CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21436/ S-38

Trade Name: **ABILIFY**

Generic Name: **Aripiprazole**

Sponsor: **Otsuka American Pharmaceutical, Inc.**

Approval Date: 12/12/2014

Indications:

ABILIFY is an atypical antipsychotic. The oral formulations are indicated for:

- Schizophrenia
- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I
- Adjunctive Treatment of Major Depressive Disorder
- Irritability Associated with Autistic Disorder
- Treatment of Tourette's disorder
- The injection is indicated for:
- Agitation associated with schizophrenia or bipolar mania

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APPLICATION NUMBER:

NDA 21436/S-38

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21436/S-038
NDA 21713/S-030
NDA 21729/S-022
NDA 21866/S-023

SUPPLEMENT APPROVAL

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: David Goldberger, RPh, RAC
Vice President, Global Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Goldberger:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received February 12, 2014 (NDA 21436/S-038), and April 3, 2014 (NDAs 21713/S-030, 21729/S-022, 21866/S-023), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abilify (aripiprazole) tablets 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg (NDA 21436), oral solution 1 mg/ml (NDA 21713), orally disintegrating tablet 10 mg, 15 mg (NDA 21729), and injectable formulation 9.75 mg/1.3 mL single-dose vial (NDA 21866).

We acknowledge receipt of your amendments dated March 7, 2014; March 26, 2014; April 30, 2014; June 10, 2014; June 20, 2014; June 26, 2014; August 29, 2014; October 28, 2014; November 14, 2014; November 24, 2014; December 2, 2014, December 8, 2014, and December 9, 2014.

Please also refer to our approval letter dated December 12, 2014. That letter contained an error in the "indications" sentence as described below:

Prior Statement: "These 'Prior Approval' supplemental new drug applications provide for labeling revisions based upon two adequate and well-controlled trials that demonstrate the efficacy for the new indication in pediatric patients with Tourette's Disorder."

Corrected Statement: "These 'Prior Approval' supplemental new drug applications provide for labeling revisions based upon two adequate and well-controlled trials that demonstrate the efficacy for the new indication in patients with Tourette's Disorder."

The effective approval date will remain December 12, 2014, the date of the original approval letter. The corrected labeling is unchanged.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment agreed upon in your communication dated November 14, 2014:

2837-1 A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of aripiprazole in the treatment of pediatric patients (6-17 years) Tourette's Disorder. This trial must include a placebo group and more than one fixed dose and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of aripiprazole. Because it is important to establish the dose-response for maintenance, this trial should randomize patients on stable doses of aripiprazole and different doses of aripiprazole (and to placebo) during the maintenance phase.

The timetable you submitted on November 25, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 01/31/2016
Trial Completion: 07/31/2021
Final Report Submission: 07/31/2022

Submit clinical protocols to your IND 116003 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to this postmarketing commitment should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call CAPT William Bender, Senior Regulatory Project Manager, at (301) 796-2145 or via email at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MITCHELL V Mathis
12/12/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21436/S-38

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ABILIFY safely and effectively. See full prescribing information for ABILIFY
ABILIFY® (aripiprazole) Tablets
ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets
ABILIFY® (aripiprazole) Oral Solution
ABILIFY® (aripiprazole) Injection FOR INTRAMUSCULAR USE ONLY
Initial U.S. Approval: 2002

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis. (5.1)
- Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.2)

---------- RECENT MAJOR CHANGES ----------

Indication, Treatment of Tourette's Disorder (1)	12/2014
Dosage and Administration, Tourette's Disorder (2.5)	12/2014
Warnings and Precautions, Metabolic Changes (5.6)	12/2014

---------- INDICATIONS AND USAGE ----------

ABILIFY is an atypical antipsychotic. The oral formulations are indicated for:

- Schizophrenia (14.1)
- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I (14.2)
- Adjunctive Treatment of Major Depressive Disorder (14.3)
- Irritability Associated with Autistic Disorder (14.4)
- Treatment of Tourette's disorder (14.5)

The injection is indicated for:

- Agitation associated with schizophrenia or bipolar mania (14.6)

---------- DOSAGE AND ADMINISTRATION ----------

		Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia – adults (2.1)		10-15 mg/day	10-15 mg/day	30 mg/day
Schizophrenia – adolescents (2.1)		2 mg/day	10 mg/day	30 mg/day
Bipolar mania – adults: monotherapy (2.2)		15 mg/day	15 mg/day	30 mg/day
Bipolar mania – adults: adjunct to lithium or valproate (2.2)		10-15 mg/day	15 mg/day	30 mg/day
Bipolar mania – pediatric patients: monotherapy or as an adjunct to lithium or valproate (2.2)		2 mg/day	10 mg/day	30 mg/day
Major Depressive Disorder – Adults adjunct to antidepressants (2.3)		2-5 mg/day	5-10 mg/day	15 mg/day
Irritability associated with autistic disorder – pediatric patients (2.4)		2 mg/day	5-10 mg/day	15 mg/day
Tourette's disorder – (2.5)	Patients < 50 kg	2 mg/day	5 mg/day	10 mg/day
	Patients ≥ 50 kg	2 mg/day	10 mg/day	20 mg/day
Agitation associated with schizophrenia or bipolar mania – adults (2.6)		9.75 mg /1.3 mL injected IM		30 mg/day injected IM

- Oral formulations: Administer once daily without regard to meals (2)
- IM injection: Wait at least 2 hours between doses. Maximum daily dose 30 mg (2.5)
- Known CYP2D6 poor metabolizers: Half of the usual dose (2.7)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg (3)
- Orally Disintegrating Tablets: 10 mg and 15 mg (3)
- Oral Solution: 1 mg/mL (3)
- Injection: 9.75 mg/1.3 mL single-dose vial (3)

---------- CONTRAINDICATIONS ----------

- Known hypersensitivity to ABILIFY (4)

---------- WARNINGS AND PRECAUTIONS ----------

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) (5.2)
- *Neuroleptic Malignant Syndrome* Manage with immediate discontinuation and close monitoring (5.3)
- *Tardive Dyskinesia* Discontinue if clinically appropriate (5.4)
- *Metabolic Changes* Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain (5.5)
  - *Hyperglycemia/Diabetes Mellitus* Monitor glucose regularly in patients with and at risk for diabetes (5.5)
  - *Dyslipidemia* Undesirable alterations in lipid levels have been observed in patients treated with atypical antipsychotics (5.5)
  - *Weight Gain* Weight gain has been observed with atypical antipsychotic use. Monitor weight (5.5)
- *Orthostatic Hypotension* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.6)
- *Leukopenia, Neutropenia, and Agranulocytosis* have been reported with antipsychotics including ABILIFY. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ABILIFY should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors (5.7)
- *Seizures/Convulsions* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.8)
- *Potential for Cognitive and Motor Impairment* Use caution when operating machinery (5.9)
- *Suicide* The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder. Closely supervise high-risk patients (5.11)

---------- ADVERSE REACTIONS ----------

Commonly observed adverse reactions (incidence ≥5% and at least twice that for placebo) were (6.1):

- Adult patients with schizophrenia: akathisia
- Pediatric patients (13 to 17 years) with schizophrenia: extrapyramidal disorder, somnolence, and tremor
- Adult patients (monotherapy) with bipolar mania: akathisia, sedation, restlessness, tremor, and extrapyramidal disorder
- Adult patients (adjunctive therapy with lithium or valproate) with bipolar mania: akathisia, insomnia, and extrapyramidal disorder
- Pediatric patients (10 to 17 years) with bipolar mania: somnolence, extrapyramidal disorder, fatigue, nausea, akathisia, blurred vision, salivary hypersecretion, and dizziness
- Adult patients with major depressive disorder (adjunctive treatment to antidepressant therapy): akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision
- Pediatric patients (6 to 17 years) with autistic disorder: sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder, and lethargy
- Pediatric patients (6 to 18 years) with Tourette's disorder: sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, increased appetite
- Adult patients with agitation associated with schizophrenia or bipolar mania: nausea

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

Dosage adjustment due to drug interactions (7.1)

Factors	**Dosage Adjustments for ABILIFY**
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers and strong CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP2D6 **or** CYP3A4 inhibitors	Administer half of usual dose
Strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers	Double usual dose over 1 to 2 weeks

---------- USE IN SPECIFIC POPULATIONS ----------

- *Pregnancy* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)
- *Nursing Mothers* Discontinue drug or nursing, taking into consideration importance of drug to the mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.2)]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution are indicated for the treatment of:

- Schizophrenia *[see CLINICAL STUDIES (14.1)]*
- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder *[see CLINICAL STUDIES (14.2)]*
- Adjunctive Treatment of Major Depressive Disorder *[see CLINICAL STUDIES (14.3)]*
- Irritability Associated with Autistic Disorder *[see CLINICAL STUDIES (14.4)]*
- Treatment of Tourette's Disorder *[see CLINICAL STUDIES (14.5)]*

ABILIFY Injection is indicated for the treatment of:

- Agitation associated with schizophrenia or bipolar mania *[see CLINICAL STUDIES (14.6)]*

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day, when administered as the tablet formulation; however, doses higher than 10 or 15 mg/day were not more effective than 10 or 15 mg/day. Dosage increases should generally not be made before 2 weeks, the time needed to achieve steady-state *[see CLINICAL STUDIES (14.1)]*.

Maintenance Treatment: Maintenance of efficacy in schizophrenia was demonstrated in a trial involving patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from those medications and randomized to either ABILIFY 15 mg/day or placebo, and observed for relapse *[see CLINICAL STUDIES (14.1)]*. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

Adolescents

The recommended target dose of ABILIFY is 10 mg/day. Aripiprazole was studied in adolescent patients 13 to 17 years of age with schizophrenia at daily doses of 10 mg and 30 mg. The starting daily dose of the tablet formulation in these patients was 2 mg, which was titrated to 5 mg after 2 days and to the target dose of 10 mg after 2 additional days. Subsequent dose increases should be administered in 5 mg increments. The 30 mg/day dose was not shown to be more efficacious than the 10 mg/day dose. ABILIFY can be administered without regard to meals *[see CLINICAL STUDIES (14.1)]*. Patients should be periodically reassessed to determine the need for maintenance treatment.

Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

2.2 Bipolar I Disorder

Acute Treatment of Manic and Mixed Episodes

Adults: The recommended starting dose in adults is 15 mg given once daily as monotherapy and 10 mg to 15 mg given once daily as adjunctive therapy with lithium or valproate. ABILIFY can be given without regard to meals. The recommended target dose of ABILIFY is 15 mg/day, as monotherapy or as adjunctive therapy with lithium or valproate. The dose may be increased to 30 mg/day based on clinical response. The safety of doses above 30 mg/day has not been evaluated in clinical trials.

Pediatrics: The recommended starting dose in pediatric patients (10 to 17 years) as monotherapy is 2 mg/day, with titration to 5 mg/day after 2 days, and a target dose of 10 mg/day after 2 additional days. Recommended dosing as adjunctive therapy to lithium or valproate is the same. Subsequent dose increases, if needed, should be administered in 5 mg/day increments. ABILIFY can be given without regard to meals *[see CLINICAL STUDIES (14.2)]*.

2.3 Adjunctive Treatment of Major Depressive Disorder

Adults

The recommended starting dose for ABILIFY as adjunctive treatment for patients already taking an antidepressant is 2 to 5 mg/day. The recommended dosage range is 2 to 15 mg/day. Dosage adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week *[see CLINICAL STUDIES (14.3)]*. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.4 Irritability Associated with Autistic Disorder

Pediatric Patients (6 to 17 years)

The recommended dosage range for the treatment of pediatric patients with irritability associated with autistic disorder is 5 to 15 mg/day.

Dosing should be initiated at 2 mg/day. The dose should be increased to 5 mg/day, with subsequent increases to 10 or 15 mg/day if needed. Dose adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week *[see CLINICAL STUDIES (14.4)]*. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.5 Tourette's Disorder

Pediatric Patients (6 to 18 years)

The recommended dosage range for Tourette's Disorder is 5 to 20 mg/day.

For patients weighing less than 50 kg, dosing should be initiated at 2 mg/day with a target dose of 5 mg/day after 2 days. The dose can be increased to 10 mg/day in patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually at intervals of no less than 1 week.

For patients weighing 50 kg or more, dosing should be initiated at 2 mg/day for 2 days, and then increased to 5 mg/day for 5 days, with a target dose of 10 mg/day on day 8. The dose can be increased up to 20 mg/day for patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually in increments of 5 mg/day at intervals of no less than 1 week. *[see CLINICAL STUDIES (14.5)]*.

Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.6 Agitation Associated with Schizophrenia or Bipolar Mania (Intramuscular Injection)

Adults

The recommended dose in these patients is 9.75 mg. The recommended dosage range is 5.25 to 15 mg. No additional benefit was demonstrated for 15 mg compared to 9.75 mg. A lower dose of 5.25 mg may be considered when clinical factors warrant. If agitation warranting a second dose persists following the initial dose, cumulative doses up to a total of 30 mg/day may be given. However, the efficacy of repeated doses of ABILIFY injection in agitated patients has not been systematically evaluated in controlled clinical trials. The safety of total daily doses greater than 30 mg or injections given more frequently than every 2 hours have not been adequately evaluated in clinical trials *[see CLINICAL STUDIES (14. 6)]*.

If ongoing ABILIFY therapy is clinically indicated, oral ABILIFY in a range of 10 to 30 mg/day should replace ABILIFY injection as soon as possible *[see DOSAGE AND ADMINISTRATION (2.1 and 2.2)]*.

Administration of ABILIFY Injection

To administer ABILIFY Injection, draw up the required volume of solution into the syringe as shown in Table 1. Discard any unused portion.

Table 1: ABILIFY Injection Dosing Recommendations

Single-Dose	Required Volume of Solution
5.25 mg	0.7 mL
9.75 mg	1.3 mL
15 mg	2 mL

ABILIFY Injection is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.7 Dosage Adjustments for Cytochrome P450 Considerations

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 2). When the coadministered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, ABILIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response.

Table 2: Dose Adjustments for ABILIFY in Patients who are known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers

Factors	**Dosage Adjustments for ABILIFY**
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers taking concomitant strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer a quarter of usual dose
Strong CYP2D6 (e.g., quinidine, fluoxetine, paroxetine) **or** CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer half of usual dose
Strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers (e.g., carbamazepine, rifampin)	Double usual dose over 1 to 2 weeks

When adjunctive ABILIFY is administered to patients with major depressive disorder, ABILIFY should be administered without dosage adjustment as specified in *DOSAGE AND ADMINISTRATION (2.3)*.

2.8 Dosing of Oral Solution

The oral solution can be substituted for tablets on a mg-per-mg basis up to the 25 mg dose level. Patients receiving 30 mg tablets should receive 25 mg of the solution *[see CLINICAL PHARMACOLOGY (12.3)]*.

2.9 Dosing of Orally Disintegrating Tablets

The dosing for ABILIFY Orally Disintegrating Tablets is the same as for the oral tablets *[see DOSAGE AND ADMINISTRATION (2.1, 2.2, 2.3, and 2.4)]*.

3 DOSAGE FORMS AND STRENGTHS

ABILIFY® (aripiprazole) Tablets are available as described in Table 3.

Table 3: ABILIFY Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
2 mg	green modified rectangle	"A-006" and "2"
5 mg	blue modified rectangle	"A-007" and "5"
10 mg	pink modified rectangle	"A-008" and "10"
15 mg	yellow round	"A-009" and "15"
20 mg	white round	"A-010" and "20"
30 mg	pink round	"A-011" and "30"

ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets are available as described in Table 4.

Table 4: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
10 mg	pink (with scattered specks) round	"A" and "640" "10"
15 mg	yellow (with scattered specks) round	"A" and "641" "15"

ABILIFY® (aripiprazole) Oral Solution (1 mg/mL) is a clear, colorless to light-yellow solution, supplied in child-resistant bottles along with a calibrated oral dosing cup.

ABILIFY® (aripiprazole) Injection for Intramuscular Use is a clear, colorless solution available as a ready-to-use, 9.75 mg/1.3 mL (7.5 mg/mL) solution in clear, Type 1 glass vials.

4 CONTRAINDICATIONS

ABILIFY is contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis *[see ADVERSE REACTIONS (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Increased Mortality

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis *[see BOXED WARNING]*.

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease

In three, 10-week, placebo-controlled studies of ABILIFY in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the adverse reactions that were reported at an incidence of ≥3% and ABILIFY incidence at least twice that for placebo were lethargy [placebo 2%, ABILIFY 5%], somnolence (including sedation) [placebo 3%, ABILIFY 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, ABILIFY 5%], excessive salivation [placebo 0%, ABILIFY 4%], and lightheadedness [placebo 1%, ABILIFY 4%].

The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with ABILIFY, assess for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration *[see also BOXED WARNING]*.

5.2 Cerebrovascular Adverse Events, Including Stroke

In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse

events (e.g., stroke, transient ischemic attack), including fatalities, in ABILIFY-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with ABILIFY. ABILIFY is not approved for the treatment of patients with dementia-related psychosis *[see also BOXED WARNING]*.

5.3 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 5.

Table 5:

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, ie, beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for ABILIFY should be written for the smallest

quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

It should be noted that ABILIFY is not approved for use in treating depression in the pediatric population.

5.4 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including ABILIFY. Rare cases of NMS occurred during ABILIFY treatment in the worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.5 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia/Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with ABILIFY *[see ADVERSE REACTIONS (6.1, 6.2)]*. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Adults

In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in ABILIFY-treated patients (+4.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 6 shows the proportion of ABILIFY-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had treatment-emergent high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 6: Changes in Fasting Glucose From Placebo-Controlled Monotherapy Trials in Adult Patients

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	ABILIFY	31/822	3.8
		Placebo	22/605	3.6
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	ABILIFY	31/176	17.6
		Placebo	13/142	9.2

At 24 weeks, the mean change in fasting glucose in ABILIFY-treated patients was not significantly different than in placebo-treated patients [+2.2 mg/dL (n=42) and +9.6 mg/dL (n=28), respectively].

The mean change in fasting glucose in adjunctive ABILIFY-treated patients with major depressive disorder (+0.7 mg/dL; median exposure 42 days; N=241) was not significantly different than in placebo-treated patients (+0.8 mg/dL; median exposure 42 days; N=246). Table 7 shows the proportion of adult patients with changes in fasting glucose levels from two placebo-controlled, adjunctive trials (median exposure 42 days) in patients with major depressive disorder.

Table 7: Changes in Fasting Glucose From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	ABILIFY	2/201	1.0
		Placebo	2/204	1.0
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	ABILIFY	4/34	11.8
		Placebo	3/37	8.1

Pediatric Patients and Adolescents

In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years), the mean change in fasting glucose in ABILIFY-treated patients (+4.8 mg/dL; with a median exposure of 43 days; N=259) was not significantly different than in placebo-treated patients (+1.7 mg/dL; with a median exposure of 42 days; N=123).

In an analysis of two placebo-controlled trials in pediatric and adolescent patients with irritability associated with autistic disorder (6 to 17 years) with median exposure of 56 days, the mean change in fasting glucose in ABILIFY-treated patients (–0.2 mg/dL; N=83) was not significantly different than in placebo-treated patients (–0.6 mg/dL; N=33).

In an analysis of two placebo-controlled trials in pediatric and adolescent patients with Tourette's disorder (6 to 18 years) with median exposure of 57 days, the mean change in fasting glucose in ABILIFY-treated patients (0.79 mg/dL; N=90) was not significantly different than in placebo-treated patients (–1.66 mg/dL; N=58).

Table 8 shows the proportion of patients with changes in fasting glucose levels from the pooled adolescent schizophrenia and pediatric bipolar patients (median exposure of 42-43 days), from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder (median exposure of 56 days), and from the two placebo-controlled trials in pediatric patients (6 to 18 year) with Tourette's Disorder (median exposure 57 days).

Table 8: Changes in Fasting Glucose From Placebo-Controlled Trials in Pediatric and Adolescent Patients

Category Change (at least once) from Baseline	Indication	Treatment Arm	n/N	%
Fasting Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	Pooled Schizophrenia and Bipolar Disorder	ABILIFY	2/236	0.8
		Placebo	2/110	1.8
	Irritability Associated with Autistic Disorder	ABILIFY	0/73	0
		Placebo	0/32	0
	Tourette's Disorder	ABILIFY	3/88	3.4
		Placebo	1/58	1.7
Fasting Glucose Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Pooled Schizophrenia and Bipolar Disorder	ABILIFY	1/22	4.5
		Placebo	0/12	0
	Irritability Associated with Autistic Disorder	ABILIFY	0/9	0
		Placebo	0/1	0
	Tourette's Disorder	ABILIFY	0/11	0
		Placebo	0/4	0

At 12 weeks in the pooled adolescent schizophrenia and pediatric bipolar disorder trials, the mean change in fasting glucose in ABILIFY-treated patients was not significantly different than in placebo-treated patients [+2.4 mg/dL (n=81) and +0.1 mg/dL (n=15), respectively].

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

There were no significant differences between ABILIFY- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and

fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

Adults

Table 9 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21 to 25 days), fasting triglycerides (pooled from eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40 to 42 days).

Table 9: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	ABILIFY	34/1357	2.5
	Placebo	27/973	2.8
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	40/539	7.4
	Placebo	30/431	7.0
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	ABILIFY	2/332	0.6
	Placebo	2/268	0.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	121/1066	11.4
	Placebo	99/794	12.5

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

Table 10 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting), fasting triglycerides, fasting LDL cholesterol, and HDL cholesterol from two placebo-controlled adjunctive trials in adult patients with major depressive disorder (median exposure 42 days).

Table 10: Changes in Blood Lipid Parameters From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	ABILIFY	3/139	2.2
	Placebo	7/135	5.2
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	14/145	9.7
	Placebo	6/147	4.1
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	ABILIFY	0/54	0
	Placebo	0/73	0
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	17/318	5.3
	Placebo	10/286	3.5

Pediatric Patients and Adolescents

Table 11 shows the proportion of adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years) with changes in total cholesterol and HDL cholesterol (pooled from two placebo-controlled trials; median exposure 42 to 43 days) and fasting triglycerides (pooled from two placebo-controlled trials; median exposure 42 to 44 days).

Table 11: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients in Schizophrenia and Bipolar Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL)	ABILIFY	3/220	1.4
	Placebo	0/116	0
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	7/187	3.7
	Placebo	4/85	4.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	27/236	11.4
	Placebo	22/109	20.2

In monotherapy trials of adolescents with schizophrenia and pediatric patients with bipolar disorder, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 0/57 (0%) vs. 0/15 (0%); Fasting Triglycerides, 2/72 (2.8%) vs. 1/14 (7.1%), respectively; and at 24 weeks, Total

Cholesterol (fasting/nonfasting), 0/36 (0%) vs. 0/12 (0%); Fasting Triglycerides, 1/47 (2.1%) vs. 1/10 (10.0%), respectively.

Table 12 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 56 days) and HDL cholesterol (median exposure 55 to 56 days) from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder.

Table 12: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Pediatric Patients with Autistic Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL)	ABILIFY	1/95	1.1
	Placebo	0/34	0
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	0/75	0
	Placebo	0/30	0
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	9/107	8.4
	Placebo	5/49	10.2

Table 13 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 57 days) and HDL cholesterol (median exposure 57 days) from two placebo-controlled trials in pediatric patients (6 to 18 years) with Tourette's Disorder.

Table 13: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Pediatric Patients with Tourette's Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL)	ABILIFY	1/85	1.2
	Placebo	0/46	0
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	5/94	5.3
	Placebo	2/55	3.6
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	4/108	3.7
	Placebo	2/67	3.0

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Adults

In an analysis of 13 placebo-controlled monotherapy trials, primarily from pooled schizophrenia and bipolar disorder, with a median exposure of 21 to 25 days, the mean change in body weight in ABILIFY-treated patients was +0.3 kg (N=1673) compared to –0.1 kg (N=1100) in placebo-controlled patients. At 24 weeks, the mean change from baseline in body weight in ABILIFY-treated patients was –1.5 kg (n=73) compared to –0.2 kg (n=46) in placebo-treated patients.

In the trials adding ABILIFY to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive ABILIFY or placebo in addition to their ongoing antidepressant treatment. The mean change in body weight in patients receiving adjunctive ABILIFY was +1.7 kg (N=347) compared to +0.4 kg (N=330) in patients receiving adjunctive placebo.

Table 14 shows the percentage of adult patients with weight gain ≥7% of body weight by indication.

Table 14: Percentage of Patients From Placebo-Controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	Patients n (%)
Weight gain ≥7% of body weight	Schizophrenia[a]	ABILIFY	852	69 (8.1)
		Placebo	379	12 (3.2)
	Bipolar Mania[b]	ABILIFY	719	16 (2.2)
		Placebo	598	16 (2.7)
	Major Depressive Disorder (Adjunctive Therapy)[c]	ABILIFY	347	18 (5.2)
		Placebo	330	2 (0.6)

[a] 4-6 weeks duration. [b] 3 weeks duration. [c] 6 weeks duration.

Pediatric Patients and Adolescents

In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years) with median exposure of 42 to 43 days, the mean change in body weight in ABILIFY-treated patients was +1.6 kg (N=381) compared to +0.3 kg (N=187) in placebo-treated patients. At 24 weeks, the mean change from baseline in body weight in ABILIFY-treated patients was +5.8 kg (n=62) compared to +1.4 kg (n=13) in placebo-treated patients.

In two short-term, placebo-controlled trials in patients (6 to 17 years) with irritability associated with autistic disorder with median exposure of 56 days, the mean change in body weight in ABILIFY-treated patients was +1.6 kg (n=209) compared to +0.4 kg (n=98) in placebo-treated patients.

In two short-term, placebo-controlled trials in patients (6 to 18 years) with Tourette's Disorder with median exposure of 57 days, the mean change in body weight in ABILIFY-treated patients was +1.5 kg (n=105) compared to +0.4 kg (n=66) in placebo-treated patients.

Table 15 shows the percentage of pediatric and adolescent patients with weight gain ≥7% of body weight by indication.

Table 15: Percentage of Patients From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	Patients n (%)
Weight gain ≥7% of body weight	Pooled Schizophrenia and Bipolar Mania[a]	ABILIFY	381	20 (5.2)
		Placebo	187	3 (1.6)
	Irritability Associated with Autistic Disorder[b]	ABILIFY	209	55 (26.3)
		Placebo	98	7 (7.1)
	Tourette's Disorder[c]	ABILIFY	105	21 (20.0)
		Placebo	66	5 (7.6)

[a] 4-6 weeks duration. [b] 8 weeks duration. [c] 8-10 weeks duration.

In an open-label trial that enrolled patients from the two placebo-controlled trials of adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years), 73.2% of patients (238/325) completed 26 weeks of therapy with ABILIFY. After 26 weeks, 32.8% of patients gained ≥7% of their body weight, not adjusted for normal growth. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of pediatric patients and adolescents by comparisons to age- and gender-matched population standards. A z-score change <0.5 SD is considered not clinically significant. After 26 weeks, the mean change in z-score was 0.09 SD.

In an open-label trial that enrolled patients from two short-term, placebo-controlled trials, patients (6 to 17 years) with irritability associated with autistic disorder, as well as *de novo* patients, 60.3% (199/330) completed one year of therapy with ABILIFY. The mean change in weight z-score was 0.26 SDs for patients receiving >9 months of treatment.

When treating pediatric patients for any indication, weight gain should be monitored and assessed against that expected for normal growth.

5.7 Orthostatic Hypotension

ABILIFY may cause orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from short-term,

placebo-controlled trials of adult patients on oral ABILIFY (n=2467) included (ABILIFY incidence, placebo incidence) orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%); of pediatric patients 6 to 18 years of age (n=732) on oral ABILIFY included orthostatic hypotension (0.5%, 0%), postural dizziness (0.4%, 0 %), and syncope (0.2%, 0%); and of patients on ABILIFY Injection (n=501) included orthostatic hypotension (0.6%, 0%), postural dizziness (0.2%, 0.5%), and syncope (0.4%, 0%). *[see ADVERSE REACTIONS (6.1)]*

The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 bpm when comparing standing to supine values) for ABILIFY was not meaningfully different from placebo (ABILIFY incidence, placebo incidence): in adult oral ABILIFY-treated patients (4%, 2%), in pediatric oral ABILIFY-treated patients aged 6 to 18 years (0.4%, 1%), or in ABILIFY injection-treated patients (3%, 2%).

ABILIFY should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) *[see DRUG INTERACTIONS (7.1)]*.

If parenteral benzodiazepine therapy is deemed necessary in addition to ABILIFY injection treatment, patients should be monitored for excessive sedation and for orthostatic hypotension *[see DRUG INTERACTIONS (7.1)*].

5.8 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trials and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including ABILIFY. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of ABILIFY at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ABILIFY in patients with severe neutropenia (absolute neutrophil count <1000/mm3) and follow their WBC counts until recovery.

5.9 Seizures/Convulsions

In short-term, placebo-controlled trials, patients with a history of seizures excluded seizures/convulsions occurred in 0.1% (3/2467) of undiagnosed adult patients treated with oral ABILIFY, in 0.1% (1/732) of pediatric patients (6 to 18 years), and in 0.2% (1/501) of adult ABILIFY injection-treated patients.

As with other antipsychotic drugs, ABILIFY should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.10 Potential for Cognitive and Motor Impairment

ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (ABILIFY incidence, placebo incidence): in adult patients (n=2467) treated with oral ABILIFY (11%, 6%), in pediatric patients ages 6 to 17 (n=611) (24%, 6%), and in adult patients (n=501) on ABILIFY Injection (9%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients and 3% (20/732) of pediatric patients (6 to 18 years) on oral ABILIFY in short-term, placebo-controlled trials, but did not lead to discontinuation of any adult patients on ABILIFY Injection.

Despite the relatively modest increased incidence of these events compared to placebo, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

5.11 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ABILIFY for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) *[see ADVERSE REACTIONS (6.2)]*.

5.12 Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses, bipolar disorder, and major depressive disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose *[see ADVERSE REACTIONS (6.1, 6.2)]*.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. ABILIFY and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see WARNINGS AND PRECAUTIONS (5.1)* and *ADVERSE REACTIONS (6.2)]*.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*
- Cerebrovascular Adverse Events, Including Stroke *[see WARNINGS AND PRECAUTIONS (5.2)]*
- Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults *[see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.3)]*
- Neuroleptic Malignant Syndrome (NMS) *[see WARNINGS AND PRECAUTIONS (5.4)]*
- Tardive Dyskinesia *[see WARNINGS AND PRECAUTIONS (5.5)]*
- Metabolic Changes *[see WARNINGS AND PRECAUTIONS (5.6)]*
- Orthostatic Hypotension *[see WARNINGS AND PRECAUTIONS (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see WARNINGS AND PRECAUTIONS (5.8)]*
- Seizures/Convulsions *[see WARNINGS AND PRECAUTIONS (5.9)]*
- Potential for Cognitive and Motor Impairment *[see WARNINGS AND PRECAUTIONS (5.10)]*
- Body Temperature Regulation *[see WARNINGS AND PRECAUTIONS (5.11)]*
- Suicide *[see WARNINGS AND PRECAUTIONS (5.12)]*

- Dysphagia *[see WARNINGS AND PRECAUTIONS (5.13)]*

The most common adverse reactions in adult patients in clinical trials (≥10%) were nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness.

The most common adverse reactions in the pediatric clinical trials (≥10%) were somnolence, headache, vomiting, extrapyramidal disorder, fatigue, increased appetite, insomnia, nausea, nasopharyngitis, and weight increased.

ABILIFY has been evaluated for safety in 13,543 adult patients who participated in multiple-dose, clinical trials in schizophrenia, bipolar disorder, major depressive disorder, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7619 patient-years of exposure to oral ABILIFY and 749 patients with exposure to ABILIFY injection. A total of 3390 patients were treated with oral ABILIFY for at least 180 days and 1933 patients treated with oral ABILIFY had at least 1 year of exposure.

ABILIFY has been evaluated for safety in 1,686 patients (6 to 18 years) who participated in multiple-dose, clinical trials in schizophrenia, bipolar mania, autistic disorder, or Tourette's disorder and who had approximately 1,342 patient-years of exposure to oral ABILIFY. A total of 959 pediatric patients were treated with oral ABILIFY for at least 180 days and 556 pediatric patients treated with oral ABILIFY had at least 1 year of exposure.

The conditions and duration of treatment with ABILIFY (monotherapy and adjunctive therapy with antidepressants or mood stabilizers) included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure.

6.1 Clinical Trials Experience

Adult Patients with Schizophrenia

The following findings are based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which oral ABILIFY was administered in doses ranging from 2 to 30 mg/day.

Commonly Observed Adverse Reactions

The only commonly observed adverse reaction associated with the use of ABILIFY in patients with schizophrenia (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) was akathisia (ABILIFY 8%; placebo 4%).

Adult Patients with Bipolar Mania

Monotherapy

The following findings are based on a pool of 3-week, placebo-controlled, bipolar mania trials in which oral ABILIFY was administered at doses of 15 or 30 mg/day.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of ABILIFY in patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 16.

Table 16: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Adult Patients with Bipolar Mania Treated with Oral ABILIFY Monotherapy

	Percentage of Patients Reporting Reaction	
Preferred Term	**ABILIFY (n=917)**	**Placebo (n=753)**
Akathisia	13	4
Sedation	8	3
Restlessness	6	3
Tremor	6	3
Extrapyramidal Disorder	5	2

Less Common Adverse Reactions in Adults

Table 17 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those reactions that occurred in 2% or more of patients treated with ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo in the combined dataset.

Table 17: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**ABILIFY (n=1843)**	**Placebo (n=1166)**
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4

Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2

[a] Adverse reactions reported by at least 2% of patients treated with oral ABILIFY, except adverse reactions which had an incidence equal to or less than placebo.

An examination of population subgroups did not reveal any clear evidence of differential adverse reaction incidence on the basis of age, gender, or race.

Adult Patients with Adjunctive Therapy with Bipolar Mania

The following findings are based on a placebo-controlled trial of adult patients with bipolar disorder in which ABILIFY was administered at doses of 15 or 30 mg/day as adjunctive therapy with lithium or valproate.

Adverse Reactions Associated with Discontinuation of Treatment

In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 12% for patients treated with adjunctive ABILIFY compared to 6% for patients treated with adjunctive placebo. The most common adverse drug reactions associated with discontinuation in the adjunctive ABILIFY-treated compared to placebo-treated patients were akathisia (5% and 1%, respectively) and tremor (2% and 1%, respectively).

Commonly Observed Adverse Reactions

The commonly observed adverse reactions associated with adjunctive ABILIFY and lithium or valproate in patients with bipolar mania (incidence of 5% or greater and incidence at least twice that for adjunctive placebo) were: akathisia, insomnia, and extrapyramidal disorder.

Less Common Adverse Reactions in Adult Patients with Adjunctive Therapy in Bipolar Mania

Table 18 enumerates the incidence, rounded to the nearest percent, of adverse reactions that occurred during acute treatment (up to 6 weeks), including only those reactions that occurred in 2% or more of patients treated with adjunctive ABILIFY (doses of 15 or 30 mg/day) and lithium or valproate and for which the incidence in patients treated with this combination was greater than the incidence in patients treated with placebo plus lithium or valproate.

Table 18: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of Adjunctive Therapy in Patients with Bipolar Disorder

	Percentage of Patients Reporting Reaction[a]	
System Organ Class Preferred Term	**ABILIFY + Li or Val* (n=253)**	**Placebo + Li or Val* (n=130)**
Gastrointestinal Disorders		
Nausea	8	5
Vomiting	4	0
Salivary Hypersecretion	4	2
Dry Mouth	2	1
Infections and Infestations		
Nasopharyngitis	3	2
Investigations		
Weight Increased	2	1
Nervous System Disorders		
Akathisia	19	5
Tremor	9	6
Extrapyramidal Disorder	5	1
Dizziness	4	1
Sedation	4	2
Psychiatric Disorders		
Insomnia	8	4
Anxiety	4	1
Restlessness	2	1

[a] Adverse reactions reported by at least 2% of patients treated with oral ABILIFY, except adverse reactions which had an incidence equal to or less than placebo.

* Lithium or Valproate

Pediatric Patients (13 to 17 years) with Schizophrenia

The following findings are based on one 6-week, placebo-controlled trial in which oral ABILIFY was administered in doses ranging from 2 to 30 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions between ABILIFY-treated and placebo-treated pediatric patients (13 to 17 years) was 5% and 2%, respectively.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of ABILIFY in adolescent patients with schizophrenia (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) were extrapyramidal disorder, somnolence, and tremor.

Pediatric Patients (10 to 17 years) with Bipolar Mania

The following findings are based on one 4-week, placebo-controlled trial in which oral ABILIFY was administered in doses of 10 or 30 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions between ABILIFY-treated and placebo-treated pediatric patients (10 to 17 years) was 7% and 2%, respectively.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of ABILIFY in pediatric patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 19.

Table 19: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (10 to 17 years) with Bipolar Mania Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction	
Preferred Term	**ABILIFY (n=197)**	**Placebo (n=97)**
Somnolence	23	3
Extrapyramidal Disorder	20	3
Fatigue	11	4
Nausea	11	4
Akathisia	10	2
Blurred Vision	8	0
Salivary Hypersecretion	6	0
Dizziness	5	1

Pediatric Patients (6 to 17 years) with Autistic Disorder

The following findings are based on two 8-week, placebo-controlled trials in which oral ABILIFY was administered in doses of 2 to 15 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions between ABILIFY-treated and placebo-treated pediatric patients (6 to 17 years) was 10% and 8%, respectively.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of ABILIFY in pediatric patients with autistic disorder (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 20.

Table 20: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 17 years) with Autistic Disorder Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction	
Preferred Term	**ABILIFY (n=212)**	**Placebo (n=101)**
Sedation	21	4
Fatigue	17	2
Vomiting	14	7
Somnolence	10	4
Tremor	10	0
Pyrexia	9	1
Drooling	9	0
Decreased Appetite	7	2
Salivary Hypersecretion	6	1
Extrapyramidal Disorder	6	0
Lethargy	5	0

Pediatric Patients (6 to 18 years) with Tourette's Disorder

The following findings are based on one 8-week and one 10-week, placebo-controlled trials in which oral ABILIFY was administered in doses of 2 to 20 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions between ABILIFY-treated and placebo-treated pediatric patients (6 to 18 years) was 7% and 1%, respectively.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of ABILIFY in pediatric patients with Tourette's disorder (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 21.

Table 21: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) with Tourette's Disorder Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction	
Preferred Term	**ABILIFY (n=121)**	**Placebo (n=72)**
Sedation	13	6
Somnolence	13	1
Nausea	11	4
Headache	10	3
Nasopharyngitis	9	0
Fatigue	8	0
Increased Appetite	7	1

Less Common Adverse Reactions in Pediatric Patients (6 to 18 years) with Schizophrenia, Bipolar Mania, Autistic Disorder, or Tourette's Disorder

Table 22 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia, up to 4 weeks in bipolar mania, up to 8 weeks in autistic disorder, and up to 10 weeks in Tourette's disorder), including only those reactions that occurred in 2% or more of pediatric patients treated with ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo.

Table 22: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**ABILIFY (n=732)**	**Placebo (n=370)**
Eye Disorders		
Blurred Vision	3	0
Gastrointestinal Disorders		
Abdominal Discomfort	2	1
Vomiting	8	7
Nausea	8	4
Diarrhea	4	3
Salivary Hypersecretion	4	1
Abdominal Pain Upper	3	2

Constipation	2	2
General Disorders and Administration Site Conditions		
Fatigue	10	2
Pyrexia	4	1
Irritability	2	1
Asthenia	2	1
Infections and Infestations		
Nasopharyngitis	6	3
Investigations		
Weight Increased	3	1
Metabolism and Nutrition Disorders		
Increased Appetite	7	3
Decreased Appetite	5	4
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	2	1
Muscle Rigidity	2	1
Nervous System Disorders		
Somnolence	16	4
Headache	12	10
Sedation	9	2
Tremor	9	1
Extrapyramidal Disorder	6	1
Akathisia	6	4
Drooling	3	0
Lethargy	3	0
Dizziness	3	2
Dystonia	2	1
Respiratory, Thoracic, and Mediastinal Disorders		
Epistaxis	2	1
Skin and Subcutaneous Tissue Disorders		
Rash	2	1

[a] Adverse reactions reported by at least 2% of pediatric patients treated with oral ABILIFY, except adverse reactions which had an incidence equal to or less than placebo.

Adult Patients Receiving ABILIFY as Adjunctive Treatment of Major Depressive Disorder

The following findings are based on a pool of two placebo-controlled trials of patients with major depressive disorder in which ABILIFY was administered at doses of 2 mg to 20 mg as adjunctive treatment to continued antidepressant therapy.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions was 6% for adjunctive ABILIFY-treated patients and 2% for adjunctive placebo-treated patients.

Commonly Observed Adverse Reactions

The commonly observed adverse reactions associated with the use of adjunctive ABILIFY in patients with major depressive disorder (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) were: akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision.

Less Common Adverse Reactions in Adult Patients with Major Depressive Disorder

Table 23 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks), including only those adverse reactions that occurred in 2% or more of patients treated with adjunctive ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with adjunctive ABILIFY was greater than the incidence in patients treated with adjunctive placebo in the combined dataset.

Table 23: Adverse Reactions in Short-Term, Placebo-Controlled Adjunctive Trials in Patients with Major Depressive Disorder

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**ABILIFY + ADT*** **(n=371)**	**Placebo + ADT*** **(n=366)**
Eye Disorders		
Blurred Vision	6	1
Gastrointestinal Disorders		
Constipation	5	2
General Disorders and Administration Site Conditions		
Fatigue	8	4
Feeling Jittery	3	1
Infections and Infestations		
Upper Respiratory Tract Infection	6	4
Investigations		
Weight Increased	3	2
Metabolism and Nutrition Disorders		
Increased Appetite	3	2
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	4	3
Myalgia	3	1
Nervous System Disorders		
Akathisia	25	4
Somnolence	6	4
Tremor	5	4

Sedation	4	2
Dizziness	4	2
Disturbance in Attention	3	1
Extrapyramidal Disorder	2	0
Psychiatric Disorders		
Restlessness	12	2
Insomnia	8	2

[a] Adverse reactions reported by at least 2% of patients treated with adjunctive ABILIFY, except adverse reactions which had an incidence equal to or less than placebo.
* Antidepressant Therapy

Patients with Agitation Associated with Schizophrenia or Bipolar Mania (Intramuscular Injection)

The following findings are based on a pool of three placebo-controlled trials of patients with agitation associated with schizophrenia or bipolar mania in which ABILIFY injection was administered at doses of 5.25 mg to 15 mg.

Commonly Observed Adverse Reactions

There was one commonly observed adverse reaction (nausea) associated with the use of ABILIFY injection in patients with agitation associated with schizophrenia and bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo).

Less Common Adverse Reactions in Patients with Agitation Associated with Schizophrenia or Bipolar Mania

Table 24 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (24-hour), including only those adverse reactions that occurred in 2% or more of patients treated with ABILIFY injection (doses ≥5.25 mg/day) and for which the incidence in patients treated with ABILIFY injection was greater than the incidence in patients treated with placebo in the combined dataset.

Table 24: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Patients Treated with ABILIFY Injection

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**ABILIFY** **(n=501)**	**Placebo** **(n=220)**
Cardiac Disorders		
Tachycardia	2	<1
Gastrointestinal Disorders		
Nausea	9	3
Vomiting	3	1
General Disorders and Administration Site Conditions		
Fatigue	2	1
Nervous System Disorders		

Headache	12	7
Dizziness	8	5
Somnolence	7	4
Sedation	3	2
Akathisia	2	0

[a] Adverse reactions reported by at least 2% of patients treated with ABILIFY injection, except adverse reactions which had an incidence equal to or less than placebo.

Dose-Related Adverse Reactions

Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with schizophrenia comparing various fixed doses (2, 5, 10, 15, 20, and 30 mg/day) of oral ABILIFY to placebo. This analysis, stratified by study, indicated that the only adverse reaction to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence [including sedation]; (incidences were placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

In the study of pediatric patients (13 to 17 years of age) with schizophrenia, three common adverse reactions appeared to have a possible dose response relationship: extrapyramidal disorder (incidences were placebo, 5.0%; 10 mg, 13.0%; 30 mg, 21.6%); somnolence (incidences were placebo, 6.0%; 10 mg, 11.0%; 30 mg, 21.6%); and tremor (incidences were placebo, 2.0%; 10 mg, 2.0%; 30 mg, 11.8%).

Bipolar Mania

In the study of pediatric patients (10 to 17 years of age) with bipolar mania, four common adverse reactions had a possible dose response relationship at 4 weeks; extrapyramidal disorder (incidences were placebo, 3.1%; 10 mg, 12.2%; 30 mg, 27.3%); somnolence (incidences were placebo, 3.1%; 10 mg, 19.4%; 30 mg, 26.3%); akathisia (incidences were placebo, 2.1%; 10 mg, 8.2%; 30 mg, 11.1%); and salivary hypersecretion (incidences were placebo, 0%; 10 mg, 3.1%; 30 mg, 8.1%).

Autistic Disorder

In a study of pediatric patients (6 to 17 years of age) with autistic disorder, one common adverse reaction had a possible dose response relationship: fatigue (incidences were placebo, 0%; 5 mg, 3.8%; 10 mg, 22.0%; 15 mg, 18.5%).

Tourette's Disorder

In a study of pediatric patients (7 to 17 years of age) with Tourette's disorder, no common adverse reaction(s) had a dose response relationship.

Extrapyramidal Symptoms

Schizophrenia

In short-term, placebo-controlled trials in schizophrenia in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for ABILIFY-treated patients was 8% vs. 4% for placebo. In the short-term, placebo-controlled trial of schizophrenia in pediatric patients (13 to 17 years), the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated patients was 25% vs. 7% for placebo; and the incidence of akathisia-related events for ABILIFY-treated patients was 9% vs. 6% for placebo.

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias). In the adult schizophrenia trials, the objectively collected data did not show a difference between ABILIFY and placebo, with the exception of the Barnes Akathisia Scale (ABILIFY, 0.08; placebo, –0.05). In the pediatric (13 to 17 years) schizophrenia trial, the objectively collected data did not show a difference between ABILIFY and placebo, with the exception of the Simpson Angus Rating Scale (ABILIFY, 0.24; placebo, –0.29).

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in adults, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between ABILIFY and placebo.

Bipolar Mania

In the short-term, placebo-controlled trials in bipolar mania in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for monotherapy ABILIFY-treated patients was 16% vs. 8% for placebo and the incidence of akathisia-related events for monotherapy ABILIFY-treated patients was 13% vs. 4% for placebo. In the 6-week, placebo-controlled trial in bipolar mania for adjunctive therapy with lithium or valproate, the incidence of reported EPS-related events, excluding events related to akathisia for adjunctive ABILIFY-treated patients was 15% vs. 8% for adjunctive placebo and the incidence of akathisia-related events for adjunctive ABILIFY-treated patients was 19% vs. 5% for adjunctive placebo. In the short-term, placebo-controlled trial in bipolar mania in pediatric (10 to 17 years) patients, the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated patients was 26% vs. 5% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 10% vs. 2% for placebo.

In the adult bipolar mania trials with monotherapy ABILIFY, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between ABILIFY and placebo (ABILIFY, 0.50; placebo, –0.01 and ABILIFY, 0.21; placebo, –0.05). Changes in the Assessments of Involuntary Movement Scales were similar for the ABILIFY and placebo groups. In the bipolar mania trials with ABILIFY as adjunctive therapy with either lithium or valproate, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive ABILIFY and adjunctive placebo (ABILIFY, 0.73; placebo, 0.07 and ABILIFY, 0.30; placebo, 0.11). Changes in the Assessments of Involuntary Movement Scales were similar for adjunctive ABILIFY and adjunctive placebo. In the pediatric (10 to 17 years), short-term, bipolar mania trial, the Simpson Angus Rating Scale showed a significant difference between ABILIFY and placebo (ABILIFY, 0.90; placebo, −0.05). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the ABILIFY and placebo groups.

Major Depressive Disorder

In the short-term, placebo-controlled trials in major depressive disorder, the incidence of reported EPS-related events, excluding events related to akathisia, for adjunctive ABILIFY-treated patients was 8% vs. 5% for adjunctive placebo-treated patients; and the incidence of akathisia-related events for adjunctive ABILIFY-treated patients was 25% vs. 4% for adjunctive placebo-treated patients.

In the major depressive disorder trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive ABILIFY and adjunctive placebo (ABILIFY, 0.31; placebo, 0.03 and ABILIFY, 0.22; placebo, 0.02). Changes in the Assessments of Involuntary Movement Scales were similar for the adjunctive ABILIFY and adjunctive placebo groups.

Autistic Disorder

In the short-term, placebo-controlled trials in autistic disorder in pediatric patients (6 to 17 years), the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated patients was 18% vs. 2% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 3% vs. 9% for placebo.

In the pediatric (6 to 17 years) short-term autistic disorder trials, the Simpson Angus Rating Scale showed a significant difference between ABILIFY and placebo (ABILIFY, 0.1; placebo, –0.4). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the ABILIFY and placebo groups.

Tourette's Disorder

In the short-term, placebo-controlled trials in Tourette's disorder in pediatric patients (6 to 18 years), the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated patients was 7% vs. 6% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 4% vs. 6% for placebo.

In the pediatric (6 to 18 years) short-term Tourette's disorder trials, changes in the Simpson Angus Rating Scale, Barnes Akathisia Scale and Assessments of Involuntary Movement Scale were not clinically meaningfully different for ABILIFY and placebo.

Agitation Associated with Schizophrenia or Bipolar Mania

In the placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for ABILIFY-treated patients was 2% vs. 2% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 2% vs. 0% for placebo. Objectively collected data on the Simpson Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) for all treatment groups did not show a difference between ABILIFY and placebo.

Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Additional Findings Observed in Clinical Trials

Adverse Reactions in Long-Term, Double-Blind, Placebo-Controlled Trials

The adverse reactions reported in a 26-week, double-blind trial comparing oral ABILIFY and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for ABILIFY vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 $\leq$49 days), and were of limited duration (7/12 $\leq$10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52 week), active-controlled study, the incidence of tremor was 5% (40/859) for ABILIFY. A

similar profile was observed in a long-term monotherapy study and a long-term adjunctive study with lithium and valproate in bipolar disorder.

Other Adverse Reactions Observed During the Premarketing Evaluation of ABILIFY

The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients:

Adults - Oral Administration

Blood and Lymphatic System Disorders:

rare - thrombocytopenia

Cardiac Disorders:

infrequent – bradycardia, palpitations, *rare* – atrial flutter, cardio-respiratory arrest, atrioventricular block, atrial fibrillation, angina pectoris, myocardial ischemia, myocardial infarction, cardiopulmonary failure

Eye Disorders:

infrequent – photophobia; *rare* - diplopia

Gastrointestinal Disorders:

infrequent - gastroesophageal reflux disease

General Disorders and Administration Site Conditions:

frequent - asthenia; *infrequent* – peripheral edema, chest pain; *rare* – face edema

Hepatobiliary Disorders:

rare - hepatitis, jaundice

Immune System Disorders:

rare- hypersensitivity

Injury, Poisoning, and Procedural Complications:

infrequent– fall; *rare* – heat stroke

Investigations:

frequent - weight decreased, *infrequent* - hepatic enzyme increased, blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transferase increased; *rare* – blood prolactin increased, blood urea inceased, blood creatinine increased, blood bilirubin increased, electrocardiogram QT prolonged, glycosylated hemoglobin increased

Metabolism and Nutrition Disorders:

frequent –anorexia; *infrequent* - *rare* - hypokalemia, hyponatremia, hypoglycemia

Musculoskeletal and Connective Tissue Disorders:

infrequent - muscular weakness, muscle tightness; *rare* – rhabdomyolysis, mobility decreased

Nervous System Disorders:

infrequent - parkinsonism, memory impairment, cogwheel rigidity, hypokinesia, myoclonus, bradykinesia; *rare* – akinesia, myoclonus, coordination abnormal, speech disorder, Grand Mal convulsion; *<1/10,000 patients* - choreoathetosis

Psychiatric Disorders:

infrequent – aggression, loss of libido, delirium; *rare* – libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking

Renal and Urinary Disorders:

rare - urinary retention, nocturia

Reproductive System and Breast Disorders:

infrequent - erectile dysfunction; *rare* – gynaecomastia, menstruation irregular, amenorrhea, breast pain, priapism

Respiratory, Thoracic, and Mediastinal Disorders:

infrequent - nasal congestion, dyspnea

Skin and Subcutaneous Tissue Disorders:

infrequent - rash, hyperhidrosis, pruritus, photosensitivity reaction, alopecia; *rare* - urticaria

Vascular Disorders:

infrequent – hypotension, hypertension

Pediatric Patients - Oral Administration

Most adverse events observed in the pooled database of 1,686 pediatric patients, aged 6 to 18 years, were also observed in the adult population. Additional adverse reactions observed in the pediatric population are listed below.

Eye Disorders

infrequent - oculogyric crisis

Gastrointestinal Disorders:

infrequent -tongue dry, tongue spasm

Investigations:

frequent - blood insulin increased

Nervous System Disorders:

infrequent - sleep talking

Renal and Urinary Disorders

frequent – enuresis

Skin and Subcutaneous Tissue Disorders:

infrequent - hirsutism

Adults - Intramuscular Injection

Most adverse reactions observed in the pooled database of 749 adult patients treated with ABILIFY injection, were also observed in the adult population treated with oral ABILIFY. Additional adverse reactions observed in the ABILIFY injection population are listed below.

General Disorders and Administration Site Conditions:

≥1/100 patients - injection site reaction; *≥1/1000 patients and <1/100 patients* - venipuncture site bruise

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ABILIFY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), and blood glucose fluctuation.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with ABILIFY

Table 25: Clinically Important Drug Interactions with ABILIFY:

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Strong CYP3A4 Inhibitors (e.g., itraconazole, clarithromycin) or strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine)	The concomitant use of ABILIFY with strong CYP 3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of ABILIFY alone *[see CLINICAL PHARMACOLOGY (12.3)]*.	With concomitant use of ABILIFY with a strong CYP3A4 inhibitor or CYP2D6 inhibitor, reduce the ABILIFY dosage *[see DOSAGE AND ADMINISTRATION (2.7)]*.
Strong CYP3A4 Inducers (e.g., carbamazepine, rifampin)	The concomitant use of ABILIFY and carbamazepine decreased the exposure of aripiprazole compared to the use of ABILIFY alone *[see CLINICAL PHARMACOLOGY (12.3)]*.	With concomitant use of ABILIFY with a strong CYP3A4 inducer, consider increasing the ABILIFY dosage *[see DOSAGE AND ADMINISTRATION (2.7)]*.
Antihypertensive Drugs	Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.	Monitor blood pressure and adjust dose accordingly *[see WARNINGS AND PRECAUTIONS (5.7)]*.
Benzodiazepines (e.g., lorazepam)	The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone *[see WARNINGS AND PRECAUTIONS (5.7)]*	Monitor sedation and blood pressure. Adjust dose accordingly.

7.2 Drugs Having No Clinically Important Interactions with ABILIFY

Based on pharmacokinetic studies, no dosage adjustment of ABILIFY is required when administered concomitantly with famotidine, valproate, lithium, lorazepam.

In addition, no dosage adjustment is necessary for substrates of CYP2D6 (e.g., dextromethorphan, fluoxetine, paroxetine, or venlafaxine), CYP2C9 (e.g., warfarin), CYP2C19 (e.g., omeprazole, warfarin, escitalopram), or CYP3A4 (e.g., dextromethorphan) when co-administered with ABILIFY. Additionally, no dosage adjustment is necessary for valproate, lithium, lamotrigine, lorazepam, or sertraline when co-administered with ABILIFY. *[see CLINICAL PHARMACOLOGY (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ABILIFY during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs (including ABILIFY) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. Adequate and well controlled studies with ABILIFY have not been conducted in pregnant women. Animal reproduction studies were conducted with aripiprazole in rats and rabbits during organogenesis, and in rats during the pre-and post-natal period. Oral and intravenous aripiprazole administration during organogenesis in rats and/or rabbits at doses higher than the maximum recommended human dose (MRHD) produced fetal death, decreased fetal weight, undescended testicles, delayed skeletal ossification, skeletal abnormalities, and diaphragmatic hernia. Oral and intravenous aripiprazole administration during the pre- and post-natal period in rats at doses higher than the maximum recommended human dose (MRHD) produced prolonged gestation, stillbirths, decreased pup weight, and decreased pup survival. Administer ABILIFY during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs (including ABILIFY) during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms.

Data

Animal Data

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg/day. Treatment at the high dose of 30 mg/kg/day caused a slight delay in fetal development (decreased fetal weight), undescended testes, and delayed skeletal ossification (also seen at 10 mg/kg/day). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 and 30 mg/kg/day), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg/day and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg/day. Some maternal toxicity was seen at 30 mg/kg/day however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rats receiving aripiprazole injection intravenously (3, 9, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose where it also caused maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30 , and 100 mg/kg/day (2 , 3, and 11 times human exposure at MRHD based on AUC and 6, 19 , and 65 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. At the high dose of 100 mg/kg/day decreased maternal food consumption, and increased abortions were seen as well as increased fetal mortality, decreased fetal weight (also seen at 30 mg/kg/day), increased incidence of a skeletal abnormality (fused sternebrae) (also seen at 30 mg/kg/day).

In pregnant rabbits receiving aripiprazole injection intravenously (3, 10, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg/day, which is 5 times the human exposure at the MRHD based on AUC and is 6 times the MRHD based on mg/m2.

In a study in which rats were treated peri- and post-natally with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m2 basis) of aripiprazole from gestation day 17 through day 21 postpartum, slight maternal toxicity, slightly prolonged gestation an increase in stillbirths and, decreases in pup weight (persisting into adulthood) and survival were seen at 30 mg/kg/day.

In rats receiving aripiprazole injection intravenously (3, 8, and 20 mg/kg/day) from gestation day 6 through day 20 postpartum, an increase in stillbirths was seen at 8 and 20 mg/kg/day, and decreases in early postnatal pup weights and survival were seen at 20 mg/kg/day; these effects were seen in presence of maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

8.3 Nursing Mothers

ABILIFY is present in human breast milk. Because of the potential for serious adverse reactions in nursing infants from ABILIFY, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients with major depressive disorder or agitation associated with schizophrenia or bipolar mania have not been established.

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in pediatric patients, 10 to 17 years of age, were similar to those in adults after correcting for the differences in body weight *[see CLINICAL PHARMACOLOGY (12.3)]*.

Schizophrenia

Safety and effectiveness in pediatric patients with schizophrenia were established in a 6-week, placebo-controlled clinical trial in 202 pediatric patients aged 13 to 17 years *[see DOSAGE AND ADMINISTRATION (2.1)*, *ADVERSE REACTIONS (6.1)*, and *CLINICAL STUDIES (14.1)*]. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Bipolar I Disorder

Safety and effectiveness in pediatric patients with bipolar mania were established in a 4-week, placebo-controlled clinical trial in 197 pediatric patients aged 10 to 17 years *[see DOSAGE AND ADMINISTRATION (2.2), ADVERSE REACTIONS (6.1), and CLINICAL STUDIES (14.2)]*. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

The efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes in pediatric patients has not been systematically evaluated. However, such efficacy and lack of pharmacokinetic interaction between aripiprazole and lithium or valproate can be extrapolated from adult data, along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Irritability Associated with Autistic Disorder

Safety and effectiveness in pediatric patients demonstrating irritability associated with autistic disorder were established in two 8-week, placebo-controlled clinical trials in 212 pediatric patients aged 6 to 17 years *[see INDICATIONS AND USAGE (1), DOSAGE AND ADMINISTRATION (2.4), ADVERSE REACTIONS (6.1), and CLINICAL STUDIES (14.4)]*. A maintenance trial was conducted in pediatric patients (6 to 17 years of age) with irritability associated with autistic disorder. The first phase of this trial was an open-label, flexibly dosed (aripiprazole 2 to 15 mg/day) phase in which patients were stabilized (defined as > 25% improvement on the ABC-I subscale, and a CGI-I rating of "much improved" or "very much improved") on ABILIFY for 12 consecutive weeks. Overall, 85 patients were stabilized and entered the second, 16-week, double-blind phase where they were randomized to either continue ABILIFY treatment or switch to placebo. In this trial, the efficacy of ABILIFY for the maintenance treatment of irritability associated with autistic disorder was not established.

Tourette's Disorder

Safety and effectiveness of aripiprazole in pediatric patients with Tourette's Disorder were established in one 8-week (aged 7 to 17) and one 10-week trial (aged 6 to 18) in 194 pediatric patients *[see DOSAGE AND ADMINISTRATION (2.5), ADVERSE REACTIONS (6.1), and CLINICAL STUDIES (14.5)]*. Maintenance efficacy in pediatric patients has not been systematically evaluated.

Juvenile Animal Studies

Aripiprazole in juvenile rats caused mortality, CNS clinical signs, impaired memory and learning, and delayed sexual maturation when administered at oral doses of 10, 20,

40 mg/kg/day from weaning (21 days old) through maturity (80 days old). At 40 mg/kg/day, mortality, decreased activity, splayed hind limbs, hunched posture, ataxia, tremors and other CNS signs were observed in both genders. In addition, delayed sexual maturation was observed in males. At all doses and in a dose-dependent manner, impaired memory and learning, increased motor activity, and histopathology changes in the pituitary (atrophy), adrenals (adrenocortical hypertrophy), mammary glands (hyperplasia and increased secretion), and female reproductive organs (vaginal mucification, endometrial atrophy, decrease in ovarian corpora lutea) were observed. The changes in female reproductive organs were considered secondary to the increase in prolactin serum levels. A No Observed Adverse Effect Level (NOAEL) could not be determined and, at the lowest tested dose of 10 mg/kg/day, there is no safety margin relative to the systemic exposures (AUC0-24) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period, and most of the drug effects in juvenile rats were also observed in adult rats from previously conducted studies.

Aripiprazole in juvenile dogs (2 months old) caused CNS clinical signs of tremors, hypoactivity, ataxia, recumbency and limited use of hind limbs when administered orally for 6 months at 3, 10, 30 mg/kg/day. Mean body weight and weight gain were decreased up to 18% in females in all drug groups relative to control values. A NOAEL could not be determined and, at the lowest tested dose of 3 mg/kg/day, there is no safety margin relative to the systemic exposures (AUC0-24) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period.

8.5 Geriatric Use

No dosage adjustment is recommended for elderly patients *[see also BOXED WARNING, WARNINGS AND PRECAUTIONS (5.1), and CLINICAL PHARMACOLOGY (12.3)]*.

Of the 13,543 patients treated with oral ABILIFY in clinical trials, 1073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. Placebo-controlled studies of oral ABILIFY in schizophrenia, bipolar mania, or major depressive disorder did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Of the 749 patients treated with ABILIFY injection in clinical trials, 99 (13%) were ≥65 years old and 78 (10%) were ≥75 years old. Placebo-controlled studies of ABILIFY injection in patients with agitation associated with schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ABILIFY is not approved for the treatment of patients with psychosis associated with Alzheimer's disease *[see also BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*.

8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see DOSAGE AND ADMINISTRATION (2.7) and CLINICAL PHARMACOLOGY (12.3)]*.

8.7 Hepatic and Renal Impairment

No dosage adjustment for ABILIFY is required on the basis of a patient's hepatic function (mild to severe hepatic impairment, Child-Pugh score between 5 and 15), or renal function (mild to severe renal impairment, glomerular filtration rate between 15 and 90 mL/minute) *[see CLINICAL PHARMACOLOGY (12.3)]*.

8.8 Other Specific Populations

No dosage adjustment for ABILIFY is required on the basis of a patient's sex, race, or smoking status *[see CLINICAL PHARMACOLOGY (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ABILIFY is not a controlled substance.

9.2 Abuse and Dependence

ABILIFY has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

MedDRA terminology has been used to classify the adverse reactions.

10.1 Human Experience

In clinical trials and in postmarketing experience, adverse reactions of deliberate or accidental overdosage with oral ABILIFY have been reported worldwide. These include overdoses with oral ABILIFY alone and in combination with other substances. No fatality was reported with ABILIFY alone. The largest known dose with a known outcome involved acute ingestion of 1260 mg of oral ABILIFY (42 times the maximum recommended daily dose) by a patient who fully recovered. Deliberate or accidental overdosage was also reported in children (age 12 and younger) involving oral ABILIFY ingestions up to 195 mg with no fatalities.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral ABILIFY overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with ABILIFY overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

10.2 Management of Overdosage

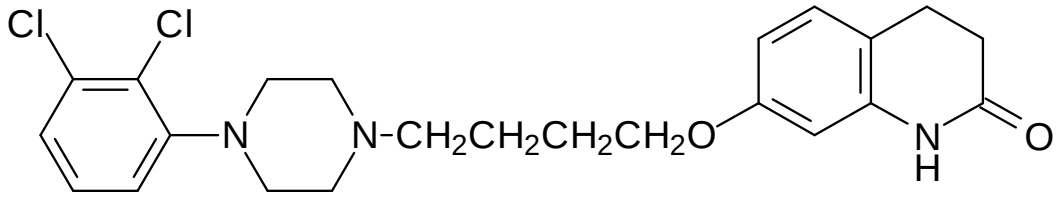
No specific information is available on the treatment of overdose with ABILIFY. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal: In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15 mg oral dose of ABILIFY, decreased the mean AUC and Cmax of aripiprazole by 50%.

Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with ABILIFY, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

11 DESCRIPTION

Aripiprazole is a psychotropic drug that is available as ABILIFY® (aripiprazole) Tablets, ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets, ABILIFY® (aripiprazole) Oral Solution, and ABILIFY® (aripiprazole) Injection, a solution for intramuscular injection. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. The empirical formula is C23H27Cl2N3O2 and its molecular weight is 448.38. The chemical structure is:



ABILIFY Tablets are available in 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg strengths. Inactive ingredients include cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

ABILIFY DISCMELT Orally Disintegrating Tablets are available in 10 mg and 15 mg strengths. Inactive ingredients include acesulfame potassium, aspartame, calcium silicate, croscarmellose sodium, crospovidone, crème de vanilla (natural and artificial flavors), magnesium stearate, microcrystalline cellulose, silicon dioxide, tartaric acid, and xylitol. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

ABILIFY Oral Solution is a clear, colorless to light-yellow solution available in a concentration of 1 mg/mL. The inactive ingredients for this solution include disodium edetate, fructose, glycerin, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose, and purified water. The oral solution is flavored with natural orange cream and other natural flavors.

ABILIFY Injection is available in single-dose vials as a ready-to-use, 9.75 mg/1.3 mL (7.5 mg/mL) clear, colorless, sterile, aqueous solution for intramuscular use only. Inactive ingredients for this solution include 199.5mg of sulfobutylether β-cyclodextrin (SBECD), 10.4 mg of tartaric acid, qs to pH 4.3 of sodium hydroxide, and qs to 1.33 mL of water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of aripiprazole in schizophrenia or bipolar mania, is unknown. However, the efficacy of aripiprazole could be mediated through a combination of partial agonist activity at D2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D2, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha1 receptors).

12.2 Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha1-adrenergic and histamine H_1 receptors (K_i values of 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K_i=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50}>1000 nM). [Aripiprazole functions as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor.]

12.3 Pharmacokinetics

ABILIFY activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for D_2 receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady-state, the pharmacokinetics of aripiprazole is dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours.

Pharmacokinetic studies showed that ABILIFY DISCMELT Orally Disintegrating Tablets are bioequivalent to ABILIFY Tablets.

ORAL ADMINISTRATION

Absorption

Tablet: Aripiprazole is well absorbed after administration of the tablet, with peak plasma concentrations occurring within 3 hours to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. ABILIFY can be administered with or without food. Administration of a 15 mg ABILIFY Tablet with a standard high-fat meal did not significantly affect the Cmax or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed Tmax by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.

Oral Solution: Aripiprazole is well absorbed when administered orally as the solution. At equivalent doses, the plasma concentrations of aripiprazole from the solution were higher than that from the tablet formulation. In a relative bioavailability study comparing the pharmacokinetics of 30 mg aripiprazole as the oral solution to 30 mg aripiprazole tablets in healthy subjects, the solution to tablet ratios of geometric mean Cmax and AUC values were 122% and 114%, respectively *[see DOSAGE AND ADMINISTRATION (2.6)]*. The single-dose pharmacokinetics of aripiprazole were linear and dose-proportional between the doses of 5 mg to 30 mg.

Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent D2 receptor occupancy indicating brain penetration of aripiprazole in humans.

Metabolism and Elimination

Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady-state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Following a single oral dose of [14C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces.

Drug Interaction Studies

Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean Cmax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 3-fold increase in mean Cmax and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

Figure 1: The effects of other drugs on aripiprazole pharmacokinetics

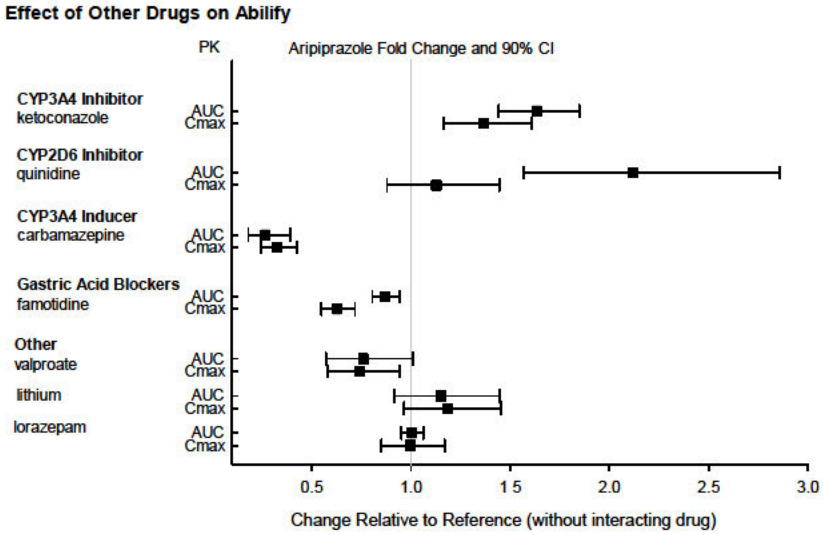
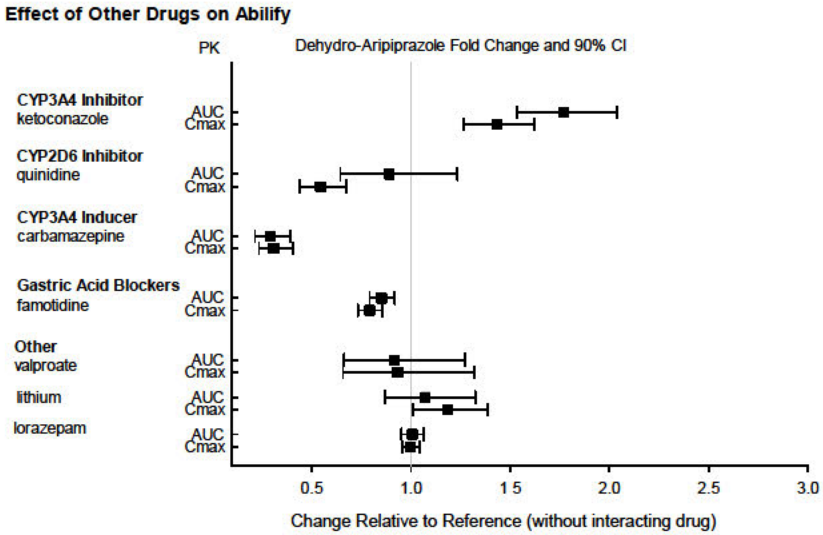


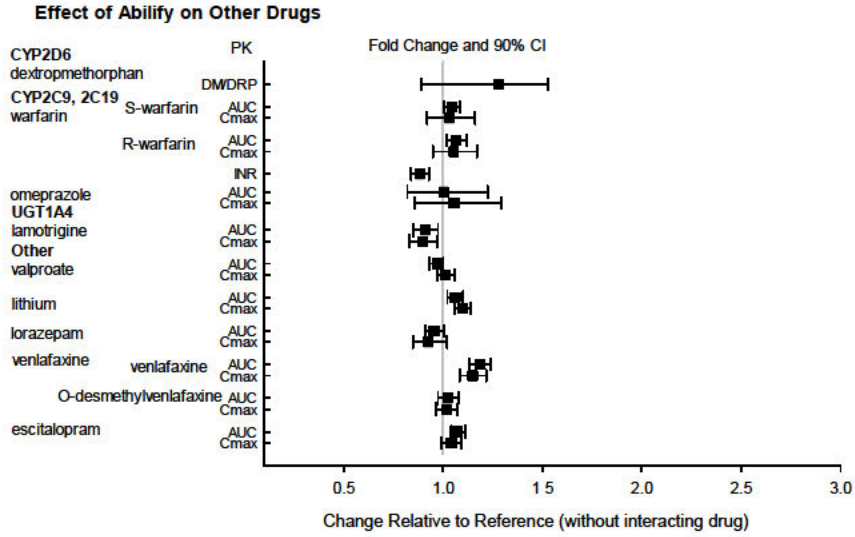
Figure 2: The effects of other drugs on dehydro-aripiprazole pharmacokinetics



The effects of ABILIFY on the exposures of other drugs are summarized in Figure 3. A population PK analysis in patients with major depressive disorder showed no substantial change in plasma concentrations of fluoxetine (20 or 40 mg/day), paroxetine CR (37.5 or 50 mg/day), or sertraline (100 or 150 mg/day) dosed to steady-state. The steady-state

plasma concentrations of fluoxetine and norfluoxetine increased by about 18% and 36%, respectively, and concentrations of paroxetine decreased by about 27%. The steady-state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these antidepressant therapies were coadministered with aripiprazole.

Figure 3: The effects of ABILIFY on pharmacokinetics of other drugs



Studies in Specific Populations

Exposures of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively. In addition, in pediatric patients (10 to 17 years of age) administered with Abilify (20 mg to 30 mg), the body weight corrected aripiprazole clearance was similar to the adults.

