the placebo group had a decrease in diastolic blood pressure (-13, -17, -17 and -20 mmHg). These data do not provide evidence for significant orthostatic hypotension in the aripiprazole group compared to the placebo group.

Height and weight

Phase 1 (open-label)
The mean and median change from baseline in height at week 26 (LOCF) were 1.8 cm and 1.5 cm respectively. The sponsor noted that there was great variability in height obtained over the weeks of the trial (e.g. week 14 mean change 1.5 cm, n = 113; week 18 mean change 2.2, n = 71) and indicated that this could reflect height measurement

errors and/or difficulty obtaining height measurements in this population. The mean and median Z-scores (LOCF) were 0.0 and -0.0 respectively.

Phase 2 (double-blind)
The mean change from baseline in height at week 16 (LOCF) was 1.4 cm in the placebo group and 1.5 cm in the aripiprazole group (not statistically significant). The adjusted mean change from baseline Z-score at week 16 (LOCF) was 0.0 for the placebo group and 0.1 for the aripiprazole group (not statistically significant).

Weight

Phase 1 (open-label)

Table 20. Weight (kg): Mean Change from Baseline – Phase 1 (open-label)

	Aripiprazole N = 155	
	n	Mean (SE)
Baseline*	152	46.2 (1.8)
Week 1	144	-0.0 (0.1)
Week 2	147	-0.0 (0.1)
Week 4	147	0.8 (0.3)
Week 6	141	1.1 (0.1)
Week 10	124	2.2 (0.2)
Week 14	115	3.0 (0.3)
Week 18	71	3.7 (0.4)
Week 22	26	3.5 (0.6)
Week 26	7	2.6 (1.0)
Week 26 (LOCF)	152	3.2 (0.3)

*Mean actual score, not mean change, provided for baseline
Source: Table S.7.19 from CSR

The unadjusted mean and median change from baseline in BMI at week 26 (LOCF) was 1.6 kg/m2 and 0.8 kg/m2.

Phase 2 (double-blind)
There was a statistically significant difference in mean weight (kg) in the aripiprazole group (2.2 kg) compared to the placebo group (0.6 kg) at week 16 (LOCF).

Table 21. Weight (kg): Mean Change from Baseline – Phase 2 (double-blind)

	Placebo N = 43		Aripiprazole N = 39	
	n	Mean (SE)	n	Mean (SE)
Baseline*	43	50.5 (3.6)	39	52.0 (3.8)
Week 2	36	0.0 (0.2)	36	0.5 (0.2)
Week 4	36	0.2 (0.2)	33	0.5 (0.2)
Week 6	33	0.4 (0.3)	29	1.0 (0.3)
Week 8	25	2.0 (1.0)	27	1.3 (0.9)
Week 10	19	0.7 (0.5)	25	1.8 (0.4)
Week 12	19	0.9 (0.6)	23	2.5 (0.5)
Week 14	19	0.8 (0.5)	23	2.8 (0.5)
Week 16	19	0.8 (0.5)	20	2.9 (0.5)
Week 16 (LOCF)	43	0.6 (0.3)	39	2.2 (0.4)
	Week 16 LOCF	Treatment difference, 95% CI: 1.67 (0.71, 2.63) $p < 0.001$		

*Mean actual score, not mean change, provided for baseline
Source: Table S.7.18 from CSR

Potentially Clinically Significant Changes
At week 16 (LOCF), 3/43 (7%) subjects in the placebo group and 8/39 (20.5%) subjects in the aripiprazole group had an increase in weight of $\geq$ 7% from baseline. Statistically, this approached significance ($p = 0.074$). For increase in weight $\geq$ 7% "at any time", significantly more subjects in the aripiprazole group (10/39, 25.6%) than in placebo group (3/43, 7%) met this criteria ($p = 0.022$).

BMI
The adjusted mean change from baseline in BMI at week 16 (LOCF) was -0.1 kg/m2 for the placebo group and 0.6 kg/m2 for the aripiprazole group ($p = 0.004$).