Figure 4: Effects of intrinsic factors on aripiprazole pharmacokinetics

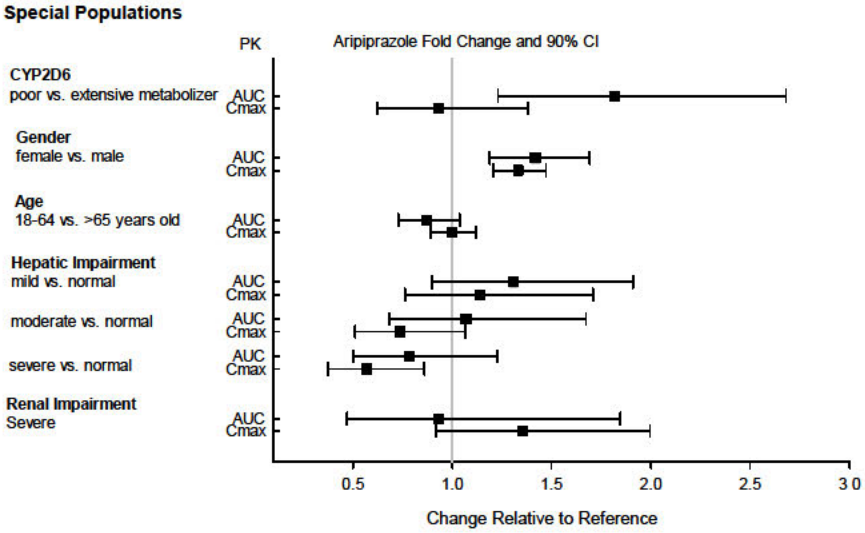
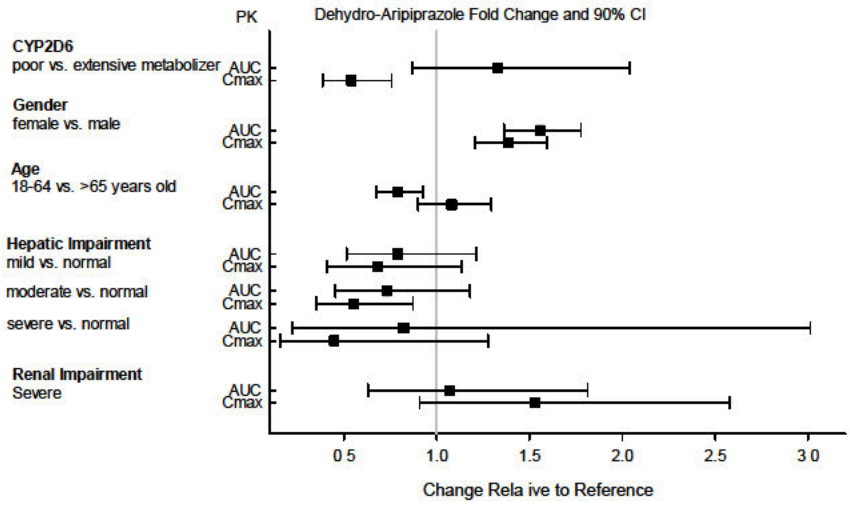


Figure 5: Effects of intrinsic factors on dehydro-aripiprazole pharmacokinetics



INTRAMUSCULAR ADMINISTRATION

In two pharmacokinetic studies of aripiprazole injection administered intramuscularly to healthy subjects, the median times to the peak plasma concentrations were at 1 hour and 3 hours. A 5 mg intramuscular injection of aripiprazole had an absolute bioavailability of 100%. The geometric mean maximum concentration achieved after an intramuscular dose was on average 19% higher than the Cmax of the oral tablet. While the systemic exposure over 24 hours was generally similar between aripiprazole injection given intramuscularly and after oral tablet administration, the aripiprazole AUC in the first 2 hours after an intramuscular injection was 90% greater than the AUC after the same dose as a tablet. In stable patients with schizophrenia or schizoaffective disorder, the pharmacokinetics of aripiprazole after intramuscular administration were linear over a dose range of 1 mg to 45 mg. Although the metabolism of aripiprazole injection was not systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice, Sprague-Dawley (SD) rats, and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 times and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m2). Aripiprazole did not induce tumors in male mice or male rats. In female mice, the incidences of pituitary gland

adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4-week and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

The mutagenic potential of aripiprazole was tested in the in vitro bacterial reverse-mutation assay, the in vitro bacterial DNA repair assay, the in vitro forward gene mutation assay in mouse lymphoma cells, the in vitro chromosomal aberration assay in Chinese hamster lung (CHL) cells, the in vivo micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the in vitro chromosomal aberration assay in CHL cells with and without metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the in vitro assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the in vivo micronucleus assay in mice; however, the response was due to a mechanism not considered relevant to humans.

Impairment of Fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg/day and decreased fetal weight was seen at 20 mg/kg/day.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m^2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

13.2 Animal Toxicology and/or Pharmacology

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40 and 60 mg/kg/day doses are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m^2 and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

14 CLINICAL STUDIES

Efficacy of the oral formulations of ABILIFY (aripiprazole) was established in the following adequate and well-controlled trials:

- Four short-term trials and one maintenance trial in adult patients and one short-term trial in adolescents (ages 13-17) with schizophrenia (14.1)
- Four short-term monotherapy trials and one 6-week adjunctive trial in adult patients and one short-term monotherapy trial in pediatric patients (ages 10-17) with manic or mixed episodes (14.2)
- One maintenance monotherapy trial and in one maintenance adjunctive trial in adult patients with bipolar I disorder (14.2)
- Two short-term trials in adult patients with MDD who had an inadequate response to antidepressant therapy during the current episode (14.3)
- Two short-term trials in pediatric patients (ages 6-17 years) for the treatment of irritability associated with autistic disorder (14.4)
- Two short-term trials in pediatric patients (ages 6-18 years) with Tourette's disorder (14.5)

Efficacy of the injectable formulation of ABILIFY (aripiprazole) was established in the following adequate and well-controlled trials:

- Three 24-hour trials in agitated adult patients with schizophrenia or manic/mixed episodes of bipolar I disorder (14.6)

14.1 Schizophrenia

Adults

The efficacy of ABILIFY in the treatment of schizophrenia was evaluated in five short-term (4-week and 6-week), placebo-controlled trials of acutely relapsed inpatients who predominantly met DSM-III/IV criteria for schizophrenia. Four of the five trials were able to distinguish ABILIFY from placebo, but one study, the smallest, did not. Three of

these studies also included an active control group consisting of either risperidone (one trial) or haloperidol (two trials), but they were not designed to allow for a comparison of ABILIFY and the active comparators.

In the four positive trials for ABILIFY, four primary measures were used for assessing psychiatric signs and symptoms. Efficacy was evaluated using the total score on the Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30 item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210. The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In a 4-week trial (n=414) comparing two fixed doses of ABILIFY (15 or 30 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score (Study 1 in Table 26), PANSS positive subscale, and CGI-severity score. In addition, the 15 mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n=404) comparing two fixed doses of ABILIFY (20 or 30 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score (Study 2 in Table 26), PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n=420) comparing three fixed doses of ABILIFY (10, 15, or 20 mg/day) to placebo, all three doses of ABILIFY were superior to placebo in the PANSS total score (Study 3 in Table 26), PANSS positive subscale, and the PANSS negative subscale.

In a 6-week trial (n=367) comparing three fixed doses of ABILIFY (2, 5, or 10 mg/day) to placebo, the 10 mg dose of ABILIFY was superior to placebo in the PANSS total score (Study 4 in Table 26), the primary outcome measure of the study. The 2 and 5 mg doses did not demonstrate superiority to placebo on the primary outcome measure.

Thus, the efficacy of 10, 15, 20, and 30 mg daily doses was established in two studies for each dose. Among these doses, there was no evidence that the higher dose groups offered any advantage over the lowest dose group of these studies.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were, by history, symptomatically stable on other antipsychotic

medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to ABILIFY 15 mg/day or placebo for up to 26 weeks of observation for relapse. Relapse during the double-blind phase was defined as CGI-Improvement score of ≥5 (minimally worse), scores ≥5 (moderately severe) on the hostility or uncooperativeness items of the PANSS, or ≥20% increase in the PANSS total score. Patients receiving ABILIFY 15 mg/day experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo (Study 5 in Figure 6).

Pediatric Patients

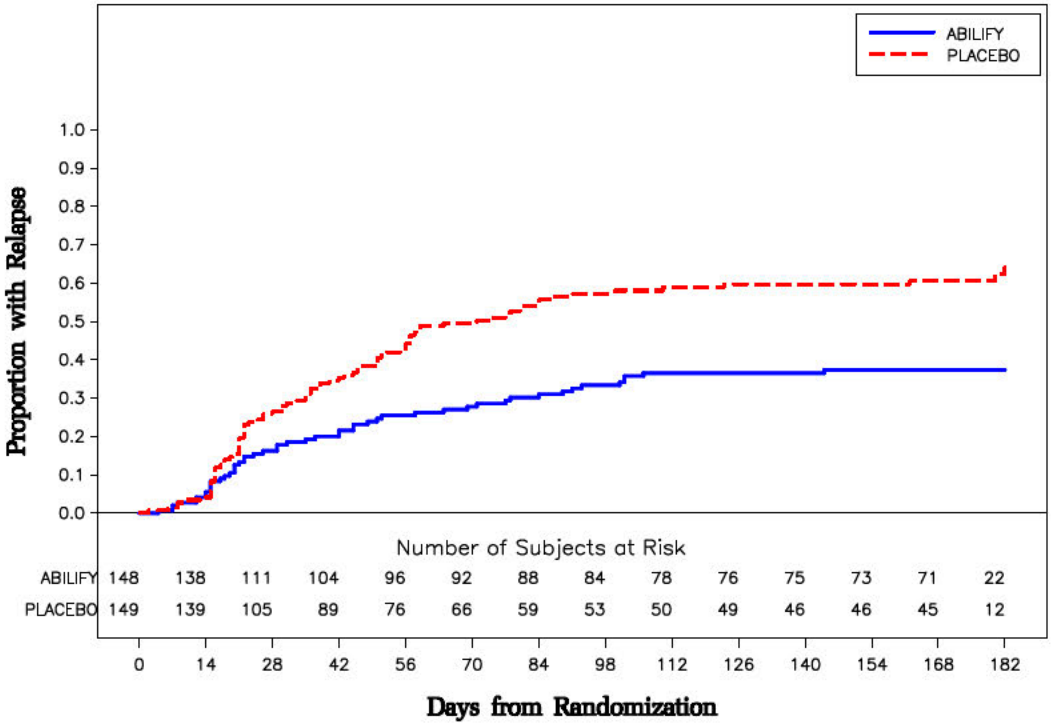
The efficacy of ABILIFY (aripiprazole) in the treatment of schizophrenia in pediatric patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled trial of outpatients who met DSM-IV criteria for schizophrenia and had a PANSS score ≥70 at baseline. In this trial (n=302) comparing two fixed doses of ABILIFY (10 or 30 mg/day) to placebo, ABILIFY was titrated starting from 2 mg/day to the target dose in 5 days in the 10 mg/day treatment arm and in 11 days in the 30 mg/day treatment arm. Both doses of ABILIFY were superior to placebo in the PANSS total score (Study 6 in Table 26), the primary outcome measure of the study. The 30 mg/day dosage was not shown to be more efficacious than the 10 mg/day dose. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Table 26: Schizophrenia Studies

Study Number	Treatment Group	Primary Efficacy Measure: PANSS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (15 mg/day)*	98.5 (17.2)	-15.5 (2.40)	-12.6 (-18.9, -6.2)
	ABILIFY (30 mg/day)*	99.0 (19.2)	-11.4 (2.39)	-8.5 (-14.8, -2.1)
	Placebo	100.2 (16.5)	-2.9 (2.36)	--
Study 2	ABILIFY (20 mg/day)*	92.6 (19.5)	-14.5 (2.23)	-9.6 (-15.4, -3.8)
	ABILIFY (30 mg/day)*	94.2 (18.5)	-13.9 (2.24)	-9.0 (-14.8, -3.1)
	Placebo	94.3 (18.5)	-5.0 (2.17)	--
Study 3	ABILIFY (10 mg/day)*	92.7 (19.5)	-15.0 (2.38)	-12.7 (-19.00, -6.41)
	ABILIFY (15 mg/day)*	93.2 (21.6)	-11.7 (2.38)	-9.4 (-15.71, -3.08)
	ABILIFY (20 mg/day)*	92.5 (20.9)	-14.4 (2.45)	-12.1 (-18.53, -5.68)
	Placebo	92.3 (21.8)	-2.3 (2.35)	--
Study 4	ABILIFY (2 mg/day)	90.7 (14.5)	-8.2 (1.90)	-2.9 (-8.29, 2.47)
	ABILIFY (5 mg/day)	92.0 (12.6)	-10.6 (1.93)	-5.2 (-10.7, 0.19)
	ABILIFY (10 mg/day)*	90.0 (11.9)	-11.3 (1.88)	-5.9 (-11.3, -0.58)
	Placebo	90.8 (13.3)	-5.3 (1.97)	--
Study 6 (Pediatric, 13-17 years)	ABILIFY (10 mg/day)*	93.6 (15.7)	-26.7 (1.91)	-5.5 (-10.7, -0.21)
	ABILIFY (30 mg/day)*	94.0 (16.1)	-28.6 (1.92)	-7.4 (-12.7, -2.13)
	Placebo	94.6 (15.6)	-21.2 (1.93)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

Figure 6: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (Schizophrenia Study 5)



14.2 Bipolar Disorder

Acute Treatment of Manic and Mixed Episodes

Adults

Monotherapy

The efficacy of ABILIFY as monotherapy in the acute treatment of manic episodes was established in four 3-week, placebo-controlled trials in hospitalized patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These studies included patients with or without psychotic features and two of the studies also included patients with or without a rapid-cycling course.

The primary instrument used for assessing manic symptoms was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). A key secondary instrument included the Clinical Global Impression-Bipolar (CGI-BP) Scale.

In the four positive, 3-week, placebo-controlled trials (n=268; n=248; n=480; n=485) which evaluated ABILIFY in a range of 15 mg to 30 mg, once daily (with a starting dose of 30 mg/day in two studies and 15 mg/day in two studies), ABILIFY was superior to placebo in the reduction of Y-MRS total score (Studies 1-4 in Table 27) and CGI-BP Severity of Illness score (mania). In the two studies with a starting dose of 15 mg/day, 48% and 44% of patients were on 15 mg/day at endpoint. In the two studies with a starting dose of 30 mg/day, 86% and 85% of patients were on 30 mg/day at endpoint.

Adjunctive Therapy

The efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in a 6-week, placebo-controlled study (n=384) with a 2-week lead-in mood stabilizer monotherapy phase in adult patients who met DSM-IV criteria for bipolar I disorder. This study included patients with manic or mixed episodes and with or without psychotic features.

Patients were initiated on open-label lithium (0.6 to 1.0 mEq/L) or valproate (50 to 125 μg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥16 and ≤25% improvement on the Y-MRS total score) to lithium or valproate were randomized to receive either ABILIFY (15 mg/day or an increase to 30 mg/day as early as day 7) or placebo as adjunctive therapy with open-label lithium or valproate. In the 6-week, placebo-controlled phase, adjunctive ABILIFY starting at 15 mg/day with concomitant lithium or valproate (in a therapeutic range of 0.6 to 1.0 mEq/L or 50 to 125 μg/mL, respectively) was superior to lithium or valproate with adjunctive placebo in the reduction of the Y-MRS total score (Study 5 in Table 27) and CGI-BP Severity of Illness score (mania). Seventy-one percent of the patients coadministered valproate and 62% of the patients coadministered lithium were on 15 mg/day at 6-week endpoint.

Pediatric Patients

The efficacy of ABILIFY in the treatment of bipolar I disorder in pediatric patients (10 to 17 years of age) was evaluated in one 4-week, placebo-controlled trial (n=296) of outpatients who met DSM-IV criteria for bipolar I disorder manic or mixed episodes with or without psychotic features and had a Y-MRS score ≥20 at baseline. This double-blind, placebo-controlled trial compared two fixed doses of ABILIFY (10 or 30 mg/day) to placebo. The ABILIFY dose was started at 2 mg/day, which was titrated to 5 mg/day

after 2 days, and to the target dose in 5 days in the 10 mg/day treatment arm, and in 13 days in the 30 mg/day treatment arm. Both doses of ABILIFY were superior to placebo in change from baseline to week 4 on the Y-MRS total score (Study 6 in Table 27).

Table 27: Bipolar Studies

Study Number	Treatment Group	Primary Efficacy Measure: Y-MRS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (30 / 15 mg/day)*	29.0 (5.9)	-12.52 (1.05)	-5.33 (-7.90, -2.76)
	Placebo	28.5 (4.6)	-7.19 (1.07)	--
Study 2	ABILIFY (30 / 15 mg/day)*	27.8 (5.7)	-8.15 (1.23)	-4.80 (-7.80, -1.80)
	Placebo	29.1 (6.9)	-3.35(1.22)	--
Study 3	ABILIFY (15 - 30 mg/day)*	28.5 (5.6)	-12.64 (0.84)	-3.63 (-5.75 , -1.51)
	Placebo	28.9 (5.9)	9.01 (0.81)	--
Study 4	ABILIFY (15 -30 mg/day)*	28.0 (5.8)	-11.98 (0.80)	-2.28 (-4.44 , -0.11)
	Placebo	28.3 (5.8)	-9.70 (0.83)	--
Study 5	ABILIFY (15 or 30 mg/day)* + Lithium/Valproate	23.2 (5.7)	-13.31 (0.50)	-2.62 (-4.29 , -0.95)
	Placebo + Lithium/Valproate	23.0 (4.9)	-10.70 (0.69)	--
Study 6 (Pediatric, 10-17 years)	ABILIFY (10 mg/day)*	29.8 (6.5)	-14.2 (0.89)	-5.99 (-8.49, -3.50)
	ABILIFY (30 mg/day)*	29.5 (6.3)	-16.5 (0.87)	-8.26 (-10.7, -5.77)
	Placebo	30.7 (6.8)	-8.2 (0.91)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses statistically significantly superior to placebo.

Maintenance Treatment of Bipolar I Disorder

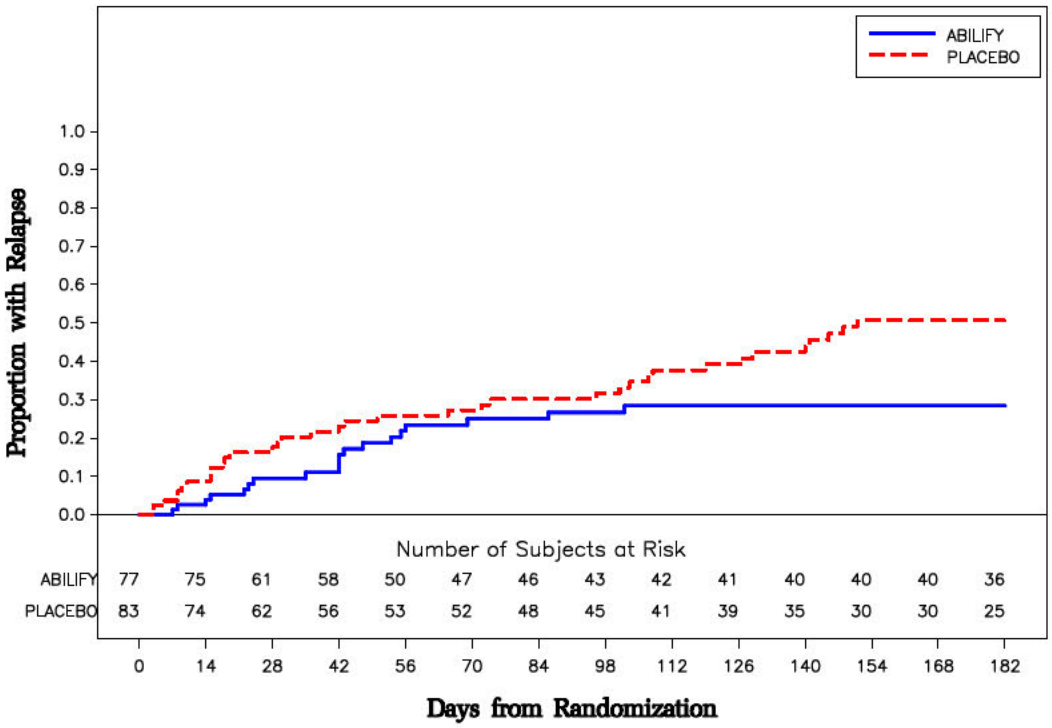
Monotherapy Maintenance Therapy

A maintenance trial was conducted in adult patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode who had been stabilized on open-label ABILIFY and who had maintained a clinical response for at least 6 weeks. The first phase of this trial was an open-label stabilization period in which inpatients and outpatients were clinically stabilized and then maintained on open-label ABILIFY (15 or 30 mg/day, with a starting dose of 30 mg/day) for at least 6 consecutive weeks. One hundred sixty-one outpatients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization and maintenance period or placebo and were then monitored for manic or depressive relapse. During the randomization phase, ABILIFY was superior to placebo on time to the number of combined affective relapses (manic plus depressive), the primary outcome measure for this study (Study 7 in Figure 7). A total of 55 mood events were observed during the double-blind treatment phase. Nineteen were from the ABILIFY group and 36 were from

the placebo group. The number of observed manic episodes in the ABILIFY group (6) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY group (9) was similar to that in the placebo group (11).

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age and gender; however, there were insufficient numbers of patients in each of the ethnic groups to adequately assess inter-group differences.

Figure 7: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (Bipolar Study 7)

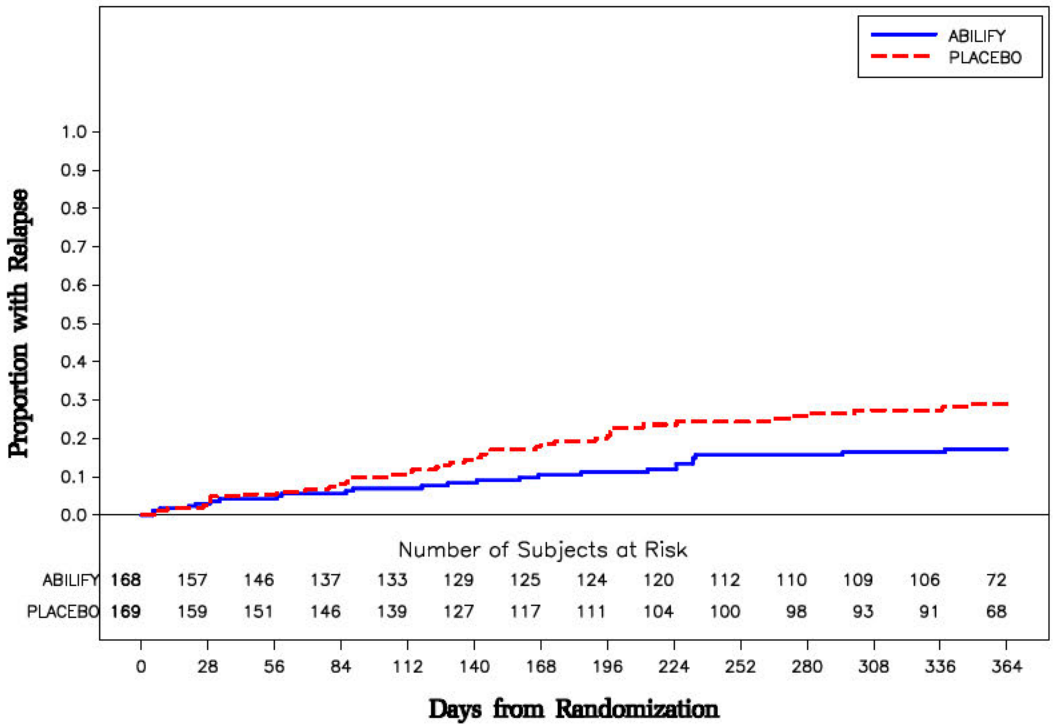


Adjunctive Maintenance Therapy

An adjunctive maintenance trial was conducted in adult patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode. Patients were initiated on open-label lithium (0.6 to 1.0 mEq/L) or valproate (50 to 125 µg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥16 and ≤35% improvement on the Y-MRS total score) to lithium or valproate received ABILIFY with a starting dose of 15 mg/day with the option to increase to 30 mg or reduce to 10 mg as early as day 4, as adjunctive therapy with open-label lithium or valproate. Prior to randomization, patients on the combination of single-blind ABILIFY and lithium or valproate were required to

maintain stability (Y-MRS and MADRS total scores ≤12) for 12 consecutive weeks. Three hundred thirty-seven patients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization period or placebo plus lithium or valproate and were then monitored for manic, mixed, or depressive relapse for a maximum of 52 weeks. ABILIFY was superior to placebo on the primary endpoint, time from randomization to relapse to any mood event (Study 8 in Figure 8). A mood event was defined as hospitalization for a manic, mixed, or depressive episode, study discontinuation due to lack of efficacy accompanied by Y-MRS score >16 and/or a MADRS >16, or an SAE of worsening disease accompanied by Y-MRS score >16 and/or a MADRS >16. A total of 68 mood events were observed during the double-blind treatment phase. Twenty-five were from the ABILIFY group and 43 were from the placebo group. The number of observed manic episodes in the ABILIFY group (7) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY group (14) was similar to that in the placebo group (18). The Kaplan-Meier curves of the time from randomization to relapse to any mood event during the 52-week, double-blind treatment phase for ABILIFY and placebo groups are shown in Figure 8.

Figure 8: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse to Any Mood Event (Bipolar Study 8)



An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age and gender; however, there were insufficient numbers of patients in each of the ethnic groups to adequately assess inter-group differences.

14.3 Adjunctive Treatment of Major Depressive Disorder

Adults

The efficacy of ABILIFY in the adjunctive treatment of major depressive disorder (MDD) was demonstrated in two short-term (6-week), placebo-controlled trials of adult patients meeting DSM-IV criteria for MDD who had had an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and who had also demonstrated an inadequate response to 8 weeks of prospective antidepressant therapy (paroxetine controlled-release, venlafaxine extended-release, fluoxetine, escitalopram, or sertraline). Inadequate response for prospective treatment was defined as less than 50% improvement on the 17-item version of the Hamilton Depression Rating Scale (HAMD17), minimal HAMD17 score of 14, and a Clinical Global Impressions Improvement rating of no better than minimal improvement. Inadequate response to prior treatment was defined as less than 50% improvement as perceived by the patient after a minimum of 6 weeks of antidepressant therapy at or above the minimal effective dose.

The primary instrument used for assessing depressive symptoms was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale used to assess the degree of depressive symptomatology. The key secondary instrument was the Sheehan Disability Scale (SDS), a 3-item self-rated instrument used to assess the impact of depression on three domains of functioning with each item scored from 0 (not at all) to 10 (extreme).

In the two trials (n=381, n=362), ABILIFY was superior to placebo in reducing mean MADRS total scores (Studies 1, 2 in Table 28). In one study, ABILIFY was also superior to placebo in reducing the mean SDS score.

In both trials, patients received ABILIFY adjunctive to antidepressants at a dose of 5 mg/day. Based on tolerability and efficacy, doses could be adjusted by 5 mg increments, one week apart. Allowable doses were: 2, 5, 10, 15 mg/day, and for patients who were not on potent CYP2D6 inhibitors fluoxetine and paroxetine, 20 mg/day. The mean final dose at the end point for the two trials was 10.7 and 11.4 mg/day.

An examination of population subgroups did not reveal evidence of differential response based on age, choice of prospective antidepressant, or race. With regard to gender, a smaller mean reduction on the MADRS total score was seen in males than in females.

Table 28: Adjunctive Treatment of Major Depressive Disorder Studies

Study Number	Treatment Group	Primary Efficacy Measure: MADRS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (5-20 mg/day)* + Antidepressant	25.2(6.2)	-8.49 (0.66)	-2.84 (-4.53 , -1.15)
	Placebo + Antidepressant	27.0 (5.5)	-5.65 (0.64)	--
Study 2	ABILIFY (5-20 mg/day)* + Antidepressant	26.0 (6.0)	-8.78 (0.63)	-3.01 (-4.66 , -1.37)
	Placebo + Antidepressant	26.0 (6.5)	-5.77 (0.67)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

14.4 Irritability Associated with Autistic Disorder

Pediatric Patients

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

Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Improvement (CGI-I) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured symptoms of irritability in autistic disorder.

The results of these trials are as follows:

In one of the 8-week, placebo-controlled trials, children and adolescents with autistic disorder (n=98), aged 6 to 17 years, received daily doses of placebo or ABILIFY 2 to 15 mg/day. ABILIFY, starting at 2 mg/day with increases allowed up to 15 mg/day based on clinical response, significantly improved scores on the ABC-I subscale and on the CGI-I scale compared with placebo. The mean daily dose of ABILIFY at the end of 8-week treatment was 8.6 mg/day (Study 1 in Table 29).

In the other 8-week, placebo-controlled trial in children and adolescents with autistic disorder (n=218), aged 6 to 17 years, three fixed doses of ABILIFY (5 mg/day, 10 mg/day, or 15 mg/day) were compared to

placebo. ABILIFY dosing started at 2 mg/day and was increased to 5 mg/day after one week. After a second week, it was increased to 10 mg/day for patients in the 10 and 15 mg dose arms, and after a third week, it was increased to 15 mg/day in the 15 mg/day treatment arm (Study 2 in Table 29). All three doses of ABILIFY significantly improved scores on the ABC-I subscale compared with placebo.

Table 29: Irritability Associated with Autistic Disorder Studies (Pediatric)

Study Number	Treatment Group	Primary Efficacy Measure: ABC-I		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (2-15 mg/day)*	29.6 (6.37)	-12.9 (1.44)	-7.9 (-11.7, -4.1)
	Placebo	30.2 (6.52)	-5.0 (1.43)	--
Study 2	ABILIFY (5 mg/day)*	28.6 (7.56)	-12.4 (1.36)	-4.0 (-7.7, -0.4)
	ABILIFY (10 mg/day)*	28.2 (7.36)	-13.2 (1.25)	-4.8 (-8.4, -1.3)
	ABILIFY (15 mg/day)*	28.9 (6.41)	-14.4 (1.31)	-6.0 (-9.6, -2.3)
	Placebo	28.0 (6.89)	-8.4 (1.39)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
a Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

14.5 Tourette's Disorder

Pediatric Patients

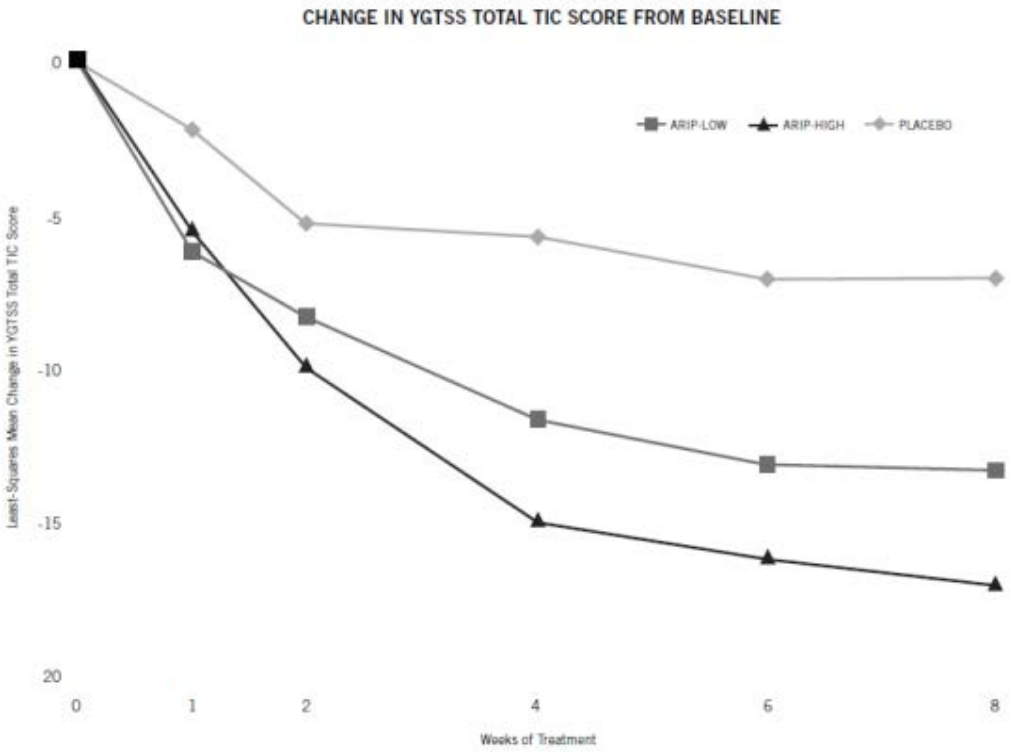
The efficacy of ABILIFY (aripiprazole) in the treatment of Tourette's disorder was established in one 8-week (7 to 17 years of age) and one 10-week (6 to 18 years of age), placebo-controlled trials in pediatric patients (6 to 18 years of age) who met the DSM-IV criteria for Tourette's disorder and had a Total Tic score (TTS) ≥ 20 - 22 on the Yale Global Tic Severity Scale (YGTSS). The YGTSS is a fully validated scale designed to measure current tic severity. Efficacy was evaluated using two assessment scales: 1) the Total Tic score (TTS) of the YGTSS and 2) the Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS), a clinician-determined summary measure that takes into account all available patient information. Over 65% of these patients were under 13 years of age.

The primary outcome measure in both trials was the change from baseline to endpoint in the TTS of the YGTSS. Ratings for the TTS are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics each. Summation of these 10 scores provides a TTS (i.e., 0-50).

The results of these trials are as follows:

In the 8-week, placebo-controlled, fixed-dose trial, children and adolescents with Tourette's disorder (n=133), aged 7 to 17 years, were randomized 1:1:1 to low dose ABILIFY, high dose ABILIFY, or placebo. The target doses for the low and high dose ABILIFY groups were based on weight. Patients < 50 kg in the low dose ABILIFY group started at 2 mg per day with a target dose of 5 mg per day after 2 days. Patients ≥ 50 kg in the low dose ABILIFY group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patients <50 kg in the high dose ABILIFY group started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patients ≥ 50 kg in the high dose ABILIFY group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a dose of 10 mg per day at day 7 and were allowed weekly increases of 5 mg per day up to a target dose 20 mg per day at Day 21. ABILIFY (both high and low dose groups) demonstrated statistically significantly improved scores on the YGTSS TTS (Study 1 in Table 30) and on the CGI-TS scale compared with placebo. The estimated improvements on the YGTSS TTS over the course of the study are displayed in Figure 9.

Figure 9: Least Square Means of Change from Baseline in YGTSS TTS by Week (Tourette's Disorder Study 1)



In the 10-week, placebo-controlled, flexible-dose trial in children and adolescents with Tourette's disorder (n=61), aged 6 to 18 years, patients received daily doses of placebo or ABILIFY, starting at 2 mg/day with increases allowed up to 20 mg/day based on clinical response. ABILIFY demonstrated statistically significantly improved scores on the YGTSS TTS scale compared with placebo (Study 2 in Table 30). The mean daily dose of ABILIFY at the end of 10-week treatment was 6.54 mg/day.

Table 30: Tourette's Disorder Studies (Pediatric)

Study Number	Treatment Group	Primary Efficacy Measure: YGTSS TTS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (low dose)*	29.2 (5.63)	-13.4 (1.59)	-6.3 (-10.2, -2.3)
	ABILIFY (high dose)*	31.2 (6.40)	-16.9 (1.61)	-9.9 (-13.8, -5.9)
	Placebo	30.7 (5.95)	-7.1 (1.55)	--
Study 2	ABILIFY (2-20 mg/day)*	28.3 (5.51)	-15.0 (1.51)	-5.3 (-9.8, -0.9)
	Placebo	29.5 (5.60)	-9.6 (1.64)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
a Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

14.6 Agitation Associated with Schizophrenia or Bipolar Mania

The efficacy of intramuscular ABILIFY for injection for the treatment of agitation was established in three short-term (24-hour), placebo-controlled trials in agitated inpatients from two diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes, with or without psychotic features). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar mania study). Patients could receive up to three injections during the 24-hour treatment periods; however, patients could not receive the second injection until after the initial 2-hour period when the primary efficacy measure was assessed. Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥15 on the five items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness, and excitement items) with at least two individual item scores ≥4 using a 1-7 scoring system (1 = absent, 4 = moderate, 7 = extreme). In the studies, the mean baseline PANSS Excited Component score was 19, with scores ranging from 15 to 34 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. A key secondary measure was the Clinical Global Impression of Improvement (CGI-I) Scale. The results of the trials follow:

In a placebo-controlled trial in agitated inpatients predominantly meeting DSM-IV criteria for schizophrenia (n=350), four fixed ABILIFY injection doses of 1 mg, 5.25 mg, 9.75 mg, and 15 mg were evaluated. At 2 hours post-injection, the 5.25 mg, 9.75 mg, and 15 mg doses were statistically

superior to placebo in the PANSS Excited Component (Study 1 in Table 31) and on the CGI-I Scale.

In a second placebo-controlled trial in agitated inpatients predominantly meeting DSM-IV criteria for schizophrenia (n=445), one fixed ABILIFY injection dose of 9.75 mg was evaluated. At 2 hours post-injection, ABILIFY for injection was statistically superior to placebo in the PANSS Excited Component (Study 2 in Table 31) and on the CGI-I Scale.

In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (manic or mixed) (n=291), two fixed ABILIFY injection doses of 9.75 mg and 15 mg were evaluated. At 2 hours post-injection, both doses were statistically superior to placebo in the PANSS Excited Component (Study 3 in Table 31).

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

Table 31: Agitation Associated with Schizophrenia or Bipolar Mania Studies

Study Number	Treatment Group	Primary Efficacy Measure: PANSS Excited Component		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Agitation Associated with Schizophrenia				
Study 1	ABILIFY (1 mg)	19.16 (3.26)	-4.47 (0.72)	-1.19 (-2.96 , 0.59)
	ABILIFY (5.25 mg)*	19.41 (3.31)	-5.65 (0.68)	-2.37 (-4.10 , -0.63)
	ABILIFY (9.75 mg)*	19.42 (2.80)	-6.69 (0.72)	-3.40 (-5.18 , -1.62)
	ABILIFY (15 mg)*	19.34 (2.38)	-5.72 (0.72)	-2.44 (-4.21 , -0.68)
	Placebo	19.18 (2.95)	-3.28 (0.70)	--
Study 2	ABILIFY (9.75 mg)*	18.82 (2.67)	-7.27 (0.59)	-2.48 (-3.77, -1.19)
	Placebo	18.74 (2.71)	-4.78 (0.69)	--
Agitation Associated with Bipolar Mania				
Study 3	ABILIFY (9.75 mg)*	18.77 (2.45)	-8.74 (0.57)	-2.99 (-4.53, -1.44)
	ABILIFY (15 mg)*	18.29 (2.49)	-8.67 (0.57)	-2.91 (-4.44, -1.38)
	Placebo	17.95 (2.63)	-5.76 (0.58)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ABILIFY® (aripiprazole) Tablets have markings on one side and are available in the strengths and packages listed in Table 32.

Table 32: ABILIFY Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code
2 mg	green modified rectangle	"A-006" and "2"	Bottle of 30	59148-006-13
5 mg	blue modified rectangle	"A-007" and "5"	Bottle of 30 Blister of 100	59148-007-13 59148-007-35
10 mg	pink modified rectangle	"A-008" and "10"	Bottle of 30 Blister of 100	59148-008-13 59148-008-35
15 mg	yellow round	"A-009" and "15"	Bottle of 30 Blister of 100	59148-009-13 59148-009-35
20 mg	white round	"A-010" and "20"	Bottle of 30 Blister of 100	59148-010-13 59148-010-35
30 mg	pink round	"A-011" and "30"	Bottle of 30 Blister of 100	59148-011-13 59148-011-35

ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets are round tablets with markings on either side. ABILIFY DISCMELT is available in the strengths and packages listed in Table 33.

Table 33: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations

Tablet Strength	Tablet Color	Tablet Markings	Pack Size	NDC Code
10 mg	pink (with scattered specks)	"A" and "640" "10"	Blister of 30	59148-640-23
15 mg	yellow (with scattered specks)	"A" and "641" "15"	Blister of 30	59148-641-23

ABILIFY® (aripiprazole) Oral Solution (1 mg/mL) is supplied in child-resistant bottles along with a calibrated oral dosing cup. ABILIFY Oral Solution is available as follows:

150 mL bottle NDC 59148-013-15

ABILIFY® (aripiprazole) Injection for intramuscular use is available as a ready-to-use, 9.75 mg/1.3 mL (7.5 mg/mL) solution in clear, Type 1 glass vials as follows:

9.75 mg/1.3 mL single-dose vial NDC 59148-016-65

16.2 Storage

Tablets

Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

Oral Solution

Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*. Opened bottles of ABILIFY Oral Solution can be used for up to 6 months after opening, but not beyond the expiration date on the bottle. The bottle and its contents should be discarded after the expiration date.

Injection

Store at 25ºC (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*. Protect from light by storing in the original container. Retain in carton until time of use.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

Discuss the following issues with patients prescribed ABILIFY:

Clinical Worsening of Depression and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior **and indicate a need for very close monitoring and possibly changes in the medication** *[see WARNINGS AND PRECAUTIONS (5.2)]*.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with ABILIFY and should counsel them in its appropriate use. A patient Medication Guide including information about "Antidepressant Medicines, Depression and other Serious Mental

Illness, and Suicidal Thoughts or Actions" is available for ABILIFY. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. It should be noted that ABILIFY is not approved as a single agent for treatment of depression and has not been evaluated in pediatric major depressive disorder.

Use of Orally Disintegrating Tablet

Do not open the blister until ready to administer. For single tablet removal, open the package and peel back the foil on the blister to expose the tablet. Do not push the tablet through the foil because this could damage the tablet. Immediately upon opening the blister, using dry hands, remove the tablet and place the entire ABILIFY DISCMELT Orally Disintegrating Tablet on the tongue. Tablet disintegration occurs rapidly in saliva. It is recommended that ABILIFY DISCMELT be taken without liquid. However, if needed, it can be taken with liquid. Do not attempt to split the tablet.

Interference with Cognitive and Motor Performance

Because ABILIFY may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that ABILIFY therapy does not affect them adversely *[see WARNINGS AND PRECAUTIONS (5.9)]*.

Nursing

Advise patients that breastfeeding is not recommended with ABILIFY treatment because of the potential for serious adverse reactions in a nursing infant *[see USE IN SPECIFIC POPULATIONS (8.3)]*.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions *[see DRUG INTERACTIONS (7)]*.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see WARNINGS AND PRECAUTIONS (5.10)]*.

Sugar Content

Patients should be advised that each mL of ABILIFY Oral Solution contains 400 mg of sucrose and 200 mg of fructose.

Phenylketonurics

Phenylalanine is a component of aspartame. Each ABILIFY DISCMELT Orally Disintegrating Tablet contains the following amounts: 10 mg, 1.12 mg phenylalanine and 15 mg, 1.68 mg phenylalanine.

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan or Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Orally Disintegrating Tablets, Oral Solution, and Injection manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

ABILIFY is a trademark of Otsuka Pharmaceutical Company.

Otsuka
Otsuka America Pharmaceutical, Inc.

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MEDICATION GUIDE

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Tablets

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Orally Disintegrating Tablets

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Oral Solution

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Injection, for intramuscular use

Read this Medication Guide before you start taking ABILIFY and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ABILIFY?

(For other side effects, also see "**What are the possible side effects of ABILIFY?**").

Serious side effects may happen when you take ABILIFY, including:

- **Increased risk of death in elderly patients with dementia-related psychosis:** Medicines like ABILIFY can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). ABILIFY is not approved for the treatment of patients with dementia-related psychosis.
- **Risk of suicidal thoughts or actions:** Antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions:

  1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**

2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
    - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
    - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.

- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

What is ABILIFY?

- **ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution** are prescription medicines used to treat:
  - Schizophrenia
  - manic or mixed episodes that happen with bipolar I disorder
  - major depressive disorder (MDD) when ABILIFY is used with antidepressant medicines
  - irritability associated with autistic disorder
  - Tourette's disorder
- **ABILIFY Injection** is a prescription medicine used to treat:
  - agitation associated with schizophrenia or bipolar mania

It is not known if ABILIFY is safe or effective in children:

- under 13 years of age with schizophrenia
- under 10 years of age with bipolar I disorder
- under 6 years of age with irritability associated with autistic disorder
- under 6 years of age with Tourette's disorder

Who should not take ABILIFY?

Do not take ABILIFY if you are allergic to aripiprazole or any of the ingredients in ABILIFY. See the end of this Medication Guide for a complete list of ingredients in ABILIFY.

What should I tell my healthcare provider before taking ABILIFY?

Before taking ABILIFY, tell your healthcare provider if you have or had:

- diabetes or high blood sugar in you or your family; your healthcare provider should check your blood sugar before you start ABILIFY and also during therapy.
- seizures (convulsions).
- low or high blood pressure.
- heart problems or stroke.
- pregnancy or plans to become pregnant. It is not known if ABILIFY will harm your unborn baby.
- breast-feeding or plans to breast-feed. ABILIFY can pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you receive ABILIFY.
- low white blood cell count.
- phenylketonuria. ABILIFY DISCMELT Orally Disintegrating Tablets contain phenylalanine.
- any other medical conditions.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ABILIFY and other medicines may affect each other causing possible serious side effects. ABILIFY may affect the way other medicines work, and other medicines may affect how ABILIFY works.

Your healthcare provider can tell you if it is safe to take ABILIFY with your other medicines. Do not start or stop any medicines while taking ABILIFY without talking to your healthcare provider first. Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ABILIFY?

- Take ABILIFY exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking ABILIFY yourself.
- ABILIFY can be taken with or without food.
- ABILIFY tablets should be swallowed whole.
- If you miss a dose of ABILIFY, take the missed dose as soon as you remember. If it is almost time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of ABILIFY at the same time.
- If you have been prescribed ABILIFY DISCMELT, take it as follows:
    - Do not open the blister until ready to take the DISCMELT tablet.
    - To remove one DISCMELT tablet, open the package and peel back the foil on the blister to expose the tablet.
    - Do not push the tablet through the foil because this could damage the tablet.
    - Immediately upon opening the blister, using dry hands, remove the tablet and place the entire ABILIFY DISCMELT Orally Disintegrating Tablet on the tongue.
    - Tablet disintegration occurs rapidly in saliva. It is recommended that ABILIFY DISCMELT be taken without liquid. However, if needed, it can be taken with liquid.
    - Do not attempt to split the DISCMELT tablet.
- If you take too much ABILIFY, call your healthcare provider or poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.

What should I avoid while taking ABILIFY?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how ABILIFY affects you. ABILIFY may make you drowsy.
- Avoid getting over-heated or dehydrated.
    - Do not over-exercise.
    - In hot weather, stay inside in a cool place if possible.
    - Stay out of the sun. Do not wear too much or heavy clothing.
    - Drink plenty of water.

What are the possible side effects of ABILIFY?

ABILIFY may cause serious side effects, including:

- **See "What is the most important information I should know about ABILIFY?"**
- **Stroke in elderly people (cerebrovascular problems) that can lead to death**
- **Neuroleptic malignant syndrome (NMS).** Tell your healthcare provider right away if you have some or all of the following symptoms: high fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and blood pressure. These may be symptoms of a rare and serious condition that can lead to death. Call your healthcare provider right away if you have any of these symptoms.
- **Uncontrolled body movements (tardive dyskinesia).** ABILIFY may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop receiving ABILIFY. Tardive dyskinesia may also start after you stop receiving ABILIFY.
- **Problems with your metabolism such as:**
  - **high blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who take ABILIFY. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes), your healthcare provider should check your blood sugar before you start ABILIFY and during your treatment.

    Call your healthcare provider if you have any of these symptoms of high blood sugar while receiving ABILIFY:

    - feel very thirsty
    - need to urinate more than usual
    - feel very hungry
    - feel weak or tired
    - feel sick to your stomach
    - feel confused, or your breath smells fruity

- **increased fat levels (cholesterol and triglycerides) in your blood.**
- **weight gain.** You and your healthcare provider should check your weight regularly.

- **Orthostatic hypotension (decreased blood pressure).** Lightheadedness or fainting may happen when rising too quickly from a sitting or lying position.
- **Low white blood cell count**
- **Seizures (convulsions)**
- **problems with control of your body temperature especially when you exercise a lot or are in an area that is very hot. It is important for you to drink water to avoid dehydration.** See "What should I avoid while receiving ABILIFY?"
- **difficulty swallowing that can cause food or liquid to get into your lungs.**

The most common side effects of ABILIFY in adults include:

- nausea
- vomiting
- constipation
- headache
- blurred vision
- upper respiratory illness
- dizziness
- anxiety
- insomnia
- restlessness
- inner sense of restlessness/need to move (akathisia)

The most common side effects of ABILIFY in children include:

- feeling sleepy
- headache
- vomiting
- fatigue
- increased or decreased appetite
- increased saliva or drooling
- insomnia
- nausea
- stuffy nose
- weight gain
- uncontrolled movement such as restlessness, tremor, muscle stiffness

These are not all the possible side effects of ABILIFY. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ABILIFY?

- Store ABILIFY at room temperature, between 68°F to 77°F (20°C to 25°C).
- Opened bottles of ABILIFY Oral Solution can be used for up to 6 months after opening, but not beyond the expiration date on the bottle.

Keep ABILIFY and all medicines out of the reach of children.

General information about the safe and effective use of ABILIFY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ABILIFY for a condition for which it was not prescribed. Do not give ABILIFY to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ABILIFY. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ABILIFY that was written for healthcare professionals.

For more information about ABILIFY visit www.abilify.com.

What are the ingredients in ABILIFY?

Active ingredient: aripiprazole

Inactive ingredients:

Tablets: cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake

ABILIFY DISCMELT Orally Disintegrating Tablets: acesulfame potassium, aspartame (which contains phenylalanine), calcium silicate, croscarmellose sodium, crospovidone, crème de vanilla (natural and artificial flavors), magnesium stearate, microcrystalline cellulose, silicon dioxide, tartaric acid, and xylitol. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake

ABILIFY Oral Solution: disodium edetate, fructose (200 mg per mL), glycerin, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose (400 mg per mL), and purified water. The oral solution is flavored with natural orange cream and other natural flavors

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan or Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Orally Disintegrating Tablets, Oral Solution, and Injection manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

ABILIFY is a trademark of Otsuka Pharmaceutical Company.

03US14L-1121

03US14L-1121C

Revised: December 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21436/S-38

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 021436/S-038

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Wang, Xiaofeng
Scales, Twanda
Birkner, Thomas
Tabacova, Sonia
Farchione, Tiffany
Holmes, Loretta
Mathis, Mitchell
Pohlman, Janice
Thompson, Susan
Dorantes, Angelica
Krudys, Kevin
Atrakchi, Aisar
Zhu, Hao
Pika-Branco, Denise

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21436/S-38

OFFICE DIRECTOR MEMO

M E M O R A N D U M

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

DATE: 10 December 2014

FROM: Mitchell V. Mathis, M.D.
Director
Division of Psychiatry Products, HFD-130

TO: File NDA 21436/S-038

SUBJECT: Summary memo and approval decision for aripiprazole tablets for the treatment of Tourette's disorder in pediatric patients ((b) (4) years)

Background

Aripiprazole is an atypical antipsychotic approved for the treatment schizophrenia (adults and adolescents), acute treatment of manic or mixed episodes associated with bipolar I disorder (adults and pediatric patients (10-17 years old)), maintenance treatment of bipolar I disorder (adults), adjunctive treatment of major depressive disorder (adults), and irritability associated with autism (ages 6-17). This supplement provides data for the treatment of (b) (4) Tourette's Disorder in pediatric patients ((b) (4) years). Currently available therapy for treating Tourette's is limited to two typical antipsychotic drugs: haloperidol and pimozide.

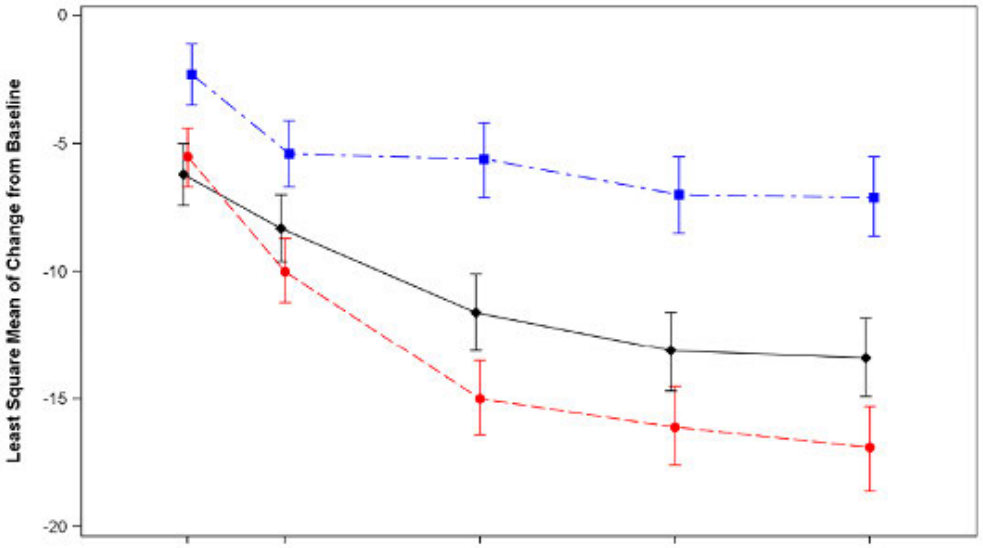
Clinical Summary and Statistics

Drs. Christina Burkhart and Mark Ritter have reviewed the clinical development program data and have recommended approval, and I agree with them. Dr. Thomas Birkner conducted the biometrics review and he too concluded that the efficacy endpoints had been met.

Two pivotal studies (one 8 weeks, the other 10 weeks) in pediatric patients were conducted multi-nationally—both support efficacy and neither identified any new safety concerns for this drug that is already approved for use in the pediatric population. Doses in the trials were based upon weight. The larger of the two studies was a fixed-dose study. Change in total tic severity score was the primary efficacy endpoint and was positive in both trials, and as noted by the reviewers, there was reduction of both motor and vocal tics.

Primary efficacy results from study 293 are presented graphically below. From the figure, dose-related decrease in tics can be seen as early as 2 weeks and the effect persists through Week 8.

LS Mean Changes from Baseline in YGTSS TTS Score by Week (MMRM) – ITT [Study 293]



P-value:					
ARIP-LOW	0.0049	0.0573	0.0014	0.0016	0.0020
ARIP-HIGH	0.0176	0.0031	<.0001	<.0001	<.0001

(Source: Study report p. 85; Error bars are least square means ± 1 standard error)

As noted in the reviews, lower weight children (less than 50 kg) randomized to the higher starting dose (10 mg per day) dropped out at a markedly higher rate compared to the lower dose groups. This led to a labeling recommendation of 5 mg/day for children less than 50 kg, with a maximum dose in this group of 10 mg/day.

Chemistry Manufacturing and Controls (CMC)

There were no CMC data submitted as part of this application. CMC recommended an approval action.

Nonclinical Pharmacology/Toxicology

No new preclinical studies were submitted as part of this application.

Office of Clinical Pharmacology (OCP)

Dr. Zhang reviewed the application. The focus of the review was assessment of the proposed dosing regimen in pediatric patients. Population PK and exposure-response analyses were conducted using data from the fixed-dose trial. These analyses confirmed that exposure in pediatric patients with Tourette's Disorder is similar to exposure in pediatric patients with other disorders, and the analyses supported the sponsor's proposed weight-based dosing which has been incorporated into labeling.

Labeling
Labeling was updated to include information from the two new studies and the sponsor has agreed with the changes.

Postmarketing Requirements/Commitments
The sponsor has agreed to conduct a standard maintenance study in pediatric patients with Tourette's Disorder.

Conclusions and Recommendations
Sufficient information has been submitted to conclude that aripiprazole is safe and effective in treating pediatric patients with Tourette's Disorder.

The labeling and Medication Guide have been negotiated to current Division standards.

The sponsor has agreed to labeling and to conduct a maintenance study post-marketing; this application should be approved by the PDUFA date.

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

/s/

MITCHELL V Mathis
12/11/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21436/S-38

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	NDA 21436/S-038
Priority or Standard	Standard
Submit Date(s)	2/12/2014
Received Date(s)	2/12/2014
PDUFA Goal Date	12/12/2014
Division / Office	DPP/OND
Reviewer Name(s)	Christina P Burkhart, M.D.
Review Completion Date	11/4/2014
Established Name	Aripiprazole
Trade Name	Abilify
Therapeutic Class	Atypical Antipsychotic
Applicant	Otsuka
Formulation(s)	Tablets: 2 mg, 5 mg,10 mg, 15 mg, 20mg, and 30mg
Dosing Regimen	< 50 kg: 2-10 mg per day > 50 kg: 2-20 mg per day
Indication(s)	[redacted] (b) (4) Tourette's Disorder in Pediatric Patients
Intended Population(s)	Pediatric Patients ([redacted] (b) (4) years)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that the Division take an Approval action for sNDA 21436, Supplement-38. Otsuka Pharmaceutical Company, Ltd has submitted two adequate and well-controlled trials that demonstrate the efficacy of Abilify in the treatment of Tourette's Disorder in pediatric patients.

The two pivotal studies in a pediatric population were as follows: a global (primarily US and Canada), short-term, placebo-controlled, fixed-dose (weight-based high and low dose) study (Trial 31-12-293) and a smaller, short-term, placebo-controlled, flexible-dose study conducted in South Korea (Trial 031-KOA-0703).

In Trial 31-12-293 (Trial 293), Abilify was efficacious in the treatment of tics in children and adolescents (aged 7-17 years) with a diagnosis of Tourette's disorder (TD). The improvement after administration of oral daily doses of 5 to 20 mg of Abilify in the primary efficacy endpoint of Yale Global Tic Severity Scale Total Tic Score (YGTSS TTS) was observed after the first week of treatment and was sustained through Week 8. The primary efficacy analysis demonstrated that both low and high doses of Abilify were superior to placebo in the treatment of tics based on the YGTSS TTS score ($p = 0.0020$ for low-dose and $p < 0.0001$ for high-dose Abilify). The key secondary efficacy analysis also showed that both low- and high-doses of Abilify were superior to placebo in Clinical Global Impressions Scale-Tourette's Syndrome (CGI-TS) improvement ($p = 0.0002$ for low-dose and $p = 0.0002$ for high-dose Abilify). In addition, oral daily doses of 5 to 20 mg of Abilify were generally well tolerated in pediatric subjects with TD and no new safety findings were identified in this population.

In the smaller, earlier trial (Trial 031-KOA-0703) conducted at six sites in South Korea; the efficacy of Abilify in the treatment of Tourette's syndrome in a pediatric population (aged 6-18 years) was also demonstrated. The primary study objective was to evaluate Abilify relative to placebo in reducing tics from randomization to final visit using the Korean version of YGTSS (K-YGTSS). Subjects were randomized 1:1 to aripiprazole or placebo. The study medication was given orally once daily for 10 weeks with incremental dose adjustment (2, 5, 10, 15, or 20 mg/day maximum) every two weeks based on TSS-CGI and AEs. The ITT analysis result showed that the mean total Tic score was changed from 29.48 at Baseline to 19.86 at the final visit for Placebo group, showing a decrease, by -9.62. For Aripiprazole group, it also changed from 28.34 at Baseline to 13.55 at the final visit, showing a greater decrease (-14.79). The difference in the change from Baseline to the final visit between the treatment groups was statistically significant (p-value=0.0196, two-sample t-test). Safety findings were consistent with the know safety profile of Abilify.

1.2 Risk Benefit Assessment

The overall benefit-risk for the use of aripiprazole in patients with Tourette's Disorder (TD) is favorable. Results from two phase 3, double-blind, placebo-controlled trials, Trials 31-12-293 and 031-KOA-0703, indicate that aripiprazole is efficacious in the treatment of (b) (4) TD. The safety and tolerability of aripiprazole have been shown in multiple indications in both adult and pediatric patients. There is an extensive safety data base. The safety findings in these two trials in pediatric patients with TD were consistent with the known safety profile of Abilify.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Routine risk minimization (i.e., FDA-approved product label) and routine pharmacovigilance will be adequate to manage the risk-benefit profile of Abilify in the treatment of Tourette's Disorder in pediatric patients.

1.4 Recommendations for Postmarket Requirements and Commitments

A PMC for a controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of aripiprazole in the treatment of Tourette's Disorder in pediatric patients (6-17 years) is recommended. This trial must include a placebo group and more than one fixed dose and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of aripiprazole.

2 Introduction and Regulatory Background

2.1 Product Information

Abilify is an atypical antipsychotic indicated for the treatment of schizophrenia (adults and adolescents); acute treatment of manic or mixed episodes associated with bipolar I disorder (adults and pediatric patients, ages 10-17); maintenance treatment of bipolar I disorder (adults); adjunctive treatment of major depressive disorder (adults); treatment of irritability associated with autistic disorder (pediatric patients, ages 6-17); and acute treatment of agitation associated with schizophrenia or bipolar I disorder (adults). The mechanism of action of aripiprazole is unknown. It has been proposed that aripiprazole's efficacy is mediated through a combination of partial agonist activity at D2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors.

2.2 Currently Available Treatments for Proposed Indications

The typical antipsychotics, Haldol (haloperidol) and Orap (pimozide), are approved for the treatment of tics in patients with Tourette's syndrome. Alpha-adrenergic agonists such as clonidine and guanfacine are also used off-label to treat tics. Atypical antipsychotics are used off-label as second line agents. However, the majority of people with Tourette's syndrome require no medication for tic suppression. Behavioral treatments such as awareness training and competing response training can also be used to reduce tics.[1]

2.3 Availability of Proposed Active Ingredient in the United States

Abilify (aripiprazole) has been marketed in the United States since 2002 and is readily available.

2.4 Important Safety Issues With Consideration to Related Drugs

Important safety issues with the atypical antipsychotics include increased incidence of cerebrovascular adverse events in the elderly with dementia-related psychosis; neuroleptic malignant syndrome; tardive dyskinesia; unfavorable metabolic changes (hyperglycemia, dyslipidemia, and weight gain); orthostatic hypotension; leukopenia, neutropenia, and agranulocytosis; seizures/convulsions; potential for cognitive and motor impairment; and the risk of suicide.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Aripiprazole was first approved for the treatment of schizophrenia in adults on 17 Jul 2002 (International Birth Date) in Mexico and subsequently in the US in 2002 and the EU in 2004. Aripiprazole was approved for use in adolescent schizophrenia in the US in 2007 and in the EU in 2009. In addition, aripiprazole was approved for acute manic or mixed episodes associated with bipolar I disorder in pediatric patients in the US in 2008. It was also approved for the treatment of irritability associated with autistic disorder in pediatric patients in 2009. Aripiprazole has not been withdrawn for any reasons of safety or efficacy from the market in any country.

Summary of Presubmission Regulatory Activity for this sNDA
The Agency's feedback on the development program was requested when the Tourette's disorder IND application (IND 116,003) was submitted on 15 Aug 2012, and FDA's feedback was provided in the "Study May Proceed" letter dated 14 Sep 2012 and in a follow-up teleconference held on 2 Oct 2012. According to the Applicant, the FDA's recommendations were instrumental in the design of one of the two pivotal studies (Trial 31-12-293), including the selection of doses to be evaluated. The Division also

[1] National Institute of Neurological Disorders and Stroke Tourette Syndrome Fact Sheet, October 2012

recommended CGI-TS as a key secondary efficacy measure and confirmed that the aggregate safety database for all indications for which oral aripiprazole has been studied in children and adolescents could be used to support the safety of aripiprazole for the Tourette's disorder indication.

A pre-NDA meeting was requested on 20 Mar 2013 to discuss the content and format of the sNDA submission. The meeting was canceled because all of the questions were addressed in the FDA's "Preliminary Meeting Comments" letter (21 May 2013), and in follow-up e-mail communications (23 May 2013) with the Senior Regulatory Project Manager, Kofi Ansah, Pharm.D.

2.6 Other Relevant Background Information

Aripiprazole has been approved for treatment of tics associated with TD in pediatric patients in Korea (patients aged 6-18 years), the Philippines, Thailand, and Egypt.

Aripiprazole for the Tourette's disorder indication is an orphan drug (Orphan Designation granted 25 Jan 2006, no. 05-2079), and in accordance with 21 CFR 314.55(d), it is therefore exempt from the requirement to submit pediatric data or request a waiver or deferral for all pediatric subpopulations.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Initially datasets were incomplete for Study 031-KOA-0703. Listing datasets did not specify the treatment administered, and analysis datasets did not have unique subject identifiers. The Applicant was notified of the problem and submitted amended datasets on 3/7/2014.

3.2 Compliance with Good Clinical Practices

Trial 031-KOA-0703 was not conducted under a US IND. The Applicant states that the trial was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements, KGCP and related regulations. The Applicant has provided documentation to demonstrate that the study meets the requirements of 21 CFR 312.120.

Trial 31-12-293 was a global trial that was conducted at sites in North America (including the United States) and Europe. This trial was conducted under IND 116,003. The Applicant states that Trial 31-12-293 was conducted in accordance with the

International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline and the applicable local laws and regulatory requirements of the countries in which the trial was conducted.

The Division requested an OSI Consult (4/9/2014) for routine inspections of the clinical sites. Two sites were inspected for the larger Study 31-12-293 (3% of sites, 25% of subjects). Six sites were inspected for the smaller (and earlier) Study 031-KOA-0703 (all sites, all 61 subjects). The following sites were inspected:

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects
510: Robert Riesenberg, M.D. Atlanta Center for Medical Research 811 Juniper Street Atlanta, GA 30308 US	31-12-293	10 Screened 10 Enrolled
533: Sohail Khattak, MD, FRCP Kids Clinic 1615 Dundas Street East, Unit 19 Whitby, ON L1N 2L1 Canada	31-12-293	27 Screened 23 Enrolled
001: Seoul University Hospital 28 Yeongeon-Dong, Jongro-Gu, Seoul (Tel: 02-2072-2114)	South Korea 031-KOA-0703	14 Screened 12 Enrolled
002: Seoul Asian Hospital 388-1 2-Dong, Poongnap, Songpa-Gu, Seoul (Tel: 1688-7575)	South Korea 031-KOA-0703	Screened 12 Enrolled 10
003: Social Welfare Corporation, Samsung Life Public Service Foundation, Samsung Medical Center 50, Ilweon-Dong, Gangnam-Gu, Seoul (Tel: 1599-3114	South Korea 031-KOA-0703	Screened 17 Enrolled 9

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects
004: Inha University Hospital 7-206, 3-Ga, Shinheung-Dong, Joong-Gu, Incheon (Tel: 032-890-2114	South Korea 031-KOA-0703	Screened 19 Enrolled 14
005: Yonsei University Medical School, Severance Hospital (134 Shinchon-Dong) 250 Seongsan-Ro, Seodaemun-Gu, Seoul (Tel: 02-2227(8)-0114	South Korea 031-KOA-0703	Screened 13 Enrolled 9
006: Chungang University Hospital 224-1 Heukseok-Dong, Dongjak-Gu, Seoul (Tel: 02-6299-1114)	South Korea 031-KOA-0703	Screened 8 Enrolled 7

The inspection outcomes are shown in the table below [excerpted from Dr. Jong Lee's Clinical Inspection Summary (9/15/2014)]:

	Clinical Investigator Site	Study, Site, Enrollment	Inspection Outcome
1	Robert Riesenberg, M.D. Atlanta Center for Medical Research Atlanta, GA, USA	Study 31-12-293 Site 510, 10 subjects	June 9 – 23, 2014 NAI
2	Sohail Khattak, M.D. Kids Clinic Whitby, Ontario, Canada	Study 31-12-293 Site 533, 23 subjects	June 17 – 20, 2014 pending preliminary NAI
3	Soo-Churl Cho, M.D. Seoul National University Hospital Seoul, South Korea	Study 031-KOA-0703 Site 001, 12 subjects	June 16 – 20, 2014 pending preliminary NAI
4	Han-Ik Yoo, M.D. Asan Hospital Seoul, South Korea	Study 031-KOA-0703 Site 002, 10 subjects	June 23 – 27, 2014 pending preliminary NAI
5	Yoo-Sook Jeong, M.D. Samsung Medical Center Seoul, South Korea	Study 031-KOA-0703 Site 003, 9 subjects	June 30 – July 7, 2014 pending preliminary VAI
6	Jeong-Seop Lee, M.D. Inha University Hospital Incheon, South Korea	Study 031-KOA-0703 Site 004, 14 subjects	June 16 – 20, 2014 VAI
7	Dong-Ho Song, M.D. Severance Hospital Seoul, South Korea	Study 031-KOA-0703 Site 005, 9 subjects	June 23 – 26, 2014 VAI
8	Young-Sik Lee, M.D. Chungang University Hospital Seoul, South Korea	Study 031-KOA-0703 Site 006, 7 subjects	June 30 – July 3, 2014 VAI

NAI = no action indicated (no significant GCP violations); VAI = voluntary action indicated (acceptable GCP violations)

Pending: The preliminary classification is based on information on Form FDA 483 and communication with the field investigator. The establishment inspection report (**EIR**) has not been received from the field office and the EIR review remains pending as of this clinical inspection summary (**CIS**).

Source: Clinical Inspection Summary, p. 4

Dr. Lee's conclusions about the data integrity are as follows:

- For Study 31-12-293, significant deficiency observations were not observed and all audited data were verifiable as reported in the NDA. The study data appear acceptable as reported in the NDA.
- For Study 031-KOA-073, many GCP deficiencies were observed at Sites 003, 004, 005, and 006 with a combined enrollment of 39 subjects (64%). The deficiencies were typically minor, isolated, or otherwise unlikely to be significant. All observations appear to be consistent with inexperienced study conduct; evidence of unblinding or biased study conduct was not observed. Deficiencies with potential impact on data integrity appear to be limited to two subjects: Subject 09 at Site 003 for inadequate subject eligibility assessment[2] and Subject 05 at Site 004 for improperly corrected efficacy data on CRFs[3]. The data for Study 031-KOA-0703 otherwise appear acceptable as reported in the NDA.
- Note: For four inspections (Site 533 in Study 31-12-293, Sites 001-003 in Study 031-KOA-0703), the EIR has not been received from the field office and the final inspection outcome classification remains pending. An addendum to this CIS will be forwarded to the review division if the outcome classification changes or if new observations of clinical or regulatory significance are discovered upon receipt and review of the EIR.

3.3 Financial Disclosures

See Appendix 9.4 and 9.5 for attached Financial Disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Reference is made to NDA 21-436 for Aripiprazole Oral Tablets for Chemistry, Manufacturing, and Controls (CMC) information. No changes to the existing approved CMC information for aripiprazole have been proposed in this sNDA.

[2] Subject 009 (Site 003) had a history of pre-existing hydrocephalus and recent neurosurgery. Subject selection criteria specify exclusion for serious cephalic damage, symptomatic neurological disorder except TD, or any condition which complicates study conduct or data interpretation. This subject was randomized to aripiprazole.

[3] Subject 005 (Site 004) had an inadequate audit trail for CRF corrections for TTS-K-YGTSS at Visit 2 (score changed from 26 to 22). Subject 005 was in the placebo group.

4.3 Preclinical Pharmacology/Toxicology

Reference is made to NDA 21-436 for Aripiprazole Oral Tablets for nonclinical information pertaining to orally administered aripiprazole. Reports of all nonclinical studies of orally administered aripiprazole have been previously submitted to NDA 21-436.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of aripiprazole is unknown. It has been proposed that aripiprazole's efficacy is mediated through a combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors.

The Applicant states that although the precise etiology of TD remains unknown, disturbances in dopaminergic and/or serotonergic pathways have been implicated because of the close association between TD and other disorders that involve imbalances in dopamine and/or serotonin (e.g., obsessive-compulsive disorder and attention-deficit hyperactivity disorder).

4.4.2 Pharmacodynamics

A population pharmacokinetic/pharmacodynamic (PK/PD) analysis based on samples obtained from subjects who participated in Trial 31-12-293 was conducted, and the report is included in this sNDA submission. A previously developed population PK model was used in the population PK/PD analysis of trial 31-12-293, and the report is also included in this submission. These reports were reviewed by Dr. Huixia Zhang (OCP). In her review, Dr. Zhang concluded that the population pharmacokinetic analysis in the current submission demonstrated similarity in PK across pediatric subjects with Tourette's disorder, schizophrenia, and bipolar disorder (see Zhang review 11/3/2014).

4.4.3 Pharmacokinetics

Please see Section 4.4.2.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Table of Clinical Trials

Listing of Clinical Trials							
Type of Trial (Trial Phase)	**Protocol Number Location of Trial**	**Trial Objective(s)**	**Trial Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Subjects Randomized[a]**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Duration**
Efficacy and Safety Trials							
Completed Placebo-controlled, Short-term Pediatric Trials in Tourette's Disorder							
Safety and efficacy (Phase 3)	31-12-293 Canada, Hungary, Italy, and United States	Efficacy and safety	Randomized, double-blind, placebo-controlled, fixed dose	OPC 2 mg QD PO OPC 5 mg QD PO OPC 10 mg QD PO OPC 15 mg QD PO OPC 20 mg QD PO Placebo QD PO	OPC: 89 Placebo: 44	Pediatric subjects aged 7-17 years with TD	8 weeks
Safety and efficacy (Phase 3)	031-KOA-0703 South Korea	Efficacy and safety	Randomized, double-blind, placebo-controlled, flexible dose	OPC 2-20 mg QD PO Placebo QD PO	OPC: 32 Placebo: 29	Pediatric subjects aged 6-18 years with chronic tic disorders or TD	10 weeks
Ongoing Open-label, Long-term Pediatric Trials in Tourette's Disorder							
Safety (Phase 3)	31-12-294 Canada, Hungary, Italy, and United States	Safety	Open-label, uncontrolled, rollover, flexible dose	OPC 2-20mg QD PO	110[a]	Pediatric subjects aged 7-17 years with TD who completed Trial 31-12-293	52 weeks

5.2 Review Strategy

The clinical study reports were reviewed in detail. Narratives of all death, SAEs, and discontinuations due to AEs were reviewed. The Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, Literature Review, Reports of Postmarketing Experience, and 120-Day Safety Update were also reviewed. Raw safety sets were

reviewed in JMP/JReview and compared to the safety detailed in the clinical study reports. The proposed labeling was also reviewed in detail.

5.3 Discussion of Individual Studies/Clinical Trials

The submission for this efficacy supplement comprises 2 pivotal studies in a pediatric population: a smaller, short-term, placebo-controlled, flexible-dose study conducted in South Korea (Trial 031-KOA-0703) and a global (primarily US and Canada), short-term, placebo-controlled, fixed-dose (weight-based high and low dose) study (Trial 31-12-293). The trial designs and efficacy results for these two pivotal trials are described in Section 6.

The two pivotal trials (Trial 31-12-293 and Trial 031-KOA-0703) also provide the primary safety data to support the basis of approval of once-daily aripiprazole as a treatment for TD. The safety results for these trials are detailed in Section 7.

An additional 52-week, open-label, flexible-dose trial (Trial 31-12-294) is ongoing. This trial will provide long-term safety data pertinent to the use of aripiprazole in the treatment of pediatric patients with TD. This trial's design and preliminary safety results are detailed in Section 7.

In addition to the trials in subjects with TD, 16 trials in pediatric subjects with other conditions have been conducted in the context of other aripiprazole clinical development programs. A brief summary of the safety data from these trials will also be provided in Section 7.

6 Review of Efficacy

Efficacy Summary

Trial 031-KOA-0703

The primary efficacy analysis was carried out on the ITT[4] population. All 61 subjects who were enrolled and randomized in six study sites were included in the ITT population; 29 in Placebo group and 32 in Aripiprazole group. The analysis results of the primary efficacy endpoint, mean change of total Tic scores in KYGTSS from randomization to the final visit showed that the mean total Tic score changed from 29.48 (±5.60) at Baseline to 19.86 (±9.54) at the final visit for Placebo group, showing a decrease, by -9.62 (±8.83). For Aripiprazole group, it changed from 28.34 (±5.51) at Baseline to 13.55 (±9.12) at the final visit, showing a greater decrease, by -14.79 (±8.42). The difference in the change from Baseline to the final visit between the treatment groups was statistically significant (p-value=0.0196, two-sample t-test).

[4] The Intention-To-Treat (ITT) population was defined as all randomized subjects.

Efficacy analysis was also carried out on the FAS[5] and PP[6] population. The difference in the change from Baseline to the final visit between the treatment groups was statistically significant for the FAS population but not the PP population.

No key secondary endpoint was specified. The Agency recommended that a retrospective analysis be done on the CGI-I results since CGI-I was the key secondary in the other pivotal trial (Trial 31-12-293). Numerical results for LS mean CGI-I at endpoint were similar to those for Trial 31-12-293. The numerical difference favored aripiprazole throughout the trial. However, statistical significance was demonstrated at Weeks 2 and 6 but not at endpoint (Week 10).

Trial 31-12-293
In Trial 293, aripiprazole was efficacious in the treatment of tics in children and adolescents (aged 7-17 years) with a diagnosis of Tourette's disorder (TD). The improvement after administration of oral daily doses of 5 to 20 mg of aripiprazole in the primary efficacy endpoint of Yale Global Tic Severity Scale Total Tic Score (YGTSS TTS) was observed after the first week of treatment and was sustained through Week 8. The treatment difference between the low-dose aripiprazole and placebo groups (-6.26) in YGTSS TTS (primary endpoint) was statistically significant ($p = 0.0020$) at Week 8; the treatment difference between the high-dose aripiprazole and placebo groups (-9.85) was also statistically significant ($p < 0.0001$) at Week 8.

The key secondary efficacy analysis also showed that both low- and high-doses of aripiprazole were superior to placebo in Clinical Global Impressions Scale-Tourette's Syndrome (CGI-TS) improvement. The treatment difference between the low-dose aripiprazole and placebo groups (-1.03) in the CGI-TS Change Score (secondary endpoint) was statistically significant ($p = 0.0001$) at Week 8; the treatment difference between the high-dose aripiprazole and placebo groups (-1.02) was also statistically significant ($p = 0.0002$) at Week 8.

6.1 Trial 031-KOA-0703

This study was not conducted under an IND though the study was conducted in accordance with GCP and Korea Otsuka SOPs for clinical investigation and documentation.

Study Period: 18 August 2008 to 21 April 2010

[5] The Full Analysis Set (FAS) population was defined as the subjects who took investigational product at least once and had evaluable primary efficacy data.
[6] The Per-Protocol (PP) population was defined as the subjects who completed the study with no major protocol violation among those included in the FAS population.

Title: "A randomized, double-blind, dose-adjustment, Placebo-controlled study to evaluate the efficacy and safety of Aripiprazole in children and adolescents with chronic Tic disorders or Tourette's disorder"

6.1.1 Methods

Objectives

Primary objective:

- To demonstrate the efficacy of aripiprazole versus placebo in the children and adolescents with chronic Tic disorders or Tourette's disorder using mean change from randomization to the final visit in total Tic scores assessed by the Korean version of Yale Global Tic Severity Scale (K-YGTSS).

Secondary objectives:

- To assess the response rate and partial response rate of treatment with Aripiprazole compared to Placebo as measured by the TS-CGI-Global Improvement scale
- To assess the efficacy of treatment with Aripiprazole compared to Placebo by measuring the mean change in TS-CGI-Global Severity of illness scale
- To assess the safety and tolerability of treatment with Aripiprazole compared to Placebo in children and adolescents

Design

This was a Phase 3, multicenter (6 sites in South Korea), double-blind, placebo-controlled, flexible-dose study. Subjects were randomized to either Aripiprazole (Abilify®) or Placebo in a 1:1 ratio on Day 1. An appropriate dose (2mg to 20mg) of Aripiprazole (Abilify®) or Placebo was administered daily for 10 weeks. The dose was administered daily at about the same time (if possible, morning) without regard to meals. All subjects visited the hospital every 2 weeks, and the investigators adjusted the investigational product (IP) dose according to the improvement of Tic symptoms and incidence of adverse events.

The dose could be increased from 2 mg/day to 5 mg/day, 10 mg/day, 15 mg/day, and 20 mg/day. The decision to increase the dose to the next higher dose was made at the visits every 2 weeks. The maximum target dose was 20 mg/day, but it was not mandatory to reach the maximum dose. The investigator made the decisions on the dose adjustments based on the improvement of Tic symptoms (score of the TS-CGI-I scale) and adverse events according to the following criteria:

- Criteria for maintaining dose: a score is 1 or 2 in the TS-CGI-I scale and tolerable adverse event(s)
- Criteria for increasing dose: a score is ≥ 3 in the TS-CGI-I scale and tolerable adverse event(s)
- Criteria for reducing dose: in case of an intolerable adverse event(s); the dose can be decreased to the previous dose or IP can be discontinued based on the

investigator's discretion. If the dose was decreased to the previous dose, the reduced dose was maintained until the final visit.

Randomization Method
The randomization list was prepared using the block randomization method stratified by the clinical trial site and the age group (children: 6-11 years; adolescent: 12-18 years). If the subject met the inclusion/exclusion criteria, the investigator accessed the study website for randomization, and entered the subject's basic information. Based on the information entered, the subject ID and treatment number were assigned.

Treatment Compliance
The drug compliance was defined as a ratio of the actually administered quantity to the planned administered quantity. If the drug compliance was < 80%, it was considered as a major protocol deviation, and the subject was excluded from the PP analysis set.

For subjects dose titration errors: if the value was below 80% or over 120%, it was considered a protocol deviation and the subject was excluded from the PP analysis set.

Subjects
Key Inclusion Criteria:

- Male or female children and adolescents aged 6 to 18 years
- Diagnosis of chronic Tic disorders (vocal Tic and motor Tic) or Tourette's disorder according to DSM-IV (using K-SADS-PL-K)
- Subjects require drug therapy
- Subjects have ≥ 22 in total Tic scores on the K-YGTSS at baseline visit (Visit 2)

Key Exclusion Criteria:

- Subjects with secondary Tic symptoms accompanied by Tardive tics, Huntington disease, neuroacanthocytosis, mental retardation, or autism
- IQ ≤ 70 (Wechsler Intelligence Scale)
- Body weight ≤ 16 kg at randomization
- Pregnant, nursing, or unwilling to use contraception during the study and up to 8 weeks after completion of the study
- History of neuroleptic malignant syndrome
- Subjects diagnosed with the following disorders according to DSM-IV (using KSADS-PLK): Schizophrenia, Mood disorders including major depressive disorder and bipolar disorder
- Subjects with comorbidity requiring drug therapy, such as attention deficit/hyperactive disorder, obsessive-compulsive disorder or Oppositional Defiant Disorder
- History of seizure disorder, serious brain injury, stroke, or other neurologic disorders

- Subjects with diseases that might cause serious adverse events during the study and make it difficult to continue the study (e.g., myocardial infarction, ischemic heart disease, arrhythmia, asthma, heart failure, or malignancy, etc.)
- Subjects with a known history of psychotropic drugs or alcohol use disorder (abuse, dependence, and/or withdrawal) during the 3 months preceding screening
- Subjects with clinically significant abnormalities in clinical laboratory tests, vital signs, 12-lead ECG, or physical examination
- Subjects who have taken antipsychotic or antiparkinson drugs within 1-2 weeks prior to randomization
- Subjects who have received fluoxetine within 4 weeks prior to randomization
- Subjects requiring cognitive-behavioral therapy (habit reversal therapy, cognitive therapy, relaxation training, etc.) during the study period
- Subjects with a history of resistance to treatment with antipsychotics
- Subjects who have previously received Aripiprazole or participated in a clinical study with Aripiprazole

Prohibited Medications

- Antidepressant, antianxiety drug, sedative, hypnotic
- Mood stabilizer or antimanic drug
- Antipsychotic drug except investigational product
- Cognitive function improver
- Inducer of CYP3A4 (e.g., Carbamazepine)
- Inhibitor of CYP3A4 (e.g., Ketoconazole)
- Inhibitor of CYP2D6 (e.g., Quinidine, Fluoxetine[7], Paroxetine)
- Stimulants
- Neuroleptic
- Dopamine secretion facilitate or dopamine receptor drug
- Antiparkinson drug[8]
- Alcohol

Criteria for Efficacy Evaluation

Primary Efficacy Outcome Measure (Primary endpoint):

- Mean change of total Tic scores in K-YGTSS from randomization to the final visit

[7] Fluoxetine administration was prohibited within 4 weeks prior to the randomization.
[8] Antiparkinson drugs were not allowed for prophylactic purposes, but could be prescribed for treatment of extrapyramidal symptom (EPS) according to the investigator's decision.

Secondary Efficacy Outcome Measures (Secondary endpoints)[9]:

- Response rate (percentage of subjects with score 1 or 2) and partial response rate (percentage of subjects with score 3) in TS-CGI-I scale at final visit
- Mean change of TS-CGI-S score from randomization to the final visit
- Percent change of total Tic scores in the K-YGTSS from randomization to the final visit:

$$\frac{\text{(total Tic score in the K–YGTSS at the final visit – total Tic score in the K-YGTSS at randomization)}}{\text{total Tic score in the K-YGTSS at randomization}} \times 100$$

Criteria for Safety Evaluation

- Serious Adverse Events (SAEs)/Adverse Events (AEs)
- Extrapyramidal symptoms as measured by mean score change of Simpson-Angus Rating Scale (SARS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movements Scale (AIMS) from randomization to the final visit
- Vital signs (blood pressure and pulse in a sitting position)
- Clinical laboratory tests including serum prolactin
- Physical examination
- 12-lead ECGs
- Changes in weight, BMI, and waist circumference

[9] No key secondary endpoint was specified.

Table 2: Trial KOA Clinical Laboratory Tests

Hematology :	Serum Chemistry :
White Blood Cell Count (WBC) with differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)	Albumin
Red Blood Cell Count (RBC)	Blood Urea Nitrogen (BUN)
Hematocrit	Creatinine
Hemoglobin	Creatinine phosphokinase (CPK)
Platelets	Aspartate Transaminase (AST or SGOT)
	Alanine Transaminase (ALT or SGPT)
Urinalysis:	Lactic Dehydrogenase (LDH)
pH	Alkaline Phosphatase (ALP)
Glucose	Total Bilirubin
Protein	Chloride
Ketones	Calcium
Blood	Glucose (fasting)
Specific gravity	Sodium
WBC	Phosphorous
	Total cholesterol (fasting)
Other:	HDL cholesterol (fasting)
Serum Prolactin	LDL cholesterol (fasting)
Insulin levels (fasting)	Triglycerides (fasting)
HbA1c (Glycosylated Hemoglobin)	Magnesium
Urine Pregnancy test (Applicable to childbearing potential women)	Potassium
	Total Protein
	Uric acid
	Gamma Glutamyl Transferase (GGT)

Source: Trial Report, p. 39

Statistical Methods

Primary Endpoint:
Paired t-test of the change from randomization in K-YGTSS total Tic scores to the final visit was performed and two-sample t-test was used to evaluate difference of change of Total Tic scores from Baseline to the final visit between treatment groups.

Sample Size Determination:
The difference in the decrease of total Tic scores in the KYGTSS from baseline to 10 weeks post-administration between Aripiprazole group and Placebo group was postulated to be 12.4. Providing that subjects would be equally divided to Aripiprazole group and Placebo group (1:1), the required number of subjects per group was calculated to be 21. If a 25 % rate of drop-out was taken into account, 28 subjects would be needed for each group. Therefore, the applicant aimed to enroll a total sample size of 56.

6.1.2 Demographics

The sixty-one ITT subjects were between 6 and 18 years old. The mean age of the ITT subjects was 10.95 years. Most of the randomized subjects were male [53 male subjects (86.89%) and 8 female subjects (13.11%)]. None of the demographics and other baseline characteristics showed a statistically significant difference between the treatment groups. All subjects were from South Korea.

Table 3: Trial KOA Summary of Demographics and Baseline Characteristics

Item		Statistic	Placebo	Aripiprazole	Total	P-value[#1]
Number of subjects in ITT population			29	32	61	
Age (years)		N	29	32	61	0.9575 [a]
		Mean	10.93	10.97	10.95	
Height (cm)		N	29	32	61	0.1927 [a]
		Mean	144.25	149.37	146.94	
Body weight (kg)		N	29	32	61	0.2755 [b]
		Mean	41.46	46.15	43.92	
		Min~Max	19.20~ 76.20	25.20~114.60	19.20~114.60	
Heart rate (beats/min)		N	29	32	61	0.7023 [a]
		Mean	82.59	83.88	83.26	
SBP (mmHg)		N	29	32	61	0.4977 [a]
		Mean	106.41	108.94	107.74	
DBP (mmHg)		N	29	32	61	0.4128 [a]
		Mean	64.83	66.91	65.92	
Waist Circumference (cm)		N	29	32	61	0.8228 [b]
		Mean	67.84	69.65	68.79	
		Min~Max	51.00~ 84.00	54.00~115.00	51.00~115.00	
Sex	Male	N (%)	23 (79.31)	30 (93.75)	53 (86.89)	0.1351 [d]
	Female	N (%)	6 (20.69)	2 (6.25)	8 (13.11)	

Source : Table 13.1
Note:
#1 P-values for the difference between treatment groups (a. Two-sample t-test, b. Wilcoxon rank sum test, c. Chi-square test, d. Fisher's exact test)

Source: Trial Report, p. 51

Psychiatric History

All 61 subjects had a diagnosis of Tourette's disorder. Past psychiatric diagnoses included attention deficit/hyperactivity disorder (ADHD) and enuresis. Current psychiatric diagnoses included ADHD, oppositional defiant disorder (ODD), and anxiety disorder.

Table 4: Trial KOA Past and Current Psychiatric Diagnoses (ITT)

Psychiatric Diagnosis	Placebo N=29 n (%)	Aripiprazole N=32 n (%)	Total N=61 n (%)
Past Psychiatric Diagnosis	0	2 (6.3)	2 (3.3)
ADHD	0	1 (3.1)	1 (1.6)
Enuresis	0	1 (3.1)	1 (1.6)
Current Psychiatric Diagnosis	2 (6.9)	6 (18.8)	8 (13.1)
ADHD	1 (3.5)	5 (15.6)	6 (9.8)
ODD	0	3 (9.4)	3 (4.9)
Anxiety Disorder	1 (3.5)	0	1 (1.6)

Source: Trial Report, p.55

Concomitant Medication

All concomitant medications were subcategorized into Pre-medication (taken before the investigational product), Concomitant medication (during the investigational product administration) and Post-medication (taken after the last investigational product). P-values computed from Chi-square tests were not significant indicating there were no difference between groups.

Table 5: Trial KOA Concomitant Medication

Medication	Placebo N=29 n (%)	Aripiprazole N=32 n (%)
Pre-medication		
Psycholeptics	8 (27.6)	6 (18.7)
Anti-Parkinson Drugs	5 (17.2)	2 (6.3)
Psychoanaleptics	3 (10.3)	2 (6.3)
Concomitant		
Analgesics	3 (10.3)	4 (12.5)
Anti-Parkinson Drugs	1 (3.5)	2 (6.3)
Antihistamines	2 (6.9)	2 (6.3)
Post-medication		
Psycholeptics	27 (93.1)	26 (81.2)
Anti-Parkinson Drugs	4 (13.7)	0
Psychoanaleptics	1 (3.5)	1 (3.1)

Source: Trial Report, p.55-57

The subjects who took prior medication or other treatment for previous episodes of psychiatric diagnosis are summarized in Table 6. The group difference was not statistically different (p-value= 0.3257).

Table 6: Trial KOA Prior Medication or Other Treatment for Previous Episodes of Psychiatric Diagnosis (ITT)

Number of subjects with prior medication or other treatment for previous episodes of psychiatric diagnosis	
Placebo N=29 n (%)	**Aripiprazole** N=32 n (%)
19 (65.5)	17 (53.1)

Source: Trial Report, p.57

6.1.3 Subject Disposition

Table 7: Trial 031-KOA-0703 Disposition of Subjects by Sites

Table 9.1 Disposition of subjects by sites

Sites[#1]	Screening	Randomized	Placebo			Aripiprazole		
			Total	Completed	Discontinued	Total	Completed	Discontinued
001	14	12	6	4	2	6	5	1
002	12	10	5	4	1	5	5	0
003	17	9	4	4	0	5	5	0
004	19	14	5	5	0	9	8	1
005	13	9	5	4	1	4	3	1
006	8	7	4	4	0	3	3	0
Total	83	61	29	25	4	32	29	3

#1 sites: 001: Seoul National University Hospital, 002: Asan Medical Center, 003: Samsung Medical Center, 004: Inha University Hospital, 005: Severance Hospital, 006: Chung-Ang University Medical Center

Source: Trial Report, p.47

Seven subjects discontinued (4 in the Placebo group and 3 in the Aripiprazole group). The reasons for discontinuation are listed in Table 8 below. Three subjects were withdrawn from participation by the investigator. Symptom aggravation was listed as the reason in all three cases. One subject in the Aripiprazole group had a protocol deviation listed as the reason for discontinuation. This protocol deviation was listed as a violation of Exclusion Criteria #9 (clinically significant abnormalities in clinical laboratory tests, vital signs, 2-lead ECG, or physical examination).

Table 8: Trial KOA Disposition of Subjects

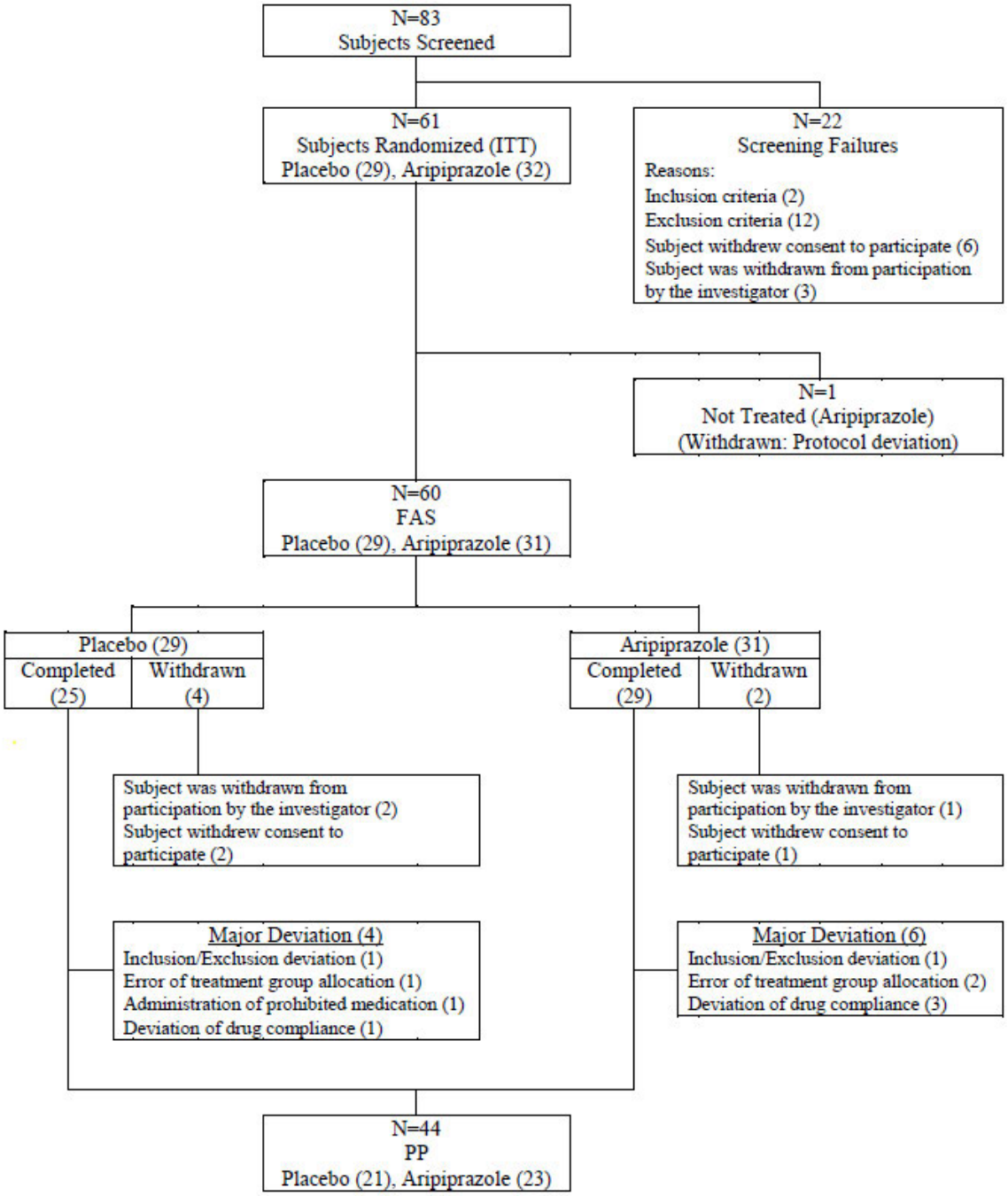
Table 9.2 Disposition of subjects

	Number of Subjects		
	Placebo	Aripiprazole	Total
Randomized	29	32	61
Treated	29	31	60
Not treated	0	1	1
Completion status for randomized subjects			
Completed	25	29	54
Discontinued	4	3	7
P-value[#1]			0.6988
Reason for discontinuation of the randomized subjects			
Lost to follow-up	0	0	0
Adverse events	0	0	0
Sponsor discontinued study	0	0	0
Subject met withdrawal criteria	0	0	0
Subject was withdrawn from participation by the investigator	2	1	3
Subject withdrew consent to participate	2	1	3
Protocol deviation	0	1	1

Note:
#1 The p-value is computed from Fisher's exact test.

Source: Trial Report, p.47

Figure 1: Trial KOA Disposition of Subjects



Source: Trial Report, p.48

Protocol Deviations

Eleven subjects were determined to have major protocol deviations (4 in the Placebo group and 7 in the Aripiprazole group). Two subjects deviated from the exclusion criteria by having previously received Aripiprazole. This deviation was considered to have a

potential impact on efficacy. These 2 subjects were excluded from the per protocol analysis set. Five subjects had deviations in drug compliance. One subject in the Aripiprazole group had less than 80% of drug compliance and four subjects (1 in the Placebo group and 3 in the Aripiprazole group) were out of the dose based drug compliance range of 80 to 120% for dose titration.

Table 9: Trial KOA Summary of Major Protocol Deviations

	Placebo	Aripiprazole
Subjects with major protocol deviations	4	7
Inclusion/exclusion deviation (Exclusion criteria #17: Previously received Aripiprazole)	1	1
Error of treatment group allocation	1	2
Administration of prohibited medication	1	0
Deviation of drug compliance	1	4

Source: Trial Report, p.49

Treatment Compliance

The mean compliance rate was 96.21% (range=89.23-100.00) for the Placebo group and 96.35% (range=78.61-104.17) for Aripiprazole group. There was no statistically significant difference between the groups (p=0.41).

Exposure

The extent of drug exposure was estimated by adding the amount of drug administration of all visits. The mean total amount of study medication taken during the study was 530.86 mg for Placebo group and 455.94 mg for Aripiprazole group. There was no statistically significant difference between the treatment groups. The mean total duration of investigational product administration was 63.75 days for Placebo group and 68.63 days for Aripiprazole group.

Average Dose

The mean average daily dose was 7.75mg for Placebo group and 6.54mg for Aripiprazole group (not statistically different). The mean final dose of the subjects who completed the study was 16.13mg for Placebo group and 10.97mg for Aripiprazole group [statistically significantly greater for Placebo group (p-value=0.0025, two-sample t-test].

Table 10: Trial KOA Average Daily and Final Dose

	Statistic	Placebo	Aripiprazole
Total number of subject of safety population	N	28	32
Average daily dose (mg)	N	28	32
	Mean	7.75	6.54
	S.D.	2.89	2.96
	Median	9.04	7.06
	Min~Max	1.87~ 10.72	1.89~ 10.70
	P-value[#1]	0.1326	
Final dose[#2] (mg)	N	24	30
	Mean	16.13	10.97
	S.D.	5.27	6.09
	Median	20.00	10.00
	Min~Max	2.00~ 20.00	2.00~ 20.00
	P-value[#1]	0.0025*	

Note:
#1: P -values for difference in extent of drug exposure between treatment groups, and p-values are computed from Wilcoxon rank sum test
#2: Only for the subjects who completed the study.

Source: KOA Study Report, p. 68-69

6.1.4 Analysis of Primary Endpoint(s)

The efficacy analysis was carried out on the following three analysis populations:

- **Intention-To-Treat (ITT) Population (major analysis set)**
- Full-Analysis Set (FAS) Population
- Per-Protocol (PP) Population

The Intention-To-Treat (ITT) population was defined as all randomized subjects. The Full Analysis Set (FAS) population was defined as the subjects who took investigational product at least once and had evaluable primary efficacy data, and the Per-Protocol (PP) population was defined as those subjects in the FAS population who completed the study with no major protocol violations.

The ITT population included the 61 randomized subjects. The FAS population included the 60 randomized subjects as one subject in the Aripiprazole group (005-0001) withdrew before investigational product administration. One subject (006-0006) who was randomized to the Placebo group took Aripiprazole due to a prescribing mistake; however this subject was analyzed as the Placebo group as per the ITT principle.

The PP population included the 44 subjects who completed the study without any major protocol violations.

Table 11: Trial KOA Data Sets Analyzed

	Number of Subjects		
	Placebo	Aripiprazole	Total
Efficacy populations			
ITT(Intention-To-Treat)	29	32	61
FAS(Full Analysis Set)	29	31	60
PP (Per-Protocol)	21	23	44

Source: Trial Report, p.50

Table 12: Trial KOA Subjects Excluded from Per Protocol Efficacy Analysis

Center No.	Subject ID	Randomization Treatment	Reason for Exclusion from Per Protocol Dataset	ITT	FAS
001	0001	Aripiprazole	Withdrawal	Yes	Yes
001	0002	Placebo	Withdrawal	Yes	Yes
001	0006	Placebo	Withdrawal	Yes	Yes
001	0007	Aripiprazole	Deviation of Drug Compliance	Yes	Yes
001	0012	Placebo	Administration of Prohibited Medication	Yes	Yes
002	0001	Aripiprazole	Inclusion/Exclusion Deviation	Yes	Yes
002	0002	Aripiprazole	Deviation of Drug Compliance	Yes	Yes
002	0003	Placebo	Withdrawal	Yes	Yes
002	0006	Placebo	Inclusion/Exclusion Deviation	Yes	Yes
003	0008	Placebo	Deviation of Drug Compliance	Yes	Yes
004	0007	Aripiprazole	Deviation of Drug Compliance	Yes	Yes
004	0011	Aripiprazole	Error of Treatment Group Allocation	Yes	Yes
004	0012	Aripiprazole	Error of Treatment Group Allocation	Yes	Yes
004	0014	Aripiprazole	Withdrawal	Yes	Yes
005	0001	Aripiprazole	Withdrawal (No IP taken)	Yes	No
005	0005	Placebo	Withdrawal	Yes	Yes
006	0006	Placebo	Error of Treatment Group Allocation	Yes	Yes

Source: Trial Report, p.770-772

The analysis results of the primary efficacy endpoint, mean change of total Tic scores in KYGTSS from randomization to the final visit for ITT, FAS and PP population are detailed in Table 13. The difference in the change from Baseline to the final visit between the treatment groups was statistically significant for the ITT and FAS populations. The difference in the change from Baseline to the final visit between the treatment groups was not statistically significant for the PP population. The Applicant states that one of the reasons for this difference in statistical significance may be due to

the exclusion of the subjects from the PP population due to dropouts from the study who had shown a poor response while taking the Placebo.

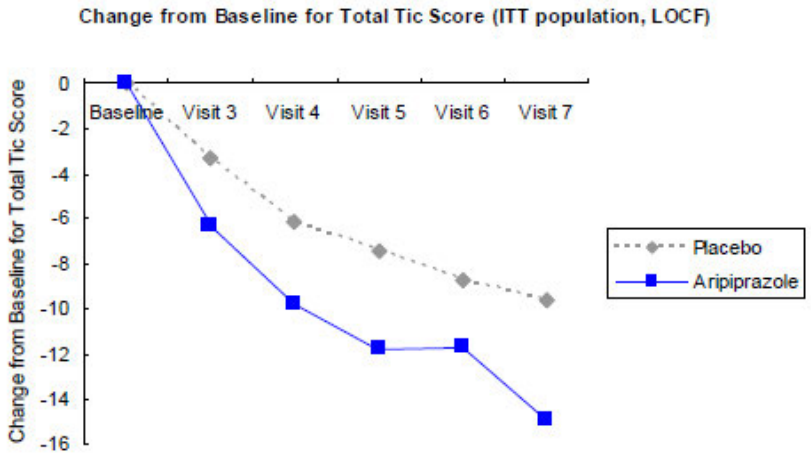
Table 13: Trial KOA Mean Change of Total Tic Scores in K-YGTSS from Randomization to the Final Visit

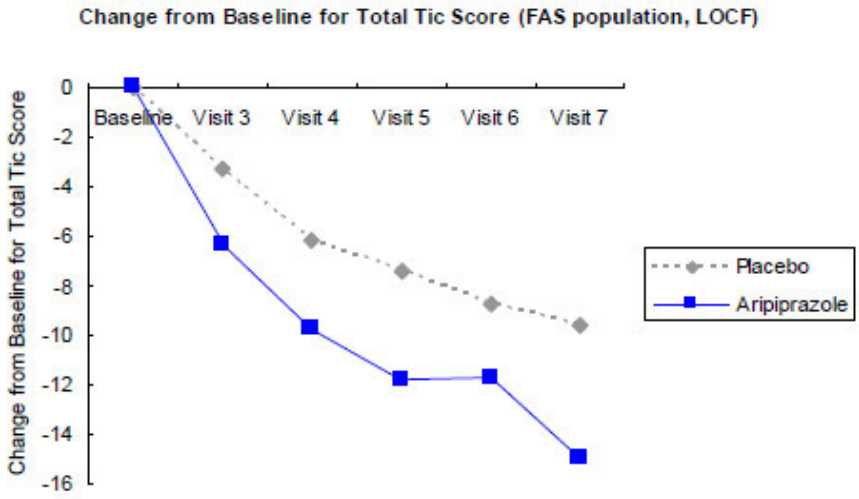
	ITT (LOCF)		FAS (LOCF)		PP	
Total Tic Score	Placebo (N=29)	Aripiprazole (N=32)	Placebo (N=29)	Aripiprazole (N=31)	Placebo (N=21)	Aripiprazole (N=23)
Baseline						
N	29	32	29	31	21	23
Mean±SD	29.48±5.60	28.34±5.51	29.48±5.60	28.52±5.51	28.19±5.72	28.35±4.65
Visit 7						
N	29	31[#2]	29	31	21	23
Mean±SD	19.86±9.54	13.55±9.12	19.86±9.54	13.55±9.12	17.24±7.44	13.87±7.27
Change from baseline						
N	29	31	29	31	21	23
Mean±SD	-9.62±8.83	-14.97±8.42	-9.62±8.83	-14.97±8.42	-10.95±7.89	-14.48±7.76
p-value[#1]	0.0196*		0.0196*		0.1427	

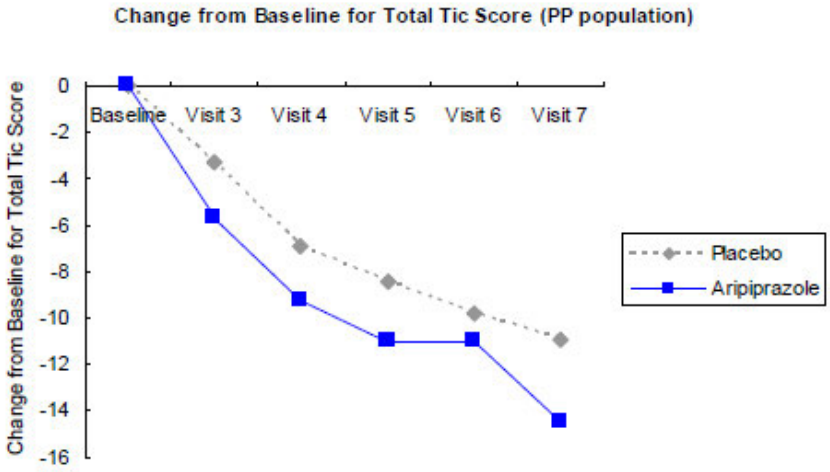
#1: P-values for difference of change from Baseline to Visit 7 between treatment groups, and p-values are computed from two-sample t-test.
#2 One subject has dropped out after making a baseline visit only.
* Statistically significant

Source: Trial Report, p.59

In addition, the same analysis was performed on the change from Baseline to each visit (Visit 3 to 6) and the significance of the change from Baseline to each visit in each treatment group was also assessed. The ITT, FAS and PP analysis results showed that the total Tic score decreased by visit and the differences from Baseline (within each treatment group) were statistically significant (paired t-test).



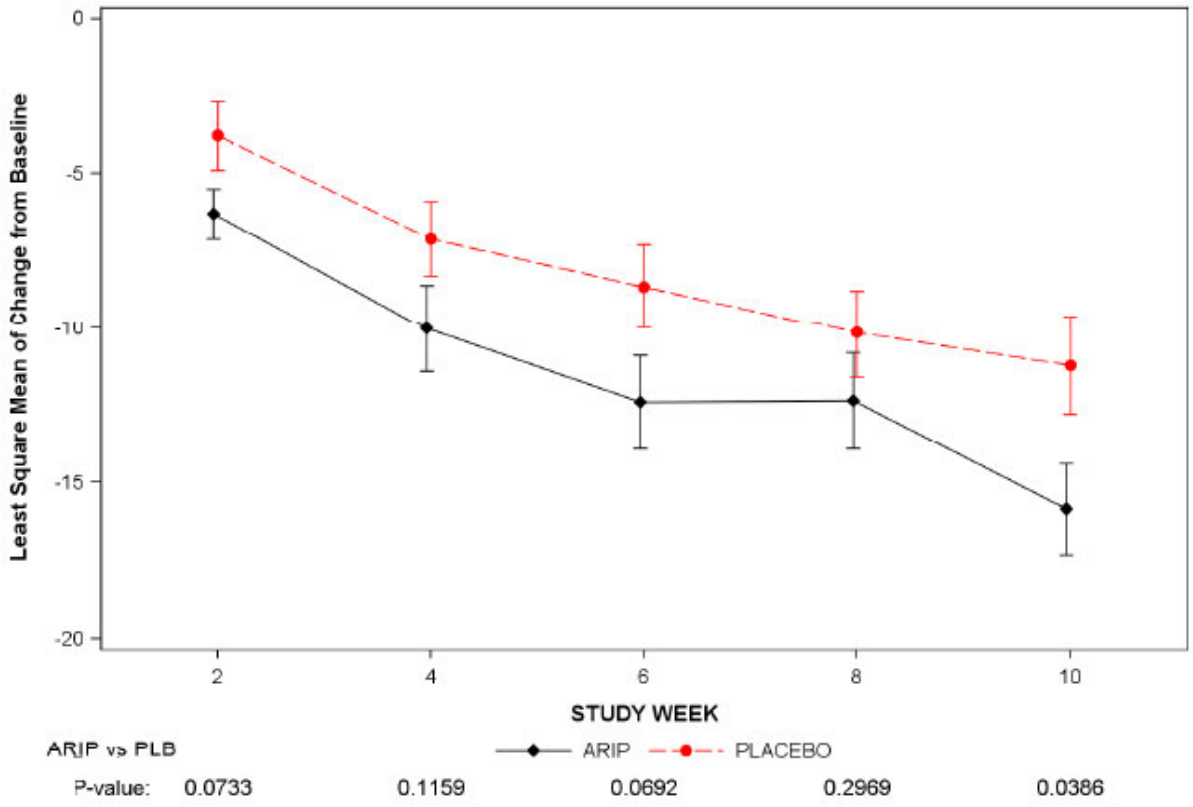




Source: Trial Report, p.59-60

ITT analysis was also carried out using MMRM. The results were similar to those for LOCF data except for the group difference at Visit 3 and 5 that were no longer significant.

Figure 2: Least Squares Mean Change from Baseline in K-YGTSS by Week, MMRM (ITT)



Source:Summary of Clinical Efficacy, p.34

6.1.5 Analysis of Secondary Endpoints(s)

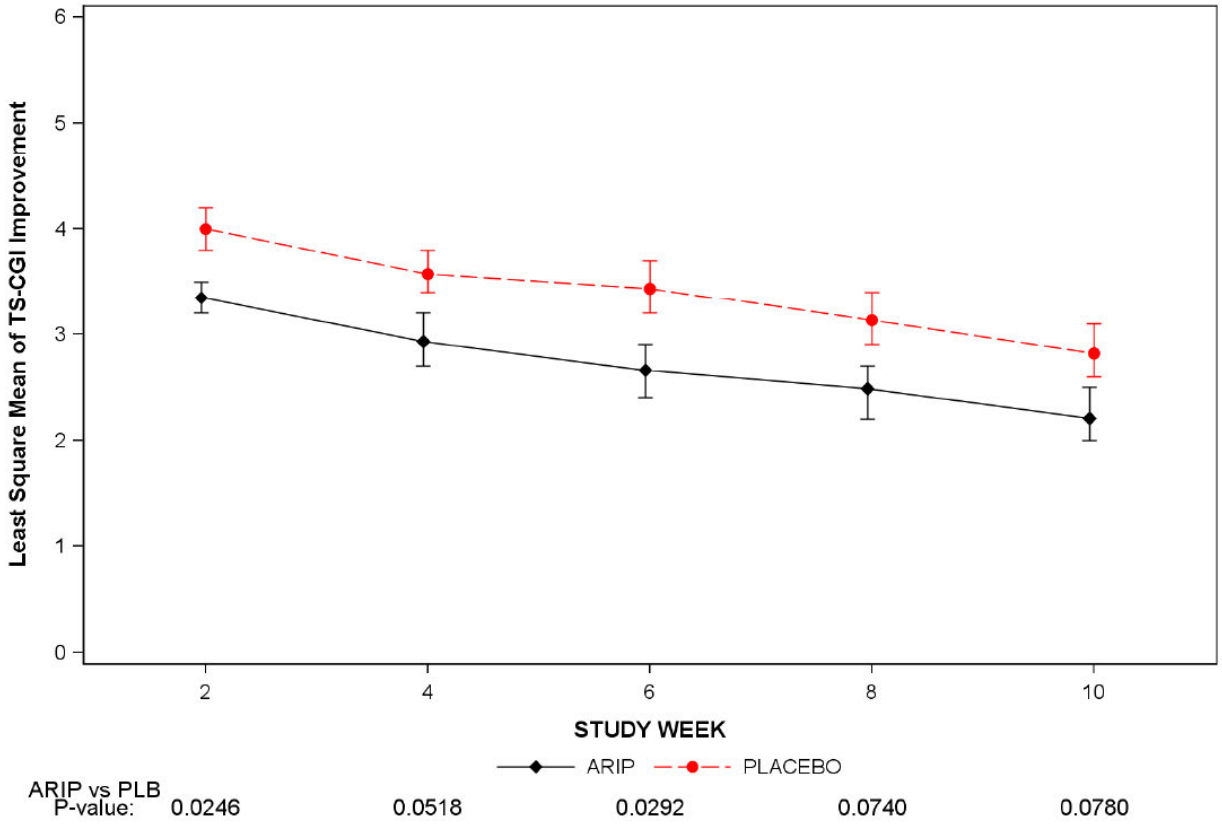
Multiple secondary endpoints were assessed for Trial 031-KOA-0703. No key secondary endpoint was specified. The Agency suggested that CGI-I results from Trial 031-KOA-0703 be analyzed retrospectively in the same manner as that specified for the Trial 31-12-293 key secondary efficacy endpoint. Numerical results for LS mean CGI-I at endpoint were similar to those for Trial 31-12-293. The numerical difference favored aripiprazole throughout the trial. However, statistical significance was demonstrated at Weeks 2 and 6 but not at endpoint (Week 10).

Table 14: Trial KOA Analysis of CGI-I at Week 10, MMRM (ITT)

						95% CI[a]		
Treatment Group	**N[a]**	**Baseline CGI-S Mean**	**LS Mean[b]**	**LS Mean SE[b]**	**Estimated Treatment Effect[b]**	**Lower Limit**	**Upper Limit**	**P-Value[b]**
Aripiprazole	29	4.5	2.21	0.24	−0.61	−1.30	0.07	0.0780
Placebo	25	4.6	2.82	0.24				

Source:Summary of Clinical Efficacy, p.37

Figure 3: Trial KOA Least Squares Mean CGI-I by Week, MMRM (ITT)



Source:Summary of Clinical Efficacy, p.38

Other Secondary Endpoints

Statistically significant differences in favor of aripiprazole compared with placebo (ITT Sample) were observed for percent change from baseline to Week 10 in K-YGTSS TTS and for mean change in CGI-S score from baseline to Week 10. No statistically significant differences were observed for response rate or partial response rate.

6.1.7 Subpopulations

This was a small study. All subjects were from South Korea. No analyses related to subpopulations were performed. The small sample sizes in subgroups would not allow reliable inferences to be made.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The mean average daily dose for the Aripiprazole group was 6.54 mg. The mean final dose of the subjects who completed the study was 10.97 mg for the Aripiprazole group. These doses are consistent with the recommended dose in the proposed label.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This short-term study was not designed to evaluate the persistence of efficacy and/or tolerance effects. A PMR/PMC for a long-term maintenance trial (randomized withdrawal) in a pediatric Tourette population to evaluate these effects is anticipated.

6.1.10 Additional Efficacy Issues/Analyses

Dr. Birkner (Biometrics) performed an additional efficacy analysis on the change from baseline in total vocal and motor tic scores. The results of this analysis demonstrate that aripiprazole had a positive effect on both motor and vocal tics. Please see his review for the details of this analysis.

6.2 Trial 31-12-293

Study Period: 01 November 2012 to 03 September 2013

Title: "A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder"

6.2.1 Methods

Objectives

Primary objective:

- To compare the efficacy of aripiprazole with placebo in the suppression of tics in children and adolescents (aged 7-17 years) with a diagnosis of Tourette's Disorder (TD)

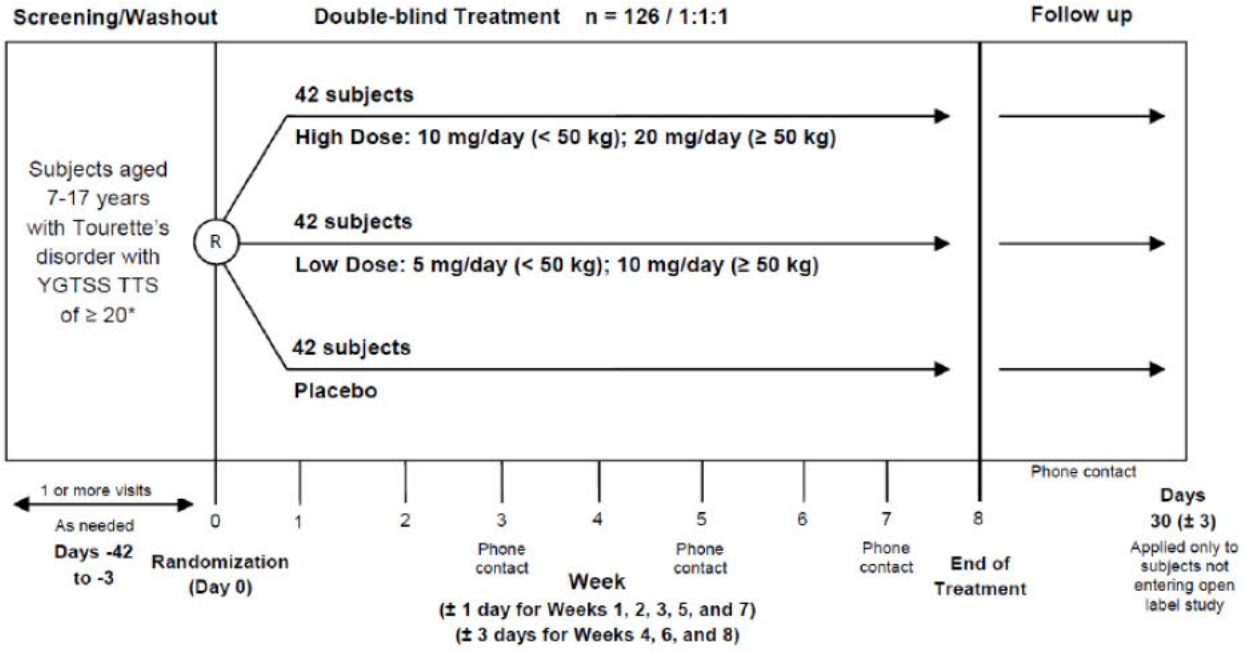
Secondary objectives:

- To evaluate the safety and tolerability of aripiprazole once-daily treatment with oral tablets in children and adolescents with a diagnosis of TD

Design

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled, fixed-dose (weight-based high and low dose), outpatient trial. A schematic of the trial design is presented in Figure 4. The study consisted of a screening/washout period, an 8-week treatment period, and a follow-up period (30±3 days) for subjects who discontinued from the trial or who did not roll over into the open-label trial. Subjects visited the clinic at Weeks 1, 2, 4, 6, and 8. A telephone call to confirm safety and tolerability was to be completed at the conclusion of Weeks 3, 5, and 7.

Figure 4: Trial 293 Trial-Design Schematic



Source: Trial Report, p. 38

Table 15: Trial 293 Medication Washout Requirements

Medication	Required Washout	Medication Allowed?
Psychostimulants (Concerta®, Metadate CR®, Ritalin LA®, Focalin, Focalin XR®)	--	Yes, if no exacerbation of tics and stable dose for at least 4 weeks
SSRIs/SNRIs	4 weeks	No
Depot neuroleptics	1 full cycle + 2 weeks	No
Clonidine, guanfacine, guanabenz, atomoxetine, and carbamazepine	2 weeks	No

Aripiprazole	30 days	--
Other Psychotropics	2 weeks	No

Source: Trial Report, p.39

Subjects were randomly assigned to low- or high-dose aripiprazole or placebo in a 1:1:1 ratio. For subjects who weighed < 50 kg at baseline, low- and high-doses of aripiprazole were 5 and 10 mg/day, respectively. For subjects who weighed ≥ 50 kg at baseline, low- and high-doses of aripiprazole were 10 and 20 mg/day, respectively. Doses were to be taken at approximately the same time every day and without regard to meals. Dosing in the morning was recommended, but dosing in the evening was allowed.

Table 16: Trial 293 Abilify Dose

Weight	Low Dose	High Dose
< 50	5 mg/day	10 mg/day
≥ 50	10 mg/day	20 mg/day

Source: Trial Report, p. 38

Subjects randomized to the aripiprazole groups began treatment at a 2-mg/day dose. After 2 days, the dose was titrated to 5 mg/day. The dose was then titrated to achieve the randomized dose according to a prespecified titration scheme (see Table 17). All subjects reached their randomized dose by Week 3. If a subject did not tolerate the randomized dose during the titration period (before his/her first dose at Week 3), he/she was discontinued from the trial. If a subject did not tolerate the randomized dose, the dose could be decreased one time after Week 3, to the next lower dose level or to 2 mg/day for the 5-mg/day group. Subjects who did not tolerate the reduced dose were discontinued from the trial.

Table 17: Trial 293 Dosing Titration Scheme

Treatment[a]	Baseline (Visit 1)		Week 1 (Visit 2)	Week 2 (Visit 3)	Week 3 (Ph Visit 4)	Week 4 (Visit 5)	Week 5 (Ph Visit 6)	Week 6 (Visit 7)	Week 7 (Ph Visit 8)	Step Down Post-Day 21 Dose[b]
	Days 0-1	Days 2-6	Days 7-13	Days 14-20	Days 21-27	Days 28-34	Days 35-41	Days 42-48	Days 49-55	
High-dose Subject ≥ 50 kg	2 mg	5 mg	10 mg	15 mg	20 mg	20 mg	20 mg	20 mg	20 mg	15 mg
High-dose Subject < 50 kg	2 mg	5 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	5 mg
Low-dose Subject ≥ 50 kg	2 mg	5 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	5 mg
Low-dose Subject < 50 kg	2 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg	2 mg
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Source: Trial Report, p. 47

Subjects

Key Inclusion Criteria:

- Male or female child or adolescent, 7 to 17 years of age
- Diagnosis of Tourette's Disorder (DSM-IV-TR)

- Diagnosis of Tourette's Disorder confirmed by K-SADS-PL, including the Diagnostic Supplement 5 (Substance Abuse and Other Diseases, i.e., Tic Disorders)
- TTS ≥ 20 on the YGTSS at screening and baseline
- Subject, caregiver, and investigator all agree that the presenting tic symptoms caused impairment in the subject's normal routines
- Females of childbearing potential had a negative pregnancy test, practiced acceptable double-barrier methods of contraception (or abstinence), and were not pregnant or lactating.

Key Exclusion Criteria:

- Medical history consistent with another neurologic condition that may have had accompanying abnormal movements (e.g., Transient tic disorder, Huntington's disease, Parkinson's disease, Sydenham's chorea, Wilson's disease, Mental retardation, Pervasive developmental disorder, Traumatic brain injury, Stroke, Restless Legs Syndrome)
- History of schizophrenia, bipolar disorder, or other psychotic disorder; history of primary mood disorder
- Subjects who received psychostimulants for the treatment of ADD/ADHD and who developed and/or had exacerbations of the tic disorder after the initiation of stimulant treatment.
- Severe OCD (CY-BOCS score > 16)
- History of taking aripiprazole within 1 month of screening
- History of neuroleptic malignant syndrome
- Sexually active males or females who would not commit to utilizing 2 of the approved birth control methods or who would not remain abstinent during the trial and for 90 days (males) or 30 days (females) following the last dose of trial drug
- Significant risk of committing suicide
- Weight < 16 kg
- Neuroleptic or antiparkinson drugs less than 14 days before randomization
- Cognitive Behavioral Therapy (CBT) for TD during the trial period
- Significant psychoactive substance use disorder within the past 3 months; + urine drug screen
- Use of any CYP2D6 and CYP3A4 inhibitors or CYP3A4 inducers within 14 days before baseline and for the duration of the trial; use of herbal medications of any kind, and nutritional or dietary supplements for TD within 7 days before baseline and for the duration of the trial
- Platelets ≤ 75,000/mm^3
- Hemoglobin ≤ 9 g/dL
- Neutrophils, absolute ≤ 1000/mm^3
- AST > 3 x ULN
- ALT > 3 x ULN
- Creatinine ≥ 2 mg/dL

- Diastolic blood pressure > 105 mmHg
- QTc ≥ 450 msec on either the QTcB or QTcF corrections on 2 of 3 timepoints

Efficacy Endpoints

Primary Efficacy Endpoint:
The primary efficacy endpoint of this trial was the change from baseline to Week 8 in Yale Global Tic Severity Scale (YGTSS) total tic score (TTS).

Key Secondary Efficacy Endpoint):
The key secondary efficacy endpoint was the Clinical Global Impressions Scale-Tourette's Syndrome (CGI-TS) Change Score at endpoint (change score obtained from CGI-TS improvement scale assessment).

Other Efficacy Endpoints:
- Mean change from baseline to endpoint in Total YGTSS Score
- Mean change from baseline to endpoint in CGI-TS Severity Score
- Response rates (clinical response was defined as > 25% improvement from baseline to endpoint in YGTSS TTS or a CGI-TS change score of 1 [very much improved] or 2 [much improved] at endpoint)
- Treatment discontinuation rates

Pharmacokinetic Endpoints
- Plasma concentrations of aripiprazole and its active metabolite, dehydro-aripiprazole, were measured in samples obtained during Weeks 6 and 8 (end of treatment or early termination [ET]).
- PK samples were to be collected either at 2 to 10 hours post last dose or at 12 hours post last dose (i.e., before the administration of the dose during the visit).

Safety Endpoints
- Adverse events (AEs)
- Laboratory tests (hematology, serum chemistry [including prolactin[10], HbA1C, and TSH], urinalysis, and pregnancy tests)
- Vital signs
- ECGs

[10] Prolactin laboratory results were monitored by an unblinded medical monitor at screening and Week 8 in the trial. This unblinded medical monitor was not a member of the clinical team (which was blinded throughout the trial) and was not involved in decisions regarding trial conduct. Without receiving actual values, trial sites were contacted by the unblinded medical monitor when prospective/enrolled subjects' prolactin results were > 45 ng/mL. If the abnormal prolactin results were accompanied by physical signs/symptoms secondary to elevated prolactin levels, the investigator was expected to assess the subjects for entry in the present trial (prompted by the unblinded medical monitor's contact at screening) and to confirm subjects' eligibility in the open-label 31-12-294 Trial.

- Simpson-Angus Scale (SAS)
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Swanson, Nolan, and Pelham-IV (SNAP-IV)[11]
- Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)
- Children's Depression Rating Scale-Revised (CDRS-R)
- Pediatric Anxiety Rating Scale (PARS)
- Body weight/Waist circumference/Body mass index (BMI)

Statistical Methods

Sample Size and Power

Assuming 5% of subjects may drop out of the trial without a postbaseline efficacy evaluation, a total of 126 subjects randomized in a 1:1:1 ratio to the aripiprazole low dose, aripiprazole high dose, and the placebo groups (42 subjects in each of the 3 groups) were required to provide at least 80% power to detect a treatment difference of -5 (common SD of 8.5) between at least 1 of 2 aripiprazole dose levels and placebo in the primary outcome.

Randomization:

The randomization code was a fixed-block, computer-generated randomization schedule stratified by region and weight group, where region was classified as North America (including US and Canada) versus Rest of the World and weight group was classified as low weight (< 50 kg) versus high weight (≥ 50 kg). Subjects were randomly assigned to treatment via IVRS/IWRS.

Data Sets

Intent-to-Treat (ITT) Sample: All subjects randomly assigned to the double-blind treatment. The ITT Sample was the primary data set for all efficacy endpoints and was analyzed according to the treatment group the subjects were randomized to.

Per-Protocol (PP) Sample: All subjects randomized to the double-blind treatment and with no major protocol violations during the trial were included in the PP Sample and analyzed according to the treatment group they were randomized to.

Safety Sample: All subjects in the ITT Sample who received at least 1 dose of IP were included. Analyses for the safety data were based on the Safety Sample according to the treatment received. If a subject randomized to placebo ever took an active aripiprazole dose, the subject was analyzed according to the highest aripiprazole dose received by the subject.

[11] Includes items to assess inattention, hyperactivity/impulsivity, and oppositional defiant symptoms

Observed Case (OC) dataset: OC dataset for ITT Sample or Safety Sample at the endpoint or at a particular Trial Week consisted of data from all subjects who had nonmissing scores at the week on the efficacy or safety variable under analysis.

Primary Endpoint:
The primary efficacy endpoint was the mean change from baseline to endpoint (Week 8) in the YGTSS TTS. A total of 2 null hypotheses were tested for the primary endpoint, aripiprazole low-dose group versus placebo and aripiprazole high dose group versus placebo. The statistical comparison was performed using a mixed model repeated measures (MMRM) linear model with terms of treatment (aripiprazole low dose, aripiprazole high dose, or placebo), region, body weight group, and visit week as factors, the baseline YGTSS TTS as a covariate and treatment-by-week interactions in the model at a significance level of 0.05 (2-sided). The Hochberg procedure was used to adjust multiplicity in testing 2 comparisons (aripiprazole low dose versus placebo and aripiprazole high dose versus placebo) of the primary endpoint. To assess the time trend of treatment effect, statistical analyses were also performed for the change from baseline in the YGTSS TTS at each clinic visit.

The primary efficacy endpoint was analyzed for the following subgroups with the MMRM model:

- Age of 7 to 12 years versus 13 to 17 years at screening
- Region of North America (US and Canada) versus the Rest of the World
- Race of white versus Other
- Baseline YGTSS TTS of < 30 versus ≥ 30

Key Secondary Endpoint:
The key secondary efficacy endpoint was CGI-TS Change Score at Week 8. The key secondary endpoint was analyzed using a similar method as described for the primary efficacy endpoint. Since CGI-TS Change Score was not measured at baseline, baseline CGI-TS Severity Score was included in the MMRM model as a covariate. Multiple comparisons of primary and key secondary efficacy endpoints were accounted for using a serial gatekeeping approach.

6.2.2 Demographics

Seventy-six (76) sites enrolled 133 subjects in 4 countries: Canada (27 subjects), Hungary (9 subjects), Italy (5 subjects), and United States (92 subjects).

Baseline demographic characteristics were similar between the low- and high-dose aripiprazole and placebo groups with the exception of a higher percentage of Black subjects in the aripiprazole low-dose group, and a lower mean body weight at baseline in the low-dose aripiprazole group compared with the other groups.

Table 18: Trial 293 Demographic Characteristics (ITT)

Demographic Characteristics	Aripiprazole Low Dose (5 and 10 mg) (N = 44)	Aripiprazole High Dose (10 and 20 mg) (N = 45)	Placebo (N = 44)
Age (years)			
n	44	45	44
Mean (SD)	11.1 (3.1)	11.8 (2.8)	11.6 (2.8)
Median	11.0	12.0	12.0
Min, Max	7.0, 17.0	7.0, 17.0	7.0, 17.0
Age Group[a]			
7 to 12 years	30 (68.2)	28 (62.2)	27 (61.4)
13 to 17 years	14 (31.8)	17 (37.8)	17 (38.6)
Sex [n (%)]			
n	44	45	44
Male	36 (81.8)	35 (77.8)	33 (75.0)
Female	8 (18.2)	10 (22.2)	11 (25.0)
Race [n (%)][a]			
White	38 (86.4)	39 (86.7)	39 (88.6)
Black or African American	6 (13.6)	1 (2.2)	4 (9.1)
American Indian or Alaska Native	0 (0.0)	1 (2.2)	0 (0.0)
Asian	0 (0.0)	3 (6.7)	0 (0.0)
Other	0 (0.0)	1 (2.2)	1 (2.3)
Ethnicity [n (%)][a]			
Hispanic or Latino	5 (11.4)	1 (2.2)	4 (9.1)
Not Hispanic or Latino	39 (88.6)	44 (97.8)	39 (88.6)
Unknown	0 (0.0)	0 (0.0)	1 (2.3)
Height (cm)			
n	44	45	44
Mean (SD)	147.9 (18.5)	149.3 (17.7)	150.7 (16.5)
Weight (kg)			
n	44	45	44
Mean (SD)	44.2 (16.0)	47.4 (20.1)	47.8 (21.8)
Weight Group[a]			
< 50 kg	28 (63.6)	30 (66.7)	29 (65.9)
≥ 50 kg	16 (36.4)	15 (33.3)	15 (34.1)
Body Mass Index (kg/m^2)			
n	44	45	44
Mean (SD)	19.5 (3.6)	20.3 (4.8)	20.1 (5.1)

Source: Trial Report, p. 81

Baseline Total Tic Severity Scores and CGI-TS were similar between groups. Total Motor Tic Severity Scores were higher than Total Vocal Tic Severity Scores for all groups.

Table 19: Trial 293 Baseline Tic and CGI-TS Severity Scores

Baseline Characteristics	Aripiprazole Low Dose (5 and 10 mg) (N = 44)	Aripiprazole High Dose (10 and 20 mg) (N = 45)	Placebo (N = 44)
Total Tic Severity Score			
n	44	45	44
Mean (SD)	29.2 (5.6)	31.2 (6.4)	30.7 (6.0)
Total Motor Tic Severity Score			
n	44	45	44
Mean (SD)	16.5 (3.3)	17.6 (2.8)	17.0 (3.4)
Total Vocal Tic Severity Score			
n	44	45	44
Mean (SD)	12.7 (3.7)	13.6 (4.7)	13.8 (4.1)
CGI-TS Severity Score			
n	44	45	43
Mean (SD)	4.3 (0.6)	4.1 (1.1)	4.2 (0.9)

Source: Trial Report, p.82

Concomitant Medications:
The most frequently reported class of prior medication and concomitant (taken during the study) medication was psychoanaleptics. Methylphenidate hydrochloride was one of the most frequently reported baseline and concomitant medications.

Table 20: Trial 293 Common Medications Taken Prior to Start of Study Medication

Medications Taken Prior to Start of Study Medication	**ARIP LOW**		**ARIP HIGH**		**Placebo**	**Total**
	ARIP 5 N=28 N (%)	**ARIP 10 N=16 N (%)**	**ARIP 10 N=30 N (%)**	**ARIP 20 N=15 N (%)**	**N=44 N (%)**	**N=133 N (%)**
Total Using ≥ 1 Baseline Medications	19(68)	7(44)	22(73)	9(60)	22(50)	79(59)
Guanfacine/guanfacine hydrochloride	1(3.6)	0	3(10)	1(6.7)	0	5(3.8)
Psychoanaleptics Methylphenidate Hydrochloride	14(50) 7(25)	1(6.3) 0	11(37) 6(20)	4(27) 0	13(29.5) 9(20.5)	43(32) 22(16)
Psycholeptics Melatonin Risperidone	4(14) 2(7.1) 2(7.1)	0 0 0	5(17) 3(10) 3(10)	1(6.7) 0 0	3(6.8) 2(4.5) 1(2.3)	13(9.8) 7(5.3) 6(4.5)

Source: Trial Report, p.170-174

Table 21: Trial 293 Concomitant Medications

Concomitant Medications (Medications taken during Study Period)	ARIP LOW		ARIP HIGH		Placebo	Total
	ARIP 5 N=28 N (%)	ARIP 10 N=16 N (%)	ARIP 10 N=30 N (%)	ARIP 20 N=15 N (%)	N=44 N (%)	N=133 N (%)
Total using ≥ 1 medication	17(61)	8(50)	19(63)	9(60)	22(50)	75 (56)
Anti-Parkinson Drugs	0	0	2(6.7)	1(6.7)	0	3 (2.3)
Benzatropine Mesilate	0	0	1	1	0	2 (1.5)
Trihexyphenidyl Hydrochloride	0	0	1	0	0	1 (0.8)
Antihistamine for Systemic Use	3(11)	0	3(10)	2(13)	5(11)	13 (9.8)
Psychoanaleptics	13(46)	1(6.3)	8(27)	1(6.7)	10(23)	33 (25)
Lisdexamfetamine/ Lisdexamfetamine Mesilate	4	1	2	0	2	9 (6.8)
Methylphenidate Hydrochloride	6	0	5	0	8	19 (14)
Psycholeptics	2(7)	0	4(13)	2(13)	2(4.5)	10 (7.5)
Diphenhydramine Hydrochloride	0	0	1	1	0	2 (1.5)
Lorazepam	0	0	0	1	0	1 (0.8)
Melatonin	2	0	3	0	2	7 (5.3)

Source: Trial Report, p.175-180

6.2.3 Subject Disposition

Of the 133 subjects randomized in the trial, 44 subjects were in the low-dose aripiprazole group (28 and 16 subjects received aripiprazole 5 and 10 mg, respectively); 45 subjects were in the high-dose aripiprazole group (30 and 15 subjects received aripiprazole 10 and 20 mg, respectively); and 44 subjects were in the placebo group. A total of 119 subjects completed the trial (i.e., completed the Week 8 Visit). Fourteen subjects prematurely discontinued from the trial because of AEs (8 subjects), consent withdrawal (4 subjects), and protocol deviations (2 subjects).

Most of the discontinuations were in the low weight/high dose aripiprazole group:

Table 22: Trial 293 Subject Disposition

	Aripiprazole Low Dose			Aripiprazole High Dose			Placebo	Total
Subjects	5 mg (< 50 kg)	10 mg (≥ 50 kg)	Total	10 mg (< 50 kg)	20 mg (≥ 50 kg)	Total		
Number (%) of Subjects	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Screened								171
Screen Failure								38
Randomized	28 (100.0)	16 (100.0)	44 (100.0)	30 (100.0)	15 (100.0)	45 (100.0)	44 (100.0)	133 (100.0)
Completed[a]	26 (92.9)	16 (100.0)	42 (95.5)	21 (70.0)	14 (93.3)	35 (77.8)	42 (95.5)	119 (89.5)
Discontinued	2 (7.1)	0 (0.0)	2 (4.5)	9 (30.0)	1 (6.7)	10 (22.2)	2 (4.5)	14 (10.5)
Analyzed for Safety[b]	28 (100.0)	16 (100.0)	44 (100.0)	30 (100.0)	15 (100.0)	45 (100.0)	44 (100.0)	133 (100.0)
Analyzed for Efficacy[c]	28 (100.0)	16 (100.0)	44 (100.0)	30 (100.0)	15 (100.0)	45 (100.0)	44 (100.0)	133 (100.0)

Note: Percentages were based on the number of subjects randomized.

Source: Trial Report, p. 77

More subjects ages 7-12 in the low weight/high dose aripiprazole group discontinued.

Table 23: Trial 293 Subject Disposition by Age

Age 7-12 years

	ARIP-LOW			ARIP-HIGH				
NUMBER OF SUBJECTS	ARIP-5 MG N (%)	ARIP-10 MG N (%)	TOTAL N (%)	ARIP-10 MG N (%)	ARIP-20 MG N (%)	TOTAL N (%)	PLACEBO N (%)	TOTAL N (%)
RANDOMIZED	26 (100.0)	4 (100.0)	30 (100.0)	26 (100.0)	2 (100.0)	28 (100.0)	27 (100.0)	85 (100.0)
COMPLETED[1]	25 (96.2)	4 (100.0)	29 (96.7)	18 (69.2)	2 (100.0)	20 (71.4)	26 (96.3)	75 (88.2)
DISCONTINUED	1 (3.8)	0	1 (3.3)	8 (30.8)	0	8 (28.6)	1 (3.7)	10 (11.8)

Age 13-17

	ARIP-LOW			ARIP-HIGH				
NUMBER OF SUBJECTS	ARIP-5 MG N (%)	ARIP-10 MG N (%)	TOTAL N (%)	ARIP-10 MG N (%)	ARIP-20 MG N (%)	TOTAL N (%)	PLACEBO N (%)	TOTAL N (%)
RANDOMIZED	2 (100.0)	12 (100.0)	14 (100.0)	4 (100.0)	13 (100.0)	17 (100.0)	17 (100.0)	48 (100.0)
COMPLETED[1]	1 (50.0)	12 (100.0)	13 (92.9)	3 (75.0)	12 (92.3)	15 (88.2)	16 (94.1)	44 (91.7)
DISCONTINUED	1 (50.0)	0	1 (7.1)	1 (25.0)	1 (7.7)	2 (11.8)	1 (5.9)	4 (8.3)

Source: Trial Report, p 137-138

Table 24: Trial 293 Subject Completion Rates (ITT)

	ARIP-LOW			ARIP-HIGH				
NUMBER OF WEEKS COMPLETED[1]	ARIP-5 MG (N=28) n (%)	ARIP-10 MG (N=16) n (%)	TOTAL (N=44) n (%)	ARIP-10 MG (N=30) n (%)	ARIP-20 MG (N=15) n (%)	TOTAL (N=45) n (%)	PLACEBO (N=44) n (%)	TOTAL (N=133) n (%)
>= 4	26 (92.9)	16 (100.0)	42 (95.5)	25 (83.3)	14 (93.3)	39 (86.7)	44 (100.0)	125 (94.0)
>= 5	26 (92.9)	16 (100.0)	42 (95.5)	23 (76.7)	14 (93.3)	37 (82.2)	43 (97.7)	122 (91.7)
>= 6	26 (92.9)	16 (100.0)	42 (95.5)	22 (73.3)	14 (93.3)	36 (80.0)	43 (97.7)	121 (91.0)
>= 7	26 (92.9)	16 (100.0)	42 (95.5)	22 (73.3)	14 (93.3)	36 (80.0)	43 (97.7)	121 (91.0)
>= 8	26 (92.9)	16 (100.0)	42 (95.5)	21 (70.0)	14 (93.3)	35 (77.8)	42 (95.5)	119 (89.5)

Source: Trial Report, p 139

Table 25: Trial 293 Subject Completion Rates by Age (ITT)

Age: 7-12 years

	ARIP-LOW			ARIP-HIGH				
NUMBER OF WEEKS COMPLETED[1]	ARIP-5 MG (N=26) n (%)	ARIP-10 MG (N=4) n (%)	TOTAL (N=30) n (%)	ARIP-10 MG (N=26) n (%)	ARIP-20 MG (N=2) n (%)	TOTAL (N=28) n (%)	PLACEBO (N=27) n (%)	TOTAL (N=85) n (%)
>= 4	25 (96.2)	4 (100.0)	29 (96.7)	22 (84.6)	2 (100.0)	24 (85.7)	27 (100.0)	80 (94.1)
>= 5	25 (96.2)	4 (100.0)	29 (96.7)	20 (76.9)	2 (100.0)	22 (78.6)	27 (100.0)	78 (91.8)
>= 6	25 (96.2)	4 (100.0)	29 (96.7)	19 (73.1)	2 (100.0)	21 (75.0)	27 (100.0)	77 (90.6)
>= 7	25 (96.2)	4 (100.0)	29 (96.7)	19 (73.1)	2 (100.0)	21 (75.0)	27 (100.0)	77 (90.6)
>= 8	25 (96.2)	4 (100.0)	29 (96.7)	18 (69.2)	2 (100.0)	20 (71.4)	26 (96.3)	75 (88.2)

Source: Trial Report, p 140

Age: 13-17 years

	ARIP-LOW			ARIP-HIGH				
NUMBER OF WEEKS COMPLETED[1]	ARIP-5 MG (N=2) n (%)	ARIP-10 MG (N=12) n (%)	TOTAL (N=14) n (%)	ARIP-10 MG (N=4) n (%)	ARIP-20 MG (N=13) n (%)	TOTAL (N=17) n (%)	PLACEBO (N=17) n (%)	TOTAL (N=48) n (%)
>= 1	2 (100.0)	12 (100.0)	14 (100.0)	4 (100.0)	13 (100.0)	17 (100.0)	17 (100.0)	48 (100.0)
>= 2	1 (50.0)	12 (100.0)	13 (92.9)	4 (100.0)	13 (100.0)	17 (100.0)	17 (100.0)	47 (97.9)
>= 3	1 (50.0)	12 (100.0)	13 (92.9)	3 (75.0)	13 (100.0)	16 (94.1)	17 (100.0)	46 (95.8)
>= 4	1 (50.0)	12 (100.0)	13 (92.9)	3 (75.0)	12 (92.3)	15 (88.2)	17 (100.0)	45 (93.8)
>= 5	1 (50.0)	12 (100.0)	13 (92.9)	3 (75.0)	12 (92.3)	15 (88.2)	16 (94.1)	44 (91.7)
>= 6	1 (50.0)	12 (100.0)	13 (92.9)	3 (75.0)	12 (92.3)	15 (88.2)	16 (94.1)	44 (91.7)
>= 7	1 (50.0)	12 (100.0)	13 (92.9)	3 (75.0)	12 (92.3)	15 (88.2)	16 (94.1)	44 (91.7)
>= 8	1 (50.0)	12 (100.0)	13 (92.9)	3 (75.0)	12 (92.3)	15 (88.2)	16 (94.1)	44 (91.7)

Source: Trial Report, p 141

Most of the discontinuations in the low weight/high dose aripiprazole group were due to adverse events:

Table 26: Trial 293 Reasons for Discontinuations (ITT)

Number of Subjects	**ARIP LOW**		**ARIP HIGH**		**Placebo**	**Total**
	ARIP 5 N=28 N (%)	**ARIP 10 N=16 N (%)**	**ARIP 10 N=30 N (%)**	**ARIP 20 N=15 N (%)**	**N=44 N (%)**	**N=133 N (%)**
Discontinued	2 (7.1)	0	9 (30)	1(6.7)	2 (4.5)	14(10.5)
Adverse Events	0	0	6 (20.0)	1(6.7)	1 (2.3)	8 (6.0)
Subject Withdrew Consent	0	0	3 (10.0)	0	1 (2.3)	4 (3.0)
Protocol Deviation	2 (7.1)	0	0	0	0	2 (1.5)

Source: Trial Report, p 142-143

Reviewer Comment: An exposure safety analysis for Trial 293 was conducted in 76 of 89 aripiprazole-treated subjects who completed 8 weeks of treatment, 12 of these 89 subjects who discontinued IMP for any reason, and 8 of these 89 subjects who discontinued IMP due to an AE. No differences in aripiprazole exposure, age, body weight, and baseline TTS were observed among the 3 groups. See Section 7.5.1 of this review for further discussion of this issue.

Protocol Deviations

The Applicant notes that while deviations termed "major" were considered important for purposes of retraining and follow up with trial personnel, many major deviations were not considered to be significant protocol violations (i.e., deviations with notable impact on subject rights or safety, primary efficacy data, or the integrity of the trial).

Table 27: Trial 293 Protocol Deviations (ITT)

Protocol Deviations	ARIP Low N=44	ARIP High N=45	Placebo N=44	Total N=133
All types	26 (59.1)	34 (75.6)	31 (70.5)	91 (68.4)
"Major"	17 (12.8)	24 (18)	23 (17.3)	64 (48)

Source: Trial Report, p 78

The applicant identified a subset of 57 major deviations across 34 subjects that represented potentially significant violations:

Table 28: Trial 293 Case-Specific Details of Major Protocol Violations

Major Violations	Case-Specific Details
Violations impacting subject rights	14-yr-old subject who completed a consent form instead of an assent form at screening
	Case involved transmission of potentially identifying personal health information from a site to members of the CST at the CRO
Violations impacting inclusion/exclusion issues	Abnormal ECG—clinically insignificant so subject allowed to continue in the study
	Abnormal ECG—early termination from study
	Abnormal ECG—early termination from study
Violations impacting subject safety	4 cases involved 4 subjects where the C-SSRS was missed (1 trial visit each), completed by an unqualified rater, or performed after the first dose of IP; no suicide-related AEs were reported for any subjects in the trial.
	4 cases involved 4 subjects who did not receive pregnancy tests as required per protocol
	3 cases involved subjects who were dosed with IP (5-mg titration cards) stored at temperatures outside of the recommended range for < 72 hours
	9 subjects (5 on active tx) with a total of 24 dosing errors that potentially impacted proper titration of IP
Violations potentially impacting primary efficacy data	1 case involved a subject who was dispensed an IP dose different from that assigned by IWRS, which affected the subject's dosing for 1 week in the trial
	3 subjects whose concomitant-medication regimen was not stable for ≥ 4 weeks before trial entry
	9 subjects had treatment compliance was < 80%. Two of the 9 early terminated from the trial.
	2 cases involved 2 subjects, where the primary endpoint measure, the YGTSS, was conducted by unqualified raters at the time the scale was administered.