Tanner Staging
Tanner staging was performed at screening and end of Phase 1 (open-label) and at the end of Phase 2 (double-blind).
Of the 155 subjects in Phase 1 (open-label), 24 advanced a Tanner stage for public hair and 21 subjects advanced a Tanner stage for breast/genitals.
In Phase 2 (double-blind), the numbers of subjects who advanced a Tanner stage were similar between the placebo and aripiprazole groups. Seven subjects advanced a Tanner stage for pubic hair (n = 4 placebo, n = 3 aripiprazole) and 9 subjects advanced a Tanner stage for breast/genitals (n = 4 placebo, n = 5 aripiprazole).

7.4.4 Electrocardiograms (ECGs)

ECGs were obtained at screening and end of Phase 1 and were available for 117 subjects. Per protocol, no ECGs were performed during Phase 2 of the protocol.

Table 22. ECG Parameters: Median Change from Baseline - Phase 1 (open-label)

	Median Change from Baseline Aripiprazole N = 155
QTcB (msec)	2
QTcF (msec)	0
PR (msec)	4
RR (msec)	-20
QRS (msec)	0
Heart rate (bpm)	2

Source: Table S.7.11 from CSR

Eleven subjects were noted to have ECG abnormalities: sinus tachycardia (n = 3), ventricle premature beat (n = 1), "other abnormalities" (n = 7). Sinus tachycardia was defined as heart rate $\geq$ 140 bpm and an increase $\geq$ 15 bpm from baseline.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6 Immunogenicity

No immunogenicity studies were conducted.

7.4.7 Assessment of Extrapyramidal Adverse Events – Rating Scales

In addition to spontaneous reports of extrapyramidal adverse events, these adverse events were also assessed via several rating scales: Simpson-Angus Scale (SAS), Barnes Akathisia Scale (BARS) and the Abnormal Involuntary Movement Scale (AIMS). These assessments were performed every 2 to 4 weeks in Phase 1 (open-label) and every 2 weeks in Phase 2 (double-blind).

For Phase 1 (open-label), the unadjusted mean change and SE from baseline in the SAS score to week 26 (LOCF) was -0.4 $\pm$ 0.16. The unadjusted mean change and SE from baseline in the BARS score to week 26 (LOCF) was -0.1 $\pm$ 0.04. The unadjusted mean change and SE from baseline in the AIMS total score to week 26 (LOCF) was -0.4 $\pm$ 0. 14.

Phase 2 data are summarized in Tables 23 - 25. The only statistical differences between the placebo and aripiprazole groups were in the mean change from baseline in the Simpson-Angus Scale scores.

Table 23. Simpson Angus Scale: Adjusted Mean Change from Baseline – Phase 2 (double-blind)

	Placebo N = 43		Aripiprazole N = 39	
	n	Mean (SE)	n	Mean (SE)
Baseline*	43	10.5 (0.22)	39	10.8 (0.23)
Week 2	36	-0.1 (0.15)	35	-0.1 (0.15)
Week 4	36	-0.1 (0.17)	32	-0.2 (0.17)
Week 6	33	0.1 (0.12)	29	-0.3 (0.13)
Week 8	25	-0.1 (0.12)	27	-0.1 (0.12)
Week 10	19	-0.2 (0.18)	25	-0.1 (0.16)
Week 12	19	0.2 (0.18)	23	-0.2 (0.17)
Week 14	19	0.2 (0.20)	23	-0.3 (0.19)
Week 16	19	0.1 (0.19)	20	-0.4 (0.20)
Week 16 (LOCF)	43	0.0 (0.13)	39	0.2 (0.18)
	Week 16 LOCF	Treatment difference, 95% CI: -0.37 (-0.73, -0.00) p = 0.050		

*Mean actual score, not mean change, provided for baseline
Source: Table S.6.29

Table 24. Barnes Akathisia Scale: Adjusted Mean Change from Baseline – Phase 2 (double-blind)

	Placebo N = 43		Aripiprazole N = 39	
	n	Mean (SE)	n	Mean (SE)
Baseline*	43	0.1 (0.07)	39	0.2 (0.07)
Week 2	36	0.1 (0.07)	36	-0.1 (0.07)
Week 4	36	-0.1 (0.03)	33	-0.1 (0.04)
Week 6	33	-0.0 (0.04)	29	-0.1 (0.05)
Week 8	25	0.1 (0.07)	27	-0.1 (0.07)
Week 10	19	-0.0 (0.06)	25	-0.1 (0.06)
Week 12	19	-0.0 (0.00)	23	-0.0 (0.00)
Week 14	19	0.1 (0.11)	23	-0.0 (0.11)
Week 16	19	-0.0 (0.05)	20	-0.1 (0.05)
Week 16 (LOCF)	43	0.0 (0.05)	39	-0.1 (0.05)
	Week 16 LOCF	Treatment difference, 95% CI: -0.10 (-0.23, -0.03) p = 0.141		

*Mean actual score, not mean change, provided for baseline
Source: Table S.6.39

Table 25. Abnormal Involuntary Movement Scale (total score): Adjusted Mean Change from Baseline – Phase 2 (double-blind)

	Placebo N = 43		Aripiprazole N = 39	
	n	Mean (SE)	n	Mean (SE)
Baseline*	43	0.0 (0.04)	39	0.1 (0.04)
Week 2	36	-0.0 (0.02)	36	-0.0 (0.02)
Week 4	36	-0.1 (0.00)	33	-0.1 (0.00)
Week 6	33	0.1 (0.16)	29	-0.1 (0.17)
Week 8	25	0.0 (0.06)	27	-0.1 (0.06)
Week 10	19	-0.1 (0.07)	25	0.0 (0.06)
Week 12	19	0.0 (0.04)	23	-0.1 (0.03)
Week 14	19	-0.0 (0.00)	23	-0.0 (0.00)
Week 16	19	-0.1 (0.00)	20	-0.1 (0.00)
Week 16 (LOCF)	43	0.1 (0.12)	39	-0.1 (0.13)
	Week 16 LOCF	Treatment difference, 95% CI: -0.15 (-0.50, 0.19) p = 0.383		

*Mean actual score, not mean change, provided for baseline
Source: Table S.6.31

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse events was not studied in this submission.

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events was not studied in this submission.

7.5.3 Drug-Demographic Interactions

The Sponsor evaluated the incidence of adverse events by gender, age and race for Phase 2. Small numbers of female subjects were included in this study. Of the 43 subjects in the placebo group, 6 were female and of the 39 subjects in the aripiprazole group, 11 were female. In the aripiprazole group, female subjects were more likely to experience adverse events (10/11, 90.9%) compared to male subjects (12/28, 42.9%). Approximately 30% of subjects in both gender cohorts in the placebo group experienced adverse events. Similar percentages of subjects in the two age cohorts experienced adverse events in the aripiprazole group: 17/31 (54.8%) in the 9-12 year old cohort and 5/8 (62.5%) in the 12 to 17 year old cohort. Approximately 30% of subjects in both age cohorts in the placebo group experienced adverse events.

White subjects experienced more adverse events in the aripiprazole group (18/29, 62.1%) compared to nonwhite subjects (4/10, 40%). This same trend was noted in the placebo group (35.7% vs. 26.7% respectively).
Approximately 55% of subjects in each of the age cohorts (9 to 12 years and 12 to 17 years) experienced adverse events in the aripiprazole group.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied in this submission.

7.5.5 Drug-Drug Interactions

No drug-drug interactions were studied in this submission.

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 occurred in this study.

7.6.3 Pediatrics and Assessment of Effects on Growth

Refer to Section 7.4.3 of the review. A meeting with the Pediatric Review Committee (PeRC) is scheduled for March 12, 2014.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose or drug abuse were identified in this clinical trial. This study did not evaluate withdrawal or rebound symptoms.

7.7 Additional Submissions / Safety Issues

Several requests for information were submitted to the sponsor including a request for datasets, literature review, case report forms for SAEs and discontinuations due to adverse events, and queries of specific questions relating to the submission. The sponsor submitted the requested information to the supplemental NDA.

8 Postmarket Experience

The sponsor did not include any data regarding the postmarket experience for aripiprazole.

9 Appendices

9.1 Literature Review/References

The sponsor provided a literature search for published articles pertaining to aripiprazole and pediatric mental disorders from June 15, 2008 through July 26, 2013. The mental disorder terms that were included in the search were: Autism, Autistic, Kanner Syndrome, Pervasive Developmental Disorder, Tourette Syndrome, Schizophrenia, Dementia Praecox, Bipolar Disorder, Manic Disorder, Maniodepressive Disorder. Nine different databases were included in this literature search. The search identified 311 references. The sponsor indicates that the references have been reviewed in detail with regard to safety and efficacy data relevant to aripiprazole and no findings were noted that would adversely affect conclusions about the safety and efficacy of aripiprazole in the current submission.