Source: Trial Report, p. 79-80

Major protocol deviations resulted in discontinuation from the trial of 2 subjects (1.5%), who received 5 mg in the low-dose aripiprazole group: Subjects 533S3067 and 788S3113 (both, Exclusion Criterion 21—abnormal ECG).

Site 555 (Site in Nashville, TN)
During the close-out visit for open-label extension Trial 31-12-294, the staff at Site 555 disclosed that Subject 555S3102 (placebo group) was not a new patient at the site at the time of enrollment in Trial 31-12-293. The subject was instead an existing patient, whose clinic chart had not been shared with the trial monitor during Trial 31-12-293. Review of Subject 555S3102's clinic chart suggested that the subject had used Zoloft (25 mg/day), Kapvay (0.1 mg/day), and Vyvanse (50 mg/day) before enrollment in Trial 31-12-293 and possibly during participation in the trial. Based on discrepancies between the clinic chart and the Trial 31-12-293 database for Subject 555S3102, the trial monitor reviewed the clinic charts of 3 other subjects at Site 555 and found similar discrepancies. The number and nature of potential issues for Site 555 subjects prompted questions about the accuracy and completeness of the site's data in the Trial 31-12-293 database and about the eligibility of its subjects. The sponsor therefore performed sensitivity analyses of the primary (change from baseline to Week 8 in YGTSS TTS) and key secondary (CGI-TS Change Score at Week 8) endpoints that excluded all 4 of Site 555's subjects. Results of these analyses confirmed that both primary and key secondary outcomes remained statistically significant after exclusion of the site's 4 subjects.

Treatment Compliance
Treatment compliance across all 3 treatment groups was 91.0%. Treatment compliance in the low- and high-dose aripiprazole and placebo groups was 90.9%, 84.4%, and 97.7%, respectively.

One subject (Subject 505S3002), who received 10 mg in the low-dose aripiprazole group, had no measurable plasma concentrations of aripiprazole or metabolite, indicating possible noncompliance with dosing. This subject is also listed as having major protocol violations as she did not take doses correctly based on dispensation instructions (dose missed or took incorrect dose on Days 0 to 4).

PK samples from 3 subjects assigned to placebo treatment had measurable concentrations of aripiprazole and/or its metabolite, dehydro-aripiprazole, during the Week 8 visit, which the Applicant says may have been due to a sample switch, as this was not observed at the Week 6 visit (Subjects 660S3084, 660S3127, and 661S3173). Subject 661S3173 is also listed as having major protocol violations: dosed from week 2 blister packs after completing week 3 dosing. Subjects 660S3084, 660S3127, and 661S3173 are from study sites in Hungary. Site 660 enrolled 3 subjects and Site 661 enrolled 6 subjects.

6.2.4 Analysis of Primary Endpoint(s)

The treatment difference between the low-dose aripiprazole and placebo groups (-6.26) in YGTSS TTS was statistically significant (p = 0.0020) at Week 8; the treatment difference between the high-dose aripiprazole and placebo groups (-9.85) was also statistically significant (p < 0.0001) at Week 8, based on a mixed effect repeated measure model. The treatment differences for both low- and high-dose aripiprazole remained significant after adjustment for multiple testing by the Hochberg procedure.

Table 29: Trial 293 Analysis of Change from Baseline to Week 8 in YGTSS TTS—MMRM (ITT)

					Treatment Difference			
Treatment Group	N[a]	BL Mean	LS Mean[b]	LS Mean SE[b]	Estimate[b]	95% CI[b] Lower limit	95% CI[b] Upper Limit	P-Value[b]
Aripiprazole Low	42	29.3	-13.35	1.59	-6.26	-10.18	-2.34	0.0020
Aripiprazole High	35	31.5	-16.94	1.61	-9.85	-13.84	-5.86	<.0001
Placebo	42	30.3	-7.09	1.55				

BL = baseline; LS = least squares; SE = standard error.
[a]Number of subjects with baseline and a Week-8 assessment of the given variable.
[b]Derived from a repeated measures linear model with treatment, week, treatment by week interaction, region, and weight group as fixed categorical effects; the baseline value as a fixed covariate; and week as the time variable for repeated measures.

Source: Trial Report, p. 84

The Per Protocol analysis was also statistically significant:

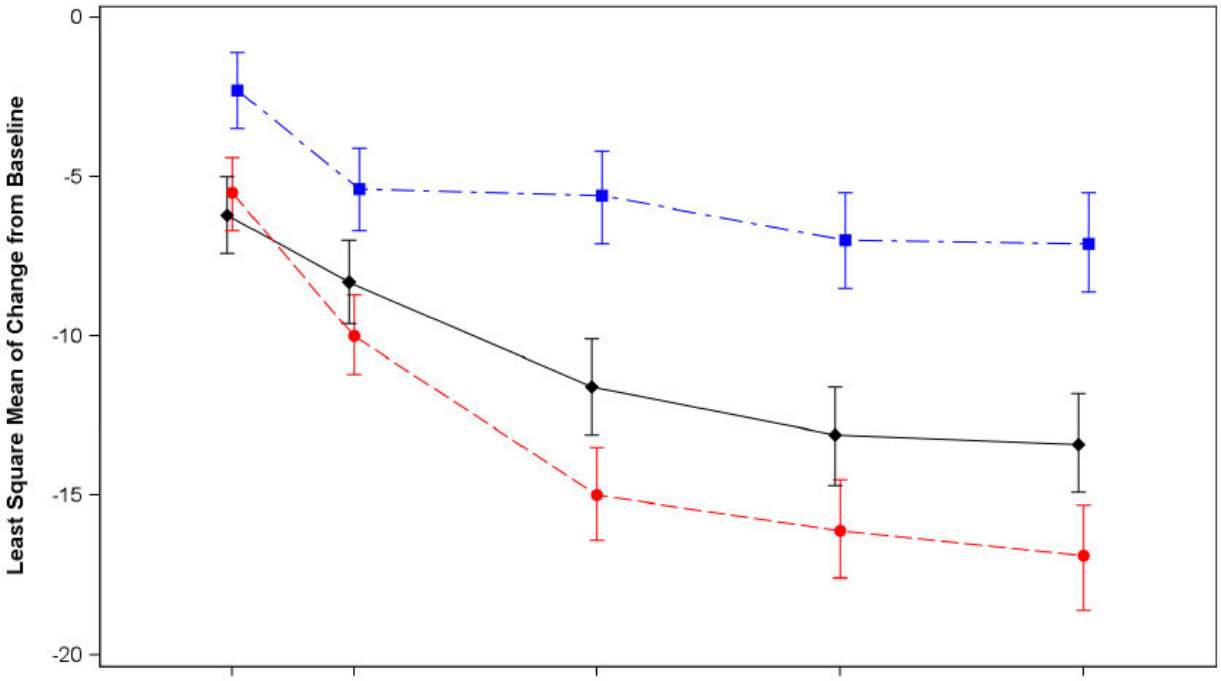
Table 30: Trial 293 Analysis of Change from Baseline in YGTSS TTS--MMRM (Per Protocol Sample)

				FROM BASELINE							
STUDY WEEK	TREATMENT GROUP	N	MEAN	N	BASE LINE MEAN	LSMEAN[1]	LSMEAN S.E.[1]	EST. TRT. DIFF.[1]	95% CI[1] LOWER LIMIT	95% CI[1] UPPER LIMIT	P-VAL[1]
BASELINE	ARIP-LOW	42	29.1								
	ARIP-HIGH	40	31.1								
	PLACEBO	44	30.7								
WEEK 8	ARIP-LOW	41	16.7	41	29.2	-12.95	1.60	-5.88	-9.73	-2.03	0.0031
	ARIP-HIGH	35	13.6	35	31.5	-17.52	1.61	-10.45	-14.39	-6.52	<.0001
	PLACEBO	42	22.7	42	30.3	-7.07	1.53				

Source: Trial Report, p. 192

The treatment difference between the aripiprazole (low and high doses) and placebo groups was statistically significant at all timepoints except at Week 2 in the low-dose aripiprazole group.

Figure 5: Trial 293 Least Square Means of Change from Baseline in YGTSS TTS Score by Week, MMRM



P-value:

ARIP-LOW	0.0049	0.0573	0.0014	0.0016	0.0020
ARIP-HIGH	0.0176	0.0031	<.0001	<.0001	<.0001

Source: Trial Report, p. 85

Subjects Taking Stepping Down Dose

A total of 7 subjects stepped down to the dose level immediately below their randomized dose: 4 subjects randomized to receive 10 mg and 1 subject randomized to receive 20 mg in the high-dose aripiprazole group; and 1 subject each, randomized to receive 5 and 10 mg in the low-dose aripiprazole group. A sensitivity analysis was performed with the 7 subjects analyzed according to the dose to which they were stepped down. The treatment effect in the YGTSS TTS remained statistically significant for both the low-dose ($p = 0.0009$) and high-dose ($p < 0.0001$) aripiprazole groups in this sensitivity analysis.

6.2.5 Analysis of Key Secondary Endpoint

The treatment difference between the low-dose aripiprazole and placebo groups (-1.03) in the CGI-TS Change Score was statistically significant (p = 0.0001) at Week 8; the treatment difference between the high-dose aripiprazole and placebo groups (-1.02) was also statistically significant (p = 0.0002) at Week 8, based on a mixed effect repeated measure model. The treatment differences for both low- and high-dose aripiprazole remained significant after adjustment for multiple testing by the Hochberg procedure.

Table 31: Trial 293 Analysis of CGI-TS Change Score at Week 8—MMRM (ITT)

				Treatment Difference			
					95% CI[b]		
Treatment Group	N[a]	LS Mean[b]	LS Mean SE[b]	Estimate[b]	Lower limit	Upper Limit	P-Value[b]
Aripiprazole Low	42	2.12	0.21	-1.03	-1.54	-0.52	0.0001
Aripiprazole High	35	2.13	0.21	-1.02	-1.54	-0.49	0.0002
Placebo	42	3.15	0.20				

LS = least squares; SE = standard error.

Source: Trial Report, p. 90

The Per Protocol Analysis was also statistically significant.

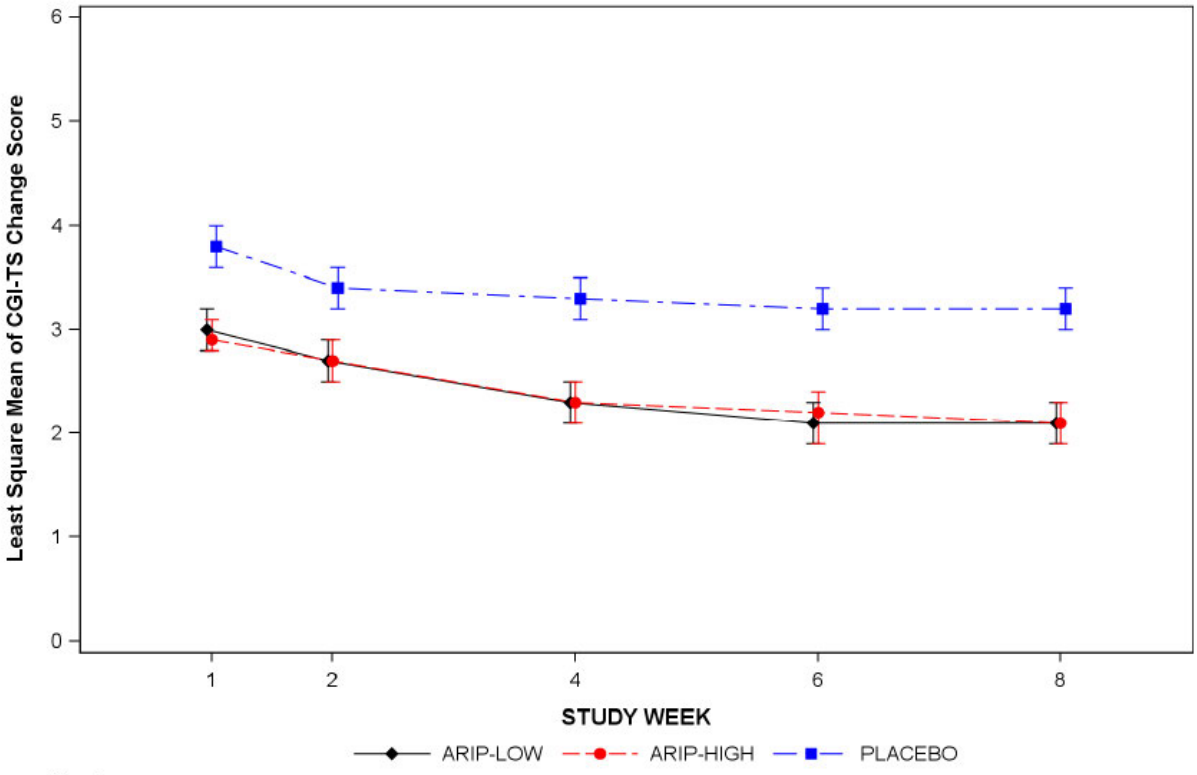
Table 32: Trial 293 Analysis of CGI-TS Change Score at Week 8—MMRM (Per Protocol Analysis)

STUDY WEEK	TREATMENT GROUP	N	LSMEAN[1]	LSMEAN S.E.[1]	EST. TRT. DIFF.[1]	95% CI[1] LOWER LIMIT	95% CI[1] UPPER LIMIT	P-VAL[1]
WEEK 8	ARIP-LOW	41	2.13	0.21	-1.01	-1.53	-0.50	0.0002
	ARIP-HIGH	35	2.05	0.22	-1.09	-1.62	-0.56	<.0001
	PLACEBO	42	3.14	0.21				

Source: Trial Report, p. 222

The treatment difference between the aripiprazole (low and high doses) and placebo groups was statistically significant at all timepoints in the trial.

Figure 6: Trial 293 Least Square Means of Change from Baseline in CGI-TS Change Score by Week, MMRM



P-value:					
ARIP-LOW	<.0001	0.0053	<.0001	<.0001	0.0001
ARIP-HIGH	<.0001	0.0025	<.0001	0.0002	0.0002

Source: Trial Report, p. 91

6.2.6 Other Secondary Endpoints

Mean Change from Baseline to Endpoint (Week 8) in the Total YGTSS Score (ITT)
The treatment difference between the low-dose aripiprazole and placebo groups (13.26) in the Total YGTSS Score was statistically significant (p = 0.0017) at Week 8; the treatment difference between the high-dose aripiprazole and placebo groups (-19.37) was also statistically significant (p < 0.0001) at Week 8, based on a mixed effect repeated measure model.

Table 33: Trial 293 Analysis of Change from Baseline to Week 8 in Total YGTSS Score--MMRM (ITT)

Treatment Group	N[a]	BL Mean	LS Mean[b]	LS Mean SE[b]	Treatment Difference			
					Estimate[b]	95% CI[b]		P-Value[b]
						Lower limit	Upper Limit	
Aripiprazole Low	42	61.2	-26.69	3.34	-13.26	-21.43	-5.08	0.0017
Aripiprazole High	35	63.2	-32.80	3.39	-19.37	-27.70	-11.04	<.0001
Placebo	42	62.0	-13.43	3.27				

BL = baseline; LS = least squares; SE = standard error.
[a]Number of subjects with baseline and a Week-8 assessment of the given variable.
[b]Derived from a repeated measures linear model with treatment, week, treatment by week interaction, region, and weight group as fixed categorical effects; the baseline value as a fixed covariate; and week as the time variable for repeated measures.

Source: Trial Report, p. 93

Mean Change from Baseline to Endpoint (Week 8) in the CGI-TS Severity Score

The treatment difference between the low-dose aripiprazole and placebo groups (-0.80) in the CGI-TS Severity Score was statistically significant (p = 0.0010) at Week 8; the treatment difference between the high-dose aripiprazole and placebo groups (-0.92) was also statistically significant (p = 0.0002) at Week 8, based on a mixed effect repeated measure model.

Table 34: Trial 293 Analysis of Change from Baseline to Week 8 in CGI-TS Severity of Illness--MMRM (ITT)

Treatment Group	N[a]	BL Mean	LS Mean[b]	LS Mean SE[b]	Treatment Difference			
					Estimate[b]	95% CI[b]		P-Value[b]
						Lower limit	Upper Limit	
Aripiprazole Low	42	4.4	-1.35	0.19	-0.80	-1.27	-0.33	0.0010
Aripiprazole High	35	4.1	-1.47	0.19	-0.92	-1.41	-0.44	0.0002
Placebo	42	4.1	-0.55	0.19				

BL = baseline; LS = least squares; SE = standard error.
[a]Number of subjects with baseline and a Week-8 assessment of the given variable.
[b]Derived from a repeated measures linear model with treatment, week, treatment by week interaction, region, and weight group as fixed categorical effects; the baseline CGI-TS Severity Score as a fixed covariate, and week as the time variable for repeated measures.

Source: Trial Report, p.94

Response Rates

Clinical response was defined as > 25% improvement from baseline to endpoint (Week 8) in YGTSS TTS or a CGI-TS change score of 1 (very much improved) or 2 (much improved at endpoint (Week 8). The response ratio for the low-dose aripiprazole group compared with the placebo group was not statistically significant; the

response ratio for the high-dose aripiprazole group compared with the placebo group was statistically significant (p = 0.0014).

Table 35: Trial 293 Response Rates at Week 8—Observed Case (ITT)

Treatment Group	Ne[a]	n[b]	(%)	Response Ratio[c] (versus placebo)	95% CI[c]		P-Value[c]
					Lower limit	Upper Limit	
Aripiprazole Low	42	31	73.8	1.36	0.98	1.88	0.0835
Aripiprazole High	35	31	88.6	1.61	1.20	2.16	0.0014
Placebo	42	23	54.8				

CMH = Cochran-Mantel-Haenszel.
[a]Ne = Number of subjects with OC YGTSS or CGI Change Score at Week 8.
[b]n = Number of responders (> 25% improvement from baseline to the specified week in YGTSS TTS or a CGI-TS change score of 1 (very much improved) or 2 (much improved) at Week 8 with the OC data.
[c]Response ratio > 1 favors aripiprazole. P-value derived from CMH General Association Test adjusting for region and weight group.
Source: Trial Report, p.96

Treatment Discontinuation Rates

The discontinuation ratio (95% CI) in the low- and high-dose aripiprazole groups, versus the placebo group, was 1.16 (0.19, 7.05) and 4.06 (1.10, 14.95), respectively. The discontinuation and hazard ratios for the low-dose aripiprazole group compared with the placebo group were not statistically significant; the discontinuation (p = 0.0132) and hazard (p = 0.0278) ratios for the high-dose aripiprazole group compared with the placebo group were statistically significant.

Due to the discontinuation rate of subjects who weighed < 50 kg and received aripiprazole 10 mg, the discontinuation rate was statistically significantly greater in the high-dose aripiprazole group compared with the placebo group.

Of the 9 subjects who discontinued IP, 8 subjects were in the aripiprazole groups:

- 1 subject who weighed ≥ 50 kg and received 20 mg in the high-dose group
- 6 subjects who weighed < 50 kg and received 10 mg in the high-dose group
- 1 subject who weighed < 50 kg and received 5 mg in the low-dose group
- 5 of the 9 subjects who discontinued from the trial did so during the titration period, receiving IP for only 2 to 15 days

Table 36: Trial 293 Discontinuation Rates (ITT)

Treatment Group	Ne[a]	n[b]	(%)	Discontinuation Ratio[c] (versus placebo)	95% CI[c]		P-Value[c]	Hazard Ratio[d] (versus placebo)	P-Value[d]
					Lower limit	Upper Limit			
Aripiprazole Low	44	2	4.5	1.16	0.19	7.05	0.9187	1.05	0.9576
Aripiprazole High	45	10	22.2	4.06	1.10	14.95	0.0132	5.51	0.0278
Placebo	44	2	4.5						

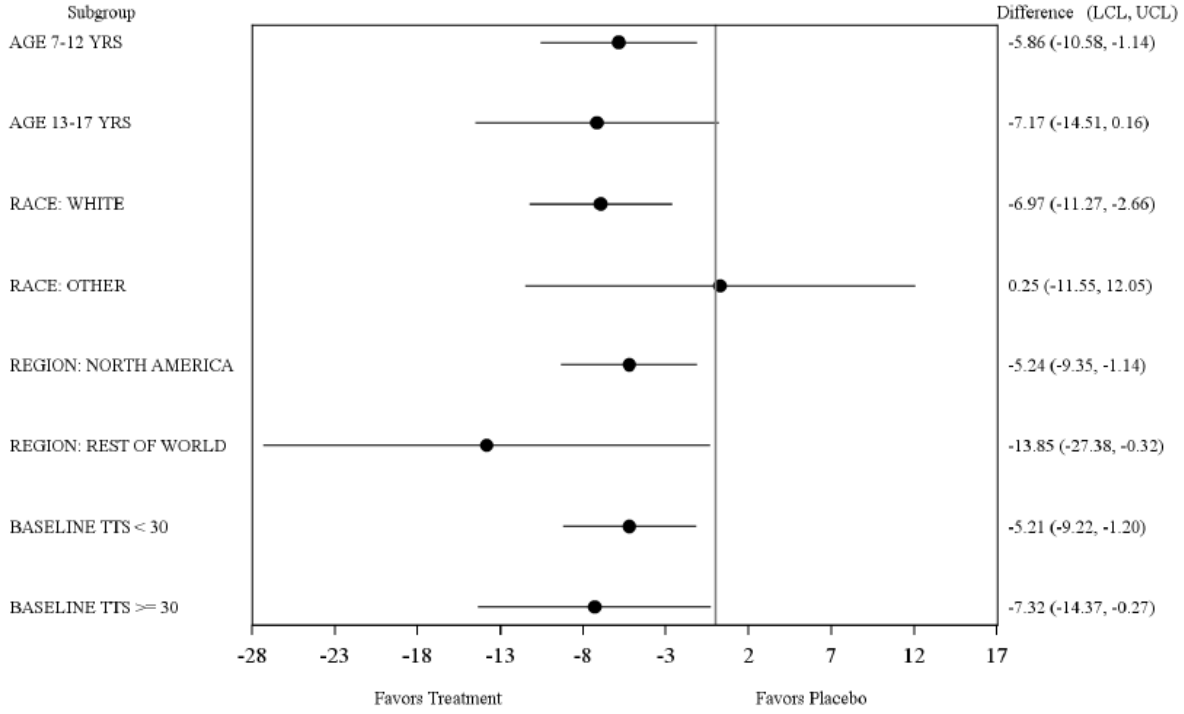
CMH = Cochran-Mantel-Haenszel.
[a]Ne = Number of randomized subjects.
[b]n = Number of discontinued subjects.
[c]Discontinuation ratio < 1 favors aripiprazole. P-value derived from CMH General Association Test adjusting for region and weight group.
[d]Hazard ratio < 1 favors aripiprazole. P-value derived from Cox proportional hazard regression adjusting for region and weight group.

Source: Trial Report, p.97

6.2.7 Subpopulations

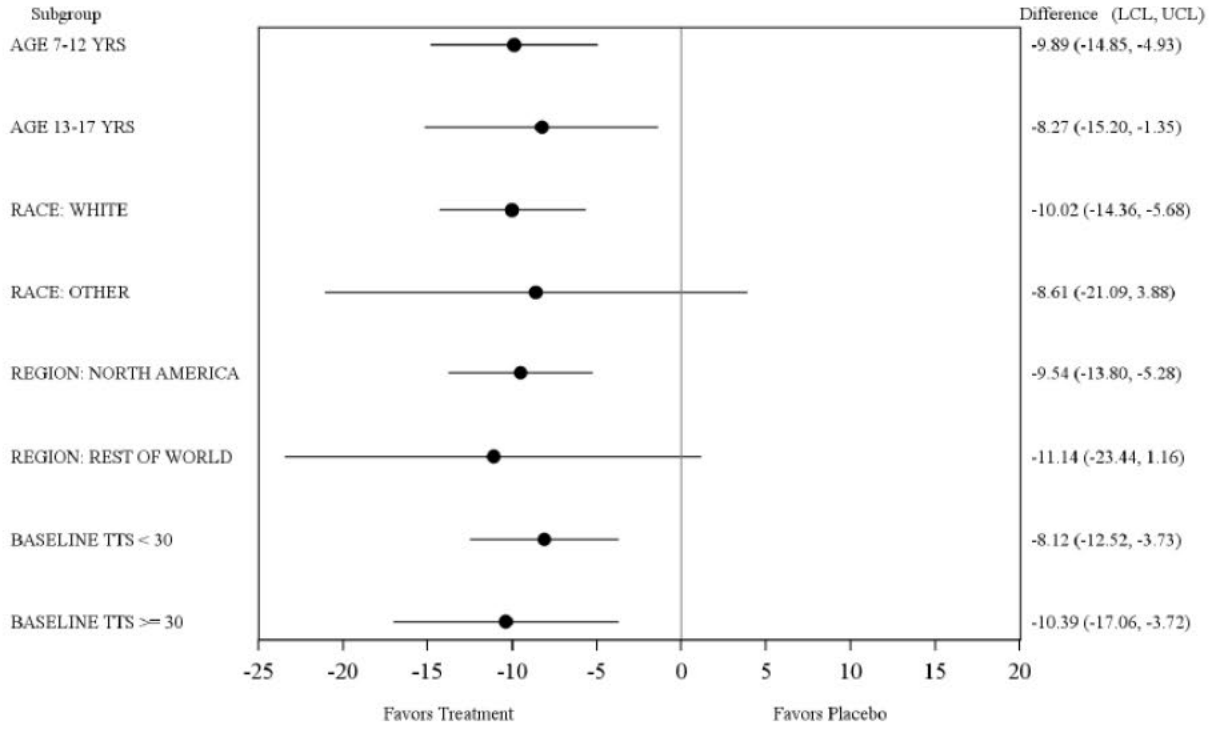
The primary efficacy endpoint of the change from baseline to Week 8 in YGTSS TTS was analyzed for the following subgroups: age, region, race, and baseline YGTSS TTS. The Applicant states that the small sample sizes in these subgroups do not allow reliable inferences to be made. Except for Race Other for the low dose group, all subgroups favored Treatment shown in Figure 7 and Figure 8.

Figure 7: Trial 293 Subgroup Analysis of Treatment Effect on YGTSS TTS Score
Aripiprazole Low Dose versus Placebo Treatment Difference and 95% CI



Source: Trial Report, p. 88

Figure 8: Trial 293 Subgroup Analysis of Treatment Effect on YGTSS TTS Score Aripiprazole High Dose versus Placebo Treatment Difference and 95% CI



Source: Trial Report, p. 89

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant's proposed dosing recommendations appear reasonable based on the clinical data:

----------DOSAGE AND ADMINISTRATION----------

	Initial Dose	Recommended Dose	Maximum Dose
(b) (4) Patients < 50 kg	2 mg/day	5 mg/day	10 mg/day
Patients > 50 kg	2 mg/day	10 mg/day	20 mg/day

Dr. Zhang (OCP, 11/3/2014 review) also concluded that the proposed dose/exposure range is acceptable. She states that the proposed doses/exposures are anticipated to be within the efficacious range and that the proposed dose/exposure is anticipated to be safe.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This short-term study was not designed to evaluate the persistence of efficacy and/or tolerance effects. A PMR/PMC for a long-term maintenance trial (randomized withdrawal) in a pediatric Tourette population to evaluate these effects is anticipated.

6.2.10 Additional Efficacy Issues/Analyses

Dr. Birkner (Biometrics) performed an additional efficacy analysis on the change from baseline in total vocal and motor tic scores. The results of this analysis demonstrate that aripiprazole had a positive effect on both motor and vocal tics. Please see his review for the details of this analysis.

7 Review of Safety

Safety Summary

Trial 31-12-293
Aripiprazole low and high doses (5 to 20 mg) were well tolerated in pediatric subjects with TD during the 8-week double-blind treatment period. No deaths or SAEs were reported during the trial. The trial completion rate was 95.5% in the low-dose aripiprazole, 77.8% in the high-dose aripiprazole, and 95.5% in the placebo groups. The rate of IMP (investigational medicinal product) discontinuation due to AEs was higher in the high-dose aripiprazole group (15.6%) than in the low-dose aripiprazole and placebo groups (2.3% in each). The number of subjects with TEAEs that led to discontinuation was greater for subjects who weighed < 50 kg in the high dose group. The most frequently reported TEAEs for both the low- and high-dose aripiprazole groups (with ≥ 5% incidence in both dose groups) were sedation, somnolence, fatigue, headache, increased appetite, nausea and nasopharyngitis. There were 1 subject (2.3%) in the low-dose and 6 subjects (13.3%) in the high-dose aripiprazole groups who experienced EPS-related TEAEs; no subjects in the placebo group experienced EPS-related events. The most frequently reported EPS-related TEAEs were dystonia and tremor (1 subject) in the low-dose aripiprazole group (5 mg) and akathisia (3 subjects) in the high-dose aripiprazole group. Weight gain-related TEAEs in the low- and high-dose aripiprazole and placebo groups were reported for 5 (11.4%), 3 (6.7%), and 1 (2.3%) subjects, respectively. There were no TEAEs related to prolactin, hyperglycemia and diabetes, lipid parameters, or suicide. The incidence of potentially clinically relevant laboratory values was similar across the low- and high-dose aripiprazole and placebo groups, except for creatine phosphokinase (CPK) and fasting glucose. The incidence of elevated CPK in the low-dose aripiprazole (2 subjects) and high-dose aripiprazole (2 subjects) groups was higher than that in the placebo group (0). The incidence of postbaseline elevated fasting glucose in the low-dose aripiprazole (2 subjects) and high-dose aripiprazole (2 subjects) groups was higher than that in the placebo group (0). No

significant findings were shown in clinical laboratory values, vital signs, and ECGs parameters. Safety findings were consistent with the know safety profile of Abilify.

Trial 031-KOA-0703
No deaths or SAEs were reported during the trial. No subjects discontinued the trial or permanently discontinued IMP due to an AE. All TEAEs were mild or moderate in severity. 75.0% of subjects treated with aripiprazole and 71.4% of subjects treated with placebo experienced at least one TEAE. The most common TEAEs in the aripiprazole group (vs placebo) were nausea (18.8% vs 7.1%), headache (15.6% vs 3.6%), and nasopharyngitis and somnolence (12.5% vs 0% each).

Three (3) subjects (9.4%) in the aripiprazole group and 2 subjects (7.1%) in the placebo group experienced a TEAE of extrapyramidal disorder. Mean changes from baseline to final visit in the SAS Total Score, AIMS Total Score, and BARS Global Score were not statistically different between the aripiprazole and placebo groups. Weight gain of ≥ 7% from baseline at Week 10 was reported in 28% of the aripiprazole group and 7% of the placebo group. No prolactin-related TEAEs were reported. Aripiprazole-treated subjects had a statistically significant mean decrease in serum prolactin at Week 10. No other changes in laboratory parameters from screening to final visit were statistically significant and clinically significant. Systolic blood pressure, diastolic blood pressure, and heart rate measurements showed no significant changes from baseline and there were no significant differences between treatment groups. ECG parameters showed no statistically significant change or significant group difference from screening to the final visit. Safety findings were consistent with the know safety profile of Abilify.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The 2 double-blind, placebo-controlled phase 3 trials (Trial 31-12-293 and Trial 031-KOA-0703) provide the primary safety data to support the basis of approval of once-daily aripiprazole as a treatment for tics in pediatric patients with TD. The trial designs and efficacy results for these trials are described in Section 6. The safety results for these trials will be detailed in this Review of Safety.

An additional trial, Trial 31-12-294, is ongoing. This 52-week, open-label, flexible-dose trial will provide long-term safety data pertinent to the use of QD aripiprazole in the treatment of tics in pediatric patients with TD. A synopsis of the trial design, subject disposition, demographics, and subject exposure for Trial 21-12-294 will be provided below. The preliminary safety results (as of cutoff date of 30 September 2013) will be discussed throughout this Review of Safety (Section 7). The 120-Day Safety Update (Section 7.8) also provides an update on this long-term, open-label trial.

In addition to the trials in subjects with TD, 16 trials in pediatric subjects with other conditions have been conducted in the context of other aripiprazole clinical development programs. A brief summary of the safety data from these trials will also be provided in this Review of Safety.

Trial 31-12-294 (Ongoing Long-Term Open-Label Trial)

Title: "An Open-Label, Multicenter Study Evaluating the Safety and Tolerability of Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder"

Trial Initiation Date: 14 January 2013

Date of last trial observation: Ongoing; cutoff date 30 Sep 2013

Objectives
Primary
- To evaluate the long-term safety and tolerability of aripiprazole once-daily treatment with oral tablets in children and adolescents (aged 7-17 years) with a diagnosis of Tourette's disorder (TD)

Secondary
- To evaluate the efficacy of once-daily aripiprazole in the suppression of tics in children and adolescents with a diagnosis of TD, as measured by the change from baseline to endpoint on the total tic score (TTS) of the Yale Global Tic Severity Scale (YGTSS).

Methodology
Trial 294 is a 52-week open-label, multicenter safety investigation of aripiprazole once-daily treatment, flexibly dosed, in pediatric subjects with a diagnosis of TD. Subjects who had successfully completed the randomized, double-blind, placebo-controlled trial of aripiprazole once daily (Trial 293) were eligible to enter this extension trial. All subjects in the open-label extension trial were assigned to aripiprazole, which was dosed once daily.

A day before the Week 8 visit of the double-blind trial, subjects took their final dose of double-blind investigational medicinal product (IMP). On Day 0 of the open-label trial, subjects began taking the open-label aripiprazole once-daily treatment. All subjects began on a dose of 2 mg/day for 2 days then the dose was to be increased to 5 mg/day. According to the investigator's discretion based on efficacy and tolerability, at the Week 1 visit, the dose of aripiprazole could have been decreased to 2 mg/day, remained at 5 mg/day, or been increased to 10 mg/day. At subsequent visits, the dose of aripiprazole could have been titrated up or down to a maximum of 20 mg/day (two 10-mg tablets) and a minimum of 2 mg/day at subsequent visits. Subjects visited the trial center at the end of Weeks 1, 2, 4, 8, 12, 20, 28, 36, 44, and 52. Telephone contacts occurred at Weeks 3, 6, 16, 24, 32, 40, and 48.

Subjects

It was anticipated that approximately 96 subjects would be enrolled in this trial and that about 48 (50%) and 38 (40%) subjects would complete the 26-week and 52-week evaluations, respectively. In actuality, 110 subjects enrolled in Trial 294, and no subjects had completed the trial as of the 30 Sep 2013 data cutoff date.

Inclusion Criteria

- Subjects with TD who successfully completed Trial 293 with no significant protocol violations or clinically relevant AEs

Exclusion Criteria

- + Urine drug screen
- Risk of suicide
- Weight < 16 kg
- Abnormal ECGs or labs

Trial Assessments

Efficacy

- YGTSS
- Clinical Global Impressions scale for Tourette's Syndrome (CGI-TS)

Safety

- AEs
- Laboratory tests: hematology, clinical chemistry including fasting lipid panel, serum prolactin, TSH, urinalysis, urine drug/alcohol screen, and serum pregnancy test
- 12-lead ECGs
- Vital signs and physical examination
- Height, body weight, waist circumference, body mass index (BMI)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Extrapyramidal symptoms (EPS) scales at every clinic visit: Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS)
- Swanson, Nolan and Pelham-IV (SNAP-IV) Rating Scale
- Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)
- Children's Depression Rating Scale - Revised (CDRS-R)
- Pediatric Anxiety Rating Scale (PARS)

Criteria for Evaluation

- **Primary endpoints** were safety endpoints: AEs, laboratory tests results, vital signs, ECGs, AIMS, SAS, BARS, C-SSRS, SNAP-IV, CY-BOCS, CDRS-R, PARS, body weight, waist circumference, and BMI
- **Secondary endpoints** were efficacy endpoints: change from baseline to endpoint in YGTSS TTS, mean CGI-TS Change Score at endpoint, change from baseline to endpoint in CGI-TS Severity Score, mean change from baseline to

endpoint in total YGTSS score, response rates (clinical response was defined as > 25% improvement from baseline to endpoint in YGTSS TTS or a CGI-TS Change Score of 1 [very much improved] or 2 [much improved] at endpoint), and treatment discontinuation rates.

Disposition

Table 37: Trial 294 Disposition of Subjects

Disposition	Number of Subjects
Enrolled	110
Completed	0 (as of cutoff date)
Discontinued	6

Source: Trial Synopsis, p.17

Table 38: Trial 294 Reasons for Discontinuation by Treatment

	ARIP-LOW		ARIP-HIGH	
NUMBER OF SUBJECTS:	ARIP-5 MG (N = 25) N (%)[1]	ARIP-10 MG (N = 13) N (%)[1]	ARIP-10 MG (N = 19) N (%)[1]	ARIP-20 MG (N = 12) N (%)[1]
ENROLLED	25 (100.0)	13 (100.0)	19 (100.0)	12 (100.0)
COMPLETED	0	0	0	0
DISCONTINUED	2 (8.0)	1 (7.7)	0	3 (25.0)
LOST TO FOLLOW UP	0	0	0	1 (8.3)
ADVERSE EVENTS	1 (4.0)	0	0	1 (8.3)
SUBJECT WITHDREW CONSENT	0	1 (7.7)	0	0
PROTOCOL DEVIATION	1 (4.0)	0	0	1 (8.3)

Source: Trial Synopsis, p.17

Demographics

The majority of subjects were male (86/110 subjects; 78%) and white (99/110 subjects; 90%). Mean subject age was 11.7 years. The mean BMI was 20.7.

Exposure

As of the cutoff date, all subjects (100%) had been exposed for at least 14 days, 98 subjects had been exposed for 29 to 56 days, and 81 subjects had been exposed for 57 to 84 days.

Table 39: Trial 294 Exposure to Aripiprazole

	TOTAL (N=110)		
TIME INTERVAL	n[1]	(%)	AVERAGE DOSE (MG)[2]
1 - 7 DAYS	110	(100.0)	4.2
8 - 14 DAYS	110	(100.0)	6.1
15 - 21 DAYS	107	(97.3)	6.9
22 - 28 DAYS	106	(96.4)	7.1
29 - 56 DAYS	98	(89.1)	7.3
57 - 84 DAYS	81	(73.6)	7.9
85 - 112 DAYS	43	(39.1)	9.0
113 - 140 DAYS	32	(29.1)	8.9
141 - 168 DAYS	24	(21.8)	9.0
169 - 196 DAYS	10	(9.1)	8.9
197 - 224 DAYS	3	(2.7)	6.7
225 - 252 DAYS	2	(1.8)	7.4
253 - 280 DAYS	1	(0.9)	0.0
281 - 308 DAYS	0	(0.0)	

Source: Trial Synopsis, p.46

7.1.2 Categorization of Adverse Events

For Trial KOA, all adverse events were classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 11.0. For Trial 293, all AEs were coded by system organ class (SOC) and Medical Dictionary for Regulatory Activities (MedDRA version 16.0) preferred term.

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

The Applicant has pooled data across many trials for the Summary of Clinical Safety. The primary pooled safety data are from the two completed placebo-controlled pivotal trials in TD, Trial KOA and Trial 293. Demographic and exposure data have also been pooled for Trial KOA, Trial 293, and Trial 294 (uncontrolled, long-term, open-label trial).

In addition, the following pooled datasets from the aggregate safety database were analyzed for safety:

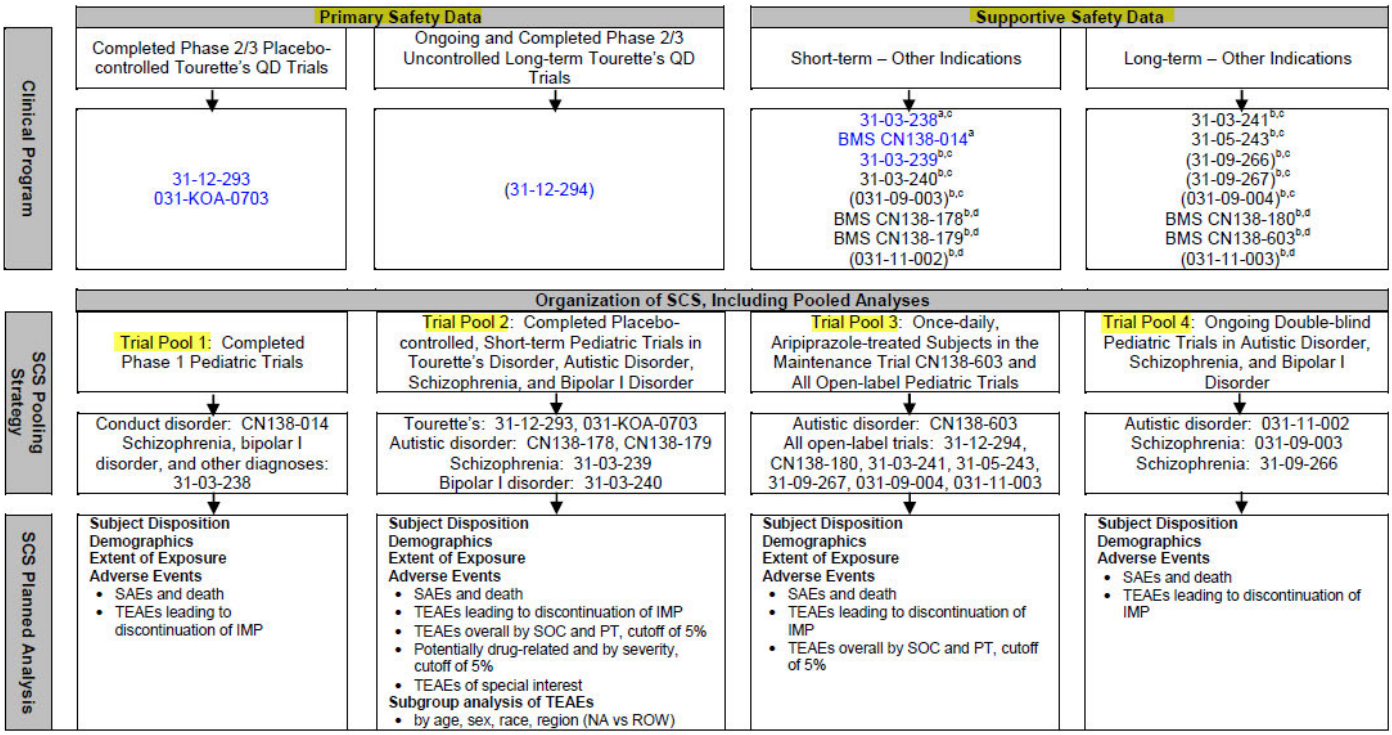
- **Trial Pool 1**: Completed phase 1 pediatric trials, including the safety samples of subjects with conduct disorder, schizophrenia, bipolar I disorder, and other diagnoses.
- **Trial Pool 2**: Completed placebo-controlled, short-term pediatric trials in subjects with TD, autistic disorder, schizophrenia, and bipolar I disorder

- **Trial Pool 3**: QD aripiprazole-treated subjects in the maintenance trial CN138-603 and all open-label pediatric trials, including the safety samples of subjects with autistic disorder, schizophrenia and bipolar I disorder
- **Trial Pool 4**: Ongoing double-blind pediatric trials in autistic disorder, schizophrenia, and bipolar I disorder (cutoff date of 30 Sep 2013)

The safety data from these pools were reviewed but only key aspects will be presented in this document. The focus of this safety review will be on the pivotal controlled trials in TD.

The organization of the pooling is presented in Figure 9 below:

Figure 9: Organization of Trials (Pools) for the Summary of Clinical Safety



Source: Summary of Clinical Safety, p. 30

7.2 Adequacy of Safety Assessments

All tests reasonably applicable were conducted to assess the safety of Abilify in the treatment of Tourette's Disorder. Safety was assessed by monitoring treatment-emergent adverse events, laboratory values, vital sign measurements, ECG data, movement disorder measures, physical examination reports, and C-SSRS.

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

There has been adequate exposure at appropriate doses. Overall, 162 subjects with TD have been exposed to aripiprazole for 46 subject-exposure years during the 3 TD trials (Trial KOA, Trial 293, and Trial 294). A total of 73 subjects (45.1%) have been exposed for at least 90 days, and 23 subjects (14.2%) have been exposed for at least 180 days.

Table 40: Cumulative Number of Subjects Who Received Once-daily Aripiprazole by Duration of Exposure (Trial 293, Trial KOA, Trial 294), Safety Sample

	Total (N=162)
Time Interval	**n[a] (%)[b]**
Subject-Exposure Years	46
≥ 1 Day	162 (100)
≥ 21 Days	152 (93.8)
≥ 42 Days	147 (90.7)
≥ 90 Days	73 (45.1)
≥ 180 Days	23 (14.2)
≥ 270 Days	0 (0.0)
≥ 360 Days	0 (0.0)

Source: Summary of Clinical Safety, p. 33

Table 41 shows exposure to aripiprazole in the pooled TD trials by dose and exposure category. Over all dose categories, 74 of the 162 subjects (45.7%) received aripiprazole for 42 to 89 days. The majority of subjects received an overall mean dose of aripiprazole >3.5 mg and ≤12.5 mg.

Table 41: Number and % of Subjects Who Received Once-daily Aripiprazole by Overall Mean Dose Category and Duration of Exposure (Trial 293, Trial KOA, and Trial 294), Safety Sample

	Aripiprazole Overall Mean Dose[a]					
	≤ 3.5 mg	> 3.5 - ≤ 7.5 mg	> 7.5 - ≤ 12.5 mg	> 12.5 - ≤ 17.5 mg	> 17.5 mg	Total
Total Duration of Exposure	**(N=13) n (%)[b]**	**(N=77) n (%)[b]**	**(N=57) n (%)[b]**	**(N=14) n (%)[b]**	**(N=1) n (%)[b]**	**(N=162) n (%)[b]**
1 - 20 Days	4 (30.8)	6 (7.8)	0 (0.0)	0 (0.0)	0 (0.0)	10 (6.2)
21 - 41 Days	0 (0.0)	1 (1.3)	4 (7.0)	0 (0.0)	0 (0.0)	5 (3.1)
42 - 89 Days	7 (53.8)	30 (39.0)	29 (50.9)	8 (57.1)	0 (0.0)	74 (45.7)
90 - 119 Days	0 (0.0)	11 (14.3)	4 (7.0)	0 (0.0)	0 (0.0)	15 (9.3)
120 - 149 Days	1 (7.7)	20 (26.0)	9 (15.8)	3 (21.4)	0 (0.0)	33 (20.4)
150 - 179 Days	0 (0.0)	0 (0.0)	1 (1.8)	1 (7.1)	0 (0.0)	2 (1.2)
180 - 269 Days	1 (7.7)	9 (11.7)	10 (17.5)	2 (14.3)	1 (100)	23 (14.2)
270 - 359 Days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
360 - 719 Days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	13 (100)	77 (100)	57 (100)	14 (100)	1 (100)	162 (100)

[a] Overall mean dose during subject's total duration of exposure, including the titration period. Categories are consistent with those used in previous submissions.

Source: Summary of Clinical Safety, p. 34

A total of 1731 pediatric subjects (6-18 years old) have received aripiprazole and contributed data to the aggregate safety database as of the data cutoff date for this sNDA submission (30 Sep 2013).

Table 42: Summary of All Pediatric Once-daily Aripiprazole Trials by Indication (Safety sample)

	Actual Treatment Group		
Pools by Indication and Trial Design	**Blinded**[a]	**Placebo**	**Aripiprazole**
Tourette's disorder			
Short-term, placebo-controlled (31-12-293, 031-KOA-0703)		72	121
Ongoing, uncontrolled/open-label (31-12-294)			110
			(69)[b]
Total Tourette's disorder		72	162
Autistic disorder			
Short-term, placebo-controlled (031-11-002, CN138-178, CN138-179)	54	101	212
Maintenance treatment placebo-controlled (CN138-603)			155
Ongoing/completed, uncontrolled/open-label (CN138-180, 031-11-003)			375
			(174)[b]
Total autistic disorder	54	101	568
Schizophrenia			
Short-term, placebo-controlled (031-09-003, 31-03-239)	55	100	202
Maintenance treatment placebo-controlled (31-09-266)	198		
Ongoing/completed, uncontrolled/open-label (031-09-004, 31-03-238, 31-03-241, 31-05-243, 31-09-267)			586
			(160)[b]
Total schizophrenia	253	100	628
Bipolar I disorder			
Short-term plus extension phase placebo-controlled (31-03-240)		97	197
Ongoing/completed, uncontrolled/open-label (31-03-238, 31-03-241, 31-09-267)			195
			(50)[b]
Total bipolar I disorder		97	342
Other indications			
Conduct disorder, uncontrolled/open-label (CN138-014)			23
Other, uncontrolled/open-label (31-03-238)			8
Total other indications			31
Total Phase 1/2/3 exposure	307	370	1731

[a]Number of subjects in the ongoing double-blinded trials
[b]Number of subjects also counted under aripiprazole in the placebo-controlled trials
Source: Summary of Clinical Safety, p. 13

Overall in the phase 2 and 3 pediatric trials, 1686 subjects with known exposure duration data available have been exposed to aripiprazole for 1342 subject-exposure years. A total of 959 subjects (56.9%) have been exposed for at least 180 days, and 556 subjects (33.0%) have been exposed for at least 360 days.

Table 43: Cumulative Number of Subjects Who Received Once-daily Aripiprazole by Duration of Exposure: All Phase 2/3 Pediatric, Ongoing Open-label and All Completed Trials (Pools 2 and 3), Safety Sample

	Total (N=1686)
Time Interval	**n[a] (%)[b]**
Subject-Exposure Years	1342
≥ 1 Day	1686 (100)
≥ 21 Days	1565 (92.8)
≥ 42 Days	1488 (88.3)
≥ 90 Days	1275 (75.6)
≥ 180 Days	959 (56.9)
≥ 270 Days	644 (38.2)
≥ 360 Days	556 (33.0)

Source: Summary of Clinical Safety, p. 35

For all phase 2 and 3 pediatric trials, 25.3% of subjects (427/1686 subjects) received aripiprazole for 360 to 719 days. Most subjects received an overall mean dose of aripiprazole >7.5 mg.

Table 44: Number and % of Subjects Who Received Once-daily Aripiprazole by Overall Mean Dose Category and Duration of Exposure: All Phase 2/3 Pediatric, Ongoing Open-label and All Completed Trials (Pools 2 and 3), Safety Sample

	Aripiprazole Overall Mean Dose[a]					
	≤ 3.5 mg	**> 3.5 - ≤ 7.5 mg**	**> 7.5 - ≤ 12.5 mg**	**> 12.5 - ≤ 17.5 mg**	**> 17.5 mg**	**Total**
Total Duration of Exposure	**(N=97) n (%)[b]**	**(N=325) n (%)[b]**	**(N=571) n (%)[b]**	**(N=298) n (%)[b]**	**(N=395) n (%)[b]**	**(N=1686) n (%)[b]**
1 - 20 Days	30 (30.9)	47 (14.5)	26 (4.6)	13 (4.4)	5 (1.3)	121 (7.2)
21 - 41 Days	6 (6.2)	17 (5.2)	29 (5.1)	7 (2.3)	18 (4.6)	77 (4.6)
42 - 89 Days	18 (18.6)	67 (20.6)	82 (14.4)	20 (6.7)	26 (6.6)	213 (12.6)
90 - 119 Days	7 (7.2)	34 (10.5)	38 (6.7)	12 (4.0)	18 (4.6)	109 (6.5)
120 - 149 Days	7 (7.2)	35 (10.8)	41 (7.2)	15 (5.0)	21 (5.3)	119 (7.1)
150 - 179 Days	5 (5.2)	15 (4.6)	38 (6.7)	14 (4.7)	16 (4.1)	88 (5.2)
180 - 269 Days	9 (9.3)	38 (11.7)	99 (17.3)	61 (20.5)	108 (27.3)	315 (18.7)
270 - 359 Days	3 (3.1)	20 (6.2)	33 (5.8)	21 (7.0)	11 (2.8)	88 (5.2)
360 - 719 Days	12 (12.4)	44 (13.5)	156 (27.3)	99 (33.2)	116 (29.4)	427 (25.3)
≥ 720 Days	0 (0.0)	8 (2.5)	29 (5.1)	36 (12.1)	56 (14.2)	129 (7.7)
Total	97 (100)	325 (100)	571 (100)	298 (100)	395 (100)	1686 (100)

[a] Overall mean dose during subject's total duration of exposure, including the titration period.

Source: Summary of Clinical Safety, p. 36

7.2.2 Explorations for Dose Response

Explorations for dose response for adverse reactions were conducted in the fixed-dose Trial 31-12-293. The Applicant states that no adverse reaction (AR) had a possible dose response relationship. The current USPI does describe dose response relationships for ARs for other indications.

With respect to efficacy, both high and low dose aripiprazole were found to be efficacious in the fixed-dose Trial 31-12-293. For the flexible-dose Trial KOA, the mean dose for the aripiprazole group was 6.54 mg (mean dose of 10.97 mg for completers). For the pooled TD trials, the majority of subjects received an overall mean dose of aripiprazole >3.5 mg and ≤12.5 mg. These data support the Applicant's proposed dosing guidelines.

7.2.4 Routine Clinical Testing

All tests reasonably applicable were conducted to assess the safety of Abilify in the treatment of Tourette's Disorder. See Sections 9.6 and 9.7 for Schedules of Assessments for details on the timing and extent of the routine clinical testing for the two controlled TD trials.

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

The Applicant adequately attempted to assess all potential adverse events that might be associated with this drug class.

7.3 Major Safety Results

The major safety findings were consistent with the known safety and tolerability profile for Abilify.

7.3.1 Deaths

No deaths were reported in the pivotal trials for this submission (Trials 293, KOA, or 294). No deaths have been reported during any of the trials in Trial Pools 1, 2, and 4. There have been 3 deaths reported as of 30 September 2013 in Trial Pool 3. Deaths were due to an accidental electrocution, bacterial pneumonia, and acute heroin toxicity. All 3 deaths were judged to be not related to IMP by the investigators.

7.3.2 Nonfatal Serious Adverse Events

Trial 293 and Trial KOA
No treatment-emergent SAEs were reported during Trial 293 or Trial KOA during the randomized treatment period. One subject in Trial KOA (Subject 003-0009) experienced

an SAE of hydrocephalus during the screening period. The investigator and sponsor judged this event to be unrelated to IMP because it occurred before administration of aripiprazole.

Trial 294
Subject 534S3011 (Aripiprazole 10 mg) experienced an SAE of severe infectious mononucleosis on Day 105 that was considered unrelated to IMP. The event resolved, and the subject did not discontinue from the trial. No other SAEs were reported as of the cutoff date of 30 Sep 2013.

Trial Pool 2
For Trial Pool 2, 3.0% of subjects in the aripiprazole group (22/732 subjects) and 2.2% of subjects in the placebo group (8/370 subjects) experienced at least one treatment-emergent SAE. Bipolar disorder (0.7%) and aggression (0.5%) were the two most frequently occurring treatment-emergent SAEs in aripiprazole-treated subjects.

Table 45: Trial Pool 2 Incidence of Treatment-emergent Non-fatal SAEs Occurring in at Least 2 Subjects

	Aripiprazole (N=732)		Placebo (N=370)	
System Organ Class Preferred Term[a]	**n**	**(%)**	**n**	**(%)**
At least 1 SAE[b]	22	(3.0)	8	(2.2)
Psychiatric Disorders	18	(2.5)	7	(1.9)
Acute Psychosis	2	(0.3)	0	(0.0)
Aggression	4	(0.5)	0	(0.0)
Bipolar Disorder	5	(0.7)	3	(0.8)
Bipolar I Disorder	2	(0.3)	1	(0.3)
Schizophrenia	2	(0.3)	0	(0.0)
Suicidal Ideation	2	(0.3)	0	(0.0)

Source: Summary of Clinical Safety, p.57

Trial Pool 3
In Trial Pool 3, 6.1% of subjects (86/1408 subjects) experienced at least one treatment-emergent SAE. The most frequently occurring SAEs were schizophrenia (1.7%), suicidal ideation (0.8%), aggression (0.6%), and bipolar disorder (0.5%).

Table 46: Trial Pool 3 Treatment-emergent Non-fatal SAEs Occurring in at Least 2 Subjects

	Total (N=1408)	
System Organ Class Preferred Term[a]	**n**	**(%)**
At least 1 SAE[b]	86	(6.1)
Injury, Poisoning and Procedural Complications	3	(0.2)
Intentional Overdose	2	(0.1)
Metabolism and Nutrition Disorders	2	(0.1)
Decreased Appetite	2	(0.1)
Psychiatric Disorders	71	(5.0)
Aggression	9	(0.6)
Agitation	3	(0.2)
Bipolar Disorder	7	(0.5)
Bipolar I Disorder	3	(0.2)
Depression	2	(0.1)
Hallucination, Auditory	3	(0.2)
Impulsive Behaviour	3	(0.2)
Intentional Self-Injury	2	(0.1)
Psychotic Disorder	3	(0.2)
Schizophrenia	24	(1.7)
Suicidal Ideation	11	(0.8)
Suicide Attempt	5	(0.4)

Source: Summary of Clinical Safety, p.58

7.3.3 Dropouts and/or Discontinuations

Trial 293

Eight (8) of 89 subjects (9.0%) discontinued the IMP due to an AE:

Table 47: Trial 293 Data for Subjects who Discontinued Aripiprazole due to an AE

Subject Identification	Age	Event (Severity)	Dose at Time of Onset	Trial Day of Onset
511S3010	12	Fatigue (moderate)	2 mg	Day 1
517S3074	13	Disturbance in attention; Fatigue; Dysarthria; Headache (all mild)	5 mg	Day 5
508S3077	8	Lethargy (severe)	5 mg	Day 5
535S3119	12	Electrocardiogram QT prolonged (mild)	10 mg	Day 31
511S3152	7	Somnolence (severe); Increased appetite (moderate)	2 mg	Day 1; Day 2
576S3170	11	Extrapyramidal disorder (moderate)	10 mg	Day 16
530S3094[a]	12	Somnambulism (severe)	5 mg	Day 28
507S3072	14	Insomnia (severe)	10 mg	Day 9

[a] Subject 530S3094 discontinued IMP due to an AE but returned to the site for the Week 8 visit and, therefore, met the protocol-specified criteria for completing the trial.

Source: Summary of Clinical Safety, p. 53[12]

An exposure safety analysis for Trial 293 was conducted in 76 of 89 aripiprazole-treated subjects (85.4%) who completed 8 weeks of treatment, 12 of these 89 subjects (13.5%) who discontinued IMP for any reason, and 8 of these 89 subjects (9.0%) who discontinued IMP due to an AE. No differences in aripiprazole exposure, age, body weight, and baseline TTS were observed among the 3 groups. The analysis revealed that aripiprazole exposure, including during the titration period, did not appear to be related to discontinuations due to AEs or discontinuations due to any reason. The majority of subjects who discontinued IMP due to AEs did so during the titration period and did not reach the 10 mg dose.

Trial KOA

No subjects discontinued the trial or permanently discontinued IMP due to an AE.

Trial 294

Three subjects prematurely discontinued from the trial due to AEs.

Table 48: Trial 294 AEs Leading to Discontinuation

Subject	Aripiprazole Dose at Time of AE	AE Leading to Discontinuation	Related	Comments
511S3164	5 mg	Emotional Poverty	Yes	Onset: Day 9

[12] Subject 530S3094 was randomized to aripiprazole 5 mg and started at a dose of 2 mg on day 1. On day 28, the subject experienced the severe event of somnambulism. The event of somnambulism was considered to be possibly related to study medication. No treatment was given for the event. Study medication was discontinued as a result of the event, and the last dose of study medication was taken on day 53. The event resolved on day 54, and the subject completed the last study visit on day 60.

		(moderate)		Drug withdrawn: Day 43 Resolved: Day 67
534S3035	10 mg	Dystonia[13] (moderate)	Yes	Onset: Day 16 Drug withdrawn: Day 16 Resolved: Day 18
565S3160	10 mg	Depression (moderate); subject "wished to be dead" and had nonspecific active suicidal thoughts	Possibly	Onset: Day 29 Drug withdrawn: Day 28 Resolved: Day 50

Source: Trial Synopsis, p. 11

Trial Pool 2
In Trial Pool 2, 9.4% of subjects treated with aripiprazole and 3.2% of subjects treated with placebo experienced at least one TEAE resulting in discontinuation of IMP. The 5 most frequently occurring TEAEs resulting in discontinuation of IMP among aripiprazole-treated subjects were sedation (1.4%), fatigue (1.0%), extrapyramidal disorder (0.8%), somnolence (0.8%), and tremor (0.7%).

Trial Pool 3
In Trial Pool 3, 6.5% of subjects experienced at least one TEAE resulting in discontinuation of IMP. The 3 most frequently occurring TEAEs resulting in discontinuation of IMP were schizophrenia (1.3%), aggression (0.7%), and weight increased (0.7%).

7.3.4 Significant Adverse Events

Trial 293
Most TEAEs were mild or moderate in severity in all treatment groups. One subject in the low-dose aripiprazole group experienced a severe TEAE of somnambulism; 4 subjects in the high-dose aripiprazole group experienced severe TEAEs of lethargy, sedation, somnolence, or insomnia.

Trial KOA
All TEAEs were mild or moderate in severity.

Trial Pool 2
Most common TEAEs that occurred in subjects treated with aripiprazole were mild or moderate in severity. A total of 22 subjects (3.0%) of the 732 aripiprazole-treated

[13] The subject reported to the emergency room and was treated with diphenhydramine (50 mg IM) and benzatropine mesylate (2 mg IM; 2 mg PO BID). The subject had a history of akathisia, for which he was concomitantly receiving benzatropine mesylate as needed.

subjects experienced a severe TEAE. The most frequently reported severe TEAE was somnolence (0.8%).

7.3.5 Submission Specific Primary Safety Concerns: Extrapyramidal Symptoms

Trial 293

One subject (2.3%) in the low-dose aripiprazole group reported EPS-related TEAEs of dystonia and tremor. They were moderate in severity and started within 2 weeks after the first dose of IMP. Six (6) of 45 subjects (13.3%) in the high-dose aripiprazole groups experienced EPS-related TEAEs. The most frequently reported EPS-related TEAE in the high-dose aripiprazole group was akathisia (6.7%). Each event was mild or moderate in severity and started within 30 days after the first dose of IMP. No subjects in the placebo group experienced EPS-related events.

In addition to reports of EPS-related TEAEs, subjects were evaluated for EPS by using the EPS rating scales (SAS, BARS, and AIMS). The EPS rating scales were assessed at baseline before dosing and at Weeks 1, 2, 4, 6 and 8. Treatment differences in the mean change from baseline to final visit between the high-dose aripiprazole and placebo groups in the SAS Total Score and the AIMS Total Score favored aripiprazole over placebo (i.e., aripiprazole showed a numerical benefit) at Week 8, based on a mixed effect repeated measure model.

Table 49: Trial 293 Analysis of Change from Baseline to Week 8 in Simpson Angus Scale Total Score --MMRM (ITT)

					Treatment Difference			
Treatment Group	N[a]	BL Mean	LS Mean[b]	LS Mean SE[b]	Estimate[b]	95% CI[b] Lower limit	95% CI[b] Upper Limit	P-Value[b]
Aripiprazole Low	42	0.4	-0.28	0.22	-0.18	-0.77	0.41	0.5502
Aripiprazole High	35	1.1	-0.74	0.22	-0.64	-1.24	-0.04	0.0357
Placebo	42	0.3	-0.10	0.21				

BL = baseline; SE = standard error.
Note: SAS total score ranges from 0 to 40 with higher score for worse condition (greater reduction from baseline for greater improvement).

Source: Study Report, p.125

Table 50: Trial 293 Analysis of Change from Baseline to Week 8 in Abnormal Involuntary Movement Scale Total Score --MMRM (ITT)

					Treatment Difference			
Treatment Group	N[a]	BL Mean	LS Mean[b]	LS Mean SE[b]	Estimate[b]	95% CI[b] Lower limit	95% CI[b] Upper Limit	P-Value[b]
Aripiprazole Low	42	5.9	-3.45	0.87	-1.46	-3.57	0.65	0.1717
Aripiprazole High	35	6.1	-4.26	0.87	-2.27	-4.42	-0.13	0.0382
Placebo	42	8.9	-1.99	0.84				

BL = baseline; LS = least squares; SE = standard error.
Note: AIMS movement score ranged from 0 to 28 with higher score for worse condition (larger reduction from baseline for greater improvement)
Source: Study Report, p.126

The treatment-differences between the aripiprazole treatment groups (low and high dose) and placebo group in the BARS global score were not statistically significant at Week 8.

Trial KOA
Three (3) subjects (9.4%) in the aripiprazole group and 2 subjects (7.1%) in the placebo group experienced a TEAE of extrapyramidal disorder.

Table 51: Trial KOA EPS-Related TEAEs

EPS-related TEAE	Aripiprazole N=32 n (%)	Placebo N=28 n (%)
Extrapyramidal Disorder	3 (9.4)	2 (7.1)
Akathisia	2 (6.3)	4 (14.3)
Dystonia	0	2 (7.1)
Bradykinesia	1 (3.1)	0

Source: Summary of Clinical Safety, p. 65

In addition to reports of EPS-related TEAEs, subjects were evaluated for EPS by using the SAS, AIMS, and BARS. Mean changes from baseline to final visit in the SAS Total Score, AIMS Total Score, and BARS Global Score were not statistically different between the aripiprazole and placebo groups.

For the pooled pivotal trials (293 & KOA), the most frequently occurring EPS-related TEAEs were akathisia and extrapyramidal disorder in the aripiprazole group, and akathisia and dystonia in the placebo group.

Table 52: Pooled Pivotal Trials (293 & KOA) EPS-Related TEAEs

EPS-related TEAE	Aripiprazole N=121 n (%)	Placebo N=72 n (%)
Total	13 (10.7)	6 (8.3)
Non-akathisia events	9 (7.4)	4 (5.6)
Akathisia	5 (4.1)	4 (5.6)
Extrapyramidal Disorder	4 (3.3)	1 (1.4)
Dystonia	2 (1.7)	3 (4.2)
Tremor	2 (1.7)	0

Source: Summary of Clinical Safety, p. 66; Supplemental data package for SCS, p. 169

Trial 294

As of the cutoff date, only EPS-related and weight gain-related AEs of special interest had been reported. Six subjects experienced EPS-related AEs.

Table 53: Trial 294 AEs Related to EPS

MedDRA Preferred Term	Low-Dose Aripiprazole (N = 38) n (%)	High-Dose Aripiprazole (N = 31) n (%)	Placebo (N = 41) n (%)
Subjects with any EPS-related AE	0 (0.0)	2 (6.5)	4 (9.8)
Akathisia	0 (0.0)	0 (0.0)	3 (7.3)
Dyskinesia	0 (0.0)	0 (0.0)	1 (2.4)
Dystonia	0 (0.0)	2 (6.5)	0 (0.0)

Source: Trial Synopsis, p. 12

Trial Pool 2

In Trial Pool 2, 23.8% of subjects treated with aripiprazole (174/732 subjects) and 9.7% of subjects treated with placebo (36/370 subjects) experienced at least one EPS-related TEAE. Among aripiprazole-treated subjects, the most frequently occurring EPS-related TEAEs were tremor (9.2%), akathisia (6.6%), and extrapyramidal disorder (6.4%). Among placebo-treated subjects, the most frequently occurring EPS-related TEAEs were akathisia (4.1%), extrapyramidal disorder (1.4%), and psychomotor hyperactivity (1.1%).

There was one treatment-emergent EPS-related SAE of extrapyramidal disorder reported by 1 of 732 subjects in the aripiprazole group. Seventeen (17) of 732 subjects (2.3%) in the aripiprazole group and 3 of 370 subjects (0.8%) in the placebo group discontinued IMP due to an EPS-related TEAE. For aripiprazole-treated subjects, the most frequently occurring EPS-related TEAEs that led to discontinuation of IMP were extrapyramidal disorder (0.8%), tremor (0.7%), akathisia (0.4%), and dystonia (0.4%). All EPS-related TEAEs leading to discontinuation of IMP for the placebo group were akathisia events

7.3.6 Submission Specific Primary Safety Concerns: Suicidal Ideation and Behavior

Trial 293

C-SSRS were assessed at screening, baseline, and at Weeks 1, 2, 4, 6 and 8. No suicide-related TEAEs were reported. The C-SSRS "Since Last Visit" questionnaire did identify 2 subjects with emergence of suicidal ideation (one subject each in the low-dose aripiprazole and placebo groups) and 4 subjects with worsening of suicidal ideation (3 subjects in the low-dose aripiprazole group and 1 subject in the placebo group). No active suicidal ideation was detected during the trial.

Table 54: Trial 293 C-SSRS-Incidence of Suicidality by Type (Aripiprazole Group)

			LOW				HIGH			
			5 MG (N=28)		10 MG (N=16)		10 MG (N=30)		20 MG (N=15)	
VISIT[1]	CATEGORY	TYPE	n[2]	(%)	n[2]	(%)	n[2]	(%)	n[2]	(%)
OVERALL	SUICIDAL BEHAVIOR	ABORTED ATTEMPT	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		PREPARATORY ACTS OR BEHAVIOR	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	SUICIDAL IDEATION	WISH TO BE DEAD	1	(3.6)	1	(6.3)	1	(3.4)	0	(0.0)
		NON-SPECIFIC ACTIVE SUICIDAL THOUGHTS	2	(7.1)	1	(6.3)	0	(0.0)	0	(0.0)
		ACTIVE SUICIDAL IDEATION WITH ANY METHODS WITHOUT INTENT TO ACT	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		ACTIVE SUICIDAL IDEATION WITH SOME INTENT TO ACT, WITHOUT SPECIFIC PLAN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		ACTIVE SUICIDAL IDEATION WITH SPECIFIC PLAN AND INTENT	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Source: Study 293 CSR, p.368

Table 55: Trial 293 C-SSRS-Incidence of Suicidality by Type (Placebo Group)

VISIT[1]	CATEGORY	TYPE	PLACEBO (N=44) n[2]	(%)
OVERALL	SUICIDAL BEHAVIOR	ABORTED ATTEMPT	0	(0.0)
		PREPARATORY ACTS OR BEHAVIOR	0	(0.0)
	SUICIDAL IDEATION	WISH TO BE DEAD	1	(2.3)
		NON-SPECIFIC ACTIVE SUICIDAL THOUGHTS	0	(0.0)
		ACTIVE SUICIDAL IDEATION WITH ANY METHODS WITHOUT INTENT TO ACT	0	(0.0)
		ACTIVE SUICIDAL IDEATION WITH SOME INTENT TO ACT, WITHOUT SPECIFIC PLAN	0	(0.0)
		ACTIVE SUICIDAL IDEATION WITH SPECIFIC PLAN AND INTENT	0	(0.0)

Source: Study 293 CSR, p.369

Trial KOA

No suicide-related TEAEs were reported during the trial. Suicidality was not assessed by the C-SSRS or any other rating scale during this trial.

Trial 294

Suicidality is being assessed by the C-SSRS during this trial. No suicide-related TEAEs were reported as of the data cutoff date.

Trial Pool 2

Two subjects (0.3%) in the aripiprazole group and 1 subject (0.3%) in the placebo group experienced suicide-related SAEs. The aripiprazole-treated subjects each experienced an SAE of suicidal ideation, while the placebo-treated subject experienced SAEs of intentional overdose and suicide attempt.

Ten subjects (1.4%) in the aripiprazole group and 8 subjects (2.2%) in the placebo group experienced suicide-related TEAEs. The most frequently reported suicide-related TEAEs in the aripiprazole group were intentional self-injury (0.8%) and suicidal ideation (0.4%). For the placebo group, the most frequently reported suicide-related TEAEs were self-injurious behavior (0.8%) and self-injurious ideation (0.5%). The C-SSRS was not used in all of the trials included in Trial Pool 2.

Table 56: Trial Pool 2 Incidence of Suicide-Related TEAEs, Safety Sample

	Aripiprazole (N=732)		Placebo (N=370)	
System Organ Class Preferred Term[a]	**n**	**(%)**	**n**	**(%)**
At least 1 Suicide-related AE[b]	10	(1.4)	8	(2.2)
Suicidal Ideation	3	(0.4)	3	(0.8)
Self-Injurious Ideation	0	(0.0)	2	(0.5)
Suicidal Ideation	3	(0.4)	1	(0.3)
Suicide Attempt	8	(1.1)	5	(1.4)
Intentional Overdose	0	(0.0)	1	(0.3)
Intentional Self-Injury	6	(0.8)	1	(0.3)
Self Injurious Behaviour	2	(0.3)	3	(0.8)
Suicide Attempt	0	(0.0)	1	(0.3)

Source: Summary of Clinical Safety, p. 69

7.3.7 Submission Specific Primary Safety Concerns: Weight Gain-Related TEAEs/Weight Changes from Baseline

Trial 293

More weight gain-related TEAEs were seen in the low-dose aripiprazole group. Potentially clinically relevant weight abnormalities (change of ≥ 7% from baseline) were also seen at a higher incidence in the low-dose aripiprazole group (18.2%) than in the high-dose aripiprazole (9.3%) and placebo groups (9.1%). In both the low- and high-dose aripiprazole groups, the majority of these subjects were in the low-weight category.

Table 57: Trial 293 Weight Gain-Related TEAEs/Weight Changes from Baseline

Weight gain-related Parameters	**ARIP Low N=44 n (%)**	**ARIP High N=45 n (%)**	**Placebo N=45 n (%)**
Total weight gain-related TEAEs	5 (11.4)	3 (6.7)	1 (2.3)
Weight increased TEAE[14]	2 (4.5)	0	0
Increased appetite TEAE	4 (9.1)	3 (6.7)	1 (2.3)
Mean increase from baseline weight (kg ± SD)	1.8 ± 2.0	1.0 ± 2.0	0.6 ± 2.1
Weight gain of ≥ 7% from baseline	8 (18.2)	4 (9.3)	4 (9.1)

Source: Summary of Clinical Safety, p. 70

[14] Subject 507S3176 (low-dose aripiprazole, 10 mg) had a TEAE of weight increased that started 44 days after the first dose of IMP. The TEAE was considered mild and probably related to IMP.
Subject 511S3012 (low-dose aripiprazole, 5 mg) group had a TEAE of weight increased that started 2 days after the first dose of IMP. The TEAE was considered moderate and not likely related to IMP.

Trial KOA

No TEAEs of weight gain or loss were reported. However, weight gain of ≥ 7% from baseline was noted in 28% of subjects in the aripiprazole group at Week 10.