Due to a corruption in this file noted late in the review, this reviewer was not able to corroborate the findings of the sponsor.

9.2 Labeling Recommendations

2 DOSAGE AND ADMINISTRATION
2.4 Irritability Associated with Autistic Disorder
Current labeling:
Maintenance Treatment: (b) (4)

Proposed:
Maintenance Treatment: The efficacy of ABILIFY for the maintenance treatment of irritability associated with autistic disorder (b) (4) not (b) (4) established *[see* (b) (4) should be periodically reassessed to determine the continued need for ~~maintenance~~ treatment.

Reviewer Comment:
In general, their proposal is acceptable with minor changes:

Maintenance Treatment: The **safety and** efficacy of ABILIFY for the maintenance treatment of irritability associated with autistic disorder **have** not been established *[see* (b) (4) ***Use in Specific Populations (8.4)***]- (b) (4)

(b) (4)
should be periodically reassessed to determine the continued need for ~~maintenance~~ treatment.

Proposed:
Section 8.4 Pediatric Use (b) (4)
not been (b) (4)
established.

14.4 Irritability Associated with Autistic Disorder

(b) (4)

Reviewer Comment:
The description of the negative clinical trial should be under Use in Specific Populations, Pediatric Use (8.4) rather than in Clinical Studies (14.4). This is consistent with placement of the negative pediatric bipolar depression trial for Seroquel XR.

In general, the clinical trial description is acceptable with minor suggested changes. The Sponsor had proposed (b) (4)
.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

(b) (4)

9.3 Advisory Committee Meeting

There was no advisory committee meeting for this submission.

9.4 Investigators and Sites for Protocol CN138603

Site No.	Principal Investigator/Site	No. Subjects Enrolled	No. Subjects Entering Phase 1	No. Subjects Randomized
001	W. Holloway Jr Oklahoma City, OK	4	2	1
002	A. Attalla Smyrna, GA	14	12	11
003	N. Handal Dothan, AL	3	2	2
004	T. Rugino Toms River, NJ	11	8	3
005	A. Robb Washington DC	4	2	1
006	A. Unis Coeur D'Alene, ID	1	1	0
007	A. Sood Richmond, VA	4	3	0
008	M. Bengtson Tampa, FL	3	3	1
009	E. Sarkis Gainesville, FL	5	3	2
010	J. Heise Kingsport, TN	2	2	2
011	E. Hurt Columbus, OH	7	6	0
013	F. Ludwig Norfolk, VA	7	6	3
014	M. Mintz Gibbsboro, NJ	10	5	2
015	R. Richter Tulsa, OK	10	10	8
016	R. Melmed Phoenix, AZ	6	3	0
017	A. Padilla Miami, FL	1	0	0
019	J. Blumer Toledo, OH	0	0	0
021	M Perez Hialeah, FL	12	10	9
022	G. Carlson Stony Brook, NY	6	5	2
023	A. Childress Las Vegas, NV	6	5	4
026	R. Malone Philadelphia, PA	0	0	0
028	T. Frazier Cleveland, OH	0	0	0
029	R. Abbey	8	4	1

	Palo Alto, CA			
030	L. Sikich Chapel Hill, NC	4	2	1
031	R. Findling Cleveland, OH	3	2	0
034	A. Hardan Stanford, CA	3	3	2
035	P. Williams Louisville, KY	0	0	0
037	S. Venkataraman Bloomfield Hills, MI	12	5	1
039	K. Sokolski Costa Mesa, CA	6	5	3
040	T. Lock Oklahoma City, OK	0	0	0
041	J. Calcagno Gresham, OR	7	5	0
043	S. Bostrom Clinton, UT	13	11	7
044	J. Carr Glendale, CA	7	6	6
045	J. Bregman Columbia, MO	0	0	0
046	R. Hendren San Francisco, CA	7	5	1
047	B. Handen Pittsburgh, PA	1	0	0
048	J. Northcutt Maitland, FL	6	5	2
049	A. Yeo Portland, OR	0	0	0
050	R. Horton Shreveport, LA	5	2	1
051	R. Shiwach Desoto, TX	12	10	7
052	H. Roane Syracuse, NY	0	0	0
054	M. Biber Newton, MA	5	4	2

Source: Appendix 1.5 from CSR

9.5 Schedule of Events for CN138603

(Sponsor Tables, from Protocol)

Table 5.1A: Screening (7 - 42 Days)

Procedure	Screen Visit 1	Visit 1A[a]	Baseline Visit 2	Notes
Eligibility Assessments				
Informed Consent	X			
Inclusion/Exclusion Criteria	X	X	X	Review and confirm entrance criteria again at Visit 1A and Baseline
Psychiatric/Medical History	X	X	X	Update medical and/or psychiatric history at Visits 1A and 2 (if applicable).
Autism Diagnostic Interview - Revised (ADI-R)	X			The ADI-R is completed only once during the Screening Phase, but portions of the interview can be conducted over interim visits if necessary.
Urine Pregnancy Test	X	(X)	X	Will only be completed once during the Screening Phase either at Visit 1 or Visit 1A, depending on whether the subject requires medication washout, but must also be done at the Baseline Visit.
Prior/Concomitant Medication	X	X	X	
Safety Assessments				
Physical Examination	X	(X)		Will only be completed once during the Screening Phase either at Visit 1 or Visit 1A, depending on whether the subject requires medication washout.
Tanner Staging	X	(X)		Will only be completed once during the Screening Phase either at Visit 1 or Visit 1A
Vital Signs, Weight and Height	X	(X)	X	Will only be completed once during the Screening Phase either at Visit 1 or Visit 1A, depending on whether the subject requires medication washout, and again at the Baseline Visit. Vitals signs to include supine and standing (or sitting) blood pressure and pulse. Blood pressure is to be taken before blood is drawn (where applicable). Weight and Height should be recorded in a consistent manner whenever scheduled to avoid confounding factors (eg, shoes on or off, excess clothing, etc, refer to Sections 5.3.3 and 5.3.4).
Clinical Lab Evaluations	X	(X)		Will only be completed once during the Screening Phase either at Visit 1 or Visit 1A, depending on whether the subject requires medication washout. Clinical Labs must be done at Visit 1A if medication washout is required. Includes a urine screen for drugs of abuse. If possible, subjects should be fasting for a minimum of 10 hours prior to all blood draws. However, if a subject is not fasting at a given visit, the blood draw should still be performed and the fasting status documented.
Electrocardiogram (ECG)	X	(X)		Will only be completed once during the Screening Phase either at Visit 1 or Visit 1A, depending on whether the subject requires medication washout. ECG must be done at Visit 1A if medication washout is required. If any clinically significant abnormalities are observed, subject must not be dispensed single blind study medication or begin Phase 1 procedures without permission of the BMS Medical Monitor
Adverse Events Assessment	X	X	X	To include the collection of serious adverse events only.
EPS Measures			X	EPS evaluations include the Simpson-Angus Scale (SAS), the Barnes Akathisia Scale (BARS) and the Abnormal Involuntary Movement Scale (AIMS).
Efficacy Assessments				
CGI-Severity	X	(X)	X	Will only be completed once during the Screening Phase either at Visit 1 or Visit 1A (depending on the need for medication washout), and again at the Baseline Visit.
CGI-Improvement				
ABC	X	(X)	X	Will only be completed once during the Screening Phase either at Visit 1 or Visit 1A (depending on the need for medication washout), and again at the Baseline Visit.

Procedure	Screen Visit 1	Visit 1A[a]	Baseline Visit 2	Notes
Outcomes Research				
PedsQL			X	
Caregiver Strain Questionnaire (CGSQ)			X	
Clinical Drug Supplies				
Dispense Study Medication			X	
Medication Compliance				

[a] Subjects needing medication washout will have an interim screen visit (Visit 1A) after medication washout is completed. For subjects requiring medication washout, only the Informed Consent, Review of Inclusion/Exclusion Criteria, and review of Psychiatric/Medical History should be completed at Visit 1. All other Screen Visit procedures and assessments should be delayed until after the completion of the washout and conducted at Visit 1A.