Table 58: Trial KOA Weight Gain-Related TEAEs/Weight Changes from Baseline

Weight gain-related Parameters	**ARIP N=32 n (%)**	**Placebo N=28 n (%)**
Increased appetite TEAE	2 (6.3)	0
Mean increase from baseline weight (kg ± SD)	1.62 ± 2.02	0.2 ± 1.84
Weight gain of ≥ 7% from baseline at Week 10	9 (28.1)	2 (7.1)

Source: Summary of Clinical Safety, p. 70; Trial KOA Study Report, p. 71, 167

The pooled weight gain/loss data from the placebo-controlled TD trials are shown in Table 59:

Table 59: Pooled Placebo-Controlled TD Trials Potentially Clinically Relevant Weight Changes and Mean Change from Baseline

Weight gain-related Parameters	**ARIP N=105 n (%)**	**Placebo N=66 n (%)**
Mean increase from baseline weight (kg)	1.5	0.4
Weight gain of ≥ 7% from baseline	21 (20)	5 (7.6)
Weight loss of ≥ 7% from baseline	0	1 (1.5)

Source: Summary of Clinical Safety, p. 71

When the data for potentially clinically relevant weight gain was analyzed by baseline BMI, the results showed that the weight gains were seen more frequently in aripiprazole-treated subjects who had lower baseline BMI. The same trend was seen in placebo-treated subjects.

Trial 294

As of the cutoff date, only EPS-related and weight gain-related AEs of special interest had been reported. 11 subjects experienced weight gain-related AEs.

Table 60: Trial 294 Weight Gain-Related AEs

MedDRA Preferred Term	**Low-Dose Aripiprazole (N = 38) n (%)**	**High-Dose Aripiprazole (N = 31) n (%)**	**Placebo (N = 41) n (%)**
Subjects with any weight gain-related AE	6 (15.8)	2 (6.5)	3 (7.3)
Weight increased	5 (13.2)	1 (3.2)	3 (7.3)
Increased appetite	3 (7.9)	1 (3.2)	0 (0.0)

Source: Trial Synopsis, p. 12

Trial Pool 2

No weight gain-related SAEs were reported. Weight increased TEAEs and increased appetite TEAE led to discontinuation of IMP for 3 of 732 subjects (0.3%) in the aripiprazole group. No placebo-treated subjects discontinued IMP due to a weight gain-related TEAE.

Table 61: Trial Pool 2 Incidence of TEAE Weight Gain-Related, Safety Sample

	Aripiprazole (N=732)		Placebo (N=370)	
System Organ Class Preferred Term[a]	**n**	**(%)**	**n**	**(%)**
At least 1 Weight Gain-related AE[b]	73	(10.0)	15	(4.1)
Investigations	26	(3.6)	6	(1.6)
Weight Increased	26	(3.6)	6	(1.6)
Metabolism and Nutrition Disorders	58	(7.9)	11	(3.0)
Increased Appetite	58	(7.9)	11	(3.0)

Source: Summary of Clinical Safety, p. 72

7.3.8 Submission Specific Primary Safety Concerns: Prolactin-Related TEAEs

Trial 293

No prolactin-related TEAEs were reported. The mean changes from baseline at Week 8 in prolactin levels for the low- and high-dose aripiprazole male groups and female groups were greater than that for the placebo group males and females.

Table 62: Trial 293 Mean (±SD) Changes from Baseline to Week 8 in Prolactin Levels (µg/L) by Treatment Group and Gender

Trial 293 Mean (±SD) Changes from Baseline at Week 8 in Prolactin Levels (µg/L) by Treatment Group and Gender			
Gender	**ARIP Low**	**ARIP High**	**Placebo**
Male	-5.82 ± 7.25	-4.32 ± 6.84	-1.48 ± 7.88
Female	-15.58 ± 23.23	-5.40 ± 7.78	-0.23 ± 4.66

Source: Summary of Clinical Safety, p. 72

Trial KOA

No prolactin-related TEAEs were reported. Aripiprazole-treated subjects had a statistically significant mean decrease in serum prolactin at Week 10 of -5.85 µg/L ($p < 0.0001$). The shift table of serum prolactin showed a significant change in the Aripiprazole group ($p< 0.0001$): 18 subjects changed from normal to abnormal-low.

The mean change in prolactin for the placebo group was -0.10 µg/L, which was not statistically significant. Differences in the mean change in prolactin were statistically significant between treatment groups ($p < 0.0001$).

Trial 294
No prolactin-related TEAEs were reported as of the cutoff date.

Trial Pool 2
No prolactin-related TEAEs were reported.

7.3.9 Submission Specific Primary Safety Concerns: Hyperglycemia- or Diabetes-Related TEAEs

Trial 293
No hyperglycemia- or diabetes-related TEAEs were reported during the trial.

Table 63: Trial 293 Mean Change in Fasting Glucose Levels at Week 8/Potentially Clinically Relevant Elevated Fasting Glucose Levels by Treatment Group

Parameter	ARIP Low	ARIP High	Placebo
Mean (±SD) change in fasting glucose at Week 8 (mg/dL)	0.06±10.2	1.40±16.9	-5.4±25
Potentially clinically relevant elevated fasting glucose (≥115) at any time after baseline [n (%)]	2 (5.1%)	2 (6.7%)	0

Source: Summary of Clinical Safety, p. 73

Trial KOA
No hyperglycemia- or diabetes-related TEAEs were reported during the trial.

Table 64: Trial KOA Mean Change in Fasting Glucose Levels at Week 8

Parameter	ARIP	Placebo
Mean (±SD) change in fasting glucose at Week 8 (mg/dL)	1.13 ± 8.7	3.67 ± 21.7

Source: Summary of Clinical Safety, p. 73

In an analysis of the two placebo-controlled trials in pediatric and adolescent patients with Tourette's disorder (6 to 18 years) with median exposure of 57 days, the mean change in fasting glucose in aripiprazole-treated patients (0.79 mg/dL; N=90) was not significantly different than in placebo-treated patients (–1.66 mg/dL; N=58).

Table 65: Mean Change from Baseline to Endpoint, Fasting Glucose--Placebo-controlled Trials for TD (-293, -KOA), Safety Sample

	ARIPIPRAZOLE			PLACEBO			ARIP - PLACEBO DIFFERENCE[1]	
VARIABLE	n	MEAN	S.E.	n	MEAN	S.E.	ESTIMATE	P-VALUE
BASELINE	117	89.37	0.83	68	92.03	2.57	0.00	
CHANGE FROM BASELINE (OC)	90	0.79	1.26	58	-1.66	3.17	1.46	0.5975

Source: Supplemental Data Package for scs, p.570

Table 66: Combined Pivotal Trials (293 and KOA) Category Change from Baseline of Fasting Glucose Levels

Parameter	ARIP N=88 n (%)	Placebo N=58 n (%)
Category changes from baseline of fasting glucose levels:normal to high (< 100 mg/dL to ≥ 126 mg/dL)	3 (3.4)	1 (1.7)
Category changes from baseline of fasting glucose levels: borderline to high (≥100 mg/dL and <126 to ≥126)	0	0

Source: Summary of Clinical Safety, p. 73

Trial 294
No hyperglycemia- or diabetes-related TEAEs were reported as of the cutoff date.

Trial Pool 2
No SAEs or TEAEs leading to discontinuation of IMP related to hyperglycemia or diabetes were reported for Trial Pool 2. No hyperglycemia- or diabetes-related TEAEs were reported for placebo-treated subjects.

Table 67: Trial Pool 2 Incidence of Hyperglycemia TEAEs

	Aripiprazole (N=732)		Placebo (N=370)	
System Organ Class Preferred Term[a]	n	(%)	n	(%)
At least 1 Hyperglycemia-related AE[b]	4	(0.5)	0	(0.0)
Investigations	4	(0.5)	0	(0.0)
Blood Glucose Increased	3	(0.4)	0	(0.0)
Glycosylated Haemoglobin Increased	2	(0.3)	0	(0.0)

Source: Summary of Clinical Safety, p. 74

7.3.10 Submission Specific Primary Safety Concerns: Lipid-Related TEAEs

Trial 293
No TEAEs related to lipid parameters were reported.

Potentially clinically relevant elevations in fasting triglyceride levels were more common in the placebo group.

Table 68: Trail 293 Potentially Clinically Relevant Elevations in Fasting Triglyceride Levels

Parameter	**ARIP Low N=39** n (%)	**ARIP High N=30** n (%)	**Placebo N=40** n (%)
Potentially clinically relevant elevation in fasting triglycerides (≥ 160 mg/dL for males or ≥ 120 mg/dL in females)	3 (7.7)	4 (13.3)	6 (15)

Source: Summary of Clinical Safety, p. 74

Trial KOA

No TEAEs related to lipid parameters were reported. No clinically significant (as judged by the investigator) changes in lipid parameters were noted in the laboratory test results.

Pooled Placebo-Controlled TD Trials

Table 69: Pooled Placebo-Controlled TD Trials Category Changes from Baseline in Select Lipid Parameters

Parameter	**ARIP N n (%)**	**Placebo N n (%)**
Category changes from baseline in fasting triglyceride levels: normal to high (< 150 mg/dL to ≥ 200 mg/dL)	94 5 (5.3)	55 2 (3.6)
Category changes from baseline in HDL: normal to low (≥ 40 mg/dL to < 40 mg/dL)	108 4 (3.7)	67 2 (3)
Category changes from baseline in total cholesterol levels: normal to high (<170 mg/dL to ≥ 200 mg/dL)	85 1 (1.2)	0

Source: Summary of Clinical Safety, p. 74-75

Trial Pool 2

Lipid-related TEAEs were experienced by 3 aripiprazole-treated subjects and 1 placebo-treated subject. None of the lipid-related TEAEs were severe. No SAEs or TEAEs leading to discontinuation of IMP related to lipid parameters were reported.

Table 70: Trial Pool 2 Incidence of Lipid-Related TEAEs

	Aripiprazole (N=732)		Placebo (N=370)	
System Organ Class Preferred Term	**n**	**(%)**	**n**	**(%)**
At least 1 Lipid Parameter-related AE	3	(0.4)	1	(0.3)
Investigations	3	(0.4)	1	(0.3)
Blood Cholesterol Increased	2	(0.3)	0	(0.0)
Blood Triglycerides Increased	1	(0.1)	1	(0.3)

Source: Summary of Clinical Safety, p. 75

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Most common adverse events indicate AEs with an incidence ≥ 5% in the aripiprazole group and ≥ 2 times that in the placebo group. In the placebo-controlled TD trials (Trials 31-12-293 and 031-KOA-0703), 50.4% of subjects treated with aripiprazole (61/121 subjects) experienced at least one TEAE that met the definition of most common. The most common TEAEs in the aripiprazole group (vs. placebo) were sedation (13.2% vs. 5.6%), somnolence (13.2% vs. 1.4%), nausea (10.7% vs.4.2%), headache (9.9% vs. 2.8%), nasopharyngitis (9.1% vs. 0%), fatigue (8.3% vs. 0%), and increased appetite (7.4% vs. 1.4%).

Trial 293
The overall incidence of TEAEs in the low- and high-dose aripiprazole groups was 65.9% and 75.6%, respectively, and 40.9% (18/44 subjects) in the placebo group. The most common TEAEs in the high-dose aripiprazole group (vs placebo) were somnolence (15.6% vs 2.3%); fatigue (15.6% vs 0%); lethargy (11.1% vs 0%); headache, nausea, and sedation (8.9% vs 2.3% each); nasopharyngitis (8.9% vs 0%); increased appetite and restlessness (6.7% vs 2.3% each); and akathisia (6.7% vs 0%) The most common TEAEs in the low-dose aripiprazole group (vs placebo) were sedation (18.2% vs 2.3%), somnolence (11.4% vs 2.3%), increased appetite (9.1% vs 2.3%), headache (6.8% vs 2.3%), nausea (6.8% vs 2.3%), fatigue (6.8% vs 0%), and nasopharyngitis (6.8% vs 0%).

Table 71: Trial 293 Overall Summary of Adverse Events (Safety Sample)

	Aripiprazole Low Dose			Aripiprazole High Dose			Placebo (N = 44)
Subjects	5 mg (< 50 kg) (N = 28)	10 mg (≥ 50 kg) (N = 16)	Total (N = 44)	10 mg (< 50 kg) (N = 30)	20 mg (≥ 50 kg) (N = 15)	Total (N = 45)	
Number (%) of Subjects	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation due to AEs	1 (3.6)	0 (0.0)	1 (2.3)	6 (20.0)	1 (6.7)	7 (15.6)	1 (2.3)
Any AEs	19 (67.9)	10 (62.5)	29 (65.9)	22 (73.3)	12 (80.0)	34 (75.6)	18 (40.9)

Source: Study report, p. 106

Table 72: Trial 293 Incidence of TEAEs Reported by 5% or More Subjects in Any Aripiprazole Group (Safety Sample)

	Aripiprazole Low Dose			Aripiprazole High Dose			Placebo (N = 44)
Subjects	5 mg (< 50 kg) (N = 28)	10 mg (≥ 50 kg) (N = 16)	Total (N = 44)	10 mg (< 50 kg) (N = 30)	20 mg (≥ 50 kg) (N = 15)	Total (N = 45)	
Adverse Event MedDRA Preferred Term	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]
Akathisia	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	2 (13.3)	3 (6.7)	0 (0.0)
Fatigue	2 (7.1)	1 (6.3)	3 (6.8)	5 (16.7)	2 (13.3)	7 (15.6)	0 (0.0)
Headache	2 (7.1)	1 (6.3)	3 (6.8)	2 (6.7)	2 (13.3)	4 (8.9)	1 (2.3)
Increased Appetite	3 (10.7)	1 (6.3)	4 (9.1)	2 (6.7)	1 (6.7)	3 (6.7)	1 (2.3)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	5 (16.7)	0 (0.0)	5 (11.1)	0 (0.0)
Nasopharyngitis	3 (10.7)	0 (0.0)	3 (6.8)	3 (10.0)	1 (6.7)	4 (8.9)	0 (0.0)
Nausea	2 (7.1)	1 (6.3)	3 (6.8)	3 (10.0)	1 (6.7)	4 (8.9)	1 (2.3)
Restlessness	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.7)	1 (6.7)	3 (6.7)	1 (2.3)
Sedation	4 (14.3)	4 (25.0)	8 (18.2)	3 (10.0)	1 (6.7)	4 (8.9)	1 (2.3)
Somnolence	3 (10.7)	2 (12.5)	5 (11.4)	6 (20.0)	1 (6.7)	7 (15.6)	1 (2.3)
Vomiting	2 (7.1)	0 (0.0)	2 (4.5)	2 (6.7)	1 (6.7)	3 (6.7)	2 (4.5)

Source: Study report, p. 108

Table 73: Trial 293 Incidence of TEAEs Considered by the Investigator as Potentially Causally Related to the IMP by 5% or Greater Incidence in Any Aripiprazole Group (Safety Sample)

	Aripiprazole Low Dose			Aripiprazole High Dose			Placebo (N = 44)
Subjects	5 mg (< 50 kg) (N = 28)	10 mg (≥ 50 kg) (N = 16)	Total (N = 44)	10 mg (< 50 kg) (N = 30)	20 mg (≥ 50 kg) (N = 15)	Total (N = 45)	
Adverse Event MedDRA Preferred Term	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]
Akathisia	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	2 (13.3)	3 (6.7)	0 (0.0)
Fatigue	1 (3.6)	1 (6.3)	2 (4.5)	5 (16.7)	2 (13.3)	7 (15.6)	0 (0.0)
Increased Appetite	3 (10.7)	1 (6.3)	4 (9.1)	2 (6.7)	0 (0.0)	2 (4.4)	1 (2.3)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	5 (16.7)	0 (0.0)	5 (11.1)	0 (0.0)
Nausea	1 (3.6)	0 (0.0)	1 (2.3)	3 (10.0)	1 (6.7)	4 (8.9)	0 (0.0)
Restlessness	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.7)	1 (6.7)	3 (6.7)	1 (2.3)
Sedation	4 (14.3)	3 (18.8)	7 (15.9)	3 (10.0)	1 (6.7)	4 (8.9)	1 (2.3)
Somnolence	3 (10.7)	2 (12.5)	5 (11.4)	6 (20.0)	1 (6.7)	7 (15.6)	1 (2.3)

Source: Study report, p. 111

Trial KOA

In Trial KOA-0703, 75.0% of subjects treated with aripiprazole (24/32 subjects) and 71.4% of subjects treated with placebo (20/28 subjects) experienced at least one TEAE. The most common TEAEs in the aripiprazole group (vs placebo) were nausea (18.8%

vs 7.1%), headache (15.6% vs 3.6%), nasopharyngitis (12.5% vs 0%), and somnolence (12.5% vs 0%). Akathisia and dizziness were lower in the aripiprazole group (6.3% and 3.1%, respectively) than in the placebo group (14.3% each).

Trial 294
Treatment-emergent AEs (TEAEs) that occurred in at least 5% of subjects were weight increased (8.2%), fatigue (7.3%), and somnolence (7.3%).

The following tables detail the most common TEAEs in the pooled pivotal trials (Table 74) and in Trial Pool 2 (Table 75):

Table 74: Common TEAEs in Pooled Placebo-Controlled TD Trials (Trial 293 and Trial KOA)

Common TEAE	Aripiprazole N=121 %	Placebo N=72 %
At least 1 TEAE	50.4%	12.5%
Sedation	13.2%	5.6%
Somnolence	13.2%	1.4%
Nausea	10.7%	4.2%
Headache	9.9%	2.8%
Nasopharyngitis	9.1%	0%
Fatigue	8.3%	0%
Increased Appetite	7.4%	1.4%

Source: Summary of Clinical Safety, p.43

Table 75: Incidence of Common TEAEs in Pediatric Subjects in Aripiprazole Group: Completed Short-term Placebo-controlled Pediatric Once-daily Aripiprazole Trials, Safety Sample (Trial Pool 2)

	Aripiprazole (N=732)		Placebo (N=370)	
System Organ Class Preferred Term[a]	**n**	**(%)**	**n**	**(%)**
At least 1 AE[b]	459	(62.7)	132	(35.7)
Gastrointestinal Disorders	117	(16.0)	32	(8.6)
Nausea	67	(9.2)	17	(4.6)
Vomiting	63	(8.6)	25	(6.8)
General Disorders and Administration Site Conditions	82	(11.2)	7	(1.9)
Fatigue	82	(11.2)	7	(1.9)
Infections and Infestations	48	(6.6)	12	(3.2)
Nasopharyngitis	48	(6.6)	12	(3.2)
Metabolism and Nutrition Disorders	58	(7.9)	11	(3.0)
Increased Appetite	58	(7.9)	11	(3.0)
Nervous System Disorders	332	(45.4)	74	(20.0)
Akathisia	48	(6.6)	15	(4.1)
Extrapyramidal Disorder	47	(6.4)	5	(1.4)
Headache	98	(13.4)	40	(10.8)
Sedation	65	(8.9)	8	(2.2)
Somnolence	122	(16.7)	14	(3.8)
Tremor	67	(9.2)	3	(0.8)
Psychiatric Disorders	40	(5.5)	31	(8.4)
Insomnia	40	(5.5)	31	(8.4)

Source: Summary of Clinical Safety, p.44

In Trial Pool 3, weight increased (14.4%), headache (11.4%), vomiting (10.8%), and somnolence (10.7%) were the most frequently occurring TEAEs.

Table 76: Incidence of Common TEAEs in Pediatric Subjects: Maintenance Trial CN138-603 and All Open-label Pediatric Once-daily Aripiprazole Trials, Safety Sample (Trial Pool 3)

	Total (N=1408)	
System Organ Class Preferred Term[a]	**n**	**(%)**
At least 1 AE[b]	817	(58.0)
Gastrointestinal Disorders	196	(13.9)
Nausea	76	(5.4)
Vomiting	152	(10.8)
General Disorders and Administration Site Conditions	148	(10.5)
Fatigue	75	(5.3)
Pyrexia	81	(5.8)
Infections and Infestations	212	(15.1)
Nasopharyngitis	135	(9.6)
Upper Respiratory Tract Infection	88	(6.3)
Investigations	203	(14.4)
Weight Increased	203	(14.4)
Metabolism and Nutrition Disorders	118	(8.4)
Increased Appetite	118	(8.4)
Nervous System Disorders	405	(28.8)
Akathisia	73	(5.2)
Headache	160	(11.4)
Somnolence	151	(10.7)
Tremor	88	(6.3)
Psychiatric Disorders	103	(7.3)
Insomnia	103	(7.3)

Source: Summary of Clinical Safety, p.45

7.4.2 Laboratory Findings

Trial 293

Clinical laboratory tests were performed at screening (considered as baseline for summaries of changes from baseline), Week 4 and Week 8. Prolactin and TSH were tested only at screening and Week 8.

Mean changes from baseline were similar across the low- and high-dose aripiprazole and placebo groups for serum chemistry, hematology, urinalysis, and other laboratory test results. No potential Hy's law cases were reported.

Table 77: Trial 293 Mean Change from Baseline to Week 8 in Select Clinical Laboratory Test Results

Clinical Laboratory Test	Mean Change from Baselline to Week 8		
	ARIP Low	ARIP High	Placebo
Alkaline Phosphatase (U/L)	7.17	1.09	-1.55
ALT (U/L)	4.31	0	-0.5
AST (U/L)	2.21	-1.71	-0.62
Total Bilirubin (mg/dL)	-0.04	-0.02	0.02
Cholesterol (mg/dL)	2.21	-1.83	1.19
CPK (U/L)	121.55	-22.69	-12.5
Creatinine (mg/dL)	0.02	0.03	0.02
Fasting Glucose (mg/dL)	0.06	1.4	-5.41
HDL (mg/dL)	2.52	3.26	-0.29
Fasting LDL (mg/dL)	-2.18	-4.16	-2.53
Fasting Triglycerides (mg/dL)	6.76	11.76	12.71
Hematocrit (%)	1.22	1.5	1.2
Hemoglobin (g/dL)	-0.04	0.10	-0.09
Hemoglobin A1C (%)	0.03	-0.10	0.08
Platelet Count (cells/uL)	-31875	-28324	-26425
WBC (Thous/µL)	-0.75	-1.10	-0.44
Fasting Insulin (µIU/mL)	3.38	3.10	2.13
TSH (µIU/mL)	0.01	0.06	-0.01

Source: Trial 293 Study Report, p. 525-628

The incidence of potentially clinically relevant laboratory values was similar across the low- and high-dose aripiprazole and placebo groups, except for creatine phosphokinase (CPK) and fasting glucose.

Table 78: Trial 293 Potentially Clinically Significant Laboratory Values

Clinical Laboratory Test	Potentially Clinically Significant Laboratory Values		
	ARIP Low N n (%)	ARIP High N n (%)	Placebo N n (%)
CPK (≥ 3xULN)	N=44 2 (4.5%)	N=41 2 (4.9%)	0
Elevated Fasting Glucose (≥115 mg/dL)	N=39 2 (5.1%)	N=30 2 (6.7%)	0

Source: Trial 293 Study Report, p. 515-518

In the summary of categorical changes in lipid parameters, the shift in all categories was similar across the low- and high-dose aripiprazole and placebo groups. The pattern of shifts in all glucose categories was also similar across all groups, except for fasting glucose, where the incidence of postbaseline increases of ≥10 mg/dL was higher in the low-dose and high-dose aripiprazole groups than in the placebo group.

Table 79: Trial 293 Postbaseline Increases in Fasting Glucose by Treatment Group

Parameter	ARIP Low N=38 n (%)	ARIP High N=30 n (%)	Placebo N=36 n (%)
Postbaseline Increases in Fasting Glucose of ≥10 mg/dL	9 (23.7)	8 (26.7)	4 (11.1)

Source: Summary of Clinical Safety, p.77-78

Two subjects in the Aripiprazole Low Dose Group (5 mg) had TEAEs related to abnormal laboratory values:

Table 80: Trial 293 Lab-related TEAEs

Subject	Treatment Group	Abnormal Lab	Related To IMP	Comments
510S3050	Low ARIP (5 mg)	↑CPK	No	Screening: 150 U/L Week 4: 160 U/L Week 8: 1146 U/L
510S3145	Low ARIP (5 mg)	neutropenia; leukopenia	No	Absolute neutrophil counts: Screening: 1.6 x 10^3 Week 8: 0.68 x 10^3 WBC: Screening: 4.19 x 10^3 Week 8: 2.96 x 10^3

Source: Summary of Clinical Safety, p.78

Trial KOA

No changes in laboratory parameters from screening to final visit were statistically significant and clinically significant. Two subjects had laboratory abnormalities at the final visit. Subject 001-0008 (placebo group) had a clinically abnormal urine protein value (1+), and Subject 002-0009 (aripiprazole group) had a clinically abnormal insulin level (24.4 µIU/mL). Both abnormalities were reported as nonserious, mild AEs with no causal relationship with the IMP.

Table 81: Trial KOA Mean Change from Baseline to Visit 7 in Select Clinical Labs

Clinical Laboratory Test	Mean Change from Baselline to Visit 7	
	Placebo	ARIP
Alkaline Phosphatase (U/L)	-12	-30.8
ALT (U/L)	1.08	2.63
AST (U/L)	0.92	-0.17
Total Bilirubin (mg/dL)	-0.02	-0.05
Cholesterol (mg/dL)	3.25	2.87
CPK (U/L)	13.88	-6.83
Creatinine (mg/dL)	0.03	0.02
Glucose (mg/dL)	3.67	1.13
HDL (mg/dL	-1.25	1.17
LDL (mg/dL)	-0.08	-0.74
Fasting Triglycerides (mg/dL)	4.25	19.52
Hematocrit (%)	0.29	0.62
Hemoglobin (g/dL)	-0.02	0.14
Hemoglobin A1C (%)	0.04	-0.04
Platelet Count	-8.25	0.77
WBC (Thous/µL)	0.17	0.15
Insulin (µIU/mL)	7.31	4.63

Source: Trial KOA Report, p. 136-143

7.4.3 Vital Signs

Trial 293

Vital sign measurements (systolic and diastolic blood pressure and heart rate) were performed at all clinic visits (screening, baseline, and at Weeks 1, 2, 4, 6 and 8). Body weight, waist circumference, and BMI were measured at baseline, Week 4, and Week 8.

The incidence of potentially clinically relevant abnormalities in vital sign measurements (heart rate, blood pressure, and body weight) was similar across the low- and high-dose aripiprazole and placebo groups, with the exception of weight gain (see Section 7.3.7).

Trial KOA

Systolic blood pressure, diastolic blood pressure, and heart rate measurements showed no significant changes from baseline in either treatment group, and there were no significant differences between treatment groups.

There were statistically significant mean changes from baseline to final visit in BMI and waist circumference for the aripiprazole group. These mean changes for BMI and waist circumference for the aripiprazole group were statistically different from the mean changes for the placebo group.

Table 82: Trial KOA Mean Change from Baseline to Final Visit in BMI and Waist Circumference

Parameter	ARIP	Placebo	p-value ARIP vs. Placebo
Mean change (±SD) in BMI from baseline to final visit (kg/m^2)	0.45 ± 0.86 p=0.0079	-0.09 ± 0.85	p=0.0243
Mean change (±SD) in waist circumference from baseline to final visit (cm)	1.83 ± 3.8 p=0.0093	-0.07 ± 2.9	p=0.0293

Source: Summary of Clinical Safety, p.80

7.4.4 Electrocardiograms (ECGs)

Trial 293

Three 12-lead ECGs (scheduled 5 minutes apart) were recorded at screening, baseline, Week 4, Week 6, and the Week 8/ET visit. A central ECG service was used for reading all ECGs in order to standardize interpretations for the safety analysis.

No subject had an increase from baseline in QTc interval of > 60 msec (by any correction method) or a QTc interval of > 500 msec (by any correction method).
One subject had an ECG-related TEAE that led to discontinuation of IMP. Subject 535S3119 (high-dose aripiprazole, 10 mg) experienced a TEAE of ECG QT prolonged, which was deemed mild and probably related to IMP. However, this TEAE did not meet the prespecified criteria for a potentially clinically relevant QTc interval prolongation (QTc interval ≥ 450 msec and ≥ 10% increase from baseline).

Three subjects had potentially clinically relevant ECG abnormalities as detailed in the table below:

Table 83: Trial 293 Potentially Clinically Relevant ECG Abnormalities

Subject	Treatment	ECG Abnormality	Comments
576S3076	ARIP Low (5 mg)	Right bundle branch block	Not present at baseline
507S3072	ARIP High (20 mg)	Supraventricular premature beat	Not present at baseline; subject discontinued due to an AE of insomnia
533S3073	ARIP High (20 mg)	Supraventricular premature beat	Not present at baseline

Source: Summary of Clinical Safety, p.80

Trial KOA
ECG parameters showed no statistically significant change or significant group difference from screening to the final visit. The shift table for overall determination of normal or abnormal ECG readings showed that 4 of 28 subjects in the placebo group and 5 of 32 subjects in the aripiprazole group shifted from normal at screening to abnormal at the final visit.

There were 2 ECG-related TEAEs in the Aripiprazole group:

Table 84: Trial KOA ECG-Related TEAEs in Aripiprazole Group

Subject	Treatment	ECG-Related TEAE	Related to IMP
001-0007	ARIP	QT prolonged-mild QTc Visit 1: 439 msec QTc Visit 7: 475 msec QTc Visit 7+1 day: 421 msec	Probably
001-0010	ARIP	QT prolonged-mild QTc Visit 1: 439 msec QTc Visit 7: 447 msec	Possibly

Source: Summary of Clinical Safety, p.81

None of the QTc intervals for these subjects met the criteria for potential clinical relevance (QTc interval ≥ 450 msec and ≥ 10% increase from baseline), as defined in the Trial 293 protocol.[15]

7.4.6 Additional Safety Variables for Study 293

Swanson, Nolan, and Pelham-IV Rating Scale (SNAP-IV)
No statistically significant difference was observed for the change in baseline between low-dose aripiprazole and placebo on any SNAP-IV rating subscale.

For the high-dose aripiprazole group, the LS mean change from baseline to Week 8 in SNAP-IV rating subscales of inattention, hyperactivity/impulsivity, and ADD/ADHD subscale average scores was -0.58, -0.58, and -0.57, respectively. High-dose aripiprazole showed significant improvement over placebo in inattention average score ($p = 0.0027$), hyperactivity/impulsivity average score ($p = 0.0352$), and ADD/ADHD average score ($p = 0.0048$).

Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)
No statistically significant difference was observed for the change from baseline between low- or high-dose aripiprazole and placebo in the CY-BOCS.

[15] *QT prolonged* is listed in the current Abilify USPI under *Other Adverse Reactions Observed During the Premarketing Evaluation of Aripiprazole.*

Children's Depression Rating Scale – Revised (CDRS-R)
No statistically significant difference was observed for the change from baseline between low- or high-dose aripiprazole and placebo in the CDRS-R.

Pediatric Anxiety Rating Scale (PARS)
No statistically significant difference was observed for the change from baseline between low- or high-dose aripiprazole and placebo in PARS.

7.5 Other Safety Explorations

Treatment-emergent AEs were evaluated by age, gender, race, severity, relationship to IMP, and exposure to IMP. For age, gender, and race, the analyses were performed for events that were most common in the overall analysis (i.e., an incidence ≥ 5% in the aripiprazole group and ≥ 2 times that in the placebo group). These analyses were performed for Trial 31-12-293 and Trial Pool 2. Exposure to IMP was evaluated in Trial 31-12-293.

7.5.1 Dose Dependency for Adverse Events

Trial 293
As stated previously, an exposure safety analysis for Trial 293 was conducted in 76 of 89 aripiprazole-treated subjects who completed 8 weeks of treatment, 12 of these 89 subjects who discontinued IMP for any reason, and 8 of these 89 subjects who discontinued IMP due to an AE. No differences in aripiprazole exposure, age, body weight, and baseline TTS were observed among the 3 groups. The analysis revealed that aripiprazole exposure, including during the titration period, did not appear to be related to discontinuations due to AEs or discontinuations due to any reason.

Although it appeared that subjects in the lower body weight category had higher rates of discontinuation due to AEs or discontinuation due to any reason, the median body weight of those subjects was the same as that of subjects who completed the trial, and the areas under the concentration-time curves (AUCs) were also comparable (Table 84).

Table 85: Trial 293 Relationship between Selected Baseline Demographic and PK Characteristics of Aripiprazole-treated Subjects and Disposition

Characteristic	AE Group (N=8)	Discontinued Group (N=12)	Completed Group (N=76)
AUC (µg·h/mL)			
Median	2.22	3.71	3.21
Minimum, Maximum	0.742, 4.08	0.714, 7.02	0.916, 11.0
Weight (kg)			
Median	42.6	40.5	42.6
Minimum, Maximum	20.9, 68.6	20.9, 72.8	19.7, 96.4
Weight Group (n [%])[a]			
< 50	7 (87.5)	10 (83.3)	47 (61.8)
≥ 50	1 (12.5)	2 (16.7)	29 (38.2)

AE group=discontinued secondary to AE
Source: Summary of Clinical Safety, p.54

7.5.3 Drug-Demographic Interactions

Age

Trial 293

For the most common TEAEs (with an incidence of ≥ 5% in any aripiprazole group and ≥ 2 times the incidence in the placebo group), the Breslow-Day Test of Homogeneity was used to assess the OR difference for age, gender, and race subgroups between the low-dose aripiprazole and placebo groups and between the high-dose aripiprazole and placebo groups.

There was a statistically significant difference (p = 0.0366) between age subgroups for the event of increased appetite (ages 7-12 year olds: 13.3% low-dose aripiprazole; 0% placebo; ages 13-17 year olds: 0% low-dose aripiprazole; 5.9% placebo), indicating that increased appetite was more prominent in younger than older subjects with TD. There was no statistically significant difference between age subgroups for the most common TEAEs for the high-dose aripiprazole versus placebo groups.

Trial Pool 2

No statistically significant differences were noted when the most common TEAEs were analyzed by age using the Breslow-Day test for homogeneity.

Sedation and somnolence were the 2 most frequently occurring TEAEs among aripiprazole-treated subjects (47/321 subjects; 14.6% each) in the 6- to 12-years age group. Somnolence was also the most frequently occurring TEAE (75/411 subjects; 18.2%) among aripiprazole-treated subjects aged 13 to 18 years.

Table 86: Comparison of Trial Pool 2 Incidence of Common TEAEs by Age (Breslow-Day Test)

	6-12 Years				13-18 Years				
	Aripiprazole (N=321)		Placebo (N=165)		Aripiprazole (N=411)		Placebo (N=205)		
Adverse Event (MedDRA Preferred Term)	n	(%)	n	(%)	n	(%)	n	(%)	P-value
Extrapyramidal Disorder	19	(5.9)	1	(0.6)	28	(6.8)	4	(2.0)	0.3586
Fatigue	39	(12.1)	3	(1.8)	43	(10.5)	4	(2.0)	0.7651
Increased Appetite	40	(12.5)	6	(3.6)	18	(4.4)	5	(2.4)	0.2847
Nasopharyngitis	26	(8.1)	5	(3.0)	22	(5.4)	7	(3.4)	0.3921
Nausea	27	(8.4)	6	(3.6)	40	(9.7)	11	(5.4)	0.6705
Sedation	47	(14.6)	5	(3.0)	18	(4.4)	3	(1.5)	0.4638
Somnolence	47	(14.6)	3	(1.8)	75	(18.2)	11	(5.4)	0.2049
Tremor	30	(9.3)	0	(0.0)	37	(9.0)	3	(1.5)	0.1192

Source: Summary of Clinical Safety, p. 48

Gender

Trial 293

There was a statistically significant difference (p = 0.0274) between gender subgroups for the event of somnolence (males: 13.9% low-dose aripiprazole; 0% placebo; females: 0% low-dose aripiprazole; 9.1% placebo), indicating that somnolence was more prominent in males than females with TD. There was no statistically significant difference between gender subgroups for the most common TEAEs for the high-dose aripiprazole versus placebo groups.

Trial Pool 2

No statistically significant differences were noted when the most common TEAEs were analyzed by gender using the Breslow-Day test for homogeneity.

Table 87: Comparison of Trial Pool 2 Incidence of Common TEAEs by Gender (Breslow-Day Test)

	Male				Female				
	Aripiprazole (N=502)		Placebo (N=261)		Aripiprazole (N=230)		Placebo (N=109)		
Adverse Event (MedDRA Preferred Term)	n	(%)	n	(%)	n	(%)	n	(%)	P-value
Extrapyramidal Disorder	30	(6.0)	3	(1.1)	17	(7.4)	2	(1.8)	0.7992
Fatigue	58	(11.6)	3	(1.1)	24	(10.4)	4	(3.7)	0.0945
Increased Appetite	44	(8.8)	7	(2.7)	14	(6.1)	4	(3.7)	0.3085
Nasopharyngitis	37	(7.4)	9	(3.4)	11	(4.8)	3	(2.8)	0.7655
Nausea	40	(8.0)	8	(3.1)	27	(11.7)	9	(8.3)	0.2719
Sedation	51	(10.2)	7	(2.7)	14	(6.1)	1	(0.9)	0.6295
Somnolence	71	(14.1)	8	(3.1)	51	(22.2)	6	(5.5)	0.9146
Tremor	39	(7.8)	2	(0.8)	28	(12.2)	1	(0.9)	0.8007

Source: Summary of Clinical Safety, p. 48

Race

Trial 293

There was no statistically significant difference between race subgroups for the most common TEAEs for the low- or high-dose aripiprazole versus placebo groups.

Trial Pool 2

No statistically significant differences were noted when the most common TEAEs were analyzed by race using the Breslow-Day test for homogeneity.

Table 88: Comparison of Trial Pool 2 Incidence of Common TEAEs by Race (Breslow-Day Test)

	White				Non-white				
	Aripiprazole (N=477)		Placebo (N=236)		Aripiprazole (N=255)		Placebo (N=134)		
Adverse Event (MedDRA Preferred Term)	n	(%)	n	(%)	n	(%)	n	(%)	P-value
Extrapyramidal Disorder	25	(5.2)	2	(0.8)	22	(8.6)	3	(2.2)	0.6389
Fatigue	62	(13.0)	7	(3.0)	20	(7.8)	0	(0.0)	0.1321
Increased Appetite	28	(5.9)	8	(3.4)	30	(11.8)	3	(2.2)	0.0980
Nasopharyngitis	35	(7.3)	8	(3.4)	13	(5.1)	4	(3.0)	0.7159
Nausea	39	(8.2)	11	(4.7)	28	(11.0)	6	(4.5)	0.5258
Sedation	44	(9.2)	4	(1.7)	21	(8.2)	4	(3.0)	0.3529
Somnolence	73	(15.3)	7	(3.0)	49	(19.2)	7	(5.2)	0.5877
Tremor	53	(11.1)	3	(1.3)	14	(5.5)	0	(0.0)	0.3723

Source: Summary of Clinical Safety, p. 49

7.5.5 Drug-Drug Interactions

No new drug interaction trials were conducted in the aripiprazole TD clinical program.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new information on human carcinogenicity was submitted to this sNDA.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported in subjects with TD. Pregnancy was reported for 2 subjects in Trial Pool 3:

Table 89: Trial Pool 3 Outcome of Pregnancies

Trial/Subject ID	Age	Indication	Duration/LMP	Pregnancy Outcome
31-09-267 617S5069	14	Bipolar I	4/1/11-12/13/11 LMP 10/26/11	Healthy female infant
31-0267 619S5402	18	Schizophrenia	6/12/12-12/2/12 LMP 10/24/12	Healthy male infant

Source: Summary of Clinical Safety, p. 82

7.6.3 Pediatrics and Assessment of Effects on Growth

No formal assessments of growth other than assessments of weight/BMI were conducted in the short-term TD trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
No TEAEs related to overdose were reported in Trials 293, KOA, or 294.

Drug Abuse, Withdrawal and Rebound
No clinical trials conducted as part of the TD development program were designed to evaluate aripiprazole's potential for abuse, tolerance, physical dependence, withdrawal or rebound. However, a search was performed of the aggregate safety AE database for the preferred terms of "drug dependence" and "drug withdrawal syndrome." No TEAEs relating to drug abuse were found. In addition, adverse events were followed for 30 days after stopping IMP.

7.7 Additional Submissions / Safety Issues

The applicant has included a brief summary of five trials investigating once-weekly formulations of oral aripiprazole in subjects with TD. Two phase 1 trials (Trials 31-09-265 and 31-09-268) have been completed, and three phase 3 trials (Trials 31-10-272, 31-10-273, and 31-10-274) are ongoing. Data for the ongoing trials are presented as of the data cutoff date (30 Sep 2013).

Table 90: Safety Data from Once-Weekly Oral Aripiprazole Trials

Trial	Design	Safety Data
Phase 1 Trial 265	Phase A: SAD, Crossover Phase B: Food effect Phase C: MAD	Deaths: 0 SAEs: A&B had none; C had SAE of affective disorder Discontinuations 2º to AE: A&B had none; C had 3 subjects who discontinued 2º to AE (nausea, orthostatic hypotension, and insomnia)
Phase 1 Trial 268	Phase A: assessed 2 dose strengths of ER[16] (fed/fasted) and 3 dose strengths of ECER[17] (fed/fasted) Phase B: multiple-dose of 2 ER and 2 ECER	Deaths: 0 SAEs: 0 Discontinuations 2º to AE: A had none; B had 1 (↑ALT)
Phase 3 Trial 272		Deaths: 0 SAEs: 7: ECG QT prolonged (3.0%), dystonia (1.5%), hyperthermia (0.7%), ↑ALT(0.7%), ↑AST(0.7%), ↑CPK (0.7%), flat affect (0.7%), and major depression (0.7%) Discontinuations 2º to AE: 7: QT prolonged (3.0%), dystonia (1.5%), hyperthermia (0.7%), ALT increased (0.7%), AST increased (0.7%), CPK increased (0.7%), flat affect (0.7%), and major depression (0.7%)
Phase 3 Trial 273		No SAEs, deaths, or discontinuations of IP due to an AE have been reported.
Phase 3 Trial 274	Subjects from 272&273; 51% have received ARIP for up to 40 weeks	Deaths: 0 SAEs: 5: appendicitis (0.6%), suicidal ideation (0.6%), TD (0.6%), tremor (0.6%), and Type 1 diabetes mellitus (0.6%) Discontinuations 2º to AE: depressed mood (0.6%), intentional self-injury (0.6%), nausea (0.6%), tonsillitis (0.6%), tremor (0.6%), and Type 1 diabetes mellitus (0.6%)

Source: Summary of Clinical Safety, p. 83-85

[16] ER=extended release, once-weekly formulation
[17] ECER= enteric-coated extended release, once-weekly formulation

7.8 120-Day Safety Update

The applicant submitted a 120-day Safety Update (SU) to the sNDA on 10 June 2014. This safety update presents a review of additional safety data from the aggregate aripiprazole pediatric safety database from 30 Sep 2013 to the cutoff date of 30 Jan 2014. This 120-day SU includes a summary of any newly reported deaths, serious adverse events (SAEs), and discontinuations due to adverse events (AEs) for Trial 31-12-294 (the ongoing 52-week open-label, flexible-dose trial), and for Trial Pools 3 and 4. There are no new data from Trial Pools 1 and 2 as these trials have been completed and final safety data were provided previously in the sNDA.

Key findings as of the 30 Jan 2014 120-day SU data cutoff date are:

- No new deaths have occurred.
- In the 3 TD trials of QD aripiprazole in pediatric subjects (Trials 31-12-293, 31-12-294, and 031-KOA-0703), total exposure for 162 subjects is 79 subject-exposure years. The majority of subjects received an overall mean dose of aripiprazole greater than 3.5 mg and up to 12.5 mg.

Table 91: Cumulative Number of Subjects Who Received Once-daily Aripiprazole by Duration of Exposure: All Tourette's Disorder Trials (31-12-293, 031-KOA-0703, 31-12-294), Safety Sample

	Total as of 30 Sep 2013 (N=162)	Total as of 30 Jan 2014[a] (N=162)
Time Interval	n (%)	n (%)
Subject-Exposure Years	46	79
≥ 1 Day	162 (100)	162 (100)
≥ 21 Days	152 (93.8)	153 (94.4)
≥ 42 Days	147 (90.7)	150 (92.6)
≥ 90 Days	73 (45.1)	105 (64.8)
≥ 180 Days	23 (14.2)	93 (57.4)
≥ 270 Days	0 (0.0)	30 (18.5)
≥ 360 Days	0 (0.0)	6 (3.7)

[a] New data for this 120-day Safety Update are from Trial 31-12-294.

Source: 120-day SU, p. 29

Table 92: Number and Percentage of Subjects who received Once-daily Aripiprazole by Overall Mean Dose Category and Duration of Exposure: All Tourette's Disorder Trials (31-12-293, 031-KOA-0703, 31-12-294), Safety Sample

	Aripiprazole Overall Mean Dose[a]					
	≤ 3.5 mg	> 3.5 - ≤ 7.5 mg	> 7.5 - ≤ 12.5 mg	> 12.5 - ≤ 17.5 mg	> 17.5 mg	Total
Total Duration of Exposure	**(N=19) n (%)[b]**	**(N=66) n (%)[b]**	**(N=60) n (%)[b]**	**(N=15) n (%)[b]**	**(N=2) n (%)[b]**	**(N=162) n (%)[b]**
1 - 20 Days	4 (21.1)	5 (7.6)	0	0	0	9 (5.6)
21 - 41 Days	0	0	3 (5.0)	0	0	3 (1.9)
42 - 89 Days	5 (26.3)	15 (22.7)	20 (33.3)	5 (33.3)	0	45 (27.8)
90 - 119 Days	0	2 (3.0)	0	0	0	2 (1.2)
120 - 149 Days	0	3 (4.5)	2 (3.3)	0	1 (50.0)	6 (3.7)
150 - 179 Days	1 (5.3)	1 (1.5)	2 (3.3)	0	0	4 (2.5)
180 - 269 Days	7 (36.8)	28 (42.4)	21 (35.0)	7 (46.7)	0	63 (38.9)
270 - 359 Days	2 (10.5)	10 (15.2)	10 (16.7)	2 (13.3)	0	24 (14.8)
360 - 719 Days	0	2 (3.0)	2 (3.3)	1 (6.7)	1 (50.0)	6 (3.7)
Total	19 (100.0)	66 (100.0)	60 (100.0)	15 (100.0)	2 (100.0)	162 (100.0)

[a]Overall mean dose during subject's total duration of exposure, including the titration period. Categories are consistent with those used in previous submissions.

Source: 120-day SU, p. 30

- A new literature search that included both clinical and nonclinical articles published since the initial sNDA cutoff date of 30 Sep 2013 through the 120-day SU cutoff date of 30 Jan 2014 found no new adverse safety information.
- Overall, the benefit-risk profile for aripiprazole remains favorable.

For Trial 31-12-294:

Table 93: Trial 294 Overall Extent of Exposure

Length of Exposure (days)	N=110 N (%)	Mean average daily dose of aripiprazole (mg)
8-14 days	110 (100)	6.1
113-140 days	100 (90.9%)	8.0
169-196 days	82 (74.5%)	7.6

Source: 120-day SU, p. 28

- As of 30 Jan 2014, 2 subjects (1.8%) have completed the trial and 21 subjects (19.1%) have discontinued prematurely. Reasons for discontinuation were withdrawal of consent (6.4%), AEs (5.5%), subject met withdrawal criteria (3.6%), protocol deviations (1.8%), and lost to follow-up (1.8%).
- AEs that lead to discontinuation included weight increased and depression.

- Three additional treatment-emergent SAEs have been reported in 2 subjects since the sNDA data cutoff: intentional overdose of IP, concussion, and appendicitis (all unrelated to IP).
- Three suicide-related nonserious treatment-emergent adverse events (TEAEs) occurred in 3 subject: 2 events of suicidal ideation and 1 event of intentional overdose.
- Most frequently reported TEAEs observed for this 120-day SU were the same as those reported in the sNDA (increased weight, fatigue, and somnolence).
- TEAEs of increased weight were reported for 19.1% (21/110 subjects). Increased weight is a labeled side effect of aripiprazole.

For Trial Pool 3:

- 6.8% (105/1534 subjects) have discontinued IP due to an AE. The 3 most frequently occurring TEAEs resulting in IP discontinuation among the 1534 subjects in Trial Pool 3 were schizophrenia (1.4%), increased weight (0.9), and aggression (0.7%).
- Eleven additional treatment-emergent SAEs have been reported in 8 subjects: schizophrenia (2), appendicitis (1), autism (1), concussion (1), delusion (1), hallucination (1), intentional overdose (1), self-injurious behavior (1), sexual abuse (1), and attempted suicide (1).
- No meaningful differences in the most frequently reported TEAEs were observed for the 120-day SU compared with those reported in the sNDA: increased weight (14.7%), headache (11.4%), somnolence (10.4%), vomiting (10.4%), and nasopharyngitis (10.0%).

For Trial Pools 2 and 3:

- Total exposure to aripiprazole for 1812 subjects is 1479 subject-exposure years. A total of 1055 subjects (58.2%) have been exposed for at least 180 days, and 594 subjects (32.8%) have been exposed for at least 360 days. Most subjects received an overall mean dose of aripiprazole greater than 7.5 mg.

Table 94: Number and Percentage of Subjects Who Received Once-daily Aripiprazole by Overall Mean Dose Category and Duration of Exposure: All Phase 2/3 Pediatric, Ongoing Open-label and All Completed Trials, Safety Sample (Trial Pools 2 and 3 Combined)

	Aripiprazole Overall Mean Dose[a]					
	≤ 3.5 mg	> 3.5 - ≤ 7.5 mg	> 7.5 - ≤ 12.5 mg	> 12.5 - ≤ 17.5 mg	> 17.5 mg	Total
Total Duration of Exposure	(N=107) n (%)[b]	(N=314) n (%)[b]	(N=611) n (%)[b]	(N=332) n (%)[b]	(N=448) n (%)[b]	(N=1812) n (%)[b]
1 - 20 Days	30 (28.0)	46 (14.6)	28 (4.6)	13 (3.9)	5 (1.1)	122 (6.7)
21 - 41 Days	6 (5.6)	13 (4.1)	27 (4.4)	5 (1.5)	18 (4.0)	69 (3.8)
42 - 89 Days	19 (17.8)	54 (17.2)	94 (15.4)	40 (12.0)	68 (15.2)	275 (15.2)
90 - 119 Days	6 (5.6)	24 (7.6)	42 (6.9)	17 (5.1)	23 (5.1)	112 (6.2)
120 - 149 Days	4 (3.7)	18 (5.7)	34 (5.6)	11 (3.3)	21 (4.7)	88 (4.9)
150 - 179 Days	3 (2.8)	16 (5.1)	40 (6.5)	15 (4.5)	17 (3.8)	91 (5.0)
180 - 269 Days	12 (11.2)	56 (17.8)	109 (17.8)	68 (20.5)	107 (23.9)	352 (19.4)
270 - 359 Days	11 (10.3)	27 (8.6)	46 (7.5)	14 (4.2)	11 (2.5)	109 (6.0)
360 - 719 Days	16 (15.0)	52 (16.6)	146 (23.9)	101 (30.4)	92 (20.5)	407 (22.5)
≥ 720 Days	0	8 (2.5)	45 (7.4)	48 (14.5)	86 (19.2)	187 (10.3)
Total	107 (100.0)	314 (100.0)	611 (100.0)	332 (100.0)	448 (100.0)	1812 (100.0)

Source: 120-day SU, p. 32

For Trial Pool 4:

- Since the sNDA data cutoff date, 9 additional TEAEs resulting in IP discontinuation have been reported for 8 subjects: psychotic disorder (5), schizophrenia (3), and attempted suicide (1).

Adverse Events of Special Interest

The applicant presented results for these analyses for Trial 31-12-294 only:

Extrapyramidal Symptoms
As of the 120-day SU data cutoff date, 1 new event of psychomotor hyperactivity was reported for a subject who had been assigned to the placebo group during Trial 31-12-293.

Suicide
Three suicide-related TEAEs (3/110 subjects; 2.7%) were reported as of the 120-day SU data cutoff date. Two events of suicidal ideation were reported for 2 subjects assigned to the low-dose aripiprazole group in Trial 31-12-293, and 1 event of intentional overdose was reported for 1 subject assigned to the placebo group in Trial 31-12-293.

Weight Gain
Weight-gain-related TEAEs were reported for 20.9% of subjects (23/110 subjects).

Prolactin/Hyperglycemia or Diabetes/Lipids
No TEAEs were reported as of the 120-day SU data cutoff date of 30 Jan 3014 for these adverse events of special interest.

Use in Pregnancy and Lactation
No pregnancies were reported in Trial 31-12-294, and no new pregnancies were reported for Trial Pools 3 and 4.

Overdose
1 newly observed event related to overdose was reported in Trial 31-12-294.

Drug Abuse
No TEAEs relating to drug abuse were found.

Post-marketing Data

Patient Exposure
Based on the information available to Otsuka Pharmaceutical and Bristol-Myers Squibb; (b) (4) mg of aripiprazole were sold during the period from 01 Jul 2002 to 31 Dec 2013. The total number of patients exposed worldwide during this period referenced is estimated to be (b) (4) ((b) (4)

According to IMS Health, a total of (b) (4) mg of aripiprazole was sold for pediatric use from 2002 through 31 Jan 2014. The total number of pediatric patients exposed in the US during this period is estimated to be (b) (4) ((b) (4) (b) (4)

Postmarketing Safety Surveillance
PSURS/PADERs: No new Periodic Safety Update Reports (PSURs) or Periodic Adverse Drug Experience Reports (PADERs) have been prepared since the sNDA was submitted on 12 Feb 2014.

Literature Search Results
A new literature search that included both clinical and nonclinical articles that were published since the 30 Sep 2013 sNDA data cutoff date was performed to ascertain if there were any new safety concerns for the use of aripiprazole. The results of this search were evaluated by a qualified medical officer. According to the applicant, all abstracts were reviewed for potential new or significant safety findings related to the use of aripiprazole. For those abstracts that were considered potentially relevant, full-text articles were reviewed. No new adverse safety information was found.

Postmarketing Conclusions
The overall benefit-risk profile for aripiprazole remains favorable based on the postmarketing experience since its first approval, and on the evaluation of the additional safety data available as of the 30 Jan 2014 SU data cutoff date.

8 Postmarket Experience

Postmarket Exposure (For updated exposure data, see **Section 7.8 120-Day Safety Update**)
An estimate of the number of treated patients has been derived from sales figures from IMS Health for the period from 01 Jul 2002 to 31 Mar 2013. Based on this information, (b) (4) mgs were sold during this period. The Applicant estimates that (b) (4) patients have been exposed to aripiprazole during this period.

According to IMS Health, a total of (b) (4) mgs of aripiprazole were sold for pediatric use from 2002 through the third quarter of 2013. The Applicant estimates that (b) (4) pediatric patients have been exposed to aripiprazole during this period.

Postmarketing Safety Surveillance

Adverse events for postmarketing safety surveillance have been summarized in Periodic Safety Update Reports (PSURs) and US Periodic Adverse Drug Experience Reports (PADERs). Twenty PSURs have been prepared since 17 Jul 2002 through 16 Jul 2013. The table below summarizes the results of the PSURs and indicates if any relevant changes were recommended for the Company Core Safety Information (CCSI).

Table 95: Summary of Cumulative Reviews in PSURs and CCSI Updates

PSUR	Cumulative Review	CCSI Update and Version Date
#1	No	No
#2	Hypersensitivity, hepatobiliary events, diabetes/hyperglycemia, increased CPK/rhabdomyolysis, syncope	No
#3	Hypersensitivity, hepatobiliary events, diabetes/hyperglycemia, increased CPK/rhabdomyolysis, syncope	Allergic reaction (eg, anaphylactic reaction, angioedema, pruritus, or urticaria), hepatobiliary events (ie, increased ALT/SGPT and increased AST/SGOT), increased CPK/rhabdomyolysis, and syncope were added to the CCSI (version: Apr 2004)

#4 (EMEA PSUR #1)	Hepatobiliary events, diabetes/hyperglycemia, pancreatitis, increased CPK/rhabdomyolysis in relation to NMS, cerebrovascular accidents, syncope	No
#5 (EMEA PSUR #2)	Hepatobiliary events, diabetes/hyperglycemia, pancreatitis, increased CPK/rhabdomyolysis in relation to NMS, cerebrovascular accidents	Diabetes mellitus, hyperglycemia, pancreatitis, increased GGT were added to the CCSI (version: Apr 2005
#6 (EMEA PSUR #3)	Bone marrow depression, cardiac events, temperature dysregulation, hepatobiliary events, diabetes/hyperglycemia, lipid abnormalities, weight gain, rhabdomyolysis/increased CPK and NMS, cerebrovascular events, extrapyramidal symptoms, renal failure, urinary incontinence and urinary retention, hypertension	Urinary incontinence, urinary retention, weight increased, hypertension, diabetic ketoacidosis, diabetic hyperosmolar coma, thrombocytopenia, leukopenia and neutropenia were added to the CCSI. In addition, rash and laryngospasm were added as part of allergic reaction, which was already listed. (version: Nov 2005)

PSUR	Cumulative Review	CCSI Update and Version Date
#7 (EMEA PSUR #4)	Cardiac events, endocrine events, hepatobiliary events, seizure events, respiratory events, photosensitivity reactions, circulatory collapse and shock, thromboembolic events	Grand mal convulsion, dysphagia, aspiration pneumonia, hepatitis, jaundice, completed suicide, suicide attempt, and suicidal ideation were added to the CCSI (version: May 2006)
#8 (EMEA PSUR #5)	Anorexia, anxiety, bone marrow depression events, dyslipidemia, hyperhidrosis, inappropriate antidiuretic secretion hormone, QT (QTc) prolongation, swollen tongue, renal failure, thromboembolic events, suicidality	Anorexia, hyponatremia, weight decreased, and hyperhidrosis were added to the CCSI (version: Dec 2006)
#9 (EMEA PSUR #6)	Blood and lymphatic system disorders, cardiac disorders, ear and labyrinth disorders, eye accommodation disorder, blindness, infections and infestations, metabolism disorders, neoplasms, psychiatric delusional symptoms, psychiatric perception disturbances, psychiatric mood alteration and manic symptoms, renal and urinary disorders, respiratory disorders, skin and connective tissue disorders, vascular disorders, drug interaction with clozapine, drug interaction with citalopram, drug interaction with escitalopram, drug interaction with levomepromazine, drug interaction with risperidone, drug interaction with venlafaxine, drug level increased	No

PSUR	Cumulative Review	CCSI Update and Version Date
#10 (EMEA PSUR #7)	Bone marrow depression events, arrhythmia events, coronary artery disease and myocardial infarction events, heart failure events, other cardiac disorder events, ear and labyrinth disorder events, hypothyroidism events, endocrine disorder events, accommodation disorder events, blindness, eye movement disorders, hepatobiliary disorders, fall events, dyslipidemia, diabetes mellitus events, weight increased, weight decreased, arthralgia, pain in extremity, joint stiffness, back pain, muscle spasm, muscle twitching, trismus, neoplasms, general hormonal disorders, male hormonal disorders, female hormonal disorders, drug interaction with escitalopram. Data regarding report rate frequencies for all of the events were provided.	No
#11 (EMEA PSUR #8)	Dystonia	Diarrhea was added to the CCSI (version: Jul 2008)
#12 (EMEA PSUR #9)	Arrhythmia events and related terms, congenital disorder events due to pregnancy exposure to aripiprazole, NMS, all health-care confirmed pediatric cases, pregnancy data since the start of the clinical program	No
#13 (EMEA PSUR #10)	Cardiac death (fatal outcomes with cardiac events)	No
#14 (EMEA PSUR #11)	PT agranulocytosis, cardiac death (fatal outcomes with cardiac events), PT inappropriate antidiuretic hormone secretion, PTs of pancreatitis and pancreatitis acute, HLGT embolism and thrombosis	No

PSUR	Cumulative Review	CCSI Update and Version Date
#15 (EMEA PSUR #12)	HLT acute and chronic pancreatitis, PT weight increased, PT blood CPK increased, HLGT movement disorders, HLGT embolism and thrombosis	No
#16 (EMEA PSUR #13)	Edema	No
#17 (EMEA PSUR #14)	Cumulative review of overdose cases	Pregnancy: the marketing authorization holder recommends adding text to the CCSI with regard to risk of extrapyramidal and/or withdrawal symptoms in neonates exposed to antipsychotic drugs during the third trimester of pregnancy
#18 (EMEA PSUR #15)	Agranulocytosis, PT pathological gambling, cases with pulmonary embolism while receiving aripiprazole therapy, cases with alopecia	Pulmonary embolism is not listed in the current aripiprazole CCSI (version 06 May 2011). Based on the information provided by these cases, no changes to the CCSI are recommended.
#19 (EMEA PSUR #16)	PTs agranulocytosis, aplastic anaemia, leukopenia, and neutropenia, pneumonia, pulmonary embolism	No
#20 (EMEA PSUR #17)	Cumulative summaries of adverse reactions from clinical trials and postmarketing data	CCSI dated 07 Jan 2013. Update of safety information in the CCSI was not recommended.

Source: Summary of Clinical Safety, p.90-93

9 Appendices

9.1 Literature Review/References

(Note: For updated literature search results, see **Section 7.8 120-Day Safety Update**)

The Applicant performed a literature (clinical and nonclinical) search to ascertain if there were any new safety concerns for the use of aripiprazole. Databases searched included Ovid MEDLINE®, Embase, BIOSIS Previews, and Current Contents/Science Edition for the time period from 15 Jun 2008 through 30 Sep 2013. Key search terms included aripiprazole, Abilitat, OPC-14597, OPC14597, OPC-31, OPC31, Abilify and terminology related to drug toxicity, drug interactions, poisoning, or adverse drug reactions.

All abstracts and relevant, full-text articles were reviewed by a medical officer. The applicant states that no new adverse safety information was found. The Applicant provided details of the search strategy, a warrant statement signed by the medical officer who evaluated the search results, and curricula vitae of the medical officer and the individual who performed the search in Module 5 of the sNDA submission.

9.2 Labeling Recommendations

The Division of Psychiatry Products (DPP) has reviewed the proposed Abilify label in detail. DPP has also consulted the Division of Medical Policy Programs (DMPP), the Office of Prescription Drug Promotion (OPDP), and the Division of Pediatric and Maternal Health (DPMH) to review the label. We are currently in the process of label negotiations with the sponsor.

Some of the proposed changes to the label include the following:

- Modify indication from (b) (4) to Treatment of Tourette's disorder.
- Update each Warning and Precaution to include a management strategy.
- Replace text with Tables for Drug Interactions.
- Update Boxed Warning to be consistent with Abilify Maintena.
- Delete language about (b) (4)
- Reformat Section 8.1 Pregnancy to be consistent with the proposed Pregnancy and Lactation Labeling Rule.
- Delete references to off-label use in (b) (4)
- Add quantities of inactive ingredients.
- Add Forest Plots to Section 12.3 Pharmacokinetics.

- Incorporate more accurate description of the pivotal fixed-dose (weight-based high and low doses) trial in Tourette's.
- Delete recommendation to avoid alcohol while taking Abilify or provide justification.

9.3 Advisory Committee Meeting

No advisory committee meeting is planned. Aripiprazole is not a new molecular entity; there is considerable premarket and postmarketing experience with aripiprazole in both adult and pediatric populations.

9.4 Financial Disclosure for Trial 031-KOA-0703

Clinical Investigator Financial Disclosure
Review Template

Application Number: **021436, Supplement-38 (Efficacy)**

Submission Date(s): **2/12/2014**

Applicant: **Otsuka**

Product: **Aripiprazole (OPC-14597/Abilify®)**

Reviewer: **Christina P. Burkhart, M.D.**

Date of Review: **3/11/2014**

Covered Clinical Trial (Name and/or Number): **031-KOA-0703**
From Applicant's Submission: "Trial 031-KOA-0703 was conducted in Korea from 2008 to 2010, and was submitted as the pivotal Trial to support the approval of a marketing application in Korea. This clinical trial was not conducted under a US IND and consequently it was not subject to 21 CFR Part 54 at that time. However, Trial 031-KOA-0703 is now included as one of the pivotal studies for the sNDA filing for Tourette's Disorder in the US. Therefore, the financial disclosure information for Trial 031-KOA-0703 has been collected retrospectively."

Was a list of clinical investigators provided:	**Yes X**	No ☐ (Request list from applicant)
Total number of investigators identified: **6 Principal Investigators; 23 Subinvestigators**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0 (For 031-KOA-0703 the Ethics, Quality and Compliance group at Otsuka searched records of payments contained in company financial systems and confirmed that none of the investigators received disclosable**		

payments from Otsuka during the trial period, or for one year following the end of the trial.)		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0 (The Applicant was able to obtain financial disclosure information from 100% (6/6) of the Principal Investigators but from only 35% (8/23) of the Subinvestigators. No disclosable financial interests were identified.)**		
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)): **NA** Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes **NA**	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes **NA**	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **15**		
Is an attachment provided with the reason:	**Yes X**	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The due diligence process for collecting the financial disclosure information from required individuals was as follows:
1. (b) (6) sent the initial request for information on financial interests along with the Financial Disclosure Form to the sites in March 2013.
2. If there was no response to the first request, Otsuka mailed reminder request letters to the study sites.
3. On a periodic basis, telephone contact to sites was also made by Otsuka personnel requesting completion of outstanding Financial Disclosure forms.

Reviewer's Comments:
All the Principal Investigator's in this study returned the Financial Disclosure forms and reported no disclosable financial interests/arrangements. The Applicant showed due diligence in trying to collect the financial disclosure information retrospectively. The Ethics, Quality and Compliance group at Otsuka also searched records of payments contained in company financial systems and confirmed that none of the investigators received disclosable payments from Otsuka during the study period, or for one year following the end of the study.

Note to File

Protocol No.	031-KOA-0703
Subject	Regarding SI who (b) (4) can't get in touch in for Financial disclosure form now

According to request from OPDC to submit data of 031-KOA-0703 study, (b) (6) attempted to get FDF from all Investigators who involved in (b) (4) study.

Because this study had been started since 2008, some of sub-investigators are not in the study site now.

We have tried to get FDF from PI and SI who we could get in touch in.

The status of getting FDF form PI and SI below.

No.	Site Name	Title	Name	Status of getting FDF(O/X)	
01	Seoul National University Hospital	PI	Soochurl Cho	O	
		SI	(b) (6)	O	
		SI		X	Out of contact
		SI		X	Out of contact
		SI		O	
		SI		X	Out of contact
		SI		O	
02	Seoul Asan Medical Center	PI	Hanik Yoo	O	
		SI	(b) (6)	O	
		SI		X	Out of contact
03	Samsung Medical Center	PI	Yoosook Chung	O	
		SI	(b) (6)	X	Out of contact
		SI		X	Out of contact
		SI		X	Out of contact
		SI		X	Out of contact
04	Inha University Hospital	PI	Jeongseop Lee	O	
		SI	(b) (6)	X	Out of contact
		SI		O	
		SI		X	Out of contact

Written by site staff, File original in ISF.
Written by sponsor staff, File original in SMF.
Version Control Number: CRGEN-F03.00
Effective Date: 2010-12-01

Page 1 of 2

Protocol No.	031-KOA-0703
Subject	Regarding SI who (b) (6) can't get in touch in for Financial disclosure form now

No.	Site Name	Title	Name	Status of getting FDF(O/X)	
05	Shinchon Severance Hospital	PI	Dongho Song	O	
		SI	(b) (6)	X	Out of contact
		SI		X	Out of contact
		SI		O	
		SI		O	
		SI		O	
06	Chung-Aang University Hospital	PI	Youngsik Lee	O	
		SI	(b) (6)	X	Out of contact
		SI		X	Out of contact
		SI		X	Out of contact

Name of the author: (b) (6) Date/Signature: 12 Jul 2013

If applicable

Comments: NA

Name of the commentator: NA Date/Signature:

Appendix C List of Investigators/Sub-Investigators who did not return financial disclosure forms

Subinvestigator	Protocol & Site No.	Participated as Principal Investigator (Yes/No)	Number of Patients Randomized at the Site	Comments/Status
(b) (6)	031-KOA-0703-001	No	12	Study conducted from 2008 – 2010. No response
	031-KOA-0703-001	No	12	Study conducted from 2008 – 2010. No response
	031-KOA-0703-001	No	12	Study conducted from 2008 – 2010. No response
	031-KOA-0703-002	No	10	Study conducted from 2008 – 2010. No response
	031-KOA-0703-003	No	9	Study conducted from 2008 – 2010. No response
	031-KOA-0703-003	No	9	Study conducted from 2008 – 2010. No response
	031-KOA-0703-003	No	9	Study conducted from 2008 – 2010. No response
	031-KOA-0703-003	No	9	Study conducted from 2008 – 2010. No response
	031-KOA-0703-004	No	14	Study conducted from 2008 – 2010. No response
	031-KOA-0703-004	No	14	Study conducted from 2008 – 2010. No response
	031-KOA-0703-005	No	9	Study conducted from 2008 – 2010. No response
	031-KOA-0703-005	No	9	Study conducted from 2008 – 2010. No response
	031-KOA-0703-006	No	7	Study conducted from 2008 – 2010. No response
	031-KOA-0703-006	No	7	Study conducted from 2008 – 2010. No response
	031-KOA-0703-006	No	7	Study conducted from 2008 – 2010. No response

9.5 Financial Disclosure for Trial 31-12-293

Clinical Investigator Financial Disclosure
Review Template

Application Number: **021436, Supplement-38 (Efficacy)**

Submission Date(s): **2/12/2014**

Applicant: **Otsuka**

Product: **Aripiprazole (OPC-14597/Abilify®)**

Reviewer: **Christina P. Burkhart, M.D.**

Date of Review: **3/11/2014**

Covered Clinical Trial (Name and/or Number): **31-12-293**

Was a list of clinical investigators provided:	**Yes X**	No ☐ (Request list from applicant)
Total number of investigators identified: **81 Principal Investigators; 285 Subinvestigators**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA		

<table>
<tr><td colspan="3">3455): <u>2 Principal Investigators and 1 Subinvestigator</u></td></tr>
<tr><td colspan="3">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: <u>0</u>

Significant payments of other sorts: <u>2</u>

Proprietary interest in the product tested held by investigator: <u>0</u>

Significant equity interest held by investigator in sponsor of covered study: <u>0</u></td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes <u>X</u></td><td>No ☐ (Request details from applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes <u>X</u></td><td>No ☐ (Request information from applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u></td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes <u>NA</u></td><td>No ☐ (Request explanation from applicant)</td></tr>
</table>

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

For Trial 31-12-293 the Ethics, Quality and Compliance group at Otsuka confirmed that the three individuals with disclosable information received payment from Bristol Myers Squibb or Lundbeck (with whom Otsuka had alliance agreements at the time) in the 2011 period, but did not receive any disclosable payments from Otsuka during the study period.

Disclosed Financial Interests:

1. [redacted] (Principal Investigator)

[redacted] Principal Investigator at Site # [redacted] in studies 31-12-293 and 31-12-294 has reported in his financial disclosure that in 2011 he was compensated $89,500 by Otsuka for serving on the speaker's bureau, participating in speaker training and serving on the Advisory Board for Otsuka. In collaboration with Otsuka RA, EQC, Legal and CM, a determination was made on 13Dec2012 that [redacted] can participate in these studies however CM will watch the enrollment at this site closely and once he has enrolled two to three subjects, CM will determine along with Biostats whether he should be allowed to enroll additional subjects. The site expects to enroll three subjects.

[redacted] staff will conduct the ICF process for each subject and regarding his financial interest, [redacted] will provide full disclosure to all subjects.

Based on the activities [redacted] will be performing, Otsuka believes that the Investigator's participation will not impact study endpoints.

2. [redacted] (Sub-investigator)

[redacted] Sub-investigator at [redacted] [Principal Investigator [redacted] in studies 31-12-293and 31-12-294, has reported in her financial disclosure that in 2011 she received compensation for promotional speaking from Otsuka partner Bristol-Meyers Squibb (BMS). Bristol Myers Squibb confirmed that [redacted] was paid $100,000 for speaking engagements between January and September 2011. [redacted] has not received any significant payments directly from Otsuka Pharmaceutical Development & Commercialization (OPDC) or Otsuka America Pharmaceutical, Inc. (OAPI). In collaboration with Otsuka Regulatory Affairs (RA), Ethics, Quality & Compliance (EQC), Legal, Quality Management (QM) and Clinical Management (CM), a determination has been made that [redacted] can participate in these studies.

It is estimated that [redacted] site will enroll approximately 1.5% (2 subjects randomized) of the total study population. CM will closely monitor the enrollment at this site and once the site has enrolled 2 subjects, CM will determine whether the site should be allowed to enroll additional subjects.

[redacted] s currently participating as a Sub-Investigator in 4 other OPDC protocols; [redacted] Audit response documents for [redacted] site from 2010 as well as letters from the FDA for two additional audits conducted in 2003 and 2007 were obtained from the study site. Findings were noted during the audits that resulted in voluntary action, but did not generate 483s.

Based on the activities the Sub-investigator [redacted] will be performing, Otsuka believes that her participation will not impact the study endpoints, because [redacted] will not perform any of the primary efficacy assessments.

3. [redacted] (Principal Investigator)

[redacted] Principal Investigator at Site #[redacted] studies 31-12-293 and 31-12-294 has reported that in 2011 he was compensated by Lundbeck $6,900 for speaker honorarium and promotional programs, as well as $2,437 for attendance at a speaker training program. These activities were not for aripiprazole but for an anti-epileptic seizure medicine. In collaboration with Otsuka RA, EQC, Legal and CM, a determination was made on 13Dec2012 that [redacted] can participate in these studies because the OPC-Lundbeck collaboration agreement does not include any revenue sharing for the formulation of aripiprazole that is under investigation in this clinical program, and further, Lundbeck will not be included as a party on the IND submitted to the USFDA at the end of the studies. Therefore, the financial disclosures made by the potential investigator with regard to income received from Lundbeck are not relevant to this clinical program and the Otsuka representatives discussing this matter concluded that there is no financial conflict of interest.

Reviewer's comment:
The Applicant's assessments seem reasonable.

9.6 Schedule for Trial 031-KOA-0703

8.4. TRIAL SCHEDULE

Table 8.1 Study Flow Chart

	STUDY VISITS								
	Screening[1] Visit 1	Baseline Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Last visit Visit 7	Safety follow up	Early Termination Visit
	Day -14 to Day 1	Day 1	Week 2 Day 14	Week 4 Day 28	Week 6 Day 42	Week 8 Day 56	Week 10 Day70	16 days after last administration	
Visit Window (day)			±4	±4	±4	±4	±4		
PROCEDURE									
Informed Consent	x								
Inclusion/Exclusion Criteria	x	x							
IQ(Wechsler Intelligence Scale)	x								
K-SADS-PL	x								
Demographics (Sex, date of birth)	x								
Medical & Psychiatric History	x								
Previous medications	x	x							
Randomization		x							
Dispense Investigational Product		x	x	x	x	x			
Drug compliance check			x	x	x	x	x		x
Concomitant medications	x	x	x	x	x	x	x	x	x
EFFICACY									
K-YGTSS evaluation	x	x	x	x	x	x	x		x
TS-CGI-Improvement evaluation			x	x	x	x	x		x
TS-CGI-Severity evaluation		x	x	x	x	x	x		x
SAFETY									
Vital Signs(BP, pulse)	x	x	x	x	x	x	x		X
Height	x	x	x	x	x	x	x		X
Body Weight	x	x	x	x	x	x	x		X
Waist Circumference		x	x	x	x	x	x		X
Physical Examination	x	x	x	x	x	x	x		X
EPS : SARS, AIMS, BARS[2]	x	x	x	x	x	x	x		x
12-Lead ECG	x						x		X
Clinical Laboratory Tests[3] (chemistry, Blood glucose, CPK, hematology, urinalysis)	x						x		x
Serum Prolactin Level	x						x		x
Pregnancy test (females of childbearing potential only)- Confirm start of menarche	x						x		x
Adverse Events[4]	x	x	x	x	x	x	x	x	x

1) Screening visit and baseline visit might be conducted at the same time regard to the subject"s wash-out period of previous drug treatment.
2) Was conducted by qualified medical specialist.
3) Subject fasted for at least 8 hours prior to the laboratory tests. (Subject"s fasting status was recorded in the source document and CRF.)
4) Adverse event was collected after obtaining written informed consent. In case of the clinical trial termination, early discontinuation or drop-out, investigated and collected pre-existing adverse event or newly occurred adverse events from the last investigational product administration day to the period of 5 times of half-life (16 days).

9.7 Schedule for Trial 31-12-293

Table 3.7-1 Schedule of Assessments

Assessments/Procedures	Screening and Washout Period (Days -42 to -3)	Treatment Period Visits									Follow-up Period 30 (±3) Days[o] (V10)
		Baseline Visit Day 0 (V1)	Wk 1 (V2)	Wk 2 (V3)	Wk 3 Phone Visit (V4)	Wk 4 (V5)	Wk 5 Phone Visit (V6)	Wk 6 (V7)	Wk 7 Phone Visit (V8)	Week 8/Early Termination (End of Treatment) (V9)	
Standard											
Informed Consent/Assent[a]	X										
Confirmation of diagnosis of Tourette's Disorder by DSM-IV-TR[b]	X										
K-SADS-PL incl. Diagnostic Supplement 5[c]	X										
Inclusion/exclusion criteria	X	X									
Demography	X										
Medical history	X										
Psychiatric history	X										
Record current neuroleptic therapy[d]	X	X	X	X	X	X	X	X	X	X	
Washout of prohibited medications, including psychotropics[d]	X										
Trial Assessments											
YGTSS[q]	X	X	X	X		X		X		X	
SNAP-IV[q]		X		X		X				X	
CDRS-R[q]		X		X		X				X	
PARS[q]		X		X		X				X	
CY-BOCS[q]	X	X		X		X				X	
CGI-TS Severity[q]		X	X	X		X		X		X	
CGI-TS Improvement[q]			X	X		X		X		X	
C-SSRS (baseline version)[e,q]	X										

Table 3.7-1 Schedule of Assessments

Assessments/Procedures	Screening and Washout Period (Days -42 to -3)	Treatment Period Visits: Baseline Visit Day 0 (V1)	Wk 1 (V2)	Wk 2 (V3)	Wk 3 Phone Visit (V4)	Wk 4 (V5)	Wk 5 Phone Visit (V6)	Wk 6 (V7)	Wk 7 Phone Visit (V8)	Week 8/Early Termination (End of Treatment) (V9)	Follow-up Period 30 (±3) Days[o] (V10)
C-SSRS (since last visit version)[e,q]		X	X	X		X		X		X	
Physical examination		X								X	
Height		X								X	
Body weight	X	X				X				X	
Waist circumference		X				X				X	
Vital signs[f]	X	X	X	X		X		X		X	
12-lead ECG[g]	X	X				X				X	
Clinical laboratory tests (hematology, serum chemistry, urinalysis)[h]	X					X				X	
Thyroid function test (TSH)[i]	X									X	
Prolactin level (blinded)	X									X	
Serum pregnancy test[j]	X	<----------						---------->		X	
Urine pregnancy test[j]		X	<----------					---------->			
Documentation of birth control status[k]	X	X	X	X		X		X		X	
Urine drug and alcohol screen[l]	X	X	<----------					---------->		X	
SAS[q]		X	X	X		X		X		X	
AIMS[q]		X	X	X		X		X		X	
BARS[q]		X	X	X		X		X		X	
Adverse Events[m]	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications[n]	X	X	X	X	X	X	X	X	X	X	X

Table 3.7-1 Schedule of Assessments

Assessments/Procedures	Screening and Washout Period (Days -42 to -3)	Treatment Period Visits: Baseline Visit Day 0 (V1)	Wk 1 (V2)	Wk 2 (V3)	Wk 3 Phone Visit (V4)	Wk 4 (V5)	Wk 5 Phone Visit (V6)	Wk 6 (V7)	Wk 7 Phone Visit (V8)	Week 8/Early Termination (End of Treatment) (V9)	Follow-up Period 30 (±3) Days[o] (V10)
Blood draw for Pharmacogenomic Analysis		X									
Blood draw for PK Analysis[p]								X		X	
Trial Management											
Register Subject in IVRS/IWR	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X		X		X			
Assess eligibility for treatment	X	X									
Drug accountability			X	X		X		X		X	

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CDRS-R = Children's Depression Rating Scale - Revised; CGI-TS = Clinical Global Impression Scale for Tourette's Syndrome; C-SSRS = Columbia-Suicide Severity Rating Scale; CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revision; ECG = Electrocardiogram; IRE = immediately reportable event; IWR = interactive web response; IVRS = interactive voice response system; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version; PARS = Pediatric Anxiety Rating Scale; SAS = Simpson-Angus Scale; SNAP-IV = Swanson, Nolan and Pelham-IV Rating Scale; TSH = thyroid-stimulating hormone; V = visit; Wk = week; YGTSS = Yale Global Tic Severity Scale.

[a] Informed consent/assent must be obtained from all legally acceptable representatives/subjects prior to initiation of any trial-related procedures.

[b] Current diagnosis of Tourette's Disorder should be made and documented at Screening by an adequately qualified clinician.

[c] K-SADS-PL including the Diagnostic Supplement 5 (Substance Abuse and Other Diseases, ie Tic Disorders): This assessment must be performed by certified personnel.

[d] Tapering rates for washout medications are at the discretion of the investigator and are to be determined on an individual basis, with consideration to subject state, dose, and known pharmacokinetics of the medication being tapered, as long as the protocol-mandated discontinuation timeframe is met. The exception is a long-acting depot medication, which cannot be tapered and would be discontinued after the informed consent is obtained. All psychotropic medications must be discontinued for at least 2 weeks (14 days) prior to the Baseline visit, with the exception of psychostimulant medications such as methylphenidate (not limited to Concerta, Metadate CR, Ritalin LA, Focalin, Focalin XR) prescribed for the treatment of symptoms of ADD/ADHD, which are permitted during the trial. Use of psychostimulant medications is only permitted if the subject did not develop and/or have an exacerbation of the tic disorder after the initiation of treatment with the psychostimulant. In addition, the dose of any psychostimulant must have been stable for at least 4 weeks

prior to Screening. All selective SSRIs/SSNIs must be discontinued at least 4 weeks (28 days) prior to the Baseline visit. In addition, long-acting (depot) neuroleptics must be discontinued for at least 1 full cycle plus 2 weeks prior to the Baseline visit. Clonidine, guanfacine, guanabenz, atomoxetine and carbamazepine are prohibited during the trial and must be discontinued for at least 2 weeks prior to Baseline. Subjects must have discontinued aripiprazole treatment at least 30 days prior to the Screening visit. Subjects not in need of medication washout may proceed to the trial Baseline visit after the inclusion/exclusion criteria have been met.

[e] The baseline ("lifetime") C-SSRS will be completed for all subjects at Screening and the "since last visit" C-SSRS will be completed at all subsequent visits.

[f] Vital signs include systolic and diastolic blood pressure and heart rate. Orthostatic assessments of blood pressure and heart rate will be made after the subject has been supine for at least 5 minutes and again after the subject has been standing for approximately 2 minutes, but not more than 3 minutes.

[g] Three 12-lead ECGs will be performed at rest after the subject has been lying down for approximately 5 minutes. Each ECG recording will be obtained approximately 5 minutes apart. ECGs will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety. All ECGs will also be evaluated by a central ECG vendor; however, the investigator or qualified designee will ultimately be responsible for determining subject eligibility and monitoring safety. Based on the QTcB and QTcF corrections, a subject will be excluded if either of the corrections are ≥ 450 msec for 2 of the 3 time points of ECGs done. If only 1 ECG time point has a corrected QTc ≥ 450 msec on either correction factor and this is not reproduced at the other 2 time points, the subject can be included in the trial. A central ECG service will be utilized to review all ECGs in order to standardize interpretations for the safety analysis. Subjects with clinically significant ECG findings at Screening may enter the treatment period only after the Screening ECG is repeated and determined by the investigator prior to treatment to have no abnormality(ies) that are clinically significant.

[h] Subjects should fast for a minimum of 8 hours prior to blood draws for all laboratory assessments. If nonfasting blood samples are obtained initially for determining eligibility for the trial, a fasting blood sample should be drawn prior to the treatment period. Subjects with clinically significant abnormal laboratory test results at Screening may enter the treatment period only after repeated laboratory test results are received and determined by the investigator prior to treatment to have no abnormality(ies) that are clinically significant.

[i] If the observed TSH level is outside of the normal range, tests of T3 (triiodthyronine) and T4 (thyroxine) levels will be performed.

[j] A serum pregnancy test for hCG will be performed at screening on all female subjects ≥ 12 years of age and all female subjects < 12 years of age if menstruation has started. Subjects with a positive result will be excluded from the study. A urine pregnancy test will be performed within 72 hours prior to the first dose of aripiprazole to reconfirm eligibility. Urine and/or serum pregnancy tests can be performed at any point during the trial if pregnancy is suspected. All positive urine pregnancy test results must be confirmed by a serum test. Treated subjects with a positive urine and serum pregnancy test must discontinue treatment, be withdrawn from the study, and an immediately reportable event (IRE) form should be completed.

[k] Abstinence will be permitted if it is confirmed and documented at every trial visit.

[l] A urine drug screen, including a urine alcohol test, is required at the designated times, but either or both can be conducted at any time during the trial at the discretion of the investigator. Subjects who have 2 positive drug screens for any drug of abuse (with the exception of caffeine, nicotine, or prescribed psychostimulants for ADD/ADHD) at any time during the trial must be discontinued.

[m] Adverse events will be recorded starting at the time the ICF/IAF is signed.

[n] A complete history of use of central nervous system (CNS)-active compounds other than neuroleptics will be recorded, as will all other medications taken within 30 days of starting study drug. In addition, all prescription and nonprescription medications taken during the trial will be recorded as concomitant medications.

[o] All subjects (completers and subjects who receive at least 1 dose of trial drug and discontinue the trial for any reason) will be followed up for safety reasons 30 days (±3 days) after the last trial visit. Follow-up will consist of telephone contact to assess any AEs experienced since the last trial visit and information on ongoing AEs and SAEs and recording of concomitant medications.

[p] PK samples will be collected during Week 6 and Week 8 visits. The actual time of the PK sample will be recorded as well as the dosing time prior to the PK sample collection. The PK samples should be collected either at 2-10 hours post last dose or at 12 hours post last dose.

[q] Benztropine (up to 4 mg/day) is not to be administered 12 hours prior to rating scales. Benzodiazepines (up to 3 mg/day benzodiazepine equivalents) are not to be administered 4 hours prior to rating scales.

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

/s/

CHRISTINA P BURKHART
11/04/2014

MARK A RITTER
11/12/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: NDA 21436 **Applicant: Otsuka** **Stamp Date: 2/12/2014**

Drug Name: Aripiprazole (OPC-14597/Abilify®) **NDA Type: NDA S-38 Efficacy (** (b) (4) [redacted]

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			Final container and carton label eCTD 0051 (1/15/2014)
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Summary of Clinical Safety per presubmission correspondence with the review division
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Summary of Clinical Efficacy per presubmission correspondence with the review division
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Clinical Overview: p.34
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product	X			

	Content Parameter	Yes	No	NA	Comment
	(*i.e.*, appropriately designed dose-ranging studies)? **Study Number: 31-12-293** Study Title: "A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder" Sample Size: 89 Abilify/44 placebo Arms: Fixed-dose Abilify and placebo arms Location in submission: 5.3.5.2 **Study Number: 031-KOA-0703** Study Title: "A randomized, double-blind, dose-adjustment, placebo-controlled study to evaluate the efficacy and safety of Aripiprazole in children and adolescents with chronic Tic disorders or Tourette's disorder" Sample Size: 32 Abilify/29 placebo Arms: Flexibly-dosed Abilify and placebo arms Location in submission: 5.3.5.1				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 31-12-293 Indication: Treatment of (b) (4) Tourette's disorder Pivotal Study #2 031-KOA-0703 Indication: Treatment of (b) (4) Tourette's disorder	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			031-KOA-0703 was not conducted under an IND but appears to meet the requirements of 21 CFR 312.120.
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			Study 31-12-293: 92 out of 133 subjects were from the United States; Study 031-KOA-0703: All 61 subjects were from South Korea.
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess	X			ECGs have been

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?				routinely assessed in all studies.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			Safety of aripiprazole for the Tourette's disorder indication is supported by the aggregate safety database for all indications for which oral aripiprazole has been studied in children and adolescents (Tourette's disorder, schizophrenia, bipolar disorder I, and autistic disorder). In addition, Study 31-12-294 is ongoing 52-week, uncontrolled, rollover, flexible-dose study for current indication.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			031-KOA-0703: AETXT, SOC, HLGT, HLT, PT, LLT
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	This sNDA is based on studies conducted in the pediatric population, ages 6 to 18 years. Aripiprazole for the Tourette's disorder indication is an orphan drug (Orphan Designation granted 25 Jan 2006, no. 05-2079), and it is therefore exempt from the requirement to submit pediatric data or request a waiver or deferral for all pediatric subpopulations.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			Study 31-12-293: 92 out of 133 subjects were from the United States; Study 031-KOA-0703: All 61 subjects were Korean.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X*			*Initially datasets were incomplete for Study 031-KOA-0703. Listing datasets did not specify the treatment administered, and analysis datasets did not have unique subject identifiers. The applicant was notified of the problem and submitted amended datasets on 3/7/2014.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X*			
37.	Are all datasets to support the critical safety analyses available and complete?	X*			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X*			
CASE REPORT FORMS					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

None

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time

Christina P Burkhart, M.D. 3/26/2014

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

CHRISTINA P BURKHART
03/26/2014

ROBERT L LEVIN
03/26/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21436/S-38

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DATE: 20 NOV 2014

TO: NDA 21436 /S-38

THROUGH: Hasmukh Patel Ph.D., Branch Chief, ONDQA/DNDQA-1

FROM: David J. Claffey, Ph.D., CMC Lead, ONDQA/DNDQA-1

SUBJECT: CMC assessment of efficacy supplement S-38

This supplement provides for an additional indication – treatment of (b) (4) Tourette's disorder in pediatric patients ((b) (4) years). The application does not provide for any changes to the drug product, manufacturing process, or specifications and there are no CMC-related labeling changes. A claim for categorical exclusion under 21 CFR Part 25.31(b) is included in the submission. Approval of the supplement may result in expanded use of the active moiety. However, the concentration of the active moiety at the point of entry into the aquatic environment will be below 1 ppb (0.224 ppb). Therefore, the claim of categorical exclusion is accepted.

Recommend approval of this application from a CMC perspective.

David J. Claffey -S
Digitally signed by David J. Claffey -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300225565, cn=David J. Claffey -S
Date: 2014.11.20 08:05:10 -05'00'

Hasmukh B. Patel -S
Digitally signed by Hasmukh B. Patel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300068254, cn=Hasmukh B. Patel -S
Date: 2014.11.20 08:18:04 -05'00'

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

/s/

MARY GRACE LUBAO
12/23/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21436/S-38

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	21,436 S-38, Abilify Tabs
	21,866 S-23, Abilify Injection
	21,729 S-22, Abilify ODT
	21,713 S-30, Abilify Oral Solution
Drug Name:	Abilify (aripiprazole) 2 - 20 mg/day tablets
Indication:	Treatment of (b) (4) Tourette's disorder (b) (4) (b) (4)
Applicant:	Otsuka
Review Priority:	Standard
Biometrics Division:	**Division of Biometrics I**
Statistical Reviewer:	Thomas Birkner, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D. (Team leader)
	Kooros Mahjoob, Ph.D. (Deputy division director)
Medical Division:	**Division of Psychiatry Products**
Clinical Team:	Christina Burkhart, M.D.
	Mark Ritter, M.D. (Team leader)
Project Manager:	William Bender

Keywords: mixed models, LOCF, retrospective analysis

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1. EXECUTIVE SUMMARY

Otsuka's submission in support of a new indication for aripiprazole (Abilify) (i.e., treatment of [redacted] Tourette's disorder [redacted] contains two pivotal studies. Study 31-12-293 (hereafter referred to as Study 293) provides strong support for the efficacy claim given the results for the primary endpoint, the Yale Global Tic Severity Scale Total Tic Score (YGTSS TTS), and for the key secondary endpoint, the Clinical Global Impression Scale for Tourette's Syndrome Improvement (CGI-TS-I). The YGTSS TTS decreased by about six points more for the low and by ten points more for the high dose group from baseline to week 8 compared to the placebo group. The CGI-TS-I is about one point lower (i.e., better) for both the low and for the high dose groups at week 8 compared to placebo. Those results are highly statistically significant at alpha = 0.05.

Study 031-KOA-0703 (hereafter referred to as Study KOA), a non-IND study, supports efficacy based on the primary endpoint (Korean version of the YGTSS TTS). Subjects treated with aripiprazole improved on average by about five points more in their TTS compared to placebo treated patients. This result is statistically significant at alpha = 0.05. A key secondary endpoint was not pre-specified. A retrospective analysis of the CGI-TS-I score at the end of study (week 10) was not statistically significant.

The primary endpoint, YGTSS Total Tic Score, is the sum of two components (vocal and motor tics). Treatment with aripiprazole had a positive effect on both components (reviewer's analysis section 3.2.4.2). This finding led the medical division to consider granting a claim for Tourette's instead of for [redacted] as proposed by the sponsor.

This reviewer obtained the same or similar results as the sponsor for the main efficacy analyses. Study KOA used the last observation carried forward (LOCF) approach to deal with missing data for the primary analysis. This technique appears justifiable given the low drop-out rate of 11.5%. Two important observations from Study 293 are the following: On the one hand lower weight subjects (<50 kg) randomized to the high dose (10 mg/day) dropped out at a markedly higher rate (30.0%) compared to the three other groups (drop-out rates of 6.7, 0, and 7.1%). On the other hand a dose of 5 mg/day might not provide the full potential efficacy (see reviewer's analysis under section 3.2.4.2.1). The sponsor proposed label reflects this trade-off between tolerability

and efficacy by recommending a dose of 5 mg/day for patients less than 50 kg (with 10 mg/day being the maximum dose).

2. INTRODUCTION

2.1 Overview

The purpose of the studies under review was to evaluate the once-daily dosing of oral aripiprazole for the treatment of tics in children and adolescents with Tourette's disorder (TD) over an 8-week (Study 31-12-293, referred to hereafter as Study 293) or 10-week (Study 031-KOA-0703, referred to hereafter as Study KOA) period. Both studies are double-blind, randomized, placebo-controlled, parallel group studies. Study 293 was conducted predominantly at North American sites employing a fixed dose regimen (low vs. high with actual dose dependent on body weight) between November 1, 2012 and September 3, 2013. Study KOA was a non-IND study conducted only in Korea between August 18, 2008 and April 21, 2010 using a flexible dosing approach. A breakdown of the number of subjects per site is provided in the appendix (Study 293 in Table A1 and Study KOA in Table A2).

Initially Otsuka had planned to study fixed doses of 5 and 10 mg in Study 293. During a teleconference with the sponsor on October 2, 2012 the Division proposed the weight-based dosing stratification to allow for a broadening of the dosing range while maintaining the safety of the study. Otsuka accepted the proposal and amended the protocol subsequently.

Table 1. List of all Studies Included in Analysis

	Phase and Design	**Treatment Period**	**# of Subjects per Arm**	**Study Population**
31-12-293 *(referred to as Study 293)*	*Phase 3*	*8 weeks*	*Low Dose: 44* *High Dose: 45* *Placebo:44*	*Children and adolescents with Tourette's Disorder*
031-KOA-0703 *(referred to as Study KOA)*	*Phase 3*	*10 weeks*	*Aripiprazole:32* *Placebo: 29*	*Children and adolescents with Tourette's disorder*

2.1 Data Sources

The electronic location of this submission is: \\cdsesub1\evsprod\\NDA021436\0045.
The response to an information request (analysis datasets with previously missing unique subject IDs and listing dataset indicating treatment assignments) can be found at: \\cdsesub1\evsprod\NDA021436\0053.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Study 293

The initial protocol for Study 293 was issued August 13, 2012. Amendment 1 to the protocol on October 16, 2012 added the weight-based dosing stratification. The final Statistical Analysis Plan (Version 2.0) is dated September 12, 2013, a date shortly after study completion (September 3, 2013). For a graphical depiction of the randomized treatment assignment over time see Figure A1 in the appendix. No randomization issues were detected. No significant deficiencies were observed during the inspection of two sites (encompassing 25% of subjects of this trial) by FDA's Office of Scientific Investigations.

Study KOA

The initial approval of the IND protocol (version 2.0) was given by the Korean FDA on February 22, 2008. The protocol was modified before and during the conduct of the study. Change tables are provided in the study report on pages 244 to 318. Most changes appear minor from a statistical point of view. Age group was added as stratification factor during randomization before the study enrolled its first patient (p. 273). A change to a central stratification by age, instead of at the institution level was made while the study was ongoing to avoid imbalances (p. 302, 304). The original SAP was approved on June 30, 2010 with a safety analysis related amendment on September 30, 2010. The database was locked on August 17, 2010. Figure A2 in the appendix displays the randomization process over time. No apparent issues were discovered.
FDA's Office of Scientific Investigations inspected all six sites involved in the Korean Study and noted many Good Clinical Practice (GCP) deficiencies at four of the six sites. However, those

deficiencies were typically minor and isolated. "Deficiencies with potential impact on data integrity appear to be limited to two subjects: subject 09 at site 003 for inadequate subject eligibility assessment and subject 05 at site 004 for improperly corrected efficacy data on CRFs" (Clinical Inspection Summary, p. 14). However, excluding those two subjects from the efficacy analysis has hardly any impact on the results (reviewer's analysis).

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study KOA

Study KOA was a randomized, double-blind, flexible dose, placebo controlled study. The randomization list was prepared using the block randomization method stratified by the clinical trial site and the age group (children: 6-11 years; adolescents: 12-18 years).

During the 10-week double-blind treatment period subjects either received aripiprazole (2-20 mg/day) or placebo. All subjects visited the hospital every 2 weeks, and the investigator could increase the dose to the next higher level according to the improvement of Tic symptoms and the incidence of adverse events. The following doses were available: 2, 5, 10, 15 and 20 mg/day. It was not mandatory to reach the maximum dose of 20 mg/day. The investigator made the dose increase decision guided by the following criteria:

- Maintain dose if the score on the improvement of Tic symptoms scale (CGI-TS-I) is 1 or 2 and adverse events are tolerable
- Increase dose if CGI-TS-I score is ≥ 3 and adverse events are tolerable
- Reduce dose or discontinue investigational product in case of intolerable adverse events. If the dose was decreased to the previous dose, the reduced dose was maintained until the final visit.

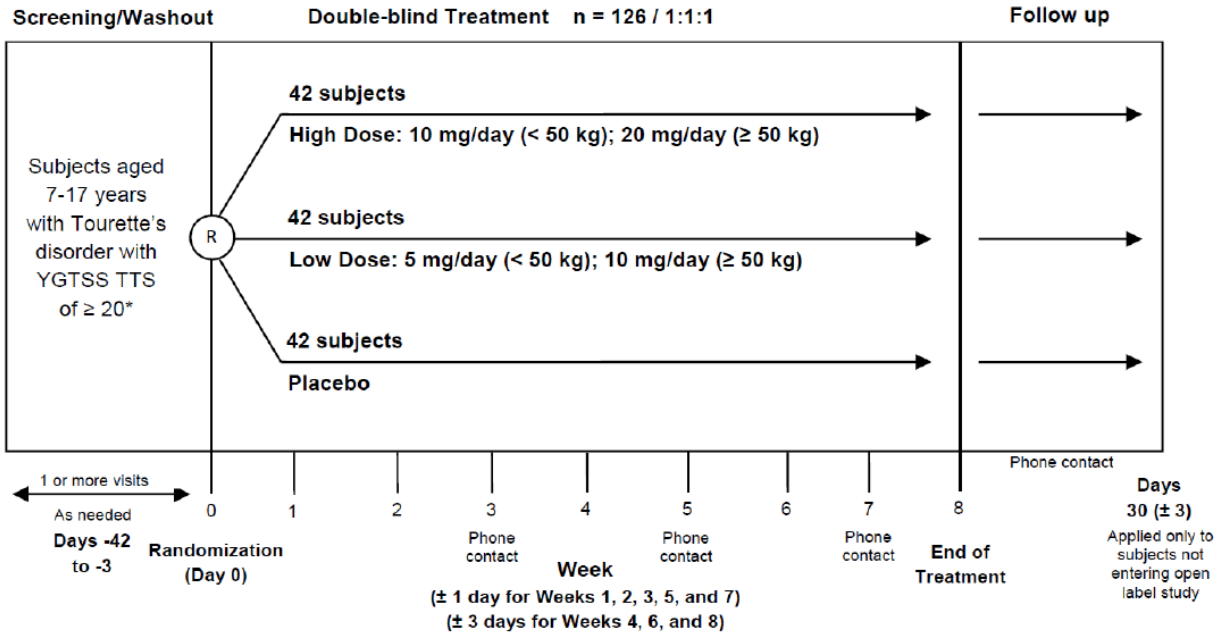
The primary efficacy outcome was the mean change in Total Tic Scores (TSS) in the Korean version of the Yale Global Tic Severity Scale (K-YGTSS). The Clinical Global Impression Tourette's Syndrome Improvement (CGI-TS-I) was assessed as part of the secondary endpoints.

Study 293

Study 293 was a multicenter, randomized, double-blind, placebo-controlled trial. After the pretreatment phase, consisting of screening and washout, subjects (male or female, 7 to 17 years of age) were randomized in a 1:1:1 ratio to low- or high-dose aripiprazole or placebo and began the 8-week double-blind treatment phase. The randomization was conducted according to a computer-generated randomization schedule stratified by region and weight group. Region was classified as North America (including US and Canada) versus Rest of the World and weight group was classified as low weight (body weight at baseline < 50 kg) versus high weight (body weight at baseline ≥ 50 kg).

All subjects randomized to the aripiprazole groups began treatment at the 2 mg/day dose, with the dose titrated to 5 mg/day after 2 days. For subjects who weighed < 50 kg at baseline, low- and high-doses of aripiprazole were 5 and 10 mg/day, respectively. For subjects who weighed ≥ 50 kg at baseline, low- and high-doses of aripiprazole were 10 and 20 mg/day, respectively. All subjects reached their randomized dose by Week 3 and should have remained on that randomized dose (one dose decrease due to tolerability issues was allowed after Week 3). Subjects visited the clinic at Weeks 1, 2, 4, 6, and 8, at which time efficacy and safety measures were taken. **Figure 1** below displays the study design.

Figure 1. Schematic of Trial Design for Study 293



(Source: Study report p. 38, *YGTSS TTS = Yale Global Tic Severity Scale Total Tic Score (0-50 score where ≥ 20 represents a moderate disease severity).

The primary efficacy endpoint of this trial was the change from baseline to Week 8 in the Yale Global Tic Severity Scale (YGTSS) total tic score (TTS). The YGTSS is a semi-structured clinical interview designed to measure current (time frame of the past 1 week) tic severity. This scale consists of a tic inventory, with 5 separate rating scales to rate the severity of symptoms, and an impairment ranking. Ratings are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics each, including number, frequency, intensity, complexity, and interference. Summation of these 10 scores provides a TTS (range 0-50), the primary outcome measure in this trial. The YGTSS ranking of impairment, also with a maximum of 50 points, is based on the impact of the tic disorder on areas of self-esteem, family-life, social acceptance, and school scores. The Total YGTSS Score (summation of TTS and impairment score) was not considered for the primary or key secondary efficacy assessment, but was analyzed as supportive analysis (see study report p. 93-94).

The key secondary efficacy endpoint was the Clinical Global Impressions Scale-Tourette's Syndrome Improvement Score (CGI-TS-I) at endpoint. The rater or investigator rated the subject's total improvement whether or not it was due to drug treatment. All responses were compared to the subject's condition at baseline (Day 0). Response choices included: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The results of a supportive analysis of the Change from Baseline to Week 8 in the CGI-TS Severity Score are included on p. 94 of the study report.

3.2.2 Statistical Methodologies

Study 293

The following analysis sets were defined for this trial: Intent-to-Treat (ITT) sample: All subjects randomly assigned to the double-blind treatment. The ITT set was the primary data set for all efficacy analyses. Per-Protocol (PP) sample: All subjects randomized to the double-blind treatment and with no major protocol violations.

Primary Efficacy Endpoint [Study 293]

The primary efficacy endpoint was the mean change from baseline to endpoint (Week 8) in the YGTSS TTS. A total of two null hypotheses were tested for the primary endpoint, aripiprazole low dose group versus placebo and aripiprazole high dose group versus placebo. The statistical comparison to placebo was performed using a mixed model repeated measures (MMRM) linear model with terms of treatment (aripiprazole low dose, aripiprazole high dose, or placebo), region, body weight group, and visit week as factors. Also included were the baseline YGTSS TTS as a covariate and the treatment-by-week interaction term. An unstructured covariance matrix was assumed for all treatment arms. Restricted maximum likelihood estimates (REML), 2-sided 95% confidence intervals (CIs) and p-values (using the Kenward-Roger degrees of freedom) from the MMRM inference on the ITT sample were obtained for the Week 8 treatment difference between each aripiprazole dose group and placebo.

MMRM analysis of the primary endpoint was also performed for the Per-Protocol Sample secondary analysis. Subjects without any post-baseline measurement of YGTSS TTS were not included in the MMRM analysis. However, such subjects were analyzed with their imputed post-baseline data in the sensitivity analyses assuming a missing not at random (MNAR) mechanism.

Sensitivity Analyses for the Primary Endpoint [Study 293]

Sensitivity analyses assuming MNAR of the primary endpoint were carried out by multiple imputation for the ITT sample. Intermittent missing values were imputed 100 times using the MCMC method in PROC MI with an IMPUTE = MONOTONE statement. The resulting 100 partially imputed datasets were further imputed under an MNAR assumption that the missing data pattern of aripiprazole subjects are similar to, worse than, or better than those of placebo subjects with similar observed outcomes for the following two scenarios:

(1) MNAR assumed for missing values resulting from discontinuation due to lack of efficacy (LOE) and AEs in the aripiprazole groups and MAR for others, and

(2) MNAR assumed for missing values resulting from discontinuation due to any reason in the aripiprazole groups and MAR for others (SAP p. 20-21).

Key Secondary Efficacy Endpoint [Study 293]

The key secondary efficacy endpoint was CGI-TS-I Score at Week 8 (obtained from the CGI-TS improvement scale assessment). The key secondary endpoint was analyzed using a similar method as described for the primary efficacy endpoint. Since CGI-TS-I Score was not measured at baseline, the baseline CGI-TS Severity Score was included in the MMRM model as a covariate.

Multiplicity

Multiple comparisons of primary and key secondary efficacy endpoints were accounted for by using a serial gatekeeping approach where families of null hypotheses were tested in a sequential manner. The comparisons of the primary endpoint (YGTSS TTS) and the key secondary endpoint (CGI-TS-I Score) formed two families of null hypotheses. The two null hypotheses (aripiprazole low dose versus placebo and aripiprazole high dose versus placebo) in the first family were tested with p-values adjusted by the Hochberg procedure, and both of the two hypotheses in this family must have been rejected at the 5% (2-sided) significance level to test the second family. If both hypotheses involving the primary endpoint were rejected, the Hochberg procedure was used to adjust p-values of testing the two hypotheses for the key secondary endpoint in order to control the overall type I error rate.

Study KOA

The efficacy analysis was carried out on the following three populations: The Intent-To-Treat (ITT) population consisting of all randomized subjects, the Full Analysis Set (FAS) population defined as the subjects who took investigational product at least once and had evaluable primary efficacy data, and the Per-Protocol (PP) population including all FAS subjects who completed the study without major protocol violations. The ITT population was the primary set used for efficacy analysis.

A two-sample t-test was employed as primary analysis to evaluate the difference in change of K-YGTSS Total Tic Score from baseline to the final visit between treatment groups. An ANCOVA adjusting for baseline total tic score, age group and study site was conducted as supportive analysis. An MMRM analysis not pre-specified in the protocol or SAP was also performed as supportive analysis.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The inclusion criteria are not identical between Study KOA and Study 293. One difference is the threshold in the baseline total tic score (TTS) to be eligible for the studies: Study KOA TTS ≥ 22 and Study 293 TTS ≥ 20. However, only 5 out of 133 subjects have a score of 20 or 21 in Study 293. Hence this theoretical difference does not translate into any meaningful practical difference between the two studies.

Study 293

A total of 171 subjects were screened for Study 293 (see **Table 2** below). Of the 133 subjects randomized 119 (89.5%) completed the trial. Reasons for discontinuations were adverse events (8 subjects), consent withdrawal (4 subjects), and protocol deviations (2 subjects). The sample sizes of the three treatment groups (i.e., aripiprazole low and high, and placebo) were about the same with 44 to 45 subjects each. Roughly two thirds of the subjects in each of the aripiprazole arms fell into the lower weight (<50 kg) strata.

Table 2. Subject Disposition [Study 293]

	Aripiprazole Low Dose			Aripiprazole High Dose			Placebo	Total
Subjects	**5 mg (< 50 kg)**	**10 mg (≥ 50 kg)**	**Total**	**10 mg (< 50 kg)**	**20 mg (≥ 50 kg)**	**Total**		
Number (%) of Subjects	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Screened								171
Screen Failure								38
Randomized	28 (100.0)	16 (100.0)	44 (100.0)	30 (100.0)	15 (100.0)	45 (100.0)	44 (100.0)	133 (100.0)
Completed[a]	26 (92.9)	16 (100.0)	42 (95.5)	21 (70.0)	14 (93.3)	35 (77.8)	42 (95.5)	119 (89.5)
Discontinued	2 (7.1)	0 (0.0)	2 (4.5)	9 (30.0)	1 (6.7)	10 (22.2)	2 (4.5)	14 (10.5)
Analyzed for Safety[b]	28 (100.0)	16 (100.0)	44 (100.0)	30 (100.0)	15 (100.0)	45 (100.0)	44 (100.0)	133 (100.0)
Analyzed for Efficacy[c]	28 (100.0)	16 (100.0)	44 (100.0)	30 (100.0)	15 (100.0)	45 (100.0)	44 (100.0)	133 (100.0)

Note: Percentages were based on the number of subjects randomized.
[a]Subjects who completed the Week 8 Visit
[b]Subjects receiving at least 1 dose of IMP were included in the safety analysis.
[c]All subjects in the ITT Sample (ie, all randomized subjects)

(Source: Study report p. 77)

Note the comparably high proportion of discontinuations (9/30) in the lower weight strata of the Arip-high group (6 of those 9 discontinued due to an adverse event, 3 withdrew consent). Figure A3 in the appendix takes a closer look at the primary efficacy measure until drop-out for the nine lower weight subjects who discontinued from the Arip-high group. Table A3 in appendix provides average and total doses by treatment assignment and weight strata.

Baseline demographic characteristics (**Table 3**) were overall similar between all treatment groups. Baseline body weight was slightly lower (by roughly 3 kg) in the low dose Aripiprazole group.

Table 3. Demographic Characteristics – ITT [Study 293]

Demographic Characteristics	Aripiprazole Low Dose (5 and 10 mg) (N = 44)	Aripiprazole High Dose (10 and 20 mg) (N = 45)	Placebo (N = 44)
Age (years)			
n	44	45	44
Mean (SD)	11.1 (3.1)	11.8 (2.8)	11.6 (2.8)
Median	11.0	12.0	12.0
Min, Max	7.0, 17.0	7.0, 17.0	7.0, 17.0
Age Group[a]			
7 to 12 years	30 (68.2)	28 (62.2)	27 (61.4)
13 to 17 years	14 (31.8)	17 (37.8)	17 (38.6)
Sex [n (%)]			
n	44	45	44
Male	36 (81.8)	35 (77.8)	33 (75.0)
Female	8 (18.2)	10 (22.2)	11 (25.0)
Race [n (%)][a]			
White	38 (86.4)	39 (86.7)	39 (88.6)
Black or African American	6 (13.6)	1 (2.2)	4 (9.1)
American Indian or Alaska Native	0 (0.0)	1 (2.2)	0 (0.0)
Asian	0 (0.0)	3 (6.7)	0 (0.0)
Other	0 (0.0)	1 (2.2)	1 (2.3)
Ethnicity [n (%)][a]			
Hispanic or Latino	5 (11.4)	1 (2.2)	4 (9.1)
Not Hispanic or Latino	39 (88.6)	44 (97.8)	39 (88.6)
Unknown	0 (0.0)	0 (0.0)	1 (2.3)
Height (cm)			
n	44	45	44
Mean (SD)	147.9 (18.5)	149.3 (17.7)	150.7 (16.5)
Median	147.5	150.0	150.0
Min, Max	106.0, 185.0	115.0, 182.0	113.0, 197.0
Weight (kg)			
n	44	45	44
Mean (SD)	44.2 (16.0)	47.4 (20.1)	47.8 (21.8)
Median	41.2	42.4	41.1
Min, Max	20.5, 77.6	19.7, 96.4	19.0, 135.0
Weight Group[a]			
< 50 kg	28 (63.6)	30 (66.7)	29 (65.9)
≥ 50 kg	16 (36.4)	15 (33.3)	15 (34.1)
Body Mass Index (kg/m^2)			
n	44	45	44
Mean (SD)	19.5 (3.6)	20.3 (4.8)	20.1 (5.1)
Median	18.7	18.8	18.6
Min, Max	12.9, 28.2	13.6, 32.6	11.8, 34.8

Max = maximum; Min = minimum.
[a]Percentages were based on the number of subjects randomized.
(Source: Study report p. 81)

Baseline measures of the primary and key secondary endpoints were similar across the three treatment groups (**Table 4**).

Table 4. Other Baseline Characteristics – ITT [Study 293]

Baseline Characteristics	Aripiprazole Low Dose (5 and 10 mg) (N = 44)	Aripiprazole High Dose (10 and 20 mg) (N = 45)	Placebo (N = 44)
Total Tic Severity Score			
n	44	45	44
Mean (SD)	29.2 (5.6)	31.2 (6.4)	30.7 (6.0)
Median	28.0	31.0	29.0
Min, Max	21.0, 42.0	20.0, 47.0	20.0, 44.0
Total Motor Tic Severity Score			
n	44	45	44
Mean (SD)	16.5 (3.3)	17.6 (2.8)	17.0 (3.4)
Median	15.0	17.0	17.0
Min, Max	12.0, 23.0	11.0, 24.0	10.0, 24.0
Total Vocal Tic Severity Score			
n	44	45	44
Mean (SD)	12.7 (3.7)	13.6 (4.7)	13.8 (4.1)
Median	13.0	14.0	13.0
Min, Max	0.0, 21.0	3.0, 24.0	5.0, 22.0
CGI-TS Severity Score			
n	44	45	43
Mean (SD)	4.3 (0.6)	4.1 (1.1)	4.2 (0.9)
Median	4.0	4.0	4.0
Min, Max	3.0, 6.0	1.0, 6.0	1.0, 6.0

Max = maximum; Min = minimum.
(Source: Study report p. 82)

Study KOA

Of the 83 subjects screened for the Korean study 61 were randomized and 54 (88.5%) completed the trial (**Table 5**).

Table 5. Subject Disposition [Study KOA]

	Placebo	Aripiprazole	Total
Number (%) of Subjects	N (%)	N (%)	N (%)
Screened			83
Screen Failure			22
Randomized	29 (100.0)	32 (100.0)	61 (100.0)
FAS	29 (100.0)	31* (96.9)	60 (98.4)
Completed	25 (86.2)	29 (90.6)	54 (88.5)
Discontinued	4 (13.8)	3 (9.4)	7 (11.5)

PPS	21 (72.4)	23 (71.9)	44 (72.1)

*One Subject not treated and not included in FAS

Demographic and other baseline characteristics (**Table 6**) in Study KOA are similar between the treatment groups, with a moderate difference in mean body weight explainable by a small number of heavier subjects in the aripiprazole group (median weights are similar).

Table 6. Demographic and Other Baseline Characteristics – ITT [Study KOA]

Item	Statistic	Placebo	Aripiprazole	Total
Number of subjects in ITT population		29	32	61
Age (years)	N	29	32	61
	Mean (SD)	10.9 (3.0)	11.0 (2.5)	11.0 (2.7)
	Median	11.0	11.0	11.0
	Min, Max	6.0, 17.0	6.0, 18.0	6.0, 18.0
Height (cm)	N	29	32	61
	Mean (SD)	144.3 (15.2)	149.4 (15.1)	146.9 (15.2)
	Median	139.8	149.4	147.3
	Min, Max	119.5, 179.5	120.1, 178.1	119.5, 179.5
Weight (kg)	N	29	32	61
	Mean (SD)	41.5 (14.7)	46.2 (17.0)	43.9 (16.0)
	Median	38.7	40.0	40.0
	Min, Max	19.2, 76.2	25.2, 114.6	19.2, 114.6
Sex Male	N (%)	23 (79.3)	30 (93.8)	53 (86.9)
Female	N (%)	6 (20.7)	2 (6.3)	8 (13.1)
Total Tic Severity Score	N	29	32	61
	Mean (SD)	29.5 (5.6)	28.3 (5.5)	28.9 (5.5)
	Median	29.0	27.5	28.0
	Min, Max	22.0, 44.0	22.0, 46.0	22.0, 46.0
Total Motor Tic Severity Score	N	28	33	61
	Mean (SD)	17.4 (3.3)	15.9 (3.9)	16.6 (3.7)
	Median	17.5	16.0	17.0
	Min, Max	9.0, 25.0	7.0, 25.0	7.0, 25.0
Total Vocal Tic Severity Score	N	28	33	61
	Mean (SD)	12.1 (4.4)	12.5 (3.6)	12.3 (4.0)
	Median	12.5	13.0	13.0
	Min, Max	5.0, 22.0	5.0, 21.0	5.0, 22.0
CGI-TS Severity Score	N	29	32	61
	Mean (SD)	4.7 (0.8)	4.5 (0.8)	4.6 (0.8)
	Median	5.0	4.0	5.0
	Min, Max	4.0, 7.0	3.0, 7.0	3.0, 7.0

(Source: Study report p. 51, 64 and Reviewer's own computations; Note slight discrepancy between number of subjects per treatment group for "Total Tic Severity Score" and the number of subjects for the component scores. Probable reason: Requested dataset "rndliste" to merge in the treatment assignments to the listing datasets (by ID) has 33 subjects in Aripiprazole group and 28 in Placebo group (in the study report there are 32 subjects randomized to Aripiprazole and 29 to placebo). The treatment variable in Rndliste seems to indicate actual treatment received vs. treatment subject was randomized to [one subject was randomized to placebo, but received Aripiprazole].)

3.2.4 Results and Conclusions

3.2.4.1 Sponsor's Results

3.2.4.1.1 Study 293

Primary Endpoint (Change in YGTSS TTS at Week 8)

The treatment difference of -6.26 at week 8 between the low-dose aripiprazole and placebo group in YGTSS TTS is statistically significant (p = 0.002); the treatment difference of -9.85 at week 8 between the high-dose aripiprazole and placebo group is also statistically significant (p<0.0001), based on the mixed effect repeated measure model (**Table 7**).

Table 7. Change from Baseline to Week 8 in YGTSS TTS (MMRM) – ITT [Study 293]

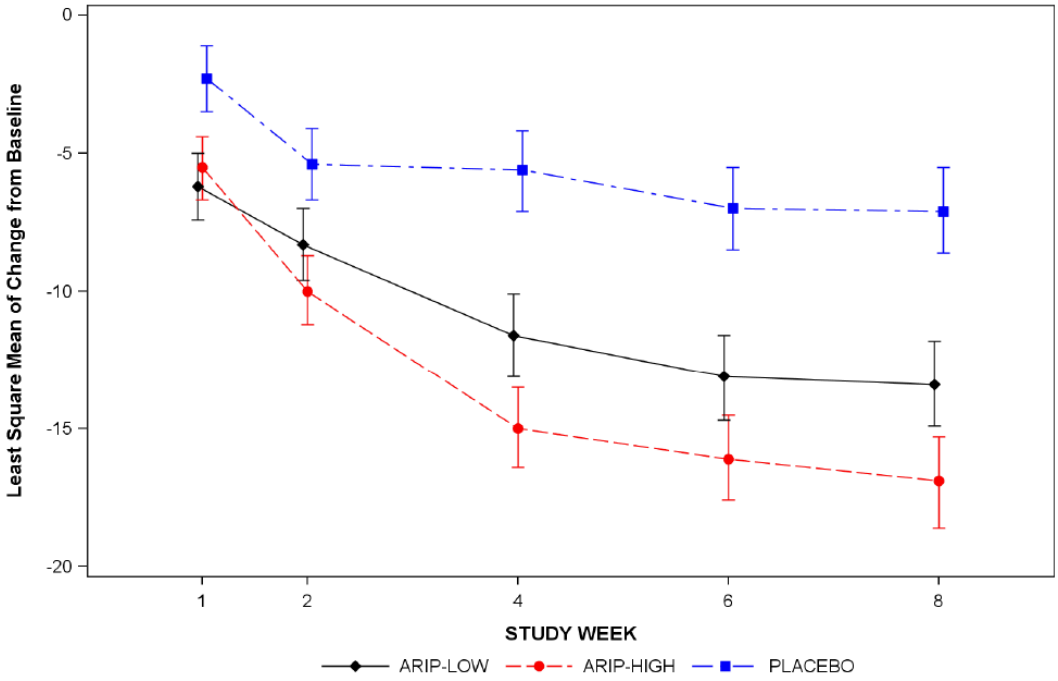
					Treatment Difference			
						95% CI[b]		
Treatment Group	N[a]	BL Mean	LS Mean[b]	LS Mean SE[b]	Estimate[b]	Lower limit	Upper Limit	P-Value[b]
Aripiprazole Low	42	29.3	-13.35	1.59	-6.26	-10.18	-2.34	0.0020
Aripiprazole High	35	31.5	-16.94	1.61	-9.85	-13.84	-5.86	<.0001
Placebo	42	30.3	-7.09	1.55				

BL = baseline; LS = least squares; SE = standard error.
Note: Total tic score ranged from 0 to 50 with higher score for more severe symptom (larger reduction from baseline for greater improvement.
[a]Number of subjects with baseline and a Week-8 assessment of the given variable.
[b]Derived from a repeated measures linear model with treatment, week, treatment by week interaction, region, and weight group as fixed categorical effects; the baseline value as a fixed covariate; and week as the time variable for repeated measures.
(Source: Study report p. 84; Results confirmed by reviewer)

Note that the MMRM analysis is based on 132 subjects. The N column in Table 7 displays the counts of subjects who had a baseline and week 8 assessment. The counts when including all subjects that contributed to the analysis are 44, 44, and 44 for low, high, placebo groups.

A treatment difference as measured by the YGTSS TTS between the aripiprazole and placebo groups was observable as early as week 1 (**Figure 2**). The high-dose aripiprazole group demonstrated a numerically greater treatment effect than the low-dose aripiprazole group beginning at week 2.

Figure 2. LS Mean Changes from Baseline in YGTSS TTS Score by Week (MMRM) – ITT [Study 293]



(Source: Study report p. 85; Error bars are least square means ± 1 standard error)

An exploration of the two components (motor and vocal) of the YGTSS TTS score is provided in the reviewer's analysis section 3.2.4.2.1. A figure displaying the mean observed YGTSS TTS scores (vs. change scores as in **Figure 2** above) over the duration of the study can be found there as well (Figure 5).

Key Secondary Endpoint (CGI-TS-I Score at Week 8)

The treatment differences between the low-dose aripiprazole and placebo group and between the high-dose aripiprazole and placebo group were statistically significant (estimated differences of -1.03 with p = 0.0001 and -1.02 with p = 0.0002 respectively) at Week 8 (**Table 8**).

Table 8. CGI-TS-I Score at Week 8 (MMRM) – ITT [Study 293]

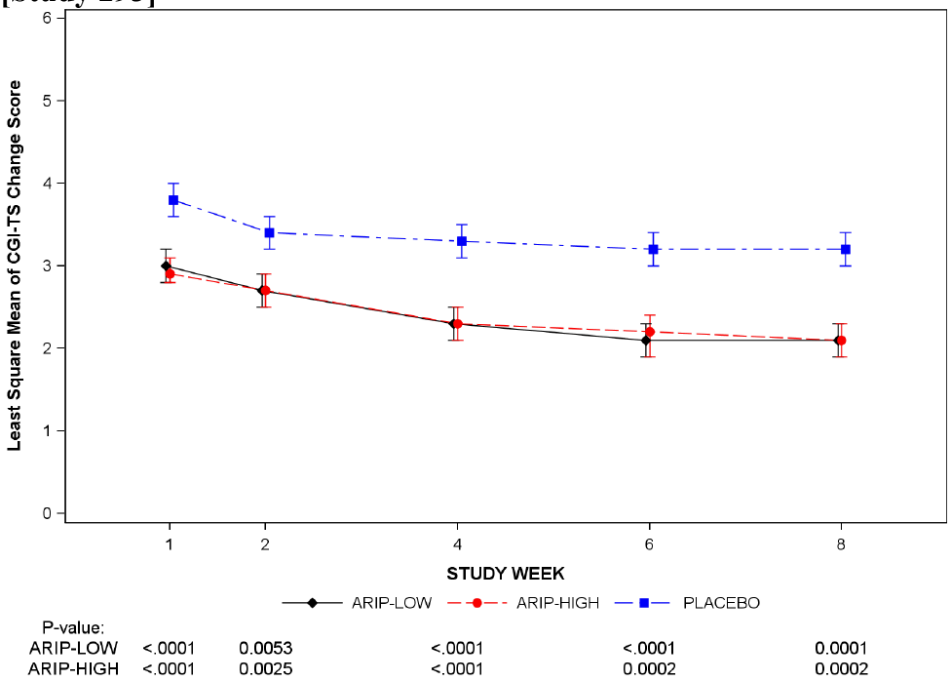
Treatment Group	N[a]	LS Mean[b]	LS Mean SE[b]	Estimate[b]	95% CI[b]		P-Value[b]
					Lower limit	Upper Limit	
Aripiprazole Low	42	2.12	0.21	-1.03	-1.54	-0.52	0.0001
Aripiprazole High	35	2.13	0.21	-1.02	-1.54	-0.49	0.0002
Placebo	42	3.15	0.20				

LS = least squares; SE = standard error.
Note: CGI Change Score (obtained from CGI-TS improvement scale) ranged from 1 to 7 with lower score for better improvement.
[a]Number of subjects with baseline and a Week-8 assessment of the given variable.
[b]Derived from a repeated measures linear model with treatment, week, treatment by week interaction, region, and weight group as fixed categorical effects; the baseline CGI-TS Severity Score as a fixed covariate, and week as the time variable for repeated measures.
(Source: Study report p. 90; Results confirmed by reviewer)

Note that the CGI-TS-I analysis was conducted on data from 131 patients (the "N" column in **Table 8** only lists subjects with a baseline and week-8 assessment).

A treatment difference between the aripiprazole groups and the placebo group was observed from Week 1 through Week 8 (**Figure 3**). There was no separation between the low- and high-dose aripiprazole groups with respect to the CGI-TS improvement scores at any assessment time in the trial.

Figure 3. LS Mean Changes from Baseline in CGI-TS Score by Week (MMRM) – ITT [Study 293]



(Source: Study report p. 90)

Sponsor's Supportive Analyses for Primary Endpoint [Study 293]

ITT Sample (ANCOVA with LOCF)

The ANCOVA model included treatment, region, and weight group as factors and the baseline value as a covariate. The estimated treatment differences to placebo for the change from baseline in YGTSS TTS at Week 8 are -6.47 for the low dose and -8.39 for the high dose aripiprazole groups (study report p. 193).

ITT Sample (ANCOVA with Observed Cases)

The ANCOVA estimates of the treatment difference to placebo in YGTSS TTS at Week 8 based on the observed cases (i.e., baseline and week 8 data available) are -6.31 for the low dose aripiprazole group and -9.17 for the high dose group (study report p. 194).

Per-Protocol Population

Using the same MMRM model as in the primary analysis the estimated treatment difference to placebo in the change from baseline to Week 8 in YGTSS TTS is -5.88 (low dose) and -10.45 (high dose) for the per-protocol population (study report p. 192).

The estimates of treatment effect from all three supportive analyses are similar to the primary analysis results (i.e., -6.26 for low dose and -9.85 for high dose).

Sponsor's Sensitivity Analyses for Primary Endpoint [Study 293]:

Data Missing Not at Random

Sensitivity analyses were performed for the primary efficacy variable to address a concern about the missingness mechanism being not missing at random. The conclusions of the primary analysis remained unchanged within a sensible range of the sensitivity parameter regardless of the subset of drop-outs for which MNAR imputation was performed (data was imputed for aripiprazole subjects (a) who had discontinued due to an adverse event or lack of efficacy or (b) discontinued due to any reason [study report p. 86]). This should not be too surprising given the completion rate of 89.5% in this study.

Step down dose

A total of seven subjects stepped down to the dose level immediately below their randomized dose: four subjects randomized to receive 10 mg and one subject randomized to receive 20 mg in the high-dose aripiprazole group; and one subject each, randomized to receive 5 and 10 mg in the low-dose aripiprazole group. The results of a sensitivity analysis analyzing the seven subjects according to the dose to which they were stepped down to were very similar to the primary analysis results [study report p. 86].

3.2.4.1.2 Study KOA

Primary analysis

The mean TTS decreased from 29.5 at baseline to 19.9 at week 10 for the placebo group (-9.6) and from 28.5 to 13.6 for the aripiprazole group (-15.0). The difference in change from baseline at week 10 between active and placebo is roughly 5.4 points, a statistically significant difference in favor of aripiprazole.

Table 9. Change from Baseline to Week 10 in K-YGTSS TTS (LOCF) – ITT [Study KOA]

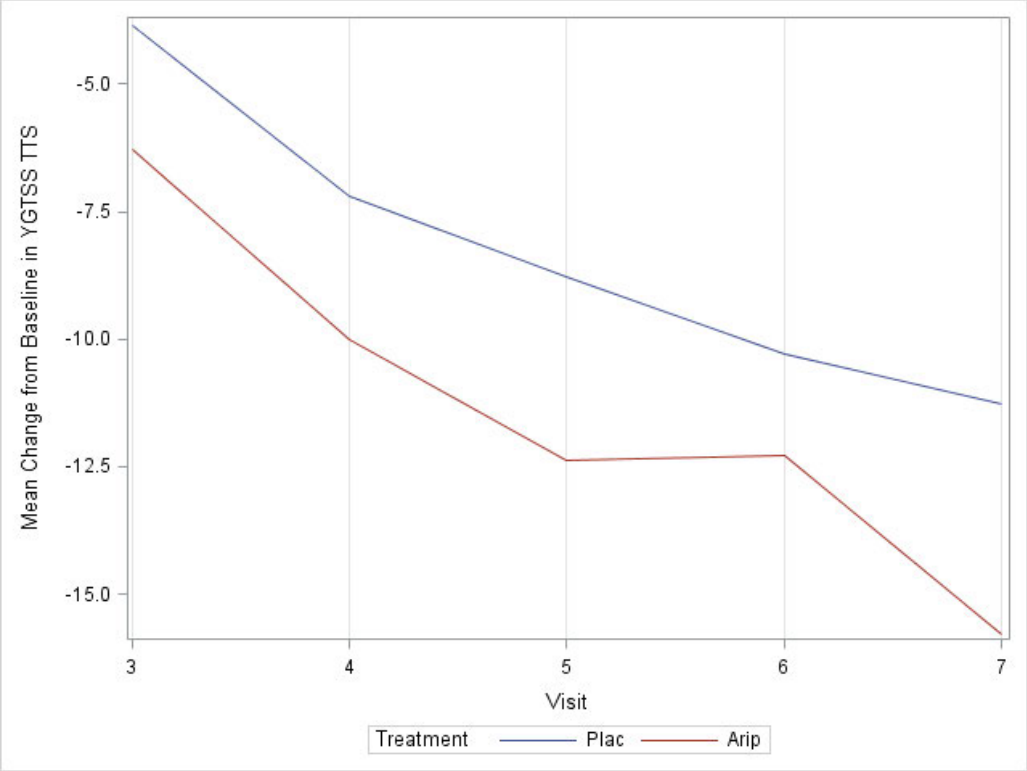
Treatment Group	N	BL Mean	Mean Change	Estimate of Treatment Effect	P-Value
Aripiprazole	32	28.3	-14.97	-5.35	0.0196
Placebo	29	29.5	-9.62		

(Source: Study report p. 59; p-value from two-sample t-test; Results confirmed by reviewer; Note that one subject randomized to aripiprazole dropped out after having the baseline visit only [never received aripiprazole], this subject contributed to the baseline mean value for the ITT population; However, the mean change was calculated without this subject. Baseline values were not carried forward in accordance with the SAP.)

Note that the results in **Table 9** above (primary analysis) are based on the observed data plus LOCF imputation. Also note that the observed decrease from baseline in the K-YGTSS TTS of roughly 10 points for the placebo subjects is far larger than the decrease of 2 points assumed for the sample size calculation.

The mean change from baseline in K-YGTSS TTS over the course of the 10 week study based on observed data only (no imputation) is displayed in **Figure 4** below by treatment group. The trajectories of the mean total tic scores (TTS) over the duration of the study are presented in Figure 10.

Figure 4. Mean Change from Baseline in K-YGTSS TTS Score by Week (Observed values) – ITT [Study KOA]



(Source: Reviewer, compare to Figure 10.1 (p. 59) in Study report)

Sponsor's <u>Supportive</u> Analyses for Primary Endpoint [Study KOA]:

Otsuka conducted several supportive analyses. Table 10 displays the primary endpoint results for the observed data without any imputation of missing data. The treatment effect estimate is about one point smaller.

Table 10. Change from Baseline to Week 10 in K-YGTSS TTS (Observed values) – ITT [Study KOA]

Treatment Group	N	BL Mean	Mean Change	Estimate of Treatment Effect	P-Value
Aripiprazole	29	28.3	-15.79	-4.51	0.0462
Placebo	25	29.5	-11.28		

(Source: Table 13.7 study report [p. 89]; Results confirmed by reviewer)

The treatment effect estimate from an analysis adjusting for age group, study site, and K-YGTSS TTS baseline is very similar to the estimate from the primary analysis (**Table 11**).

Table 11. Change from Baseline to Week 10 in K-YGTSS TTS (ANCOVA LOCF) – ITT [Study KOA]

					Treatment Difference			
Treatment Group	N	BL Mean	LS Mean	LS Mean SE	Estimate	95% CI		P-Value
						Lower limit	Upper limit	
Aripiprazole	32	28.3	-14.51	1.61	-5.17	-9.72	-0.61	0.0269
Placebo	29	29.5	-9.34	1.66				

(ANCOVA with age group, study site and baseline as predictors; Note that age group and study site were included in the model though they were both not significant. ANCOVA LOCF p-value provided on p. 88 of study report and confirmed by reviewer)

An analysis on the per protocol set also results in a treatment effect estimate favoring aripiprazole, albeit roughly two points smaller compared to the primary analysis (**Table 12**). This estimate does not reach statistical significance at alpha = 0.05, mainly due to the decrease in sample size.

Table 12. Change from Baseline to Week 10 in K-YGTSS TTS – Per Protocol Set [Study KOA]

Treatment Group	N	BL Mean	Mean Change	Estimate of Treatment Effect	P-Value
Aripiprazole	23	28.4	-14.48	-3.53	0.1427
Placebo	21	28.2	-10.95		

(Source: Table 10.12 study report [p. 59])

Supplemental report

Per request of the Korean FDA the sponsor conducted an analysis excluding five additionally randomized subjects (above sample size target) and two subjects with major protocol violations (new n = 53). The estimated difference in change in TTS between aripiprazole and placebo at Week 10 for this modified analysis set with a value of -5.63 is similar to the estimate from the primary analysis set (-5.35).

Sponsor MMRM for KOA

In the summary of clinical effectiveness the sponsor presents results from a post-hoc MMRM model as supportive analysis (recall that MMRM is the primary analysis in Study 293). The treatment effect estimated using this model with a value of -4.63 is very similar to the effect

estimated by the pre-specified primary analysis. The p-value of 0.04 is somewhat larger. This reviewer obtained similar results when running this analysis.

Table 13. Change from Baseline to Week 10 in K-YGTSS TTS (MMRM) – ITT [Study KOA]

					Treatment Difference			
Treatment Group	N	BL Mean	LS Mean	LS Mean SE	Estimate	95% CI		P-Value
						Lower limit	Upper limit	
Aripiprazole	29	28.1	-15.86	1.48	-4.63	-9.00	-0.25	0.0386
Placebo	25	28.8	-11.23	1.60				

(MMRM Model with treatment, week, and treatment-by-week interaction as fixed effects, baseline as a covariate, and week as the time variable for repeated measures; Source: Summary of Clinical Effectiveness p. 33; Reviewer obtained similar results)

The summary of clinical effectiveness also includes the results of a retrospective analysis of the Clinical Global Impression Scale for Tourette's Improvement (CGI-TS-I). This assessment was conducted in the Korean Study, but had not been pre-specified as a key secondary endpoint. Aripiprazole subjects experienced numerically a somewhat greater improvement on average compared to the placebo subjects (**Table 14**); the difference however is small (but similar to Study 293) and not statistically significant at the week 10 endpoint (nor the week 8 visit).

Table 14. Retrospective Analysis of CGI-TS-I Change Score at Week 10 (MMRM) – ITT [Study KOA]

					Treatment Difference			
Treatment Group	N	BL Mean	LS Mean	LS Mean SE	Estimate	95% CI		P-Value
						Lower limit	Upper limit	
Aripiprazole	29	4.5	2.21	0.24	-0.61	-1.30	-0.07	0.0780
Placebo	25	4.6	2.82	0.24				

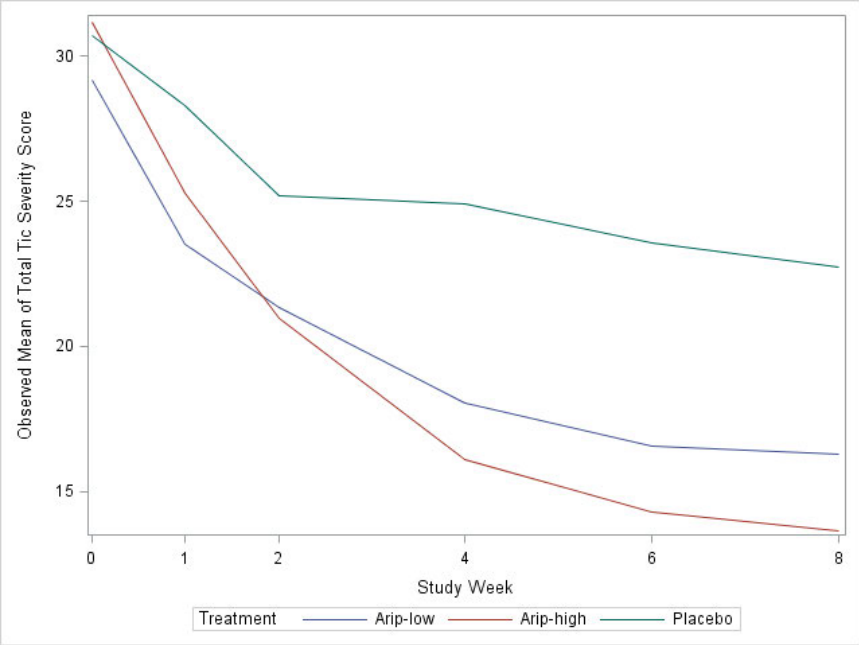
(Source: Summary of Clinical Effectiveness p. 37, Reviewer obtained similar results; Improvement Score [CGI-TS-I] is dependent variable)

3.2.4.2 Reviewer's Analyses

3.2.4.2.1 Study 293

The average YGTSS TTS scores based on the observed data are displayed in **Figure 5**. The baseline (week 8) average scores are 30.7 (22.7) for the placebo, 29.2 (16.3) for the arip-low and 31.2 (13.6) for the arip-high arm.

Figure 5. Mean YGTSS TTS by Treatment Group (observed) – ITT [Study 293]



(Source: Reviewer)

Motor versus Vocal Tics

The YGTSS Total Tic Score is the sum of two components: motor and vocal tics. The score for both components is within the range of 0 to 25 each. Note that in Study 293 the mean baseline total motor tic score with a value of 17.0 is somewhat larger compared to the mean baseline total vocal tic score with a value of 13.4. It is of interest to assess whether both types of tics are affected by the treatment. Figure 6 and Figure 7 below display the estimated change from baseline in YGTSS total motor and total vocal tic scores derived by using the primary analysis model (MMRM) on both tic score components separately. Table 15 and Table 16 provide the model estimates. Both low and high dose aripiprazole groups separate numerically in both

components from placebo, with the high dose group exhibiting a greater degree of separation for both motor and vocal tics. The estimated treatment differences to placebo in the total motor tic score at Week 8 for the high and low dose aripiprazole groups are -5.32 and -4.04 respectively. For the total vocal tic score the estimated differences to placebo at Week 8 are -4.45 (high dose) and -2.13 (low dose). Figures A8 through A11 in the appendix provide the average observed total and change scores by visit for the motor and vocal tics. The observed and estimated change scores are very similar.

Table 15. Change from Baseline to Week 8 in YGTSS Total Motor Tic Score (MMRM) – ITT [Study 293]

Treatment Group	N	BL Mean	LS Mean Change	LS Mean Change SE	Treatment Difference		
					Estimate	95% CI	
						Lower Limit	Upper Limit
Aripiprazole Low	44	16.5	-6.73	0.85	-4.04	-6.15	-1.93
Aripiprazole High	44	17.6	-8.01	0.87	-5.32	-7.47	-3.16
Placebo	44	17.0	-2.69	0.83			

(Source: Reviewer)

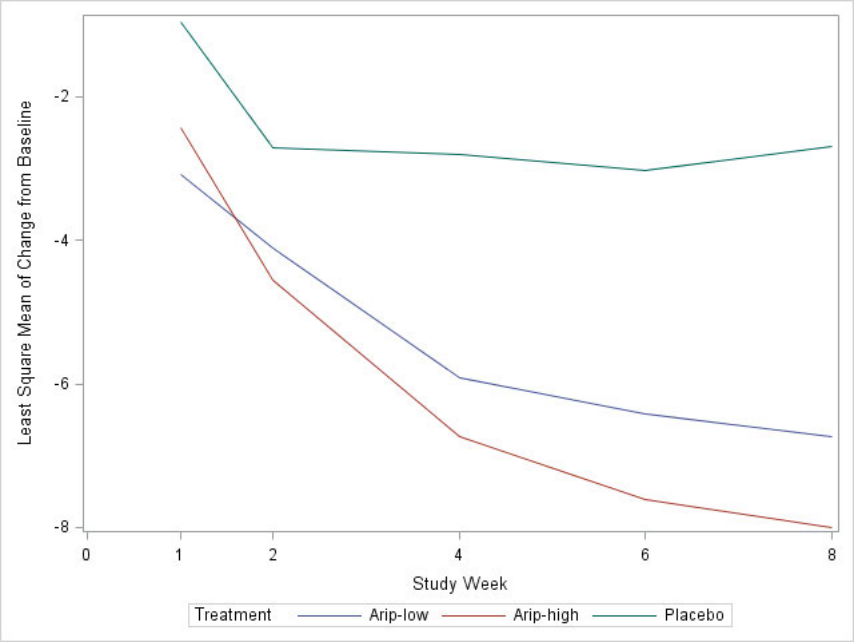
Aripiprazole at both doses reduces the total motor tic score over an eight week course of treatment more than placebo. The same applies for the total vocal score. However, placebo treatment appears to decrease the total vocal score more than it decreases the total motor score. This results in a lower treatment effect estimate for the vocal tic compared to the motor tic component.

Table 16. Change from Baseline to Week 8 in YGTSS Total Vocal Tic Score (MMRM) – ITT [Study 293]

Treatment Group	N	BL Mean	LS Mean Change	LS Mean Change SE	Treatment Difference		
					Estimate	95% CI	
						Lower Limit	Upper Limit
Aripiprazole Low	44	12.7	-6.58	0.90	-2.13	-4.33	0.06
Aripiprazole High	44	13.6	-8.90	0.91	-4.45	-6.68	-2.22
Placebo	44	13.8	-4.45	0.87			

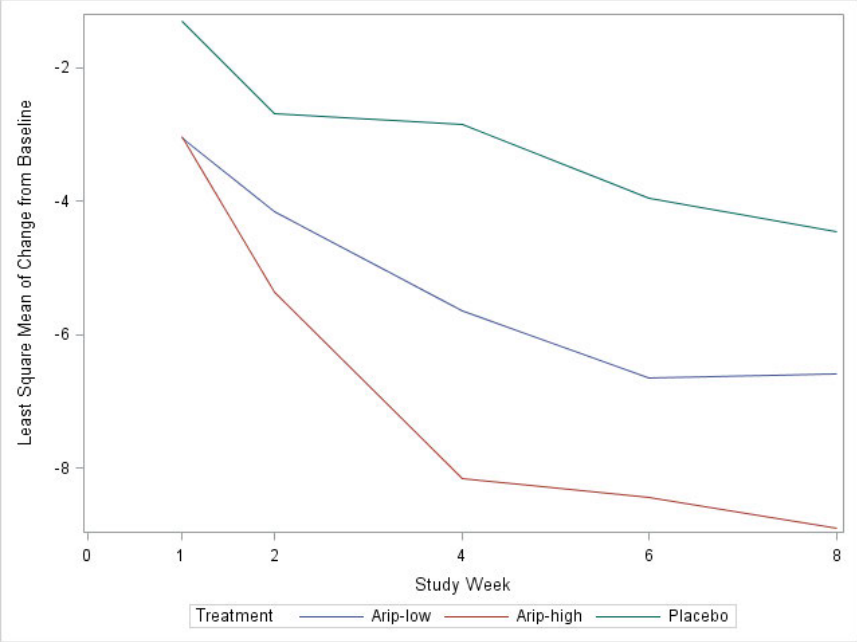
(Source: Reviewer)

Figure 6. Change from Baseline in Total Motor Tic Severity Score – ITT [Study 293]



(Source: Reviewer)

Figure 7. Change from Baseline in Total Vocal Tic Severity Score – ITT [Study 293]



(Source: Reviewer)

Exploratory Analysis: Change from Baseline to Week 8 in YGTSS TTS and CGI-TS by combination of randomized dose level and baseline body weight (MMRM) [Study 293]

An exploratory analysis was conducted subdividing the low dose and high dose groups into two groups each (grouping by actual dosage which in turn depended on the baseline weight of the subject). Note, that the groups used in this exploratory analysis are not formed by randomization, but by a combination of randomized assignment and baseline weight grouping (<50 kg or ≥ 50 kg). Also note that the sponsor provided a descriptive analysis by dose (observed cases only) in the study report on pages 195-196. The observed means by dose presented by the sponsor are similar to LS means obtained from the exploratory model below.

Statistical note: The models used for the estimates in the tables and figures below are based on the primary efficacy analysis model (MMRM) with two modifications:

1) Treatment assignment variable (Placebo, Arip-low, Arip-high) has been replaced by the new grouping variable (Placebo, Arip-low and < 50kg, Arip-low and ≥ 50kg, Arip-high and < 50kg, Arip-high and ≥ 50kg);
2) The predictor weight grouping (<50 kg or ≥ 50kg) has been removed from the model, since this factor has been incorporated into the new grouping variable.

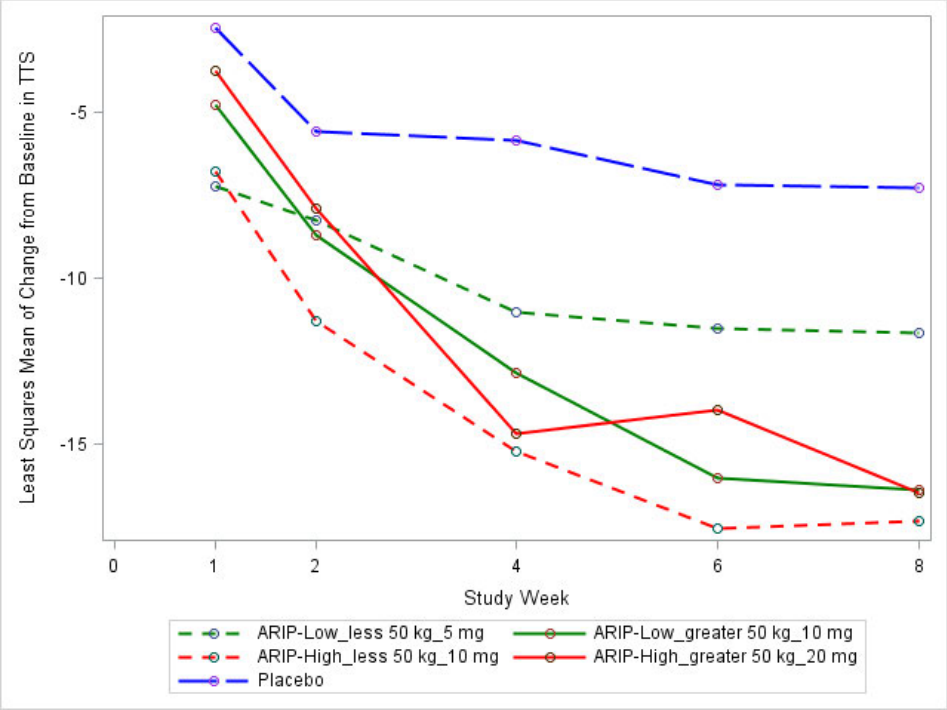
Table 17 provides the estimates of the change from baseline to week 8 in the total tic score by the exploratory grouping. Figure 8 displays the LS mean estimates of the change for each visit.