Table 5.1B: Phase 1: Stabilization Phase (Single-blind Treatment)

Procedure	Phase 1: Single Blind Treatment[a]														
	V 3	V 4	V 5	V 6	Phone V 1	V 7	Phone V 2	V 8	Phone V 3	V 9	Phone V 4	V 10	Phone V 5	V 11	Notes
	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8[b]	Wk 10	Wk 12[b]	Wk 14	Wk 16[b]	Wk 18	Wk 20[b]	Wk 22	Wk 24[b]	Wk 26/ET	
Eligibility Assessments															
Inclusion/Exclusion Criteria														X	Eligibility criteria for entry into the Randomization Phase to be assessed. For subjects entering the Randomization Phase, Week 26/ET assessments will be utilized as randomization baseline scores. At time of randomization, all Wk 26/ET procedures must be completed.
Safety Assessments															
Physical Examination														X	
Tanner Staging														X	

Procedure	Phase 1: Single Blind Treatment[a]														
	V 3	V 4	V 5	V 6	Phone V 1	V 7	Phone V 2	V 8	Phone V 3	V 9	Phone V 4	V 10	Phone V 5	V 11	Notes
	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8[b]	Wk 10	Wk 12[b]	Wk 14	Wk 16[b]	Wk 18	Wk 20[b]	Wk 22	Wk 24[b]	Wk 26/ET	
Vital Signs, Weight and Height	X	X	X	X		X		X		X		X		X	Vital signs to include supine and standing (or sitting) blood pressure and pulse. Blood pressure is to be taken before blood is drawn (when applicable). Weight and Height should be recorded in a consistent manner whenever scheduled to avoid confounding factors (eg, shoes on or off, excess clothing, etc, refer to Sections 5.3.3 and 5.3.4).
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Lab Evaluations														X	Includes a urine screen for drugs of abuse at the discretion of the investigator at anytime during the study. If possible, subjects should be fasting for a minimum of 10 hours prior to all blood draws. However, if a subject is not fasting, the blood draw should still be performed, and the fasting status documented.

Procedure	Phase 1: Single Blind Treatment[a]														
	V 3	V 4	V 5	V 6	Phone V 1	V 7	Phone V 2	V 8	Phone V 3	V 9	Phone V 4	V 10	Phone V 5	V 11	Notes
	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8[b]	Wk 10	Wk 12[b]	Wk 14	Wk 16[b]	Wk 18	Wk 20[b]	Wk 22	Wk 24[b]	Wk 26/ET	
Urine Pregnancy Test		X		X		X		X		X		X		X	
ECG														X	If any clinically significant abnormalities are observed, subject must not be randomized into Phase 2 without permission of the BMS Medical Monitor
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EPS Measures	X	X	X	X		X		X		X		X		X	EPS evaluations include the Simpson-Angus Scale (SAS), the Barnes Akathisia Scale (BARS) and the Abnormal Involuntary Movement Scale (AIMS).
Efficacy Assessments															
CGI- Severity	X	X	X	X		X		X		X		X		X	
CGI-Improvement	X	X	X	X		X		X		X		X		X	
ABC	X	X	X	X		X		X		X		X		X	

Procedure	Phase 1: Single Blind Treatment[a]														
	V 3	V 4	V 5	V 6	Phone V 1	V 7	Phone V 2	V 8	Phone V 3	V 9	Phone V 4	V 10	Phone V 5	V 11	Notes
	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8[b]	Wk 10	Wk 12[b]	Wk 14	Wk 16[b]	Wk 18	Wk 20[b]	Wk 22	Wk 24[b]	Wk 26/ET	
Outcomes Research															
PedsQL			X			X				X				X	
CGSQ			X			X				X				X	
Clinical Drug Supplies															
Dispense Study Medication	X	X	X	X		X		X		X		X		X	
Medication Compliance	X	X	X	X		X		X		X		X		X	

[a] At their discretion, investigators may schedule additional interim visits or initiate telephone contact to further monitor safety and tolerability. For Phases 1 and 2, every effort should be made to conduct assessments ± 2 days from the scheduled visit date, except where an interim visit is warranted for reasons of safety, tolerability, or efficacy.