Table 17. Exploratory Analysis of Change from Baseline to Week 8 in YGTSS TTS by Combination of Randomized Assignment and Baseline Weight (MMRM) – ITT [Study 293]

Group	N	BL Mean	LS Mean Change	LS Mean Change SE	Treatment Difference		
						95% CI	
					Estimate*	Lower limit	Upper limit
Arip-low_less50kg_5mg	28	28.43	-11.66	1.94	-4.39	-8.85	0.07
Arip-low_ge50kg_10mg	16	30.44	-16.40	2.37	-9.12	-14.39	-3.86
Arip-high_less50kg_10mg	30	31.37	-17.33	1.96	-10.06	-14.60	-5.51
Arip-high_ge50kg_20mg	15	30.80	-16.48	2.46	-9.21	-14.65	-3.76
Placebo	44	30.73	-7.27	1.54			

(Source: Reviewer; *Derived from a repeated measures linear model with group, week, group by week interaction, and region as fixed categorical effects; the baseline value as a fixed covariate; and week as the time variable for repeated measures)

Figure 8: Exploratory Analysis of LS Mean Changes from Baseline in YGTSS TTS Score by Week (MMRM) – ITT [Study 293]



(Source: Reviewer; n = 133; Color associates lines by treatment assignment [Arip-Low vs. Arip-High vs. Placebo], Solid vs. Short Dashed lines stand for the grouping by baseline weight; the weight based dosing does not apply to the placebo group)

Observations:

The Arip-low treatment group is represented by the green dashed (lower weight, 5 mg subjects) and green solid (higher weight, 10 mg subjects) lines in **Figure 8**. Both subgroups show an improvement over placebo (blue long dash). The green dashed and green solid lines separate, particularly past study week 4, with the higher weight, higher dose subjects (green solid line) showing greater improvement in their total tic score (roughly 5 points difference at week 8). The lower weight, 5 mg subjects appear to reach some plateau around week 4.

The Arip-high treatment group is represented by the red dashed (lower weight, 10 mg subjects) and red solid (higher weight, 20 mg subjects) lines. Both subgroups show improvement over placebo. The decrease in the Total Tic Score is similar for both subgroups, in particular at week 8 (last visit). The nearly identical results of an analysis including only the completers are given in Figure A4 in the appendix.

Comparisons based on baseline weight:

Lower weight subjects (<50 kg): Consider green dashed and red dashed lines

The model appears to suggest that putting the lower weight subjects on 10 mg instead of 5 mg/day would result in a greater reduction in the Total Tic Score (roughly by 6 points).

Higher weight subjects (≥ 50 kg): Consider green solid and red solid lines

The model appears to suggest that the expected reduction in the Total Tic Score at week 8 is about the same, regardless of dose (10 vs. 20 mg/day), for the higher weight subjects.

Key Secondary Endpoint CGI-TS

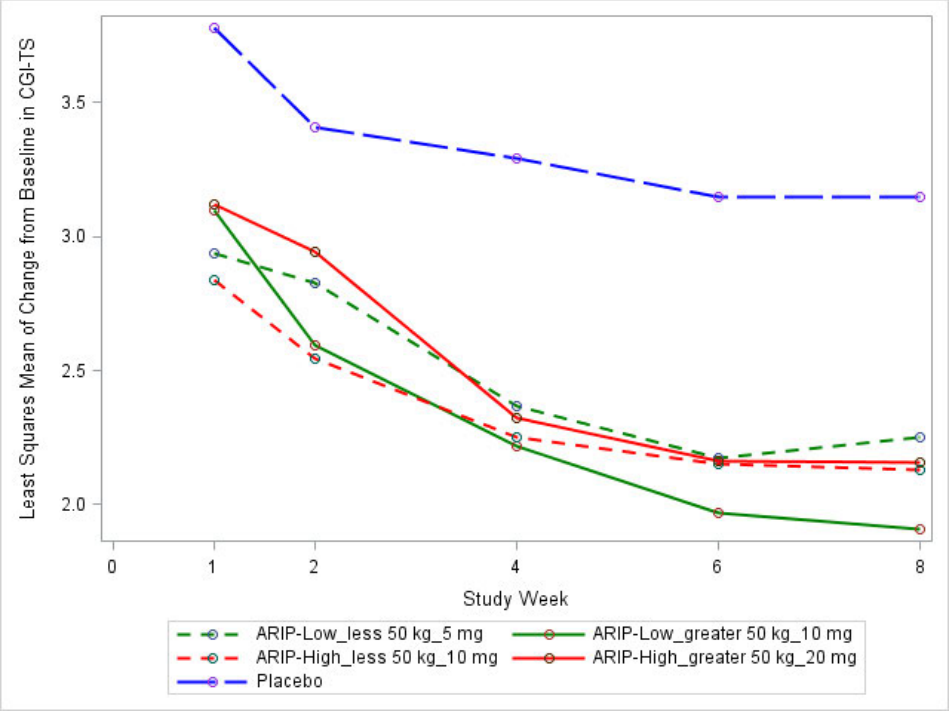
Recall that the scores for improvement in CGI-TS scale are: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change … ("smaller value is better"). Table 18 and Figure 9 and provide the MMRM estimates and trajectories over the course of the study for the key secondary endpoint CGI-TS-I for the exploratory grouping by the combination of randomized assignment and baseline weight.

Table 18: Exploratory Analysis of Improvement Scores from Baseline to Week 8 in CGI-TS by Combination of Randomized Assignment and Baseline Weight (MMRM) – ITT [Study 293]

					Treatment Difference		
Group	**N**	**BL Mean***	**LS Mean****	**LS Mean SE**		**95% CI**	
					Estimate**	**Lower limit**	**Upper limit**
Arip-low_less50kg_5mg	28	4.29	2.25	0.26	-0.90	-1.49	-0.31
Arip-low_ge50kg_10mg	16	4.44	1.91	0.31	-1.24	-1.93	-0.55
Arip-high_less50kg_10mg	30	4.00	2.13	0.26	-1.02	-1.63	-0.41
Arip-high_ge50kg_20mg	15	4.20	2.16	0.33	-0.99	-1.71	-0.27
Placebo	44	4.21	3.15	0.21			

(Source: Reviewer; *CGI-TS Severity Score; **Derived from a repeated measures linear model with group, week, group by week interaction, and region as fixed categorical effects; the baseline severity value as a fixed covariate; and week as the time variable for repeated measures)

Figure 9: Exploratory Analysis of LS Mean Changes from Baseline in CGI-TS-I Score by Week (MMRM) – ITT [Study 293]



(Source: Reviewer; CGI-TS has been measured in two ways in the trial: Severity Score and Improvement Score; the model estimates the CGI-TS-I mean scores [Improvement compared to BL, not the mean change from BL in the Severity score]; this is in line with the primary analysis model for the key secondary endpoint as specified in SAP)

Observation:

All four active drug groups separate from the placebo group (i.e., show greater improvement), and the estimated improvement as measured by CGI-TS scale is fairly homogenous among the active drug groups.

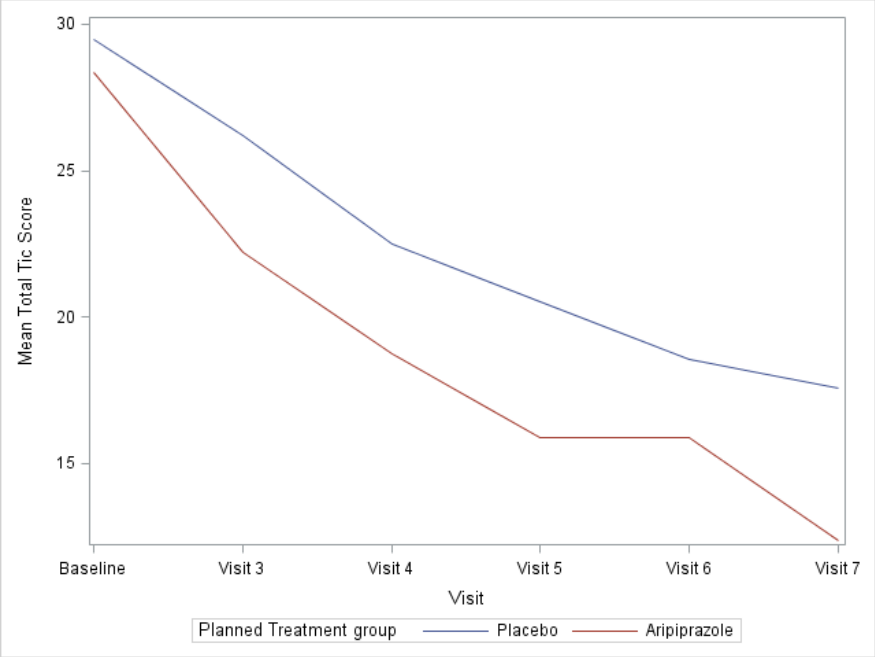
Overall conclusions for this exploratory analysis:

The 5 mg/day dose might be too low to achieve the full efficacy potential as measured by the Total Tic Score (YGTSS TTS) in the lower weight subjects (caveat: tolerability of the 10 mg/day dose in lower weight subjects). However, there appears to be no difference in the key secondary endpoint (CGI-TS) between the 5 mg and 10 mg/day groups for the lower weight subjects. The 20 mg/day dose might not be necessary for the higher weight subjects, given comparable efficacy as measured by YGTSS TTS and CGI-TS at 10 mg/day.

3.2.4.2.2 Study KOA

Figure 10 displays the mean total tic scores based on the observed (not imputed) data over the course of the 10 week study. The baseline and week 10 [visit 7] mean total tic scores are 29.5 (17.6) for the placebo subjects and 28.3 (12.3) for the aripiprazole subjects. Note the generally decreasing scores, with the aripiprazole group starting out below the placebo group. The difference in mean scores increased gradually over the duration of the study, with the aripiprazole subjects improving more compared to placebo subjects. Note there is no change in the mean TTS from Visit 5 (week 6) to Visit 6 (week 8) for the aripiprazole subjects. Patient level trajectories for the TTS over the course of the study are provided in Figures A5 (aripiprazole subjects) and A6 (placebo subjects) in the appendix.

Figure 10. Mean Total Tic Score (observed) – ITT [Study KOA]



(Source: Reviewer)

Exploration of ANCOVA (LOCF) Results

At first glance it might appear strange that the p-value from the ANCOVA LOCF for the treatment difference in the primary endpoint at week 10 with a value of 0.0269 is greater than the p-value obtained from the two-sample t-test with a value of 0.0196 (for those results see study

report p. 88 – 89 or section 3.2.4.1.2 in this review). Recall that the exploratory ANCOVA model adjusts by age group, study site and baseline TTS. The inclusion of those predictors resulted in a somewhat smaller treatment effect estimate and slightly larger standard error for the LOCF data. Also note that age group and study site were included in the model though they were not statistically significant (type-3 test p-values of 0.73 and 0.44).

ANCOVA Observed Values

Six subjects discontinued early from Study KOA (two on aripiprazole, four on placebo; two after week 2, 4, and 6 each). Table A4 in the appendix lists the drop-outs and their last TTS measure. The six drop-outs result in about 18 imputed values total per variable when carrying forward the last available assessment.

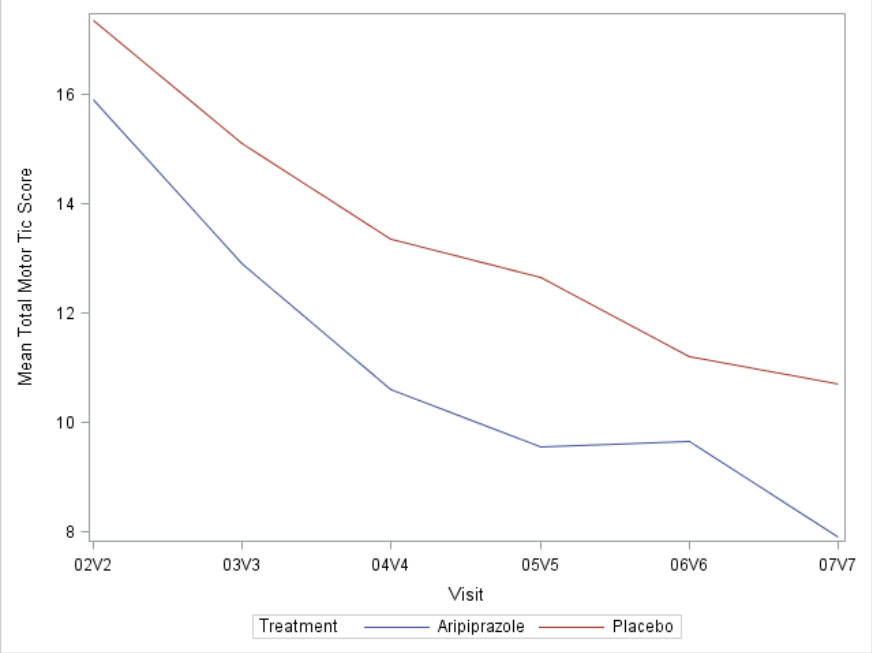
When analyzing only the observed data the p-values for the treatment difference at week 10 in the primary endpoint line up as expected: two-sample t-test: 0.0462, ANCOVA model: 0.0196.

Exploration of No Change between Week 6 and Week 8 in TTS in Aripiprazole group

In Figure 10 above (K-YGTSS TTS) we observe a generally decreasing mean total tic score over the course of the study, besides between week 6 (visit 5) and week 8 (visit 6), where the mean score remained essentially unchanged in the aripiprazole group. As can be seen in

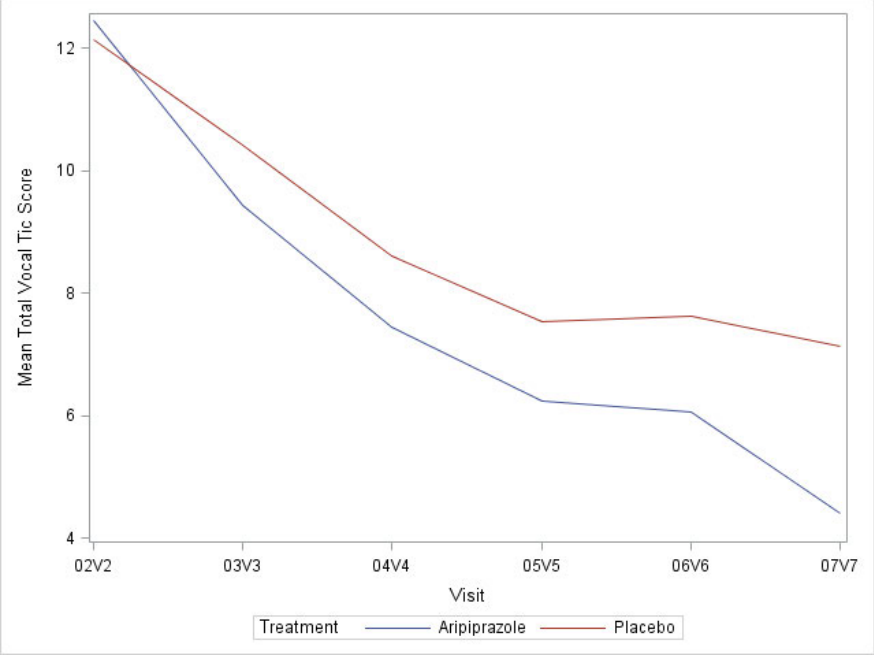
Figure 11 and Figure 12 this phenomenon encompasses both the motor and the vocal tic component of the total score. It appears that this event is driven by two out of the total of six sites in the study. Site 1 and Site 2 exhibit an increase in the mean total tic score between week 6 and week 8 by 5 and 1.5 points respectively whereas all other sites had a modest mean decrease (see Table A5 in appendix). The ultimate reason for the "flatness" between weeks 6 and 8 (vs. the general decreasing trend) appears to be the small sample size. Figure A7 in the appendix shows that two subjects at Site 1 and one subject at Site 2 have rather large increases in their total tic scores between weeks 6 and 8. The data from those three subjects have a strong enough impact on the overall mean score to achieve the flat trajectory.

Figure 11. Mean Total Motor Tic Score by Visit (observed data) [Study KOA]



(Source: Reviewer)

Figure 12. Mean Total Vocal Tic Score by Visit (observed data) [Study KOA]



(Source: Reviewer)

3.3 Evaluation of Safety

The reader is referred to the clinical review for the comprehensive safety analysis. This reviewer looked only at treatment related weight gain because it appears to be a pertinent side effect for this drug.

Body Weight

Study 293

Body weight was measured at screening, baseline, week 4 and week 8. Weight gain-related TEAEs in the low- and high-dose aripiprazole and placebo groups were reported for 5 (11.4%), 3 (6.7%), and 1 (2.3%) subjects, respectively (study report p. 117, 472). **Table 19** presents mean body weight by treatment group for the four measurement times based on observed data (no imputation). We see that body weight did hardly change between screening and baseline (screening days -42 to -3). However, a trend of increasing body weight is observed between baseline and week 8, with numerically larger increases for the actively treated groups compared to placebo (3.9 vs. 2.2 vs. 0.9 kg).

Table 19. Mean Body Weight by Treatment Group (Observed Cases) – ITT [Study 293]

Treatment	Mean Weight in kg (SD) n				Change from Baseline to Week 8 in kg (%)
	Screening	Baseline	Week 4	Week 8	
Placebo	47.3 (22.2) 44	47.8 (21.8) 44	48.0 (21.9) 43	48.7 (21.7) 42	0.9 (1.9)
Arip-Low	43.9 (15.9) 44	44.2 (16.0) 44	45.0 (16.6) 42	46.4 (16.6) 41	2.2 (5.0)
Arip-High	47.3 (20.1) 45	47.4 (20.1) 45	50.2 (21.1) 36	51.3 (21.4) 34	3.9 (8.2)

(Source: Computed by reviewer based on weight variable in vital signs dataset)

Drop-outs (missing data) might have had substantial impact on the mean estimates in Table 19 (e.g., recall the higher drop-out rate for high dose subjects weighing less than 50 kg). Table 20 considers completers only and we notice similar estimates of body weight changes as before for the placebo and arip-low groups. The estimate of change for the arip-high group is lower by

about two points mainly because of the exclusion (due to drop-out) of lower weight subjects increasing the mean baseline weight by about two kilograms.

Table 20. Mean Body Weight by Treatment Group (Completers) – ITT [Study 293]

Treatment	Mean Weight in kg (SD) n				Change from Baseline to Week 8 in kg (%)
	Screening	Baseline	Week 4	Week 8	
Placebo	47.6 (22.7) 42	48.1 (22.3) 42	48.2 (22.2) 42	48.7 (21.7) 42	1.1 (2.3)
Arip-Low	44.0 (16.2) 42	44.3 (16.3) 42	45.0 (16.6) 42	46.4 (16.6) 41*	2.4 (5.5)
Arip-High	49.7 (21.1) 35	49.8 (21.2) 35	50.2 (21.4) 35	51.3 (21.4) 34*	1.6 (3.2)

(Source: Computed by reviewer based on weight variable in vital signs dataset; *this reviewer could not resolve why the number of subjects is dropping by one subject for both active treatment arms from week 4 to week 8 when selecting completers by "termstat = 1", which should select completers only [two subjects likely completed the trial, but have missing weight measurements at week 8])

Study KOA

The mean change in bodyweight was 1.62 kg (SD = 2.02) in the Aripiprazole group and 0.20 kg (SD = 1.84) in the Placebo group. Two subjects (7.1%) in the placebo group and 9 subjects (28.1%) in the aripiprazole group had gained more than 7% in body weight from baseline to the week 10 visit (study report p. 76-77, 164-167). In conclusion, weight gain appears associated with treatment with aripiprazole.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Study KOA

The sponsor did not perform any subgroup analysis in Study KOA. The trial was conducted in its entirety in Korea with 53 male and 8 female participants.

Given the age range from 6 to 18 years it appears prudent to consider an exploratory subgroup analysis by child vs. adolescent. The efficacy dataset "adeff" (ITT LOCF) contains the categorical variable "agegr", which classifies subjects 6 to 11 years of age as children and subjects 12 to 18 years of age as adolescents. This reviewer computed the mean change in TTS at

week 10 as an exploratory analysis for the two age groups. Results from Study 293 (ignoring dose group) are also included for comparison (see Table 21 below).

Table 21. Exploratory Analysis of Change from BL at Final Visit in TTS by Children vs. Adolescents (Observed data) - ITT

	Study KOA				**Study 293**	
Children	6-11 years		6-12 years		7-12 years	
	N	Mean	N	Mean	N	Mean
Placebo	16	-12.0	17	-11.3	26	-7.2
Aripiprazole	19	-17.9	22	-17.0	49	-14.9
Difference		5.9		**5.7**		**7.7**
Adolescents	12-18 years		13-18 years		13-17 years	
	N	Mean	N	Mean	N	Mean
Placebo	9	-10.0	8	-11.3	16	-8.2
Aripiprazole	10	-11.8	7	-12.1	28	-15.8
Difference		1.8		**0.9**		**7.6**

(Source: Reviewer; The definition of the age groups is slightly different between the Korean [e.g., children 6 – 11] and the global study [e.g., children 6 – 12])

The effect of aripiprazole treatment on the Total Tic Score (TTS) is consistent over the age groups (children vs. adolescents) in Study 293, but appears quite different in the Korean Study (i.e., difference of 5.7 for the child vs. 0.9 for the adolescent group). However, the sample sizes for those exploratory subgroup analyses are small.

When combining data from both trials (KOA and 293) roughly 2/3 of the ITT subjects fall into the 6-12 year age bracket and 1/3 of the subjects fall into the 13-18 years of age bracket (see Summary of Clinical Efficacy p. 25). TTS efficacy results provided by the sponsor for the combined data are similar over both age brackets (Summary of Clinical Efficacy p. 40 – 41).

Study 293

The sponsor analyzed the primary efficacy endpoint of change from baseline to week 8 in YGTSS TTS for the following subgroups:

- Age of 7 to 12 years versus 13 to 17 years at screening
- Region of North America (US and Canada) versus the Rest of the World
- Race of White versus Other

Gender

No analysis by gender was performed by the sponsor. This is reasonable since more than 75% of subjects in the trial are male.

Race

More than 86% of the subjects in Trial 293 were White. There were only 5 to 6 subjects (mostly African American or Asian) per treatment group who were not White. The sponsor provides a subgroup analysis by White vs. Other for the primary endpoint on p. 88-89 of the study report. The results though are not very meaningful due to the small sample size for the "Other" race group.

Age

The average age of participants in Study 293 is 11.5 years. The sponsor performed an analysis for change in TTS dividing participants into two groups: 7 to 12 year olds versus 13 to 17 year olds at screening. The average reduction in TTS at week 8 ranges between -5.86 to -9.89 with no consistent trend given low or high dose and age group.

Geographic Region

The analysis of subjects from the "Rest of the World" (i.e., Hungary and Italy) does not provide meaningful results due to the small sample size of 14 subjects.

The estimated changes in TTS when considering only North American (US and Canada) subjects (N=118) are as follows: Arip-low -5.24 and Arip-high -9.54. Those values are very similar to the estimates when considering US subjects only (N = 92): Arip-low -5.33 and Arip-high -8.24.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No major statistical issues were discovered. The in hindsight too small sample size in the Korean study, due to a higher than expected placebo response, attenuates the Korean study's contribution to the total body of evidence supporting efficacy.

5.2 Collective Evidence

The non-IND Korean study is the smaller trial with 61 subjects. Its primary outcome measure, the change in K-YGTSS TTS from baseline at week 10, is statistically significantly different from placebo (estimate = -5.35; p = 0.0196). Various supportive analyses arrive at similar results. A key secondary endpoint was not pre-specified. A retrospective analysis of CGI-TS-I does not reach statistical significance (estimate of difference to placebo: -0.61; p = 0.078).

Study 293 is the larger study with 133 randomized subjects. Low and high dose aripiprazole groups separate in a statistically significant manner from the placebo group on the primary outcome (estimates of YGTSS TTS differences to placebo at week 8: low dose -6.26 [p = 0.002], high dose -9.85 [p < 0.0001]). Both aripiprazole groups also show statistically significant improvements over placebo on the CGI-TS-I at week 8, the key secondary outcome measure (estimated differences of roughly one point with p-values of 0.0001 and 0.0002). The high dose group shows numerically better efficacy compared to the low dose group on the primary endpoint. There is however no numerical separation between the high and low dose aripiprazole groups for the key secondary endpoint. This reviewer arrived at the same or similar results when replicating the major efficacy analyses for both studies.

An exploratory analysis of the four dosage groups (i.e., 5, 10, 10, 20 mg/day) formed by the combination of randomized treatment assignment and baseline body weight suggests that a dose of 5 mg/day might be too small to achieve full efficacy in subjects weighing less than 50 kg. However, this finding needs to be balanced with potential tolerability issues at the 10 mg/day dose for lower weight subjects as indicated by a clearly higher drop-out rate (9/30), mainly due to adverse events, in this group. The exploratory analysis also suggests that a dose of 20 mg/day may on average not add much to the efficacy obtained at 10 mg/day for subjects weighing 50 kg or more.

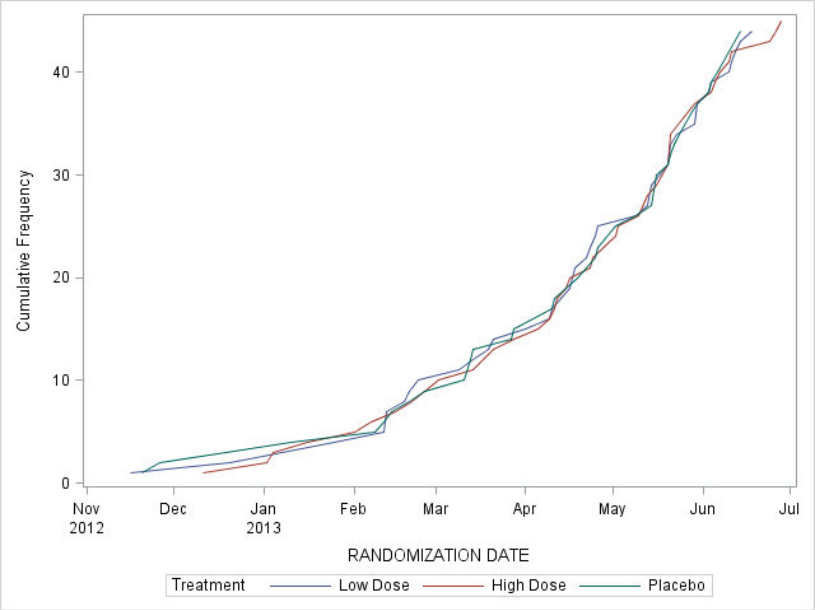
It appears that treatment with aripiprazole reduces both motor and vocal tics components of the YGTSS TTS.

5.3 Conclusions and Recommendations

The statistical results provide adequate evidence to support the claim (treatment of (b) (4) (b) (4) Tourette's disorder (b) (4).

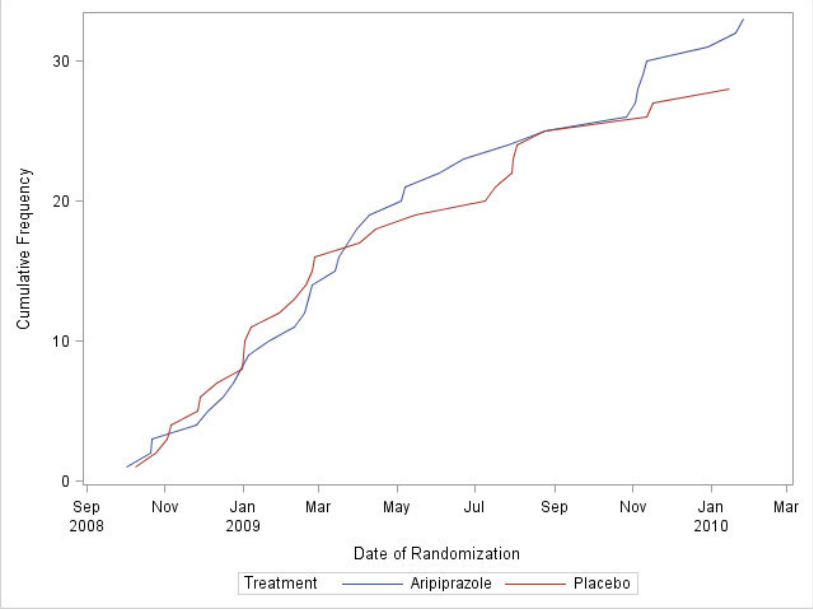
6. APPENDICES

Figure A1. Randomization [Study 293]



(Source: Reviewer)

Figure A2. Randomization [Study KOA]



(Source: Reviewer)

Table A1. Sites [38] in Descending Order by Number of ITT Subjects [Study 293]

Site Number	Frequency	Percent	Country
533	23	17.29	Canada
511	11	8.27	USA
510	10	7.52	USA
595	7	5.26	USA
507	6	4.51	USA
514	6	4.51	USA
661	6	4.51	Hungary
555	4	3.01	USA
576	4	3.01	USA
582	4	3.01	USA
588	4	3.01	USA
520	3	2.26	USA
530	3	2.26	USA
534	3	2.26	USA
563	3	2.26	USA
660	3	2.26	Hungary
788	3	2.26	Italy
502	2	1.50	USA
503	2	1.50	USA
508	2	1.50	USA
535	2	1.50	Canada
552	2	1.50	USA
554	2	1.50	USA
562	2	1.50	USA
590	2	1.50	Canada
780	2	1.50	Italy
505	1	0.75	USA
517	1	0.75	USA
518	1	0.75	USA
528	1	0.75	USA
537	1	0.75	USA
542	1	0.75	USA
547	1	0.75	USA

Site Number	Frequency	Percent	Country
551	1	0.75	USA
565	1	0.75	USA
574	1	0.75	USA
577	1	0.75	USA
591	1	0.75	USA
	133	**100.00**	

Table A2. Number of ITT Subjects per Site [Study KOA]

Site Number	Frequency	Percent
001	12	19.67
002	10	16.39
003	9	14.75
004	14	22.95
005	9	14.75
006	7	11.48
	61	**100.00**

Table A3. Average and Total Doses by Treatment Assignment and Weight Strata [Study 293]

	Aripiprazole Low Dose		Aripiprazole High Dose	
	5 mg (< 50 kg)	10 mg (≥ 50 kg)	10 mg (< 50 kg)	20 mg (≥ 50 kg)
N	28	16	30	15
Average Daily Dose (SD)	4.7 (0.65)	9.1 (0.65)	7.9 (2.21)	15.1 (2.67)
Average Total Dose (SD)	251.4 (70.53)	507.9 (47.50)	386.4 (191.44)	822.3 (226.97)

(Source: Computed by Reviewer based on dataset dose0)

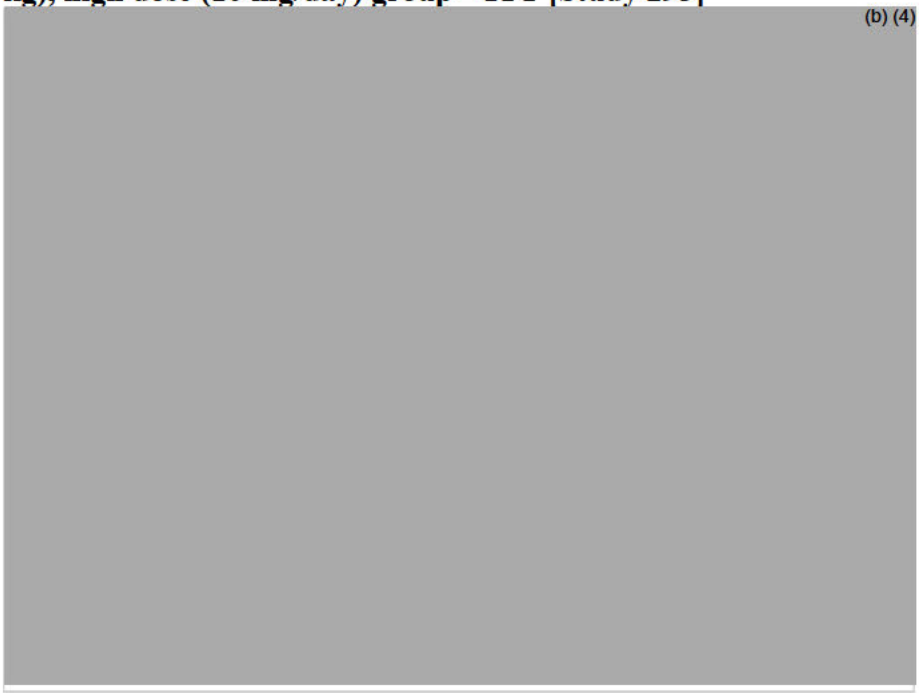
Note the differences in average daily dose and average total dose between the groups of subjects both slated to receive 10 mg but with a body weight above or below 50 kg at baseline. The group of patients with a baseline body weight below 50 kg took numerically on average a lower daily dose and also a lower average total dose. Four subjects weighing less than 50 kg at baseline in the 10 mg group had their dose stepped down to 5 mg. This occurred to only one subject

weighing more or equal to 50 kg also scheduled for the 10 mg dose. The values for total dose in the table above are impacted by the duration a subject stays on treatment/in the trial; the calculation of the average dose should adjust for that. The observed differences are of numeric nature, but provide further indication (additional to the higher incidence of adverse events) that the 10 mg dose could cause some tolerability issues for some of the lower weight subjects.

From the Korean study which was operating with a flexible dose schedule it is also apparent that subjects with baseline bodyweight less than 50 kg ended the study on a lower dose than subjects with a bodyweight greater 50 kg at baseline (i.e., means of 11.4 vs. 14.6 mg).

Examination of the relatively large proportion of discontinuations (9 out of 30) in the lower weight, high dose group [Study 293]

Figure A3: Observed Total Tic Scores for the nine drop-outs from the lower weight (<50 kg), high dose (10 mg/day) group – ITT [Study 293]



(Source: Reviewer; curves above ignore intermittent missing values; for a different type of visualization of the missing data pattern see study report p. 198)

Lower weight (<50 kg), high dose (10 mg/day) group: Six subjects discontinued due to an adverse event and three subjects withdrew consent (one each at baseline, week 2, and week 4).

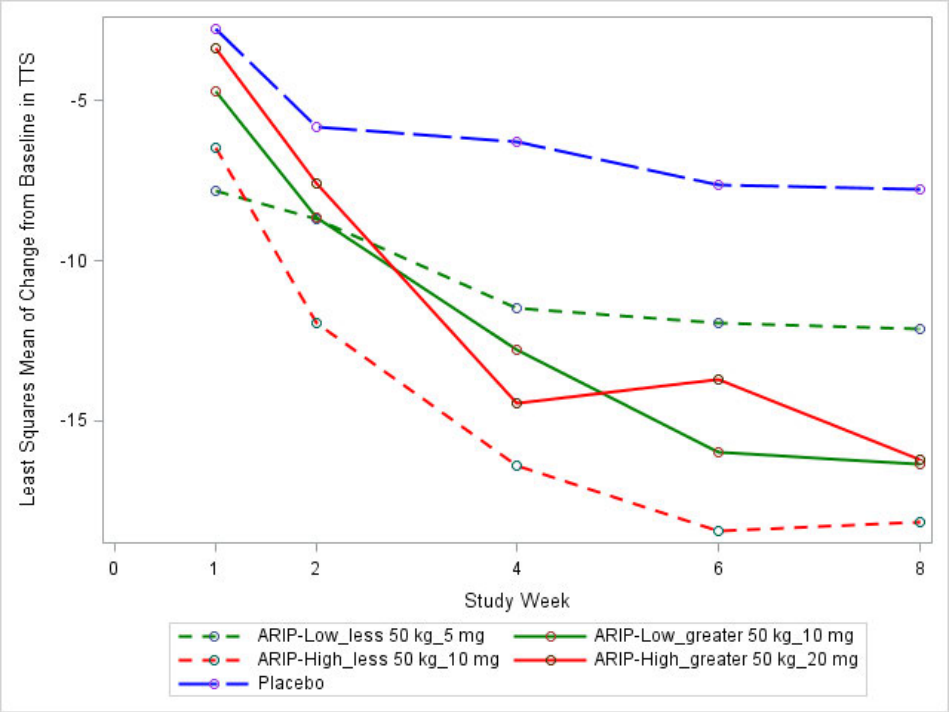
Note that at least for some of the subjects the Total Tic Score did not improve for several weeks prior to drop-out (lack of efficacy appears associated with discontinuation).

A comparison of the drop-out profiles with other weight groups is not very meaningful, because there are only three other drop-outs (two in the low dose [5 mg], lower weight group due to protocol deviations and one in the high dose [20 mg], higher weight group due to an adverse event). There were also two drop-outs on placebo (one due to an adverse event and one due to withdrawal of consent).

Primary Endpoint YGTSS TTS – Completers Only

Purpose: Explore the possible impact of the 9 out of 30 drop-outs in the lower weight, high dose group on the results above.

Figure A4: Exploratory Analysis of LS Mean Changes from Baseline in YGTSS TTS Score by Week (MMRM) – Completers only [Study 293]



(Source: Reviewer; n = 119)

There are only minimal differences between the estimates when considering all subjects (as in **Figure 8**) vs. completers only (as in Figure A4). The separation between the curves for the lower weight subjects on 5 mg and the lower weight subjects on 10 mg remains unchanged.

Table A4. LOCF subjects - Last Visit before Discontinuation [Study KOA]

Obs	Unique Patient Identifier for Clintrial	Site Number	Planned Treatment group (c)	Visit (c)	Baseline Total Tic score	Total Tic score	Change from baseline in Total Tic score
1	001S00010001	001	Aripiprazole	Visit 4	46	43	-3
2	001S00020002	001	Placebo	Visit 4	36	36	0
3	001S00060006	001	Placebo	Visit 3	26	27	1
4	002S00040003	002	Placebo	Visit 5	37	31	-6
5	004S00170014	004	Aripiprazole	Visit 5	22	19	-3
6	005S00090005	005	Placebo	Visit 3	35	43	8

(b) (4)

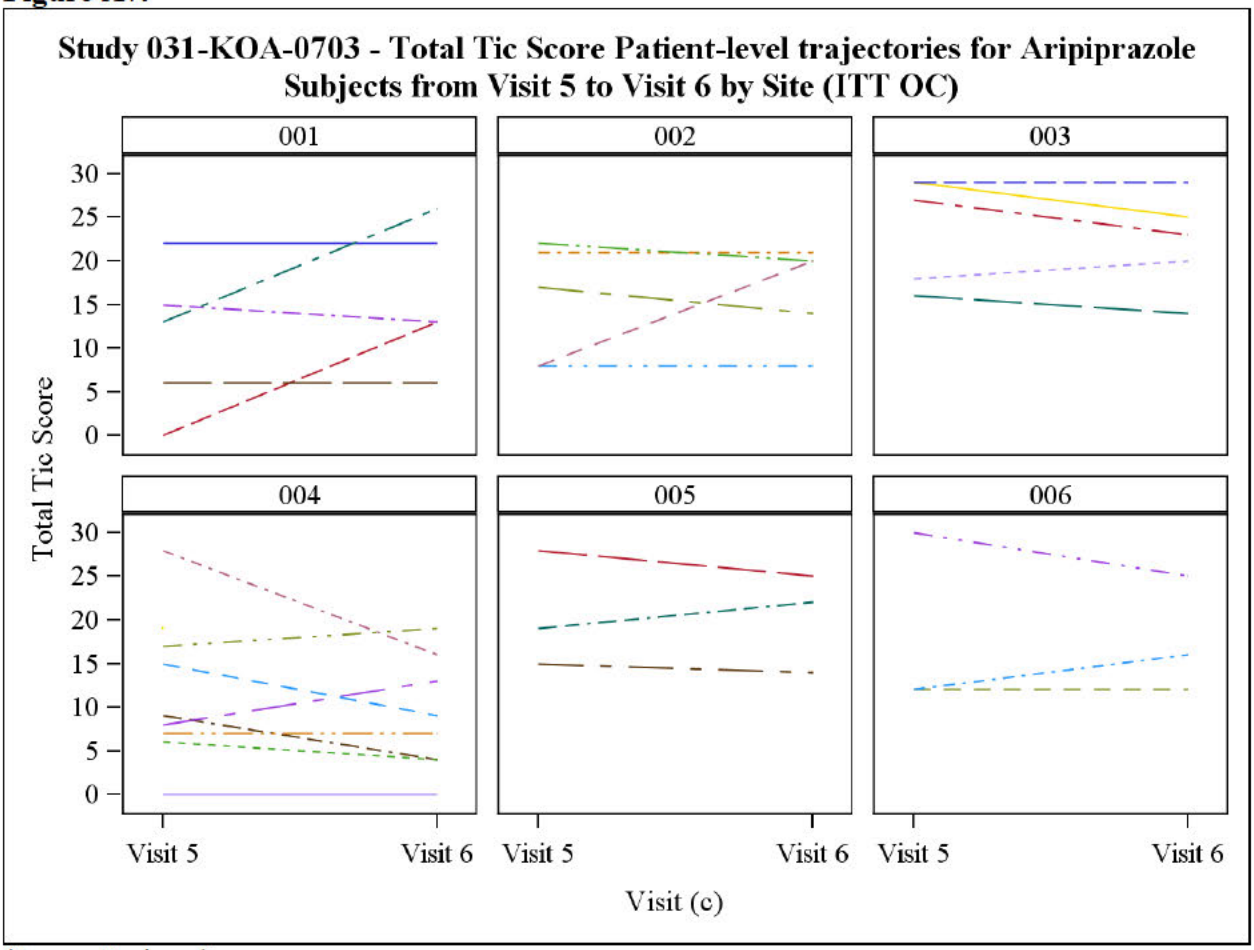
Table A5. Mean TTS in Aripiprazole Group (Observed data) on Visit 5 (week 6) and Visit 6 (week 8) by Site [Study KOA]

Site Number	Visit (c)	N Obs	Mean
001	Visit 5	5	11.2
001	Visit 6	5	16.0
002	Visit 5	5	15.2
002	Visit 6	5	16.6
003	Visit 5	5	23.8
003	Visit 6	5	22.2
004	Visit 5	9	12.1
004	Visit 6	8	9.0

Site Number	Visit (c)	N Obs	Mean
005	Visit 5	4	20.7
005	Visit 6	4	20.3
006	Visit 5	3	18.0
006	Visit 6	3	17.7

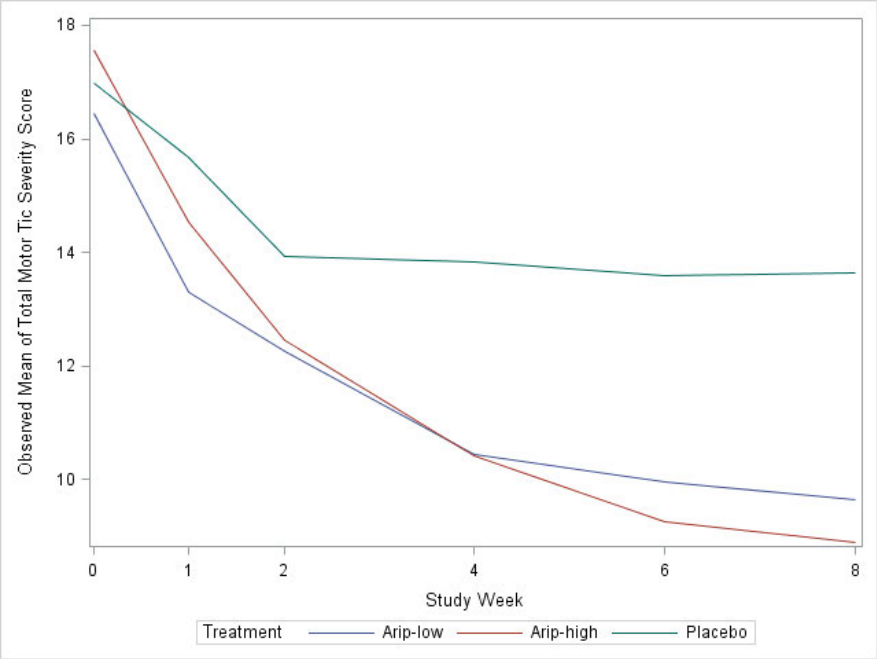
(Source: Reviewer)

Figure A7.



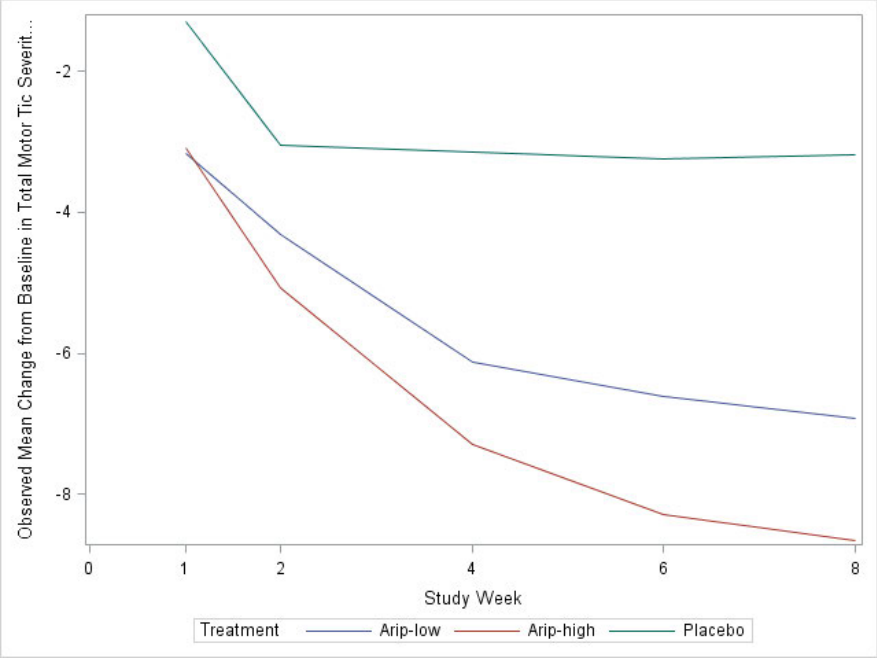
(Source: Reviewer)

Figure A8. Observed Means of Total Motor Tic Severity Score – ITT [Study 293]



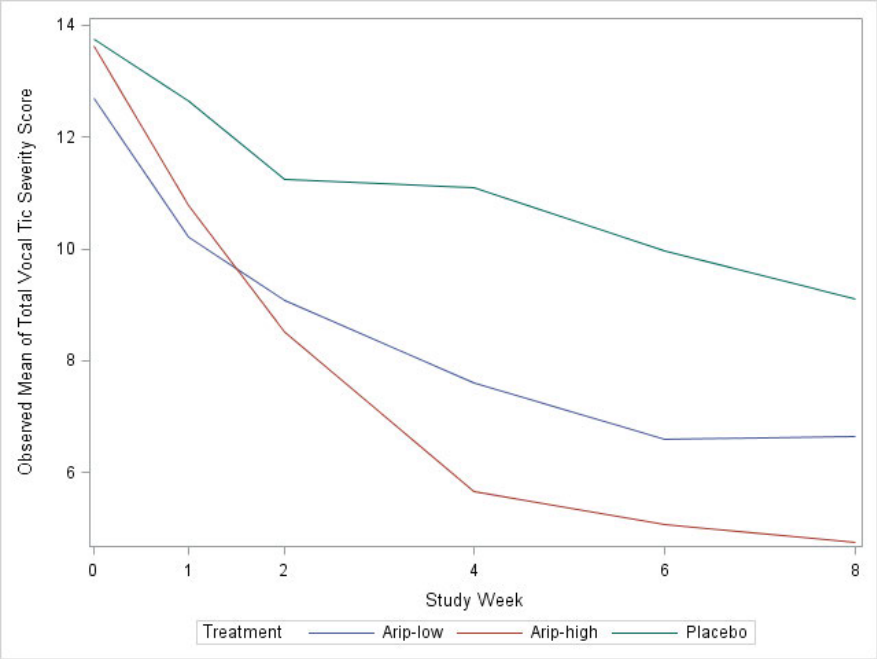
(Source: Reviewer)

Figure A9. Observed Mean Changes in Total Motor Tic Severity Score – ITT [Study 293]



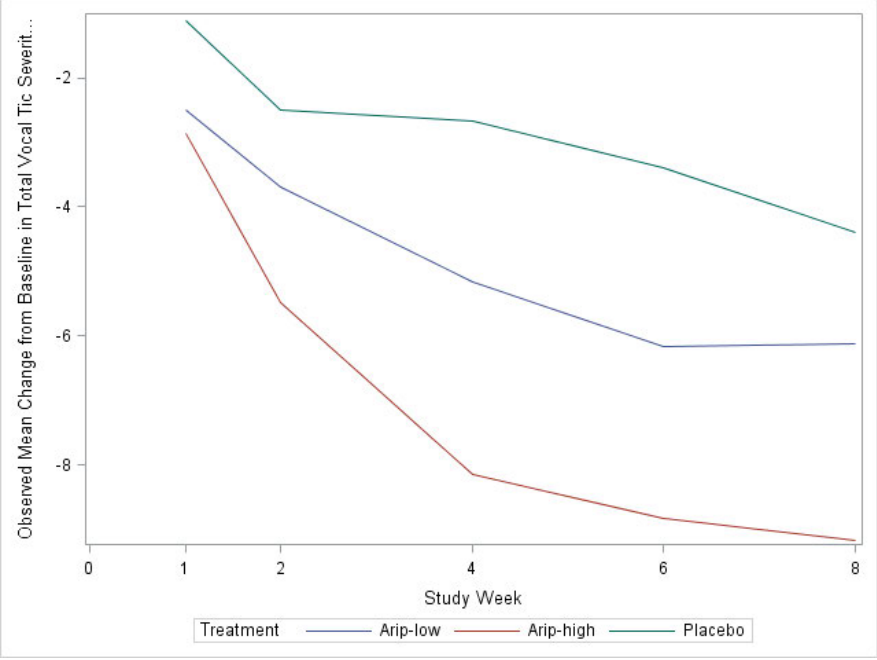
(Source: Reviewer)

Figure A10. Observed Means of Total Vocal Tic Severity Score – ITT [Study 293]



(Source: Reviewer)

Figure A11. Observed Mean Changes in Total Vocal Tic Severity Score – ITT [Study 293]



(Source: Reviewer)

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/s/

THOMAS BIRKNER
10/31/2014

PEILING YANG
10/31/2014

KOOROS MAHJOOB
10/31/2014
I concur with the review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 21,436 S-38 **Applicant: Otsuka** **Stamp Date: 02/12/2014**

Drug Name: Abilify **NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			No separate ISS, ISE
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			No subgroup analyses in Korean study; Analyze by Age (child vs. adolescent) and gender
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			Need SAS code with formats for Study 293; at least some listing datasets for Study 293 miss treatment group variable

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Appropriate references for novel statistical methodology (if present) are included.			**X**	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	**X**			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	**X**			LOCF used in Korean study, comparison with OC results provided; further investigation of drop-outs warranted

Thomas Birkner 03/25/2014

Reviewing Statistician Date

Peiling Yang 03/25/2014

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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

/s/

THOMAS BIRKNER
03/24/2014

PEILING YANG
03/26/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21436/S-38

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA/Supplement/Serial #:	21,436/S038/0045
Brand Name:	Abilify
Generic Name:	Aripiprazole
Dosage Form:	Tablet
Strengths (mg):	2, 5, 10, 15, 20, 30
Sponsor:	Otsuka Pharmaceuticals
Indication:	(b) (4)
Relevant IND:	116,003
Submission Date:	2/12/2014
Review Type:	Pediatric sNDA
Review Team:	Huixia Zhang, Xiaofeng Wang, Kevin Krudys, Hao Zhu

Table of Contents

1. Executive Summary

Abilify (aripiprazole) oral tablet has been approved since 2002. The approved indications in pediatric patients include: schizophrenia (13-17 years), bipolar mania (monotherapy or as an adjunct to lithium or valproate, 10-17 years), and irritability associated with autistic disorder (6-17 years). In the current submission, Otsuka is seeking approval of Abilify in treatment of (b) (4) Tourette's disorder in pediatric patients (b) (4)

The primary evidence for the safety and efficacy of aripiprazole in treatment of Tourette's is provided by two pivotal placebo-controlled trials:

- **Trial 31-12-293**: A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder
- **Trial 031-KOA-0703**: A Randomized, Double-bind, Dose-adjustment, Placebo-controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder

The focus of the analyses performed by the Office of Clinical Pharmacology (OCP) is to assess the proposed dosing regimen in pediatric patients with Tourette's disorder (Table 1). Population PK and exposure-response analyses were performed using data from one of the pivotal trials conducted in the US (Trial 31-12-293). The results are **in support of the proposed dosing regimen**. In addition, population PK analysis confirmed that aripiprazole PK in pediatric patients with Tourette is **similar** to other pediatric patients (i.e., schizophrenia, and bipolar).

Table 1: Summary of the Proposed Dosing Regimen

Patient Group	Initial Dose	Recommended Dose	Maximum Dose
Patients < 50 kg	2 mg/day	5 mg/day	10 mg/day
Patients ≥ 50 kg	2 mg/day	10 mg/day	20 mg/day

1.1 Clinical Pharmacology Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology I has reviewed the submission, and concluded that there is sufficient evidence to support a recommendation of approval for Abilify in the treatment of (b) (4) Tourette's in pediatric patients (b) (4), provided an agreement on the label can be reached with the sponsor. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP	Recommendation and Comments		
Overall	☒ Yes ☐ No ☐ NA	Pending labeling agreement with the sponsor		
Evidence of effectiveness	☒ Yes ☐ No ☐ NA	Trial 31-12-293 and Trial 031-KOA-0703		
Proposed dose in pediatric patients (b) (4)	☒ Yes ☐ No ☐ NA	Dose (mg/day)	Patients <50kg	Patients ≥50kg
		Initial dose	2	2
		Recommended dose	5	10
		Maximum dose	10	20
Labeling	☐ Yes ☒ No ☐ NA	Pending satisfactory agreement with the sponsor.		

1.2 PMR/PMC Recommendation

None

1.3 Labeling Recommendation

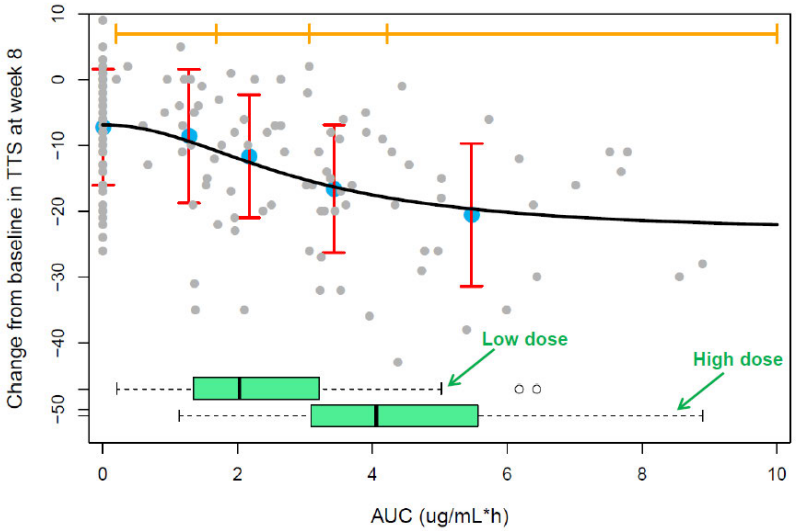
No labeling changes pertinent to clinical pharmacology was proposed in the current submission.

1.4 Summary of Clinical Pharmacology Key Findings

Population PK data collected from the efficacy and safety trial (Trial 31-12-293) was analyzed and exposure/response analysis was performed. It is found that:

- The pharmacokinetic features of aripiprazole in pediatric patients with Tourette's disorder are sufficiently similar to pediatric patients in other disease populations (i.e., schizophrenia, and bipolar disorder).
- Increasing doses from the recommended levels (5 mg/day or 10 mg/day) to the maximum levels (10 mg/day or 20 mg/day) is anticipated to improve drug response. Doses beyond the maximum levels (10 mg/day or 20 mg/day) are only anticipated to provide limited additional treatment benefit, because the exposure-response curve is reaching its plateau in this range (Figure 1).
- The proposed dosing regimen with both recommended and maximum doses reduced by half in pediatric patients less than 50 kg (Table 1) is acceptable. It is shown that the proposed dose/exposure range is anticipated to be safe and efficacious. Following the proposed dosing regimen, the mean and variability of aripiprazole exposure (i.e., AUC) in low and high body weight groups are comparable. Under the extreme scenario, pediatric patients, weighted 40-50 kg, are anticipated to yield the lowest exposure as compared to patient groups with other body weights, following the proposed dosing regimen. The low exposure appears to affect more on patients receiving recommended dose (i.e., 5 mg/day) and less on the maximum dose (i.e., 10 mg/day). With the option to increase dose to the maximum level, potential lack of efficacy does not appear to be a concern.

Figure 1: Change from Baseline in TTS at Week 8 versus AUC



- Note: black solid line is the typical exposure-response curve; grey points represent the observed change from baseline in TTS values for all subjects; orange line on the top represents AUC range for 4 exposure bins; blue points and red bars represent mean and standard deviation of the observed change from baseline in TTS values for placebo group (the first set) and 4 AUC bins;

two green box plots at bottom represent the AUC distribution of the low dose and high dose treatment groups, respectively.

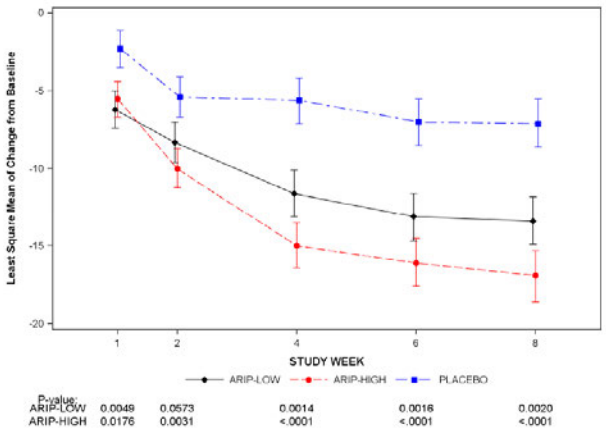
2. Question-Based Review

2.1 Is there evidence of effectiveness for Abilify in treatment of (b) (4) Tourette in pediatrics aged (b) (4) years?

Yes. The efficacy of Abilify in patients aged (b) (4) years old was demonstrated in two efficacy trials: Trial 31-12-293 and Trial 031-KOA-0703.

Trial 31-12-293 was a multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of fixed-dose once-daily oral aripiprazole in children and adolescents (aged 7-17 years) with Tourette's disorder. Qualified subjects were randomly assigned to low- or high-dose aripiprazole or placebo in a 1:1:1 ratio. For subjects who weighed < 50 kg at baseline, low and high doses of aripiprazole were 5 and 10 mg/day, respectively. For subjects who weighed ≥ 50 kg at baseline, low and high doses of aripiprazole were 10 and 20 mg/day, respectively. All subjects randomized to the aripiprazole groups were titrated to the target doses from an initial dose of 2 mg/day according to a pre-specified titration scheme. Approximately 126 subjects were planned for randomization in this trial from an estimated 120 sites worldwide. A total of 171 subjects were screened for the trial and 133 randomized.
The primary efficacy endpoint was the change from baseline to endpoint (Week 8) on the total tic score (TTS) of the Yale Global Tic Severity Scale (YGTSS). The treatment difference between the low-dose aripiprazole and placebo groups (-6.26) was statistically significant (p = 0.0020) for the primary efficacy endpoint (change from baseline to Week 8 in YGTSS TTS); the treatment difference between the high-dose aripiprazole and placebo groups (-9.85) was also statistically significant (p < 0.0001), based on a mixed effect repeated measure model (Figure 2).

Figure 2: Least Square Means of Change from Baseline in YGTSS TTS Score By Week, MMRM

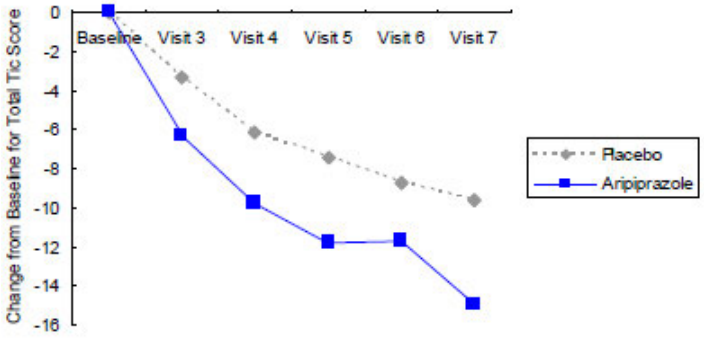


- Source: Figure 11.4.1.1-1 Clinical Study Report, Page 85

Trial 031-KOA-0703 was randomized, double-blind, dose-adjustment, placebo-controlled study to evaluate the efficacy and safety of aripiprazole in children and adolescents with chronic Tic disorders or Tourette's disorder in Korea. Patients who satisfied all the inclusion/exclusion criteria were randomized to either aripiprazole or placebo and was administered the investigational products for 10 weeks. An appropriate dose (2mg to 20mg) of aripiprazole or placebo was administered daily at about the same time without regard to meal. A total of 61 subjects were randomized.

The primary efficacy endpoint was the mean change from baseline to endpoint of total Tic scores in K-YGTSS from randomization to the final visit. The results showed that the mean total Tic score changed from 29.48 (±5.60) at Baseline to 19.86 (±9.54) at the final visit for placebo group, showing a decrease, by -9.62 (±8.83). For aripiprazole group, it changed from 28.34 (±5.51) at Baseline to 13.55 (±9.12) at the final visit, showing a greater decrease, by -14.97 (±8.42). The difference in the change from Baseline to the final visit between the treatment groups was statistically significant (p-value=0.0196, two-sample t-test) (Figure 3).

Figure 3: Change from Baseline for Total Tic Score (ITT population, LOCT)



- Source: Figure 10.1 Clinical Study Report, Page 59

2.2 Is the proposed dose/exposure range appropriate?

Yes, the proposed dose/exposure range is acceptable. Per the sponsor's proposal, depending on patient body weight, the pediatric dose can range between low dose (5mg/day or 10 mg/day) and high dose (10 mg/day or 20 mg/day).

The proposed doses/exposures are anticipated to be within the efficacious range. Our exposure-response analysis using data from Trial 31-12-293 showed that more efficacy benefit can be expected by increasing the dose from recommended levels (5 mg/day or 10 mg/day) to maximum levels (10 mg/day or 20 mg/day). Doses beyond the maximum levels (10 mg/day or 20 mg/day) are only anticipated to provide limited additional treatment benefit, because the exposure-response curve is reaching its plateau (Figure 1).

The proposed dose/exposure range is anticipated to be safe. Population pharmacokinetic analysis in the current submission demonstrated similarity in PK across pediatric subjects with Tourette's disorder, schizophrenia, and bipolar disorder. Since the proposed dose range of 5 mg/day to 20 mg/day has been approved in pediatric patients

of similar age in other indications, dose selection is also acceptable form a safety perspective.

2.3 Is the proposed body-weight based dosing regimen with the body weight cutoff of 50 kg acceptable?

Yes, the proposed body-weight based dosing regimen with the weight cutoff of 50 kg is acceptable. In the current submission, the sponsor proposed a weight-based dosing regimen in order to narrow the concentration distribution within each pediatric dose range. The proposed body weight cut off is 50 kg. The recommended and maximum doses in low body weight pediatric patients are half of those in high body weight pediatric patients (Table 2).

Table 2: Proposed Dosing Regimen By the Sponsor

Patient Group	Initial Dose	Recommended Dose	Maximum Dose
Patients < 50 kg	2 mg/day	5 mg/day	10 mg/day
Patients ≥ 50 kg	2 mg/day	10 mg/day	20 mg/day

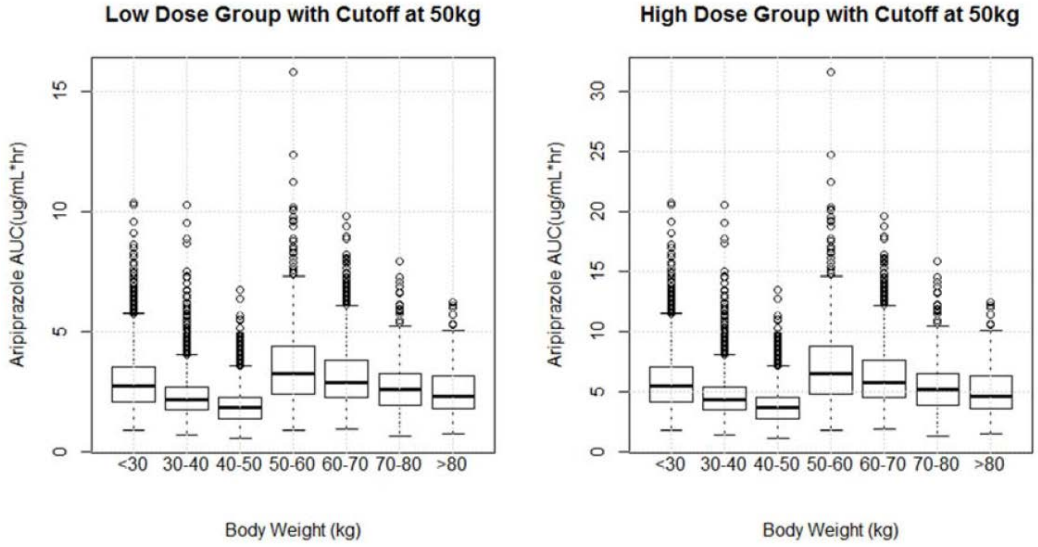
Our population pharmacokinetic simulation demonstrated that, following the body weight cut off of 50 kg, the mean and variability of aripiprazole exposure (i.e., AUC) in low and high body weight groups are comparable (Table 3). Mean exposure in patients with low body weight (<50 kg) is approximately 30% lower than that in patients with high body weight (≥ 50 kg) following the proposed dosage regimens (for both low and high dose groups).

Table 3: Mean (±SD) AUC Comparison in Low Dose and High Dose Groups Based on Body Weight

	Low Dose Group		High Dose Group	
Dose (mg)	5 mg (n=30)	10 mg (n=15)	10 mg (n=19)	20 mg (n=11)
Body weight (kg)	<50	≥50	<50	≥50
AUC (hr*ng/mL)	2.41±1.12	3.26±1.65	4.34±1.34	6.24±3.22
% CV	46.5	50.5	30.9	51.7

Following the proposed dosing regimen, the lowest exposure levels are anticipated in patients weighing from 40 to 50 kg (Figure 4). To check if efficacy is compromised by lower exposure in this weight group, observed response levels were compared between patients weighing 40 to 50 kg and all other patients. The results showed that although patients from 40 to 50 kg appear to have lower response than the other patients at recommended dose levels (5 mg/day or 10 mg/day), such difference in response levels were minimal at the maximum dose levels (10 mg/day or 20 mg/day) (Table 4). Since there is the option for subjects from 40 to 50 kg to increase the dose to the maximum level, lack of efficacy should not be a concern.

Figure 4: Simulated Exposure versus Body Weight Groups, Dose Given by Body Weight Cutoff at 50 kg



Source: Study 31-13-299 report (Feb. 12, 2014), Figure 4.3.6-1, Page 47.

Table 4: Comparison of Observed Response Levels between Patients Weighing 40-50 kg and the Others in Study 31-12-293

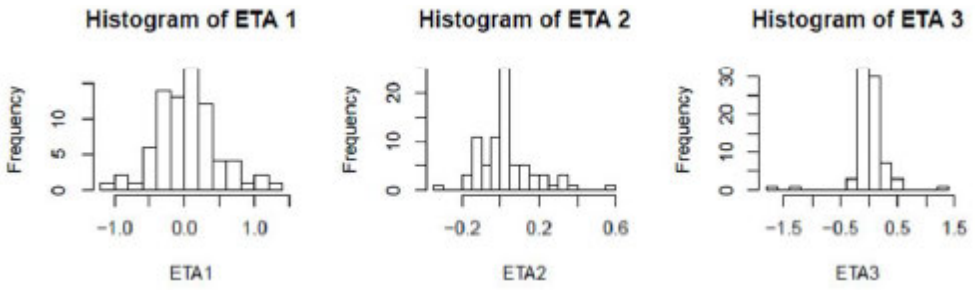
Dose Levels	Body Weight Groups	Change from Baseline in TTS at Week 8 Mean(SD)
Recommended (5 mg/day or 10 mg/day)	40 – 50 kg (n=8)	-5.75 (6.54)
	The others (n=35)	-13.38 (10.78)
Maximum (10 mg/day or 20 mg/day)	40 – 50 kg (n=10)	-14.1 (4.93)
	The others (n=35)	-17.67 (12.2)
Placebo	40 – 50 kg (n=10)	-8.3 (10.24)
	The others (n=34)	-6.85 (8.47)

2.4 Is aripiprazole PK in patients with Tourette similar to other patient populations?

Yes. Consistent PK properties of aripiprazole were shown in pediatric patients with Tourette's disorder as compared to other pediatric patient populations. Model evaluation (Figure 5) indicated that the previously developed pediatric population PK model based on pediatric schizophrenia and bipolar patients was able to describe well the PK data from Trial 31-12-293. The results suggest that the pharmacokinetic features of aripiprazole in pediatric patients with Tourette's Disorder are sufficiently similar to pediatric patients in other disease populations.

Figure 5: Diagnostic Plots Resulted from Fitting PK Data of Trial 31-12-293 with the PK Model and Parameter Estimates from the Previous Trials in Schizophrenia and Bipolar Pediatric Patients

(b) (4)



Note: Histograms of Eta1, Eta2, and Eta3 were for CL/F, V/F, and ka, respectively.
-source: Figure 4.2.2-1 and Figure 4.2.2-2 of Population PK/PD Reports 31-13-299.pdf

SIGNATURES

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Office of Clinical Pharmacology

Xiaofeng Wang
Reviewer, Pharmacometrics
Office of Clinical Pharmacology

Kevin Krudys
Team Leader, Pharmacometrics
Office of Clinical Pharmacology

RD/FT, Initialized by Hao Zhu, Ph.D.
Team leader, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology
Cc: NDA 21,520 (Mehta, Uppoor, Zhu, Krudys, Wang, Zhang)

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3. Appendix

3.1 Population PK Review

3.1.1 Summary of Findings

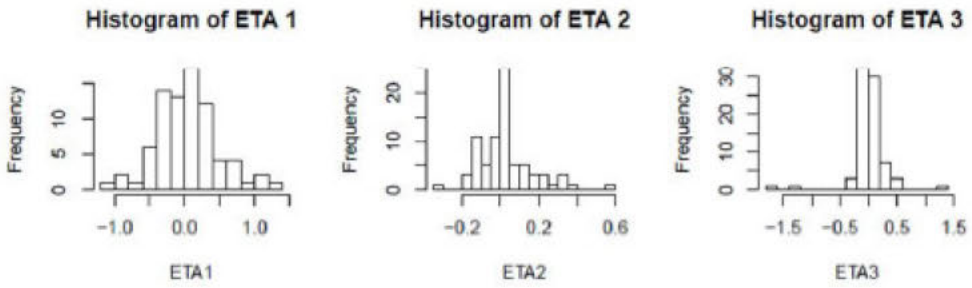
3.1.1 Key Review Questions

The purpose of this review is to address the following key questions.

3.1.1.1 Does aripiprazole demonstrate consistent PK properties in pediatric patients with Tourette Disorder compared to other patient populations?

Yes. Consistent PK properties of aripiprazole were shown in pediatric patients with Tourette Disorder (TD) as compared to other pediatric patient populations. Model evaluation (Figure 1) indicated that the previously developed pediatric population PK model based on pediatric schizophrenia and bipolar patients was able to describe well the PK data from Trial 31-12-293 conducted in pediatric patients with Tourette Disorder. The results suggest that the pharmacokinetic features of aripiprazole (i.e., underlying pharmacokinetic structure model and parameters) in pediatric patients with Tourette Disorder are sufficiently similar to pediatric patients in other disease populations.

Figure 1: Diagnostic Plots Resulted from Fitting PK Data of Trial 31-12-293 with the PK Model and Parameter Estimates from the Previous Trials in Schizophrenia and Bipolar Pediatric Patients



Note: Histograms of Eta1, Eta2, and Eta3 were for CL/F, V/F, and ka, respectively.

Source: Figure 4.2.2-2 on Page 32 of Population PK/PD Reports 31-13-299.pdf

3.1.1.2 Is the body weight cutoff value of 50 kg supported by PopPK analysis?

Yes. The proposed body weight cut off of 50 kg is supported by population pharmacokinetic analysis. The proposed dosing regimen for the treatment of (b) (4) Tourette's Disorder in pediatric patients, which suggested different recommended dosage and maximum dosage in pediatric patients at the body weight cut off at 50 kg, is shown in Table 1.

Table 1: Proposed dosage for treatment of (b) (4) Tourette's disorder in pediatric patients (b) (4)

	Initial Dosage (mg/day)	Recommended Dosage (mg/day)	Maximum Dosage (mg/day)
Patients (<50 kg)	2	5	10
Patients (≥ 50 kg)	2	10	20

Our population pharmacokinetic simulation demonstrated that, following the body weight cut off of 50 kg, the mean and variability of aripiprazole exposure (i.e., AUC) in low and high body weight groups are comparable (Table 2) in each dosing group. Exposure in patients with low body weight (<50 kg) is approximately 30% lower than that in patients with high body weight (≥ 50 kg) following the recommended dosage regimen.

Table 2: Mean AUC comparison in low dose and high dose groups based on body weight

	Low Dose Group		High Dose Group	
Dose (mg)	5 mg	10 mg	10 mg	20 mg
Body weight (kg)	<50	≥50	<50	≥50
Mean AUC (hr*ng/mL)	2.41	3.26	4.34	6.24
Sd	1.12	1.65	1.34	3.22
% CV	46.5	50.5	30.9	51.7
# of patients	30	15	19	11

3.1.1.2 Recommendations

Division of Clinical Pharmacology I has reviewed the pharmacokinetic analysis conducted by the sponsor, and concluded that there is sufficient evidence to support a recommendation of approval for Abilify in the treatment of (b) (4) Tourette Disorder (TD) in pediatric patients (b) (4), provided a labeling agreement can be reached with the sponsor.

3.1.2 Pertinent regulatory background

Abilify (aripiprazole) Oral Tablets has been approved for use in several indications since original approval in 2002. The approved indications in pediatric patients include: schizophrenia (13-17 years), bipolar mania (monotherapy or as an adjunct to lithium or valproate, 10-17 years), irritability associated with autistic disorder (6-17 years). In the current submission, Otsuka is seeking approval to add a new indication, treatment of (b) (4) (b) (4) Tourette's disorder in pediatric patients (b) (4) to the labeling for this product, based on safety and efficacy data from trials 31-12-293 and 031-KOA-0703.