[b] Telephone visit to check subject status. It is recommended to maintain contact with subject and caregiver between study visit intervals to assist in the assessment of subject well-being, compliance and the need for an interim study visit to be scheduled. If needed, subject should be brought in for an interim study visit to further assess status, investigator can substitute an office visit for a phone visit when subject is potentially eligible for randomization.

Table 5.1C: Phase 2: Randomization Phase (Double-Blind Treatment)

Procedure	Phase 2: Double-Blind Treatment[a]										
	Phone V 1	V 2	Phone V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	Notes
	Wk 1[b]	Wk 2	Wk 3[b]	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16/ End of Treatment	
Eligibility Assessments											
Inclusion/Exclusion Criteria											
Safety Assessments											
Physical Examination										X	
Tanner Staging										X	
Vital Signs, Weight and Height		X		X	X	X	X	X	X	X	Vital signs to include supine and standing (or sitting) blood pressure and pulse. Blood pressure is to be taken before blood is drawn (when applicable). Weight and Height should be recorded in a consistent manner whenever scheduled to avoid confounding factors (eg, shoes on or off, excess clothing, etc, refer to Sections 5.3.3 and 5.3.4).
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	

Procedure	Phase 2: Double-Blind Treatment[a]										
	Phone V 1	V 2	Phone V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	Notes
	Wk 1[b]	Wk 2	Wk 3[b]	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16/ End of Treatment	
Clinical Lab Evaluations										X	If possible, subjects should be fasting for a minimum of 10 hours prior to all blood draws. However, if a subject is not fasting, the blood draw should still be performed, and the fasting status documented.
Urine Pregnancy Test				X		X		X		X	
ECG											
Adverse Events	X	X	X	X	X	X	X	X	X	X	
EPS Measures		X		X	X	X	X	X	X	X	EPS evaluations include the Simpson-Angus Scale (SAS), the Barnes Akathisia Scale (BARS) and the Abnormal Involuntary Movement Scale (AIMS)
Efficacy Assessments											
CGI- Severity		X		X	X	X	X	X	X	X	
CGI-Improvement		X		X	X	X	X	X	X	X	
ABC		X		X	X	X	X	X	X	X	

Procedure	Phase 2: Double-Blind Treatment[a]										
	Phone V 1	V 2	Phone V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	Notes
	Wk 1[b]	Wk 2	Wk 3[b]	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16/ End of Treatment	
Outcomes Research											
PedsQL				X		X		X		X	
CGSQ				X		X		X		X	
Clinical Drug Supplies											
Dispense Study Medication		X		X	X	X	X	X	X		
Medication Compliance		X		X	X	X	X	X	X	X	

[a] Interim visits to be scheduled as needed to assess criteria for relapse. At their discretion, investigators may also schedule additional interim visits or initiate telephone contact to further monitor safety and tolerability. For Phases 1 and 2, every effort should be made to conduct assessments ± 2 days from the scheduled visit date, except where an interim visit is warranted for reasons of safety, tolerability, or efficacy. If a subject scores the following at a scheduled study visit: ABC Irritability Subscale ≥ a 25% increase compared to the randomization visit (end of Phase 1) score AND a CGI-I rating of 'Much Worse' or 'Very Much Worse,' they will be brought back to the site in approximately one week to repeat these assessments to determine if they meet criteria for relapse (an interim visit will occur if a regular study visit is not scheduled to occur within the approximate one week time frame). After relapse criteria are met on one visit, the second visit should occur in approximately one week to repeat these assessments to determine if the subject continues to meet full criteria for relapse. If the criteria for relapse is met (ie, scores on the ABC Irritability Subscale and CGI-I again meet the above criteria), the site will conduct the full Early Termination Visit assessments and procedures and study medication will be discontinued.

[b] Telephone visit to check subject status. It is recommended to maintain contact with subject and caregiver between study visit intervals to assist in the assessment of subject well-being, compliance and the need for an interim study visit to be scheduled. If needed, subject should be brought in for an interim study visit to further assess status, investigator can substitute an office visit for a phone visit when subject is potentially eligible for randomization

9.6 Inclusion and Exclusion Criteria for Protocol CN138603

Inclusion Criteria

1. Written informed consent must be obtained from a legally authorized representative (e.g. guardian or caregiver), in accordance with requirements of the study center's institutional review board, prior to the initiation of any protocol-required procedures. Where applicable, subject assent should also be obtained.
2. The subject is a male or female child or adolescent 6 to 17 years of age, inclusive, at the time of the baseline visit.
3. The subject and/or the designated guardian or caregiver are able to comprehend and satisfactorily comply with the protocol requirements, in the opinion of the investigator.
4. The subject meets current DSM-IV-TR diagnostic criteria for Autistic disorder and also demonstrates behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems. Diagnosis of autistic disorder will be confirmed by the Autism Diagnostic Interview-Revised.
5. The subject has an ABC-Irritability subscale score $\geq$ 18 and a CGI-S score $\geq$ 4 at the screening and baseline visits.
6. The subject has a mental age of at least 24 months, as assessed by the investigator.
7. Females of childbearing potential and males must be using an acceptable method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the last dose of investigational product in such a manner that the risk of pregnancy is minimized.
8. Females must have a negative serum or urine pregnancy test within 72 hours prior to the start of investigational product.
9. Females must not be breastfeeding.

Exclusion Criteria

1. The subject is considered treatment resistant to antipsychotic medication, in the opinion of the investigator, based on lack of therapeutic response to 2 different antipsychotics after treatment of at least 3 weeks each.
2. The subject was previously treated with aripiprazole for at least 3 weeks in duration at an adequate daily dose and did not demonstrate a clinically meaningful response in the judgment of the investigator.
3. The subject has a lifetime diagnosis of bipolar disorder, psychosis, or schizophrenia, or a current diagnosis of major depressive disorder.
4. The subject is diagnosed with Pervasive Developmental Disorder-Not Otherwise Specified, Asperger's Syndrome, Rett's Syndrome, Childhood Disintegrative Disorder or Fragile X Syndrome.
5. The subject has a history of Neuroleptic malignant syndrome

6. The subject represents a significant risk of committing suicide based on history or routine psychiatric status examination.
7. The subject has had a seizure within the past year.
8. The subject has a history of severe head trauma or stroke.
9. The subject has a history or current evidence of any unstable medical conditions that would expose them to undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the trial.
10. The subject has a history of a clinically significant low white blood cell count or a drug-induced leukopenia/neutropenia.
11. The following lab test results, vital sign and ECG findings are exclusionary: QTc > 475 msec, platelets $\leq$ 75,000/mm^3, hemoglobin $\leq$ 9 g/dL, neutrophils $\leq$ 1 x E3/mm^3 (or equivalent), AST or ALT > 3x upper limit of normal, creatinine $\geq$ 2 mg/dL.
12. Subject should be excluded if they have any other abnormal laboratory test result, vital sign or ECG finding that, in the investigator's judgment, is medically significant, in that it would impact the safety of the subject or the interpretation of the study results.
13. The subject weighs < 15 kg.
14. The subject has taken an investigational agent within one month of the screening visit.
15. Subjects who are likely to require prohibited concomitant therapy during the trial.
16. The subject has a known allergy or hypersensitivity to aripiprazole or other dihidrocarbostyrils.
17. Females of child bearing potential who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 8 weeks after the study.
18. Subjects who are pregnant or breastfeeding.
19. Subjects with a positive pregnancy test on enrollment or prior to study drug administration.
20. Prisoners or subjects who are involuntarily incarcerated.
21. Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness.

9.7 Clinical Laboratory: Potentially Clinically Significant Abnormalities

Lab Parameter	Criterion
Chemistry	
AST	≥ 3x ULN
ALT	≥ 3x ULN
Alkaline Phosphatase	≥ 3x ULN
LDH	≥ 3x ULN
Creatinine	≥ 2 mg/dL
Uric Acid	≥ 10.5 mg/dL (males), > 8.5 mg/dL (females)
Bilirubin (total)	≥ 2 mg/dL
Hematology	
Hematocrit	≤ 33%
Hemoglobin	< 11.3 g/dL
WBC	≤ 2800 mm or ≥ 16000 mm
Eosinophils	> 17%
Neutrophils	< 15%
Platelet count	≤ 75,000 mm or ≥ 700,000 mm

Source: Appendix 4 of Protocol CN138603

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

/s/

CARA L ALFARO
02/27/2014

SILVANA BORGES
03/04/2014

MITCHELL V Mathis
03/24/2014