3.1.3 Results of Sponsor's Analysis

From Sponsor's report 31-13-299-report-body.pdf

A previously developed population PK model of aripiprazole based on pediatric patients aged 10 to 17 years with schizophrenia, or bipolar 1 disorder, a one compartment model with first-order absorption, first-order elimination, and allometrically scaled PK parameters, was used to describe the PK data from Trial 31-12-293 conducted in pediatric patients with Tourette Disorder through Bayesian analysis.

Previously Developed PopPK model: The population PK of aripiprazole in children and adolescent subjects aged 10 to 17 years was previously described by a one-compartment model with first-order absorption rate constant (ka) and elimination.

The equations for PK parameters include a fixed power value of 0.75 for CL/F and 1.0 for V/F.

$$(Cl/F) = (Cl/F)_{TV} \cdot \left(\frac{LBW_i}{LBW_{ref}}\right)^{0.75}$$

$$(V/F) = (V/F)_{TV} \cdot \left(\frac{Wt_i}{Wt_{ref}}\right)^{1.0}$$

Table 3: Typical population PK parameters used in the model given the reference covariates (70 kg weight and 50 kg lean body mass).

Parameters	Parameter Estimates	%RSE[a]	95% CI	
			Lower Bound	Upper Bound
CL (L/hr)	3.44	2.76	3.26	3.63
V (L)	255	4.98	231	231, 283
Ka (hr^{-1})	1.67	25.5	0.748	4.28

[a]%RSE is percent relative standard error(100%xSE/EST)

Data Source for Original Model: The pharmacokinetic data file for analysis contained 1444 plasma samples of 343 patients from the following 3 studies:
Study 31-03-238: An Open-Label Dose Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of Orally Administered Aripiprazole Tablets in Children and Adolescent Patients with Mania Associated with Bipolar Disorder.
Study 31-03-239: A Multicenter, Randomized, Double-Blind, Placebo- Controlled Study of Two Fixed Oral Doses of Aripiprazole (10 mg or 30 mg) in the Treatment of Adolescent Patients with Schizophrenia.
Study 31-03-240: A Multicenter, Randomized, Double-Blind, Placebo- Controlled Study of Two Fixed Oral Doses of Aripiprazole (10 mg and 30 mg) in the Treatment of Child and Adolescent Patients, Ages 10-17 Years, with Bipolar I Disorder, Manic or Mixed Episode with or without Psychotic Features.
New PK Source: New PK analysis was conducted using 138 PK samples from 78 subjects in the aripiprazole arm in Trial 31-12-293.

Trial Description**:** Trial 31-12-293 was a phase 3, multicenter, randomized, double-blind, placebo controlled, outpatient trial designed to assess the safety and efficacy of oral aripiprazole once-daily tablets in children and adolescents with TD aged 7 to 17 years at screening. Qualified subjects were randomly assigned to low- or high-dose aripiprazole or placebo in a 1:1:1 ratio. For subjects who weighed < 50 kg at baseline, low and high doses of aripiprazole were 5 and 10 mg/day, respectively. For subjects who weighed ≥ 50 kg at baseline, low and high doses of aripiprazole were 10 and 20 mg/day, respectively.

Dose Administration: All subjects randomized to the aripiprazole groups began treatment at a 2 mg/day dose, with the dose titrated to 5 mg/day after 2 days. The dose was titrated to achieve the randomized dose according to a pre-specified titration scheme. All subjects reached their randomized dose by Week 3 and should have remained on that randomized dose.

Pharmacokinetic Sample Collection: Sparse PK samples were collected 2-10 or 12 hours post last dose (i.e., before the administration of the dose during the visit), during visits at Week 6 and 8.

Population Pharmacokinetic Analysis Methodology: NONMEM v7.2 was used for population PK and PK/PD modeling. R 2.15.1 and SAS v9.3 were used for data exploration and management, creation of graphs and tables.

PK data from Trial 31-12-293 were fitted with the previously developed population PK model described above. Bayesian analysis was conducted by setting MAXEVAL = 0 in NONMEM (software used for PK/PD modeling). Model evaluation was performed to determine whether the previously developed population PK model was adequate to describe PK data from Trial 31-12-293.

Typical diagnostic plots, visual predictive check (VPC), and distribution of interindividual variability (η) were visually examined to determine the adequacy of the

previously developed PK model and parameters in describing the PK data from Trial 31-12-293. Typical diagnostic or goodness of fit plots included individual predicted (IPRED) and population predicted (PRED) versus observed concentrations, and conditional weighted residuals (CWRES) versus PRED and time. VPC was conducted by generating one thousand Monte Carlo simulation replicates of the PK dataset using the population PK model; the 5th, 50th, and 95th percentile of aripiprazole concentrations were compared between the simulated data and the observed data. Histograms of η values were generated to determine whether the η values for CL/F, V/F, and ka were normally distributed, as assumed.

Results:

Model Evaluation Diagnostic plots, distribution of the inter-individual random effect, and VPCs were used to determine the adequacy of the previously developed PK model in describing the PK data from Trial 31-12-293. Typical diagnostic plots resulted from the fitting are presented in Figure 1.

Figure 1: Diagnostic Plots Resulted from Fitting PK Data of Trial 31-12-293 with the PK Model and Parameter Estimates from the Previous Trials

Note: circles for observed data; blue line for Loess fitting line, grey line for linear regression
Source: Figure 4.2.2-1 on Page 32 of Population PK/PD Reports 31-13-299.pdf

Figure 1 demonstrates that the previously developed population PK model was able to adequately describe the PK data from Trial 31-12-293. Although the diagnostic plots showed slight under-prediction towards the high concentrations, according to the sponsor, the same prediction trend was observed in the previous trial where the population PK model was developed.

The predictive performance of the model was assessed by VPC shown in Figure 2. The aripiprazole concentration-time course was simulated using 1000 replicates of the PK dataset "293PKEX.xpt". Due to the sparse sampling time, simulated concentrations and the observed concentrations were binned by Week 6 and Week 8 for the 5th, 50th, and 95th percentiles. The 5th, 50th, and 95th percentiles of the observed concentrations for other time points were not calculated, since there were only 1 to 3 data points for each sampling time. The previously developed model showed good predictive performance as the 5th, 50th, and 95th percentiles of the observed concentrations-time profiles agreed with the respective intervals of the model simulated data (Figure 2).

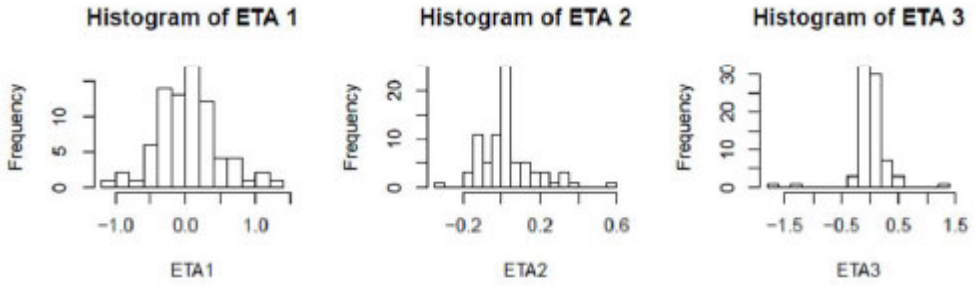
Figure 2: Visual Predictive Check of the Population PK Model

Note: Circles represent the observed data; dashed lines represent the 5th (green), 50th (blue), and 95th (red) percentiles of the observed data; solid lines are corresponding percentiles of the simulated data.
Bands represent the 5th (lower bound) to 95th (upper bound) percentiles of the corresponding percentiles.

Source: Figure 4.2.2-3 on Page 34 of Population PK/PD Reports 31-13-299.pdf

Histograms of inter-individual variability of parameters (Etas) estimated for subjects in Trial 31-12-293 presented in Figure 3 indicated that, in general, the IIV for each parameter is normally distributed with mean 0. The fact that the distribution of Etas follows normal distribution with mean at 0 further suggested that the previous population PK model was able to describe the PK data from Trial 31-12-293 without bias.

Figure 3: Histograms of Eta1, Eta2, and Eta3



Note: Histograms of Eta1, Eta2, and Eta3 were for CL/F, V/F, and ka, respectively.

Source: Figure 4.2.2-2 on Page 32 of Population PK/PD Reports 31-13-299.pdf

3.1.4 Reviewer's Analysis

The reviewer conducted independent analysis using the data and pharmacokinetic models submitted by the sponsor.

3.1.4.1 Introduction

The aim of reviewer's analysis is to confirm the analysis submitted by the sponsor, and to assess the appropriateness of body weight cut off of 50 kg in the proposed pediatric dosing.

3.1.4.2 Methods

3.1.4.2.1 Data Sets

Data sets used are summarized in Table 4.

Table 4. Analysis Data Sets

Study Number	Name	Link to EDR
31-12-293	293PKEX.xpt	<\\CDSESUB1\evsprod\NDA021436\0045\m5\53-clin-stud-rep\535-rep-effic-safety-stud\tourettes\5351-stud-rep-contr\study-31-12-293>

3.1.4.2.2 Software

NONMEM® (Version 7.2), and SAS® (Version 9.3)

3.1.4.2.3 Models Methods

The pharmacokinetic models submitted by the sponsor were employed in the evaluation. Similar analysis using Bayesian approach was conducted to compare PK data obtained from pediatric Tourette's patients with existing data collected from pediatric schizophrenia and bipolar patients. The simulation analysis aimed to evaluate the appropriateness of the proposed dosage-whether comparable exposure could be obtained under current dosing recommendation for different body weight groups.

3.1.4.3 Results

Assessment of model performance
In general, the reviewer was able to reproduce what the sponsor has performed, and agreed with the sponsor that the model adequately described the data from Trial 31-12-293. PK properties of aripiprazole are not different in the pediatric patients with Tourette's from patients in other indications (i.e., schizophrenia, or bipolar disorder).

Assessment of dosing recommendations
Exposure to aripiprazole in the pediatric Tics population demonstrated a high variability of about 60% (Table 5). The dosing regimen based on body weight (50 kg cut off) decreased the PK variability by roughly 9-12%.

Table 5: Aripiprazole exposure in pediatric patients with Tourette's disorder

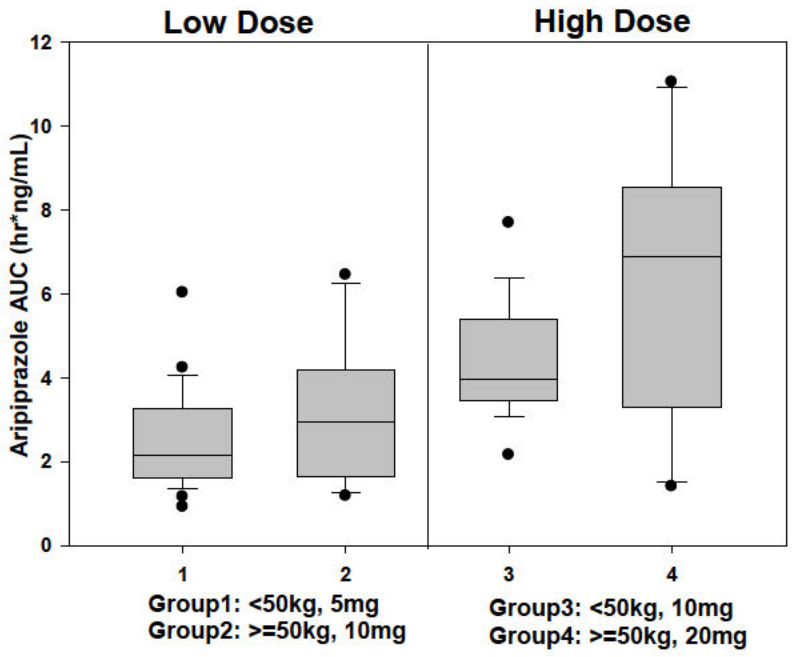
	All patients	Low body Weight group	High body weight group	Low dose group	High dose group
Mean AUC (hr*ng/mL)	3.63	3.16	4.52	2.70	5.04
Sd	2.15	1.53	2.82	1.36	2.36
% CV	59.2	48.4	62.4	50.5	46.8
# of patients	75	49	26	45	30

To determine whether 50 kg cutoff for dosing is appropriate, the exposure to aripiprazole was compared between the low dose group and high dose group stratified by body weight (Table 6, Figure 4).

Table 6: Mean (±SD) aripiprazole AUC in low dose group and high dose group

	Low Dose Group		High Dose Group	
Dose (mg)	5 mg (n=30)	10 mg (n=15)	10 mg (n=19)	20 mg (n=11)
Body weight (kg)	<50	≥50	<50	≥50
Mean AUC (hr*ng/mL)	2.41±1.12	3.26±1.65	4.34±1.34	6.24±3.22
% CV	46.5	50.5	30.9	51.7

Figure 4: Aripiprazole AUC comparison between low dose group and high dose groups



Our population pharmacokinetic simulation demonstrated that, following the body weight cut off of 50 kg, the mean and variability of aripiprazole exposure (i.e., AUC) in low and high body weight groups is comparable (Table 2) in each dosing group. Exposure in patients with low body weight (<50 kg) is approximately 30% lower than that in patients with high body weight (>= 50 kg) following the recommended dosage regimen. And the percent difference is smaller than the PK inter-subject variability.

3.2 Exposure-Response Analysis

3.2.1 Summary of Findings

3.2.1.1 Key Review Questions

The purpose of this review is to address the following key questions.

3.2.1.1.1 Is the proposed dose/exposure range appropriate?

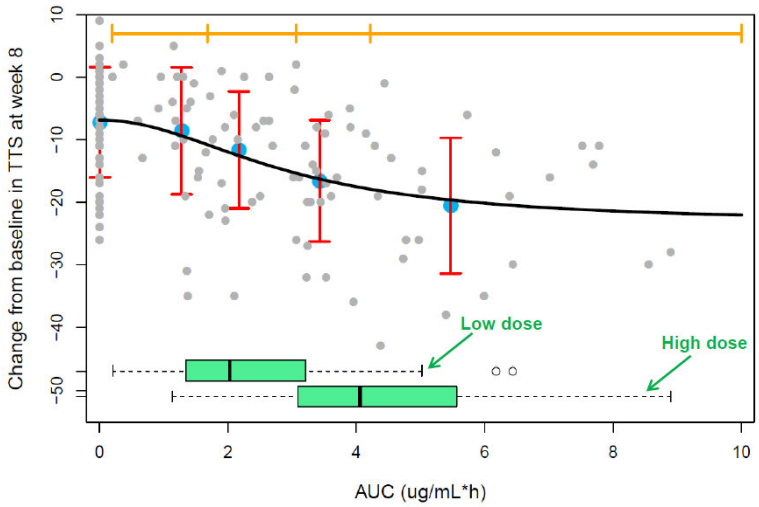
Yes, the proposed dose/exposure range is acceptable. In the current submission, the sponsor proposed a weight-based dosing regimen in order to narrow the concentration distribution within each pediatric dose range (Table 1).

Table 3 Summary of the Proposed Dosing Regimen

Patient Group	Initial Dose	Recommended Dose	Maximum Dose
Patients < 50 kg	2 mg/day	5 mg/day	10 mg/day
Patients ≥ 50 kg	2 mg/day	10 mg/day	20 mg/day

Our exposure-response analysis using data from Trial 31-12-293 showed that more efficacy benefit can be expected by increasing the dose from recommended levels (5 mg/day or 10 mg/day) to maximum levels (10 mg/day or 20 mg/day), but that the exposure-response curve is reaching its plateau at maximum dose levels (Figure 1).

Figure 1 Change from Baseline in TTS at Week 8 versus AUC



Note: black solid line is the typical exposure-response curve; grey points represent the observed change from baseline in TTS values for all subjects; orange line on the top represents AUC range for 4 exposure bins; blue points and red bars represent mean and standard deviation of the observed change from baseline in TTS values for placebo group (the first set) and 4 AUC bins; two green box plots at bottom represent the AUC distribution of the low dose and high dose treatment groups, respectively.

Population pharmacokinetic analysis in the current submission demonstrated similarity in PK across pediatric subjects with Tourette's disorder, schizophrenia, or bipolar disorder. Since the proposed dose range of 5 mg/day to 20 mg/day has been approved in pediatric patients of similar age in other indications, dose selection is also acceptable form the safety perspective.

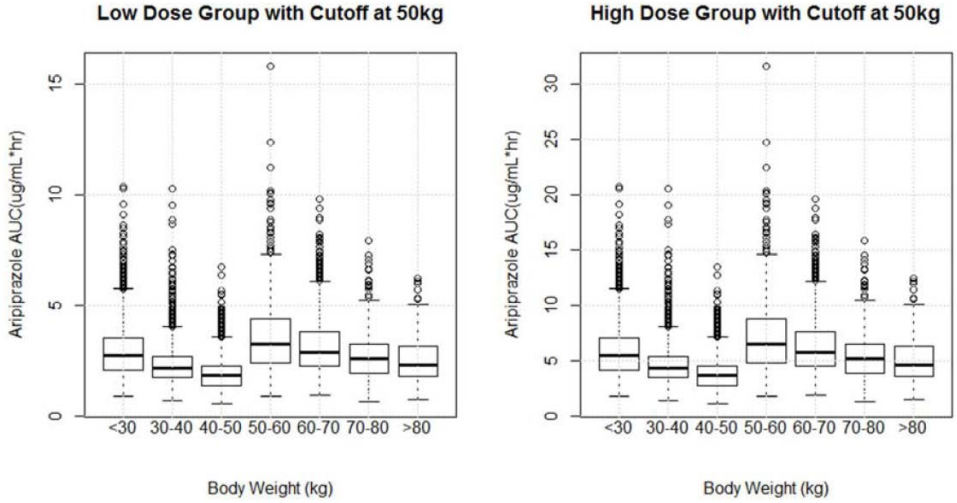
3.2.1.1.2 Is the proposed body-weight based dosing regimen with the body weight cutoff of 50 kg acceptable?

Yes, the proposed body-weight based dosing regimen with the body weight cutoff of 50 kg is acceptable. Such a weight cutoff would result in the lowest exposure levels in patients weighing from 40 to 50 kg (Figure 2). To check if efficacy is compromised by lower exposure in this weight group, observed response levels were compared between patients weighing 40 to 50 kg and all other patients. The results showed that although patients from 40 to 50 kg appear to have lower response than the other patients at recommended dose levels (5 mg/day or 10 mg/day), such difference in response levels were minimal at the maximum dose levels (10 mg/day or 20 mg/day) (Table 2). Since there is the option for subjects from 40 to 50 kg to increase the dose to the maximum level, lack of efficacy should not be a concern.

Table 4 Comparison of Observed Response Levels between Patients Weighing 40-50 kg and the Others in Study 31-12-293

Dose Levels	Body Weight Groups	Change from Baseline in TTS at Week 8 Mean(SD)
Recommended (5 mg/day or 10 mg/day)	40 – 50 kg (n=8)	-5.75 (6.54)
	The others (n=35)	-13.38 (10.78)
Maximum (10 mg/day or 20 mg/day)	40 – 50 kg (n=10)	-14.1 (4.93)
	The others (n=35)	-17.67 (12.2)
Placebo	40 – 50 kg (n=10)	-8.3 (10.24)
	The others (n=34)	-6.85 (8.47)

Figure 2 Simulated Exposure versus Body Weight Groups, Dose Given by Body Weight Cutoff at 50 kg



Source: Study 31-13-299 report (Feb. 12, 2014), Figure 4.3.6-1, Page 47.

3.2.1.2 Recommendations

The sponsor's proposed dosing regimen is acceptable.

3.2.2 Pertinent regulatory background

Aripiprazole is approved for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder in adults in the United States (US), the European Union (EU), Canada, and several other countries, and as adjunctive treatment in adult patients with major depressive disorder in the US. Aripiprazole extended release injectable suspension, for intramuscular use, was recently approved in the US and EU as a treatment for schizophrenia in adults. Aripiprazole is also approved in the US, EU, and Canada as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder in adult patients, and these indications have been approved in children and adolescents in the US. In addition, aripiprazole is approved for the treatment of schizophrenia in adolescents in the US (aged 13-17 years) and EU (aged 15-17 years), for the treatment of bipolar I disorder in the US in children and adolescents (aged 10-17 years) and in EU (aged 13-17 years), and for the treatment of irritability associated with autistic disorder in the US in children and adolescents (aged 6-17 years).

Otsuka Pharmaceutical Company Ltd. submitted a supplemental new drug application on 2/12/2014 requesting approval to add a new indication, treatment of (b) (4) Tourette's disorder in pediatric patients (b) (4) to the labeling for this product based on safety and efficacy data from trials 31-12-293 and 031-KOA-0703.

3.2.3 Results of Sponsor's Analysis

3.2.3.1 Summary of Clinical Trial 31-12-293

Study 31-12-293 was a multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of fixed-dose once-daily oral aripiprazole in

children and adolescents (aged 7-17 years) with Tourette's disorder. After qualifying for enrollment, subjects were randomly assigned to low- or high-dose aripiprazole or placebo in a 1:1:1 ratio. For subjects who weighed < 50 kg at baseline, low and high doses of aripiprazole were 5 and 10 mg/day, respectively. For subjects who weighed ≥ 50 kg at baseline, low and high doses of aripiprazole were 10 and 20 mg/day, respectively. All subjects randomized to the aripiprazole groups were titrated to the target doses from an initial dose of 2 mg/day according to a pre-specified titration scheme. Approximately 126 subjects were planned for randomization in this trial from an estimated 120 sites worldwide. A total of 171 subjects were screened for the trial and 133 randomized.

The primary efficacy endpoint was the change from baseline to endpoint (Week 8) on the total tic score (TTS) of the Yale Global Tic Severity Scale (YGTSS). The treatment difference between the low-dose aripiprazole and placebo groups (-6.26) was statistically significant ($p = 0.0020$) for the primary efficacy endpoint (change from baseline to Week 8 in YGTSS TTS); the treatment difference between the high-dose aripiprazole and placebo groups (-9.85) was also statistically significant ($p < 0.0001$), based on a mixed effect repeated measure model.

No deaths or any other serious TEAEs were reported during the trial. Discontinuation of aripiprazole due to a TEAE occurred in 9 subjects: 1 subject (2.3%) each, in the low-dose aripiprazole and placebo groups and 7 subjects (15.6%) in the high-dose aripiprazole group. The overall incidence of TEAEs in the low- and high-dose aripiprazole groups was 65.9% and 75.6%, respectively, and 40.9% in the placebo group. The most frequently reported TEAEs that occurred in the low- and high-dose aripiprazole groups (with an incidence of ≥ 5% in both aripiprazole groups) were sedation (18.2% and 8.9%, respectively), somnolence (11.4% and 15.6%, respectively), increased appetite (9.1% and 6.7%, respectively), fatigue (6.8% and 15.6%), and headache, nasopharyngitis, and nausea (6.8% and 8.9%, respectively, each).

Subjects visited the clinic at Weeks 1, 2 (± 1 day), 4, 6, and 8 (± 3 days), at which time efficacy, safety, and outcome measures were collected. Blood samples were collected during Weeks 6 and 8, and plasma concentrations of aripiprazole and its active metabolite, dehydro-aripiprazole, were assessed. The PK samples were collected either at 2 to 10 hours post last dose or at 12 hours post last dose (ie, before the administration of the dose during the visit).

3.2.3.2 Exposure-Efficacy Analysis

A population PK/efficacy analysis was performed to characterize the exposure-efficacy relationship for the changes in TTS of the Yale Global Tic Severity Scale (YGTSS) from baseline following administration of aripiprazole using data from study 31-12-293. Model simulation was then performed to support dose regimen selection for this population of pediatric subjects with Tourette's disorder.

3.2.3.2.1 Exposure-Response Modeling

The primary endpoint of efficacy, the change of TTS from baseline with time, was explored graphically and the results indicated that the longer the treatment duration and the higher the aripiprazole exposure, the greater the decrease of the TTS (Figure 3). To assess the effect of aripiprazole on TTS reduction, the change in TTS with time was

characterized by adding a drug effect model on top of a placebo effect model, which incorporated baseline estimate (BASE), placebo effect (EFF_P), and drug effect (EFF_d) (Equation 1):

$$TTS = BASE \times (1\text{-}EFF_P) \times (1\text{-}EFF_d) \quad (1)$$

The placebo effect, EFF_P, was described by a Weibull model (Equation 2), where $Pmax_p$ represents the maximum placebo effect; k represents the time to reach $Pmax_p$; γ is the power term defining the shape of the curve.

$$EFF_P = P\max_p(1 - e^{-(kt)^\gamma}) \quad (2)$$

The drug effect was described using a time- and exposure-dependent model with nonlinear relationships (Equation 3), where Imax is the maximum effect of aripiprazole; AUC50 is the aripiprazole AUC required to elicit half of the maximum effect; TD50 represents time to achieve half of maximum aripiprazole effect.

$$EFF_d = \frac{\mathrm{Im}ax \cdot Time \cdot AUC}{(TD50 + Time)(AUC50 + AUC)} \quad (3)$$

Final parameter estimates of the model are shown in Table 3 and model diagnostic plots are shown in Figure 4. In addition, VPC was carried out to evaluate the predictive performance of the final model (Figure 5).

3.2.3.2.2 Exposure-Response Simulation

Model simulation was conducted to assess the expected efficacy for different body weight (BW) subgroups with the proposed dosing regimen. Specifically, 100 replicates of the dataset of Trial 31-12-293 were simulated. A high dose (10 m/day for low BW group, 20 mg/day for high BW group) and a low dose (5 mg/day for low BW group, 10 mg/day for high BW group) of aripiprazole were assigned to subjects by BW cutoff at 50 kg. The median AUC for each group is shown in Table 4. The AUC values for different BW subgroups are shown in Figure 2.

Given the cutoff BW at 50 kg, low-dose and high-dose treatment groups would achieve a median value of 32% (daily aripiprazole exposure [AUC] = 2.16 μg/mL*h) to 35% (AUC = 2.82 μg/mL*h), and 39% (AUC = 4.32 μg/mL*h) to 41% (AUC = 5.64 μg/mL*h) reduction in TTS in addition to the placebo effect (26.7% reduction) with 8 weeks of treatment duration. At AUC ≥ 6.48 μg/mL*h, further increased aripiprazole exposure will not improve the response. Changing the body weight cutoff value, for example, from 50 to 40 kg, will double the exposure for subjects weighing 40 to 50 kg from 3.61 to 7.22 μg/mL*h, as the high dose for these subjects will be 20 mg instead of 10 mg once-daily tested in Trial 31-12-293. However, the expected increase in the reduction of TTS will only be approximately 4%.

To summarize, given a dose from 5 to 20 mg, significant improvement in efficacy compared with placebo group is expected. A dose between 10 and 20 mg will provide similar response across all subjects.

Reviewer's Comments:

1. *The sponsor's population exposure-efficacy analysis appears appropriate.*
2. *We conducted our independent exposure-response analysis to further support the proposed dosing regimen. (See reviewer's analysis section)*

3.2.3.3 Exposure-Safety Analysis

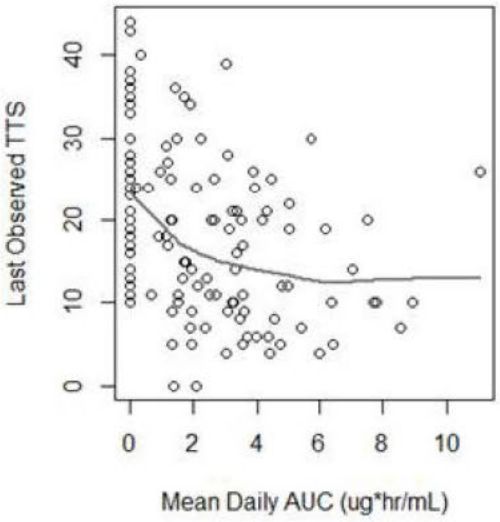
Among the 88 subjects who were treated with aripiprazole, 76 (86.4%) subjects completed the trial and 12 (13.6%) subjects discontinued before Week 8. There were 8 subjects who stopped aripiprazole due to AEs. No difference in aripiprazole, age, BW, and baseline TTS was observed among those who stopped aripiprazole due to AE (n=8), those who discontinued (n=12), and those who completed the trial (n=76).

To explore whether subjects who discontinued IMP due to AE or who discontinued from the trial during the titration period had higher aripiprazole exposure, CL/F values were compared among subjects who stopped IMP due to AE, who discontinued, and who completed the trial. No difference in CL/F was observed for subjects in different groups, indicating no exposure-AEs or exposure-dropout relationship (Figure 6).

Reviewer's Comments: The sponsor's exposure-safety analysis appears appropriate.

Figure 3 Graphical Analysis of the Primary Efficacy Endpoint

(b) (4)



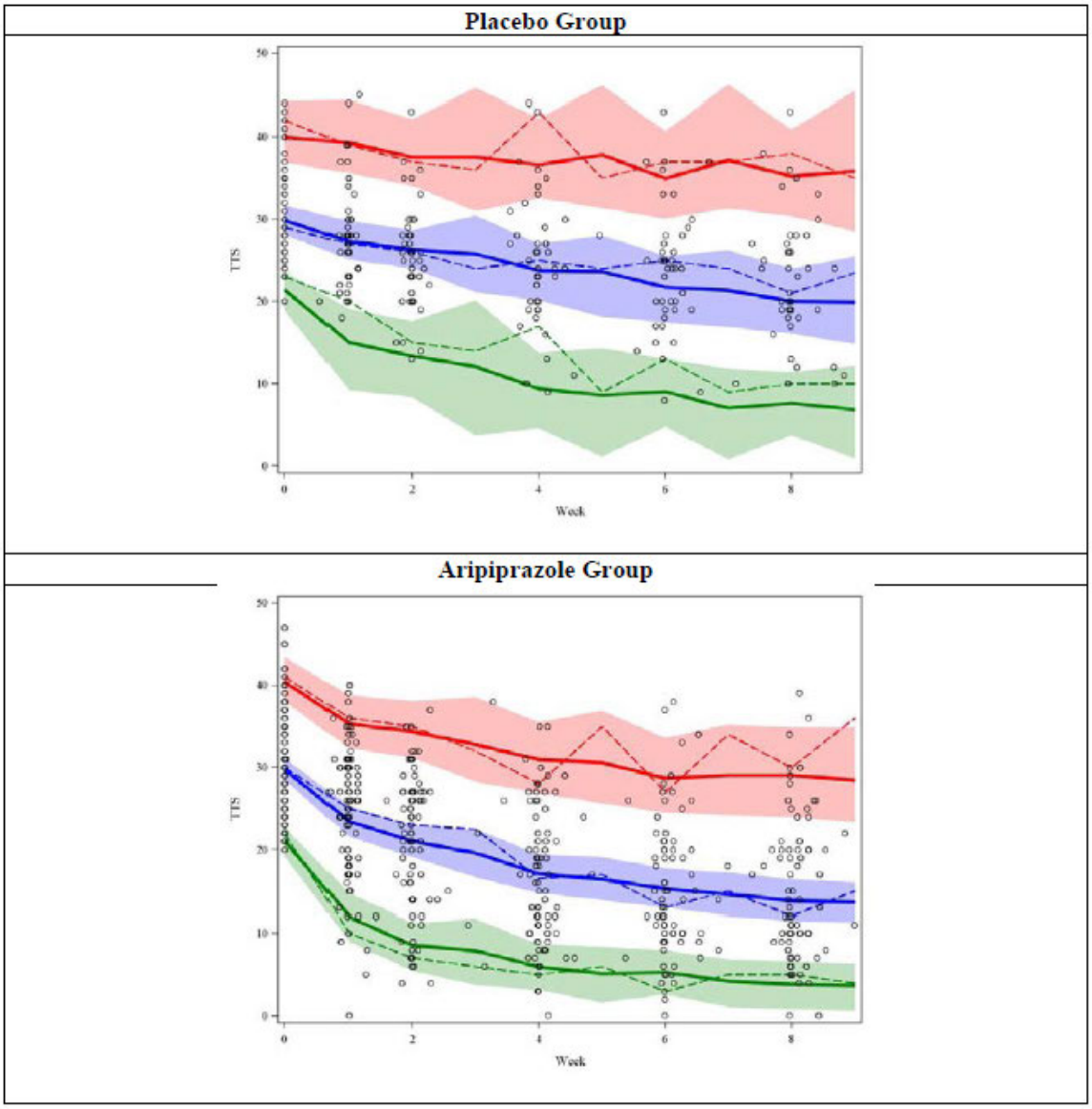
Note: The left panel shows observed TTS versus time; the right panel shows last observed TTS versus mean daily AUC

Source: Study 31-13-299 report (Feb. 12, 2014), Figure 4.3.1-1, 4.3.1-2, Page 38.

Figure 4 Diagnostic Plots for the Final Exposure-efficacy Model

Source: Study 31-13-299 report (Feb. 12, 2014), Figure 4.3.5.1-1, Page 44.

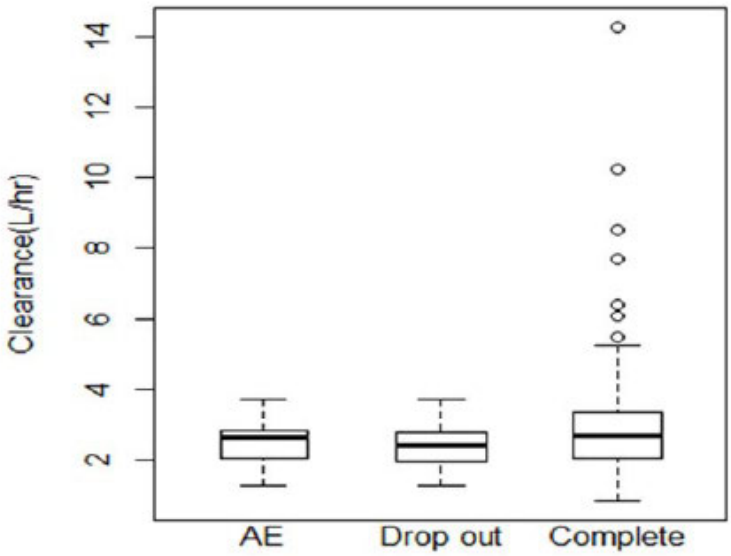
Figure 5 Visual Predictive Check of the Final Population Exposure-efficacy



Note: Circles represent the observed data; dashed lines represent the 5th (green), 50th (blue), and 95th (red) percentiles of the observed data; solid lines are corresponding percentiles of the simulated data. Bands represent the 5th (lower bound) to 95th (upper bound) percentiles of the corresponding percentiles.

Source: Study 31-13-299 report (Feb. 12, 2014), Figure 4.3.5.1-2, Page 46.

Figure 6 Comparison of Clearance Values Among Subjects with Different Trial Completion Statuses



AE = adverse event; IMP = investigational medicinal product.
Note: AE refers to subjects who stopped IMP due to AEs, Dropout refers to subjects who discontinued before Week 8, and Complete refers to subjects who completed the trial.

Source: Study 31-13-299 report (Feb. 12, 2014), Figure 4.4.1-1, Page 51.

Table 5 Final Parameter Estimates of the Exposure-efficacy Model

Parameter	Parameter Explaination	Parameter Estimate	%RSE[a]	
THETA				
TTS0	Baseline Total Tic Score	29.7	1.88%	
Logit P_{maxp}	Logit maximum placebo effect	0.272	57.40%	
P_{maxp}[b]	Maximum placebo effect	0.568		
K (1/day)	Rate of reaching maximum placebo effect	0.0146	16.85%	
λ	Power parameter in Weibull function	2.26	21.95%	
I_{max}	The maximum aripiprazole effect	0.607	11.25%	
AUC_{50}	Aripiprazole AUC to achieve half of its maximum effect	1.11	42.07%	
TD_{50} (days)	Parameter describing the time to achieve half of maximum aripiprazole effect	13.1	35.34%	
OMEGA				IIV
IIV TTS0 (1,1)	Inter-individual variability (IIV) in TTS0	0.0314	18.50%	17.72%
IIV LOGP (2,2)	IIV in logit P_{maxp}	0.747	67.47%	
	P_{maxp}[b]			8.91%
IIV LOGP,K (3,2)	Correlation between IIVs in Logit P_{maxp} and K	0.503	156.46%	
IIV K (3,3)	IIV in K	1.81	28.73%	134.54%
IIV λ (4,4)	IIV in λ	2.68	27.09%	163.71%
IIV AUC_{50} (5,5)	IIV in AUC_{50}	0.629	92.21%	79.31%
IIV TD_{50} (6,6)	IIV in TD_{50}	6.05	39.01%	245.97%
SIGMA				
ERR1	Additive residual error	7.09	3.64%	

AUC_{50} = AUC of aripiprazole required to achieve half of its maximum effect; IIV = inter-individual variability; I_{max} = maximum aripiprazole effect; K = rate to reach maximum placebo effect; P_{maxp} = maximum placebo effect; RSE = residual standard error; SE = standard error; TD_{50} = time to achieve half of maximum aripiprazole effect; TTS0 = Baseline Total Tic Score.

Source: Study 31-13-299 report (Feb. 12, 2014), Table 4.3.4-1, Page 43.

Table 6 Simulated Steady State Daily AUC (ug*hr/mL) with a Cutoff Body Weight of 50 kg (Subjects, n=7800)

Dose Group	BW Group	DOSE	MEAN	SD	5th Percentile	50th Percentile	95th Percentile
LOW	< 50 kg	5 mg	2.45	1.13	1.13	**2.16**	4.68
	≥ 50 kg	10 mg	3.13	1.42	1.47	**2.82**	5.92
HIGH	< 50 kg	10 mg	4.89	2.26	2.27	**4.32**	9.36
	≥ 50 kg	20 mg	6.25	2.84	2.94	**5.64**	11.83

AUC = area under the curve; BW = body weight; SD = standard deviation.

Source: Study 31-13-299 report (Feb. 12, 2014), Table 4.3.6-1, Page 47.

3.2.4 Reviewer's Analysis

3.2.4.1 Introduction

In the current submission, the sponsor conducted population PK/efficacy analysis for efficacy using a longitudinal model describing the change of TTS with time following aripiprazole administration. Simulation was then utilized to support the proposed dosing regimen. We therefore performed an independent exposure-response analysis to confirm the sponsor's results and conclusions.

3.2.4.2 Objectives

Analysis objective is to explore the relationship between aripiprazole exposure and the primary efficacy endpoint, change from baseline in TTS at week 8, to support dosing regimen selection.

3.2.4.3 Methods

3.2.4.3.1 Data Sets

Data sets used are summarized in 3.2.5.

Table 7 Analysis Data Sets

Study Number	Name	Link to EDR
31-12-293	ttsmd293	\\cdsesub1\evsprod\nda021436\0045\m5\datasets\31-13-299\analysis\ttsmd293.xpt

3.2.4.3.2 Software

NONMEM (Version 7.2, ICON Development Solutions) and R (Version 3.0.2, Insightful Inc.) were used in the analysis.

3.2.4.4 Results

3.2.4.4.1 Exposure-response model

Instead of using the observed TTS at various time points as the response variable in the sponsor's population PK/efficacy analysis, the primary efficacy endpoint, change from baseline in TTS at week 8, was directly modeled against aripiprazole AUC at week 8 using an Emax model, which adequately described the exposure-response relationship. The typical exposure-response curve of change from baseline in TTS at week 8 against aripiprazole exposure is presented as the solid black line in Figure 1. Our exposure-response model showed that more efficacy benefit is expected by increasing the dose from recommended levels (5 mg/day or 10 mg/day) to maximum levels (10mg/day or 20 mg/day), and exposure response curve is reaching its plateau at maximum dose levels. Our results confirmed the sponsor's exposure-efficacy analysis and provided additional support for the proposed dosing regimen.

3.2.5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
emax.mod	Model input file	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Aripiprazole_NDA21436_XW\ER Analyses
emax model.lst	Model output file	\\cdsnas\pharmacometrics\Reviews\Ongoing

		PM Reviews\Aripiprazole_NDA21436_XW\ER Analyses
emax.csv	dataset	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Aripiprazole_NDA21436_XW\ER Analyses

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/s/

HUIXIA ZHANG
10/31/2014

XIAOFENG WANG
10/31/2014

KEVIN M KRUDYS
11/03/2014

HAO ZHU
11/03/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**21,436/S38**	**Brand Name**	**Abilify**
OCP Division (I, II, III, IV, V)	**DCPI**	**Generic Name**	**Aripiprazole**
Medical Division	**Division of Psychiatry Product**	**Drug Class**	**Antipsychotics**
OCP Reviewer	**Huixia Zhang**	**Indication(s)**	**Treatment of (b) (4) (b) (4) Tourette's disorder**
OCP Team Leader	**Hao Zhu**	**Dosage Form**	**IR tablet**
Pharmacometrics Reviewer	**Xiaofeng Wang**	**Dosing Regimen**	**QD**
Date of Submission	**2/12/2014**	**Route of Administration**	**PO**
Estimated Due Date of OCP Review	**11/4/2014**	**Sponsor**	**Otsuka**
Medical Division Due Date	**11/12/2014**	**Priority Classification**	**Standard**
PDUFA Due Date	**12/12/2014**		

Summary

This supplemental application proposes modifications to the labeling based on safety and efficacy data from trials 31-12-293 and 031-KOA-0703 for the treatment of (b) (4) Tourette's disorder in pediatric patients (b) (4) Additionally, one PK/PD study report (31-13-299) is also included in the submission.

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**x**	**1**		
Population Analyses -				
Data rich:				
Data sparse:	**x**	**1**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the			X	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	NDA legible so that a substantive review can begin?				
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Orphan drug indication
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Huixia Zhang 3/28/2014

Reviewing Clinical Pharmacologist Date

Hao Zhu 3/28/2014

Team Leader/Supervisor Date

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/s/

HUIXIA ZHANG
07/24/2014

HAO ZHU
07/24/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21436/S-38

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: December 5, 2014
NDA: **21436/S-038, 21713/S-030, 21729/S-022, 21866/S-023**
Drug: Abilify (aripiprazole) 2, 5, 10, 15, 20, 30 mg tablets (NDA 21436); Abilify (aripiprazole) 1 mg/mL oral solution (NDA 21713); Abilify (aripiprazole) 10 and 15 mg ODT (NDA 21729); Abilify (aripiprazole) 9.75 mg/1.3 mL injection for IM use (NDA 21866)
Sponsor: Otsuka Pharmaceutical Development & Communications, Inc.
Proposed Change(s): Tourette's Disorder in children ages (b) (4) years.

Labeling Supplements Under Review:

NDA	Supplement	Dated	Action
Abilify (aripiprazole) 2, 5, 10, 15, 20, & 30 mg Tables (NDA 21436)			
21436	S-036	3/15/13,and Class 1 RS 5/13/14	Approval letter dated 6/9/14
21436	S-038	2/12/2014	Pending
Abilify (aripiprazole) 1mg/mL Oral Solution (NDA 21713)			
21713	S-028	3/15/13, and Class 1 RS 5/13/14	Approval letter dated 6/9/14
21713	S-030	4/3/2014	Pending
Abilify (aripiprazole) 10 mg and 15 mg ODT (NDA 21729)			
21729	S-020	3/15/13, and Class 1 RS 5/13/14	Approval letter dated 6/9/14
21729	S-022	4/3/2014	Pending
Abilify (aripiprazole) 9.75 mg/1.3 mL injection for IM use (NDA 21866)			
21866	S-021	3/15/13, and Class 1 RS 5/13/14	Approval letter dated 6/9/14
21866	S-023	4/3/2014	Pending

NOTES

- The last approved labeling, for comparison purposes, was the labeling attached to the 6/09/2014 approval letter for supplemental applications 21436/S-036, 21713/S-028, 21729/S-020, 21866/S-021.
- This review will only encompass PA Efficacy S-038 (NDA 21436), S-030 (NDA 21713), S-022 (NDA 21729), and S-023 (NDA 21866).
- All 4 NDA formulations share the same labeling.

REVIEW

21436/S-038, 21713/S-030, 21729/S-022, 21866/S-023
Date: 02/12/2014 for 21436/S-038 and 04/03/2014 for 21713/S-030, 21729/S-022, & 21729/S-023
CBE: No
Reviewed by Clinical and Statistical Reviewers: Yes: 11/12/2014(Clinical) and 10/31/2014 (Statistical) respectfully.

The sponsor has proposed to update the following sections of their label based on two studies that displayed the safety and efficacy of Abilify for the treatment of Tourette's Disorder in children: Indications and Usage (1); Dosage and Administration (2.5); and Warnings and Precautions, Metabolic Changes (5.6). .

Additionally, many edits to labeling were provided by the ADL as a result of an initiative to promote consistency across our Psychotropic Products per the PLR including changes to section 1: Indications and Usage; section 2: Dosage and Administration; section 5: Warnings and Precautions; section 6: Adverse Reactions; section 7: Drug Interactions; section 8: Use in Specific Populations; section 12: Clinical Pharmacology; section 14: Clinical Studies; section 17: Patient Counseling Information; and the Medication Guide. We reached agreement, verbatim, with the sponsor regarding labeling on December 09, 2014.

CONCLUSIONS

1. These supplements only provide for the labeling revisions listed above when compared to the last approved labeling (see approval letter dated 06/09/2014). Please see attached documentation denoting the revisions made to labeling compared to the last approved label for Abilify; approval letter dated 06/09/2014).

2. I recommend issuing an approval letter for these pending efficacy supplements.

William H. Bender, R.Ph., MS HCA, Senior Regulatory Project Manager

Paul David, CPMS

Enclosure: 1) Labeling agreement email dated 12/09/2014, from sponsor, and 2) Annotated labeling changes- Full Prescribing Information and Medication Guide

Bender, William

From: Guinn, Patrick <Patrick.Guinn@otsuka-us.com>
Sent: Tuesday, December 09, 2014 5:44 PM
To: Bender, William
Cc: Goldberger, David; Prindle, Ann; Guinn, Patrick
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children
Attachments: CLEAN - nda21436s03812092014cleanWB - Response - 9-Dec-14.doc.doc; nda21436s03812092014cleanWB - Response - 9-Dec-14.doc.doc

Hi Bill,

Please refer to the attachments for revised labeling incorporating the most recent FDA comment sent this afternoon, Dec 9.

> **FDA Comment #3: RECENT MAJOR CHANGES, Warnings and Precautions, Metabolic Changes (5.6) 12/2014 - These are new data for Tourette's patients. The labeling will need to have the black line along the side accordingly.**
> ***Otsuka's Response**: Formatting changes have been addressed.*

These revisions have been incorporated into the label along with previous comments provided by FDA this morning, Dec 9.

> **FDA Comment #1: Page 2, Full Prescribing Information Comments - Please move this horizontal line and FULL PRESCRIBING INFORMATION: CONTENTS* to the top of the next page as you did for your application of Abilify Maintena, NDA 202971.**
>
> ***Otsuka's Response**: Formatting errors have been addressed.*
>
> **FDA Comment #2: Page 47, Section 7.2, Drugs Having No Clinically Important Interactions with ABILIFY - *Based on the labeling and published data, it seems that CYP2C19 contributes more to the metabolism of (es)citalopram, compared to CYP3A4 and CYP2D6.***
>
> ***Otsuka's Response**: FDA edits have been accepted.*

The formal submission will be sent electronically later today.

Regards, Patrick.

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Tuesday, December 09, 2014 11:15 AM
To: Guinn, Patrick
Cc: Goldberger, David; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Hi Patrick,
We have addressed your below comment regarding escitalopram. Also, the "Full Prescribing Information Contents" and horizontal line are still on the first page and not on the TOC page (top of the second page) as you did for your Abilfiy Maintena application. Please edit that part accordingly and let us know if you accept our escitalopram comment. If so, please send back a clean word version and the version addressing our comments as you have been doing. I am suspecting that this can be done by COB today.
Thanks,
Bill

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Monday, December 08, 2014 11:09 AM
To: Bender, William
Cc: Goldberger, David; Prindle, Ann; Guinn, Patrick
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Hi Bill,

Please refer to the attachments for labeling that addresses FDA's comments as well as a clean copy of the labeling as requested.

We accept the revised labeling as requested by FDA on Friday, Dec 5.
We are requesting one clarification regarding the deleted text and the revised text provided by FDA in Section 7.2. It appears that escitalopram (highlighted in the deleted text) was inadvertently omitted from the revised text provided by FDA. Otsuka added escitalopram back into the text for the list of substrates of (b) (4) Please provide confirmation that this is acceptable or any additional FDA comments regarding this matter.

In Section 7.2 Drugs Having No Clinically Important Interactions with ABILIFY

(b) (4)

Regards, Patrick.

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Friday, December 05, 2014 11:33 AM
To: Guinn, Patrick
Cc: Goldberger, David; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Hi Patrick,
We have some very minor edits to the label (attached). Please use this label to address our comments and send back to me (also please include a clean word version).
Thanks and please let me know if you have any questions.
Thanks,
Bill

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Tuesday, December 02, 2014 4:57 PM
To: Bender, William
Cc: Goldberger, David; Guinn, Patrick; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Dear Bill,

Please refer to the attachments for the Cover Letter, marked up labeling, and clean copy labeling, as requested by FDA.

Reference is made to Otsuka Pharmaceutical Company, Ltd.'s (OPC) New Drug Applications (NDAs) 21-436 (aripiprazole tablets), approved on November 15, 2002, 21-713 (aripiprazole oral solution) approved on December 10, 2004, 21-729 for Abilify Discmelt (aripiprazole orally disintegrating tablets) approved on June 7, 2006 and 21-866 (aripiprazole intramuscular injection) approved on September 20, 2006.

Reference is also made to the made to the supplemental new drug application (sNDA) requesting approval to add a new indication, treatment of (b) (4) Tourette's disorder in pediatric patients (b) (4) to the labeling for this product, which was submitted on February 12, 2014.

Further reference is made to the draft labeling provided by FDA on November 30, 2014, in an email from CDR William Bender, Senior Regulatory Project Manager, request for additional revisions to the overall Abilify package insert.

We have accepted and incorporated all text changes requested by FDA. In addition, there were four comments from FDA included in the draft labeling. Comments made by the FDA are stated in bold and are followed by Otsuka's response.

- **FDA Comment #1: Use this clean label as a base document. Please carefully review this label and correct any formatting errors (including the 42-item checklist) and typos. Address all outstanding requests noted in comments and track all changes. Delete comments, once you have addressed them in labeling.**

  ***Otsuka's Response**: Formatting errors have been addressed and all comments that have been addressed in the past have been deleted at requested.*

- **FDA Comment #2: Edits made for consistency with Abilify Maintena labeling (Section 5.8).**

  ***Otsuka's Response**: FDA edits have been accepted.*

- **FDA Comment #3: Have there been any premarketing cases of rhabdomyolysis that were not associated with neuroleptic malignant syndrome? If yes, rhabdomyolysis should be re-added.**

  ***Otsuka's Response**: Rhabdomyolysis has been re-added.*

- **FDA Comment #4: Please add PK changes for venlafaxine, escitalopram, fluoxetine, paroxetine, sertraline to the forest plot. If cannot be added to the plot, please provide brief description as text (Drug Interaction Studies, Figure 3).**

  ***Otsuka's Response**: The PK data for venlafaxine (CSR CN138462) and escitalopram (CSR CN138463) was added to Figure 3. The text summary was added for other ADTs.*

Regards, Patrick.

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Tuesday, December 02, 2014 7:55 AM
To: Guinn, Patrick
Subject: FW: NDA 21436 s038 Abilify for Tourette's in Children

Good Morning Patrick,
Do you think that you will be able to respond today?
Thanks,
Bill

From: Bender, William
Sent: Sunday, November 30, 2014 9:50 PM
To: Guinn, Patrick
Cc: Goldberger, David; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Hi Patrick,

Attached is hopefully our last labeling negotiation. Please use this clean version as your base label, delete the comments that have been addressed, and track any additional changes (if you have any). Since there are a few comments, please send back to me by COB Tuesday, December 2nd.
Thanks,
Bill

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Friday, November 21, 2014 5:16 PM
To: Bender, William
Cc: Goldberger, David; Prindle, Ann; Guinn, Patrick
Subject: NDA 21436 s038 Abilify for Tourette's in Children

Hi Bill,

Please refer to the attachments for the Cover Letter and responses to FDA comments in the labeling.

- Attachment 1: Cover Letter
- Attachment 2: Labeling with responses to FDA comments

The electronic submission is expected to be sent through the FDA e-gateway tonight.

Regards, Patrick.

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Thursday, November 20, 2014 11:43 AM
To: Guinn, Patrick
Cc: Goldberger, David; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Hi Patrick,
We have some minor changes to the label (attached). Please respond to these changes by Monday, November 24th. Please let me know if you have any questions.
Thanks,
Bill

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Friday, November 14, 2014 2:14 PM
To: Bender, William
Cc: Goldberger, David; Guinn, Patrick; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Dear Bill,

Please refer to the attachments for responses to your e-mail correspondence dated 10 Nov 2014.
The electronic submission is scheduled to be submitted through the FDA e-gateway later today.

- Attachment #1 - Cover Letter (responses)
- Attachment #2 – Draft Clean Word labeling
- Attachment #3 – Draft Marked Up Word labeling

Please let me know if you have any questions.

Regards, Patrick.

Patrick F. Guinn, RAC
Associate Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.

2440 Research Blvd.
Rockville, MD 20850 USA
Phone: 1-240-683-3277
Mobile: 1-301-335-2967
Email: Patrick.Guinn@otsuka-us.com

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Monday, November 10, 2014 8:43 AM
To: Guinn, Patrick; Prindle, Ann; Goldberger, David
Subject: NDA 21436 s038 Abilify for Tourette's in Children

Good Morning Mr. Guinn,

Please refer to your Supplemental New Drug Application (sNDA) for Abilify, s-038 for Tourette's in children. We also refer you to the labeling that was sent to you on October 10, 2014 and your response on October 27, 2014. Additionally, we refer you to our April 24, 2014 "Filing Letter" in which we notified you of our target date of November 21, 2014 form communicating labeling changes and postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures-Fiscal Years 2013 Through 2017."

We have proposed revisions to the label that are attached to this email (both a tracked-changes and clean word version). We request that you resubmit labeling that addresses these issues by COB Friday, November 14, 2014. The resubmitted labeling will be used for further labeling negotiations if needed, therefore, please send both a tracked-changes and clean version in word format.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drugs and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We have the following proposed Postmarketing Commitment:

PMC: A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of aripiprazole in the treatment of pediactric patients (6-17 years) Tourette's Disorder. This trial must include a placebo group and more than one fixed dose and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of aripiprazole. Because it is important to establish the dose-response for maintenance, this trial should randomize patients on stable doses of aripiprazole and different doses of aripiprazole (and to placebo) during the maintenance phase.

Please let me know if you agree with this Postmarketing Commitment and if you have any questions.
Thanks,
Bill

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/s/

WILLIAM H BENDER
12/10/2014

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/s/

WILLIAM H BENDER
12/11/2014

PAUL A DAVID
12/11/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: **October 24, 2014**

To: William Bender, RPh, RAC
Senior Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah K. O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 021436 S-038**
Abilify® (aripiprazole) Tablets

OPDP has reviewed the draft product labeling (PI) and Medication Guide (MG) for Abilify® (aripipraazole) Tablets (Abilify) as requested in the consult from DPP dated April 29, 2014.

OPDP's comments on the draft PI and MG for Abilify are based on the version provided by William Bender via email on October 14, 2014.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials. Thank you!

(b) (4)

98 Pages(s)of Draft Labeling have been witheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SUSANNAH O'DONNELL
10/24/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 24, 2014
To:	Mitchell Mathis, M.D. Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ABILIFY (aripiprazole)
Dosage Form and Route:	Oral Tablets
Application Type/Number:	NDA 21436
Supplement Number:	038
Applicant:	Otsuka Pharmaceutical Company Ltd. (Otsuka)

1 INTRODUCTION

On February 11, 2014, Otsuka submitted for the Agency's review a Supplemental New Drug Application (sNDA) for ABILIFY (aripiprazole) Oral Tablets (NDA 21436 S038). This supplement was submitted requesting approval to add a new indication for treatment of (b) (4) Tourette's disorder in pediatric patients (b) (4) to the labeling for this product. ABILIFY (aripiprazole) Oral Tablets was approved on November 15, 2002 and is indicated for the treatment of Schizophrenia.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Psychiatry Products (DPP) on May 21, 2014, for DMPP to review of the Applicant's proposed Medication Guide (MG) for ABILIFY (aripiprazole) Oral Tablets.

2 MATERIAL REVIEWED

- Draft ABILIFY (aripiprazole) Oral Tablets MG received on February 11, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on October 8, 2014.
- Draft ABILIFY (aripiprazole) Oral Tablets Prescribing Information (PI) received on February 11, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on October 8, 2014.

3 REVIEW METHODS

In our focused review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Consult DMPP during the next review cycle for a comprehensive review of the Patient Labeling to bring it up to current Patient Labeling standards.
- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

19 Pages(s) of Draft labeling have been withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

TWANDA D SCALES
10/24/2014

SHAWNA L HUTCHINS
10/24/2014

LASHAWN M GRIFFITHS
10/24/2014

LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 19, 2014
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 021436/S-038
Product Name and Strength:	Abilify (Aripiprazole) Tablets 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Otsuka Pharmaceutical Corporation, Ltd.
Submission Date:	February 12, 2014
OSE RCM #:	2014-895
DMEPA Primary Reviewer:	Loretta Holmes, BSN, PharmD
DMEPA Associate Director:	Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

Otsuka submitted supplement NDA 021436/S-038 which provides for the addition of a new indication, treatment of [redacted] (b) (4) Tourette's disorder in pediatric patients [redacted] (b) (4), to the prescribing information (PI) for Abilify. There were no new strengths or new product formulations proposed in this supplement.

The Division of Psychiatry Products (DPP) requested we review the proposed changes to the Prescribing Information (PI) to determine if they can contribute to confusion that can lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Labeling Review

Materials Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E
Other	F (N/A)
Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the updates to the Dosage and Administration sections of the Prescribing Information (PI). Additions were made to these sections of the labeling. We noted that Section 2.5 Treatment of Tourette's Disorder in Full Prescribing Information (FPI) contains the error-prone symbol "<". It is considered error-prone because it can be misinterpreted as having the opposite meaning. This symbol is on the Institute for Safe Medication Practices' List of Error-Prone Abbreviations, Symbols, and Dose Designations.[1] The symbol "≥" is also used in

[1] Institute for Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dose Designations. Available at http://www.ismp.org/Tools/errorproneabbreviations.pdf.

this section of the FPI and can also be considered error-prone. Replacing these symbols in this section of the FPI with their written meaning will provide clarity and prevent potential confusion associated with interpreting the symbols. We acknowledge these symbols are also used in the dosing chart in the Highlights of Prescribing, Dosage and Administration section of the PI. However, in that location, they facilitate reading of the information in the chart and, thus, we do not recommend their replacement there.

We have no safety concerns with the other additions made to the Dosage and Administration sections to accommodate the newly proposed indication.

4 CONCLUSION & RECOMMENDATION

Our review of the insert labeling noted there are areas where information can be more clearly presented in order to help minimize potential confusion. We provide a recommendation in Section 4.1 below and recommend its implementation prior to approval of this supplement.

4.1 RECOMMENDATION FOR THE DIVISION

A. Full Prescribing Information, Section 2.5 Treatment of Tourette's Disorder

Consider replacing the symbols "<" and "≥" with their written meanings in order to prevent confusion that can be caused by misinterpreting the symbols.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Abilify that Otsuka submitted on February 12, 2014.

Table 2. Relevant Product Information for Abilify

Active Ingredient	Aripiprazole
Indication	Treatment of schizophrenia; acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate; maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate; adjunctive treatment of major depressive disorder (MDD); treatment of irritability associated with autistic disorder; treatment of agitation associated with schizophrenia or bipolar I disorder; and treatment of (b) (4) Tourette's disorder (proposed indication)
Route of Administration	Oral
Dosage Form	Tablets
Strengths	Tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg
Dose and Frequency	

	Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia – adults (2.1)	10-15 mg /day	10-15 mg /day	30 mg /day
Schizophrenia – adolescents (2.1)	2 mg /day	10 mg /day	30 mg /day
Bipolar mania – adults: monotherapy (2.2)	15 mg /day	15 mg /day	30 mg /day
Bipolar mania – adults: adjunct to lithium or valproate (2.2)	10-15 mg /day	15 mg /day	30 mg /day
Bipolar mania – pediatric patients: monotherapy or as an adjunct to lithium or valproate (2.2)	2 mg /day	10 mg /day	30 mg /day
As an adjunct to antidepressants for the treatment of major depressive disorder – adults (2.3)	2-5 mg /day	5-10 mg /day	15 mg /day
Irritability associated with autistic disorder – pediatric patients (2.4)	2 mg/day	5-10 mg/day	15 mg/day
(b) (4) Tourette's disorder – Patients < 50 kg	2 mg/day	5 mg/day	10 mg/day
(b) (4) Patients ≥ 50 kg	2 mg/day	10 mg/day	20 mg/day
Agitation associated with schizophrenia or bipolar mania – adults (~~2.5~~ 2.6)	9.75 mg /1.3 mL injected IM		30 mg/day injected IM

<table>
<tr><td>How Supplied</td><td>
<table>
<tr><th>Tablet Strength</th><th>Tablet Color/Shape</th><th>Tablet Markings</th><th>Pack Size</th></tr>
<tr><td>2 mg</td><td>green modified rectangle</td><td>“A-006” and “2”</td><td>Bottle of 30</td></tr>
<tr><td>5 mg</td><td>blue modified rectangle</td><td>“A-007” and “5”</td><td>Bottle of 30
Blister of 100</td></tr>
<tr><td>10 mg</td><td>pink modified rectangle</td><td>“A-008” and “10”</td><td>Bottle of 30
Blister of 100</td></tr>
<tr><td>15 mg</td><td>yellow round</td><td>“A-009” and “15”</td><td>Bottle of 30
Blister of 100</td></tr>
<tr><td>20 mg</td><td>white round</td><td>“A-010” and “20”</td><td>Bottle of 30
Blister of 100</td></tr>
<tr><td>30 mg</td><td>pink round</td><td>“A-011” and “30”</td><td>Bottle of 30
Blister of 100</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>Store at 25˚C (77˚F); excursions permitted between 15˚C to 30˚C (59˚F to 86˚F)</td></tr>
</table>

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

A FAERS search was not conducted since ongoing surveillance has not identified any signals that need to be addressed for Abilify at this time.

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive and AIMS on September 12, 2014 using the term, "Abilify" to identify reviews previously performed by DMEPA.

C.2 Results

Park J. Medication Errors Postmarketing Safety Review (NDA 021436). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2008 Mar 10. 29 p. OSE RCM No.: 2007-979.

We did not identify any concerns in the aforementioned review that need to be carried over to our current review.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on September 12, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the labeling.

ISMP Newsletters Search Strategy	
Date Range	No Limits
ISMP Newsletter Search Strategy	Match Exact word or phrase
Search Terms	Abilify

E.2 Results

None of the articles retrieved were pertinent to this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Abilify labeling submitted by Otsuka on February 12, 2014.

- Prescribing Information

G.2 Labeling Images

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

LORETTA HOLMES
09/19/2014

LUBNA A MERCHANT
09/19/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: September 15, 2014

TO: William Bender, R.Ph., Regulatory Project Manager
Christina Burkhart, M.D., Medical Officer
Robert Levin, M.D., Team Leader
Division of Psychiatry Products

FROM John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATION: NDA 021436 S-038

APPLICANT: Otsuka Pharmaceutical Development, Inc.

DRUG: Abilify® (Aripiprazole)

NME: No

INDICATION: Treatment of (b) (4) Tourette's disorder (TD)

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: April 11, 2014

INSPECTION SUMMARY GOAL DATE: October 12, 2014

REGULATORY ACTION GOAL DATE: November 12, 2014

PDUFA DUE DATE: December 12, 2014

I. BACKGROUND

Otsuka Pharmaceutical Development and Commercialization, Inc. (**Otsuka**) submitted this supplemental NDA 21436 S-038 to add a new indication to the product labeling for Abilify® (aripiprazole), treatment of (b) (4) Tourette's disorder (**TD**) in children and adolescents (age (b) (4) years). As an orphan indication, Otsuka receives seven years of orphan exclusivity at NDA approval.

TD is a neuropsychiatric disorder of childhood onset characterized by involuntary motor and vocal tics. Symptoms may appear as early as two years of age, with a mean age of onset of seven years. Early adolescents (age 10 to 15 years) are disproportionately affected. Disturbances in dopaminergic and/or serotonergic neuronal pathways have been implicated based on the observed association of TD with other disorders of dopamine and/or serotonin imbalance (comorbid in 84% of TD patients), including obsessive-compulsive disorder (**OCD**) and attention deficit hyperactivity disorder (**ADHD**). As a rare disorder primarily of childhood, FDA designated TD as an orphan disorder in 2006.

Otsuka originally developed aripiprazole for treatment of schizophrenia. As a second-generation agent (partial dopamine and serotonin receptor agonist), its mechanism of action is thought to differ from those of other antipsychotic agents, with efficacy also for TD as shown in limited studies. First generation agents including haloperidol and pimozide are approved for TD, but not in children under age 12 years. At present, alpha-2 agonists including clonidine and guanfacine are often used as first-line agents for TD, but inadequate efficacy and unacceptable side effects often limit their use.

This NDA is supported by two pivotal studies, Study 31-12-293 conducted primarily in the United States (**US**) and Canada in follow up of the initial Study 031-KOA-0703 conducted in South Korea. Both studies were audited at good clinical practice (**GCP**) inspections of eight study sites, two sites (of 76) for Study 31-12-293 and all six sites for Study 031-KOA-0703. The two studies are described below with emphasis on study features relevant to inspection (primarily Study 031-KOA-0703).

Study 31-12-293

A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder

This randomized, double-blind, placebo-controlled study was conducted over 10 months (November 2012 to September 2013) in 133 pediatric subjects (age 7-17 years) with TD at 76 sites in the US (> 60% enrollment), Canada, and Europe. Subjects were randomized in equal ratio to low-dose aripiprazole, high-dose aripiprazole, or placebo. The study medication was given orally once daily for eight weeks, initially at 2 mg/day and titrated up to the target dose (5 or 10 mg/day) by Week 3. The primary efficacy endpoint was the change from baseline to Week 8 in the total tic score on Yale Global Tic Severity Scale (**TTS-YGTSS**). The major secondary efficacy endpoint was the change in Tourette's syndrome score on Clinical Global Impressions Scale (**TSS-CGI**). Major safety evaluations included adverse event (**AE**) monitoring, including systematic scaled screening for new motor dysfunction. The sponsor reports: (1) relative to placebo, TTS-YGTSS decreased by 6.3 ($p = 0.002$) for low-dose aripiprazole and by 9.9 ($p < 0.0001$) for high-dose aripiprazole, by mixed repeated measures (**MRM**) analysis, (2) TSS-CGI results were consistent with TTS-YGTSS results, and (3) new safety concerns were not identified.

Study 031-KOA-0703

A Randomized, Double-blind, Dose-adjustment, Placebo-controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder

This randomized, double-blind, placebo-controlled study was conducted over 20 months (August 2008 to April 2010) in 61 subjects at six sites in South Korea. In comparison with Study 31-12-293, this study was smaller (61 & 133 subjects), earlier (completed 2010 & 2013), and longer (20 & 10 months). The primary study objective was to evaluate aripiprazole relative to placebo in reducing tics from baseline Visit 2 (Week 0) to end-of-therapy (**EOT**) Visit 7 (Week 10) using the Korean version of YGTSS (**K-YGTSS**).

Subjects were randomized in equal ratio to aripiprazole or placebo. The study medication was given orally once daily for 10 weeks with incremental dose adjustment (2, 5, 10, 15, or 20 mg/day maximum) every two weeks based on TSS-CGI and AEs: (1) no adjustment for TSS-CGI of 1 or 2 with no intolerable treatment-related AEs (**ITAEs**), (2) next higher dose for TSS-CGI $\geq$ 3 with no ITAEs, and (3) previous lower dose for any ITAE with dose maintained through EOT unless decreased again or suspended.

Subject Eligibility

Children and adolescents of age 6-18 years requiring drug therapy for TD diagnosed per *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (**DSM-IV**), confirmed using Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime, Korean Version (**K-SADS-PL-K**) with baseline total tic score on K-YGTSS (**TTS-K-YGTSS**) $\geq$ 22, with none of the following exclusion criteria:

- Per DSM-IV and (as applicable) K-SADS-PL-K: schizophrenia and other psychotic disorders; major depressive disorder (**MDD**), bipolar disorder (**BD**), and other mood disorders; substance abuse or dependence (including alcohol) within three months; ADHD, OCD, or oppositional defiant disorder (**ODD**) requiring drug therapy
- Tardive tics, Huntington's chorea, neuroacanthocytosis, mental retardation, and autism with tics; intelligence quotient < 70 on Wechsler Intelligence Scale; history of neuroleptic malignant syndrome, seizure (except febrile seizure), or any serious cephalic damage (including stroke)
- Any current symptomatic neurological disorder (except TD); any condition that complicates safe and interpretable study conduct, including clinically significant abnormalities in laboratory tests, physical examination (**PE**), vital signs, and electrocardiogram (**ECG**); body weight < 16 kg, pregnancy, breast-feeding, or inadequate contraception
- Use of antipsychotic agents within two weeks, drugs for parkinsonism within two weeks, or fluoxetine within four weeks; on-going requirement for concurrent drug and behavioral therapies; aripiprazole hypersensitivity or intolerance to antipsychotic drugs; participation in aripiprazole study at any time or in any clinical trial within one month
- Use of prohibited medications for one to four weeks before study (as applicable for each medication, per investigator evaluation): psychotropic drugs, CYP3A4 inducers or inhibitors, CYP2D6 inhibitors, drugs for parkinsonism, anticonvulsants, and alcohol

Major Study Endpoints

- Efficacy: mean (primary endpoint) and percent (major secondary endpoint) reduction in TTS-K-YGTSS, from baseline Visit 2 to EOT Visit 7 (Week 10)
- Safety: AEs including extrapyramidal symptoms (**EPS**), PE, laboratory testing, ECG, body mass index (**BMI**), waist circumference (**WC**), and body weight (**BW**)
- Scaled screening for new motor dysfunction: Simpson-Angus Rating Scale (**SARS**), Barnes Akathisia Rating Scale (**BARS**), and Abnormal Involuntary Movements Scale (**AIMS**)

Sponsor Report of Major Findings

- Primary endpoint (relative to placebo): decrease in mean TTS-K-YGTSS by 5.6 ($p = 0.03$) using two sample t-test and modified full analysis set of 53 subjects (eight subjects excluded)
- Major secondary endpoints (relative to placebo): (1) 19% change in TTS-K-YGTSS ($p = 0.02$) using two sample t-test), (2) decrease in mean TSS-CGI by 0.6 ($p = 0.03$) using Wilcoxon rank sum test), and (3) 21% percent change in TSS-CGI (statistically not significant)
- AE profile: similar for aripiprazole and placebo including nature of events, seriousness, severity, and occurrence rates (aripiprazole 47%, placebo 50%)

II. GCP INSPECTIONS

Studies 31-12-293 and 031-KOA-0703 were audited at inspections of eight study sites. For Study 31-12-293 conducted globally (US primarily, Canada and Europe), Sites 510 in US and Site 533 in Canada were selected as the two largest sites. For Study 031-KOA-0703 conducted in South Korea, all six sites were inspected. The inspection outcomes are shown below.

Clinical Investigator Site		Study, Site, Enrollment	Inspection Outcome
1	Robert Riesenberg, M.D. Atlanta Center for Medical Research Atlanta, GA, USA	Study 31-12-293 Site 510, 10 subjects	June 9 – 23, 2014 NAI
2	Sohail Khattak, M.D. Kids Clinic Whitby, Ontario, Canada	Study 31-12-293 Site 533, 23 subjects	June 17 – 20, 2014 pending preliminary NAI
3	Soo-Churl Cho, M.D. Seoul National University Hospital Seoul, South Korea	Study 031-KOA-0703 Site 001, 12 subjects	June 16 – 20, 2014 pending preliminary NAI
4	Han-Ik Yoo, M.D. Asan Hospital Seoul, South Korea	Study 031-KOA-0703 Site 002, 10 subjects	June 23 – 27, 2014 pending preliminary NAI
5	Yoo-Sook Jeong, M.D. Samsung Medical Center Seoul, South Korea	Study 031-KOA-0703 Site 003, 9 subjects	June 30 – July 7, 2014 pending preliminary VAI
6	Jeong-Seop Lee, M.D. Inha University Hospital Incheon, South Korea	Study 031-KOA-0703 Site 004, 14 subjects	June 16 – 20, 2014 VAI
7	Dong-Ho Song, M.D. Severance Hospital Seoul, South Korea	Study 031-KOA-0703 Site 005, 9 subjects	June 23 – 26, 2014 VAI
8	Young-Sik Lee, M.D. Chungang University Hospital Seoul, South Korea	Study 031-KOA-0703 Site 006, 7 subjects	June 30 – July 3, 2014 VAI

NAI = no action indicated (no significant GCP violations); VAI = voluntary action indicated (acceptable GCP violations)

Pending: The preliminary classification is based on information on Form FDA 483 and communication with the field investigator. The establishment inspection report (**EIR**) has not been received from the field office and the EIR review remains pending as of this clinical inspection summary (**CIS**).

1. Robert Riesenberg, M.D.

a. What was inspected:

- Study records review: study monitoring, clinical investigator (**CI**) financial disclosure, drug accountability and disposition, and subject records
- Subject records review: subject eligibility, informed consent, randomization, study blind, treatment compliance, and major data verification
- Data verification: primary and major secondary efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 31-12-293, Site 510: 10 subjects were screened, all were enrolled, all completed the primary study, and eight continued into the optional extension study. Subject records for all subjects were completely reviewed for the primary study.

No significant deficiencies were identified and a Form FDA 483 was not issued. Study conduct and monitoring appeared adequate, including informed consent, AE reporting, and drug accountability. Source records were well organized and appeared complete and accurate. All audited endpoint data were verifiable among source records, case report forms (**CRFs**), and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

2. Sohail Khattak, M.D.

a. What was inspected:

- Records review: sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records review: subject eligibility, informed consent, randomization, study blind, treatment compliance, and major data verification
- Data verification: primary and major secondary efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 31-12-293, Site 533: 27 subjects were screened, 23 enrolled, and 20 completed the study. Subject records were reviewed for 17 subjects, including detailed review for 11 enrolled subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct and monitoring appeared adequate. All subjects signed the informed consent document. Drug accountability was well documented. Source records appeared complete and accurate. All audited study data were verifiable among source records, CRFs, and NDA data listings. Three minor deficiencies were verbally discussed:

- Protocol deviations: One subject was enrolled for two days until receipt of abnormal (prolonged QT) ECG report, and two subjects lacked a baseline urine drug screen.
- Drug accountability: A comparison of the original records (retrieved upon request) against uncertified photocopies (readily available) revealed one minor discrepancy for one subject, a note about a missed study medication dose recorded only on the copy (apparently after filing the original).

c. Assessment of data integrity: Data from this study site appear reliable.

Note: These observations are based on preliminary communication with the field investigator. The EIR has not been received and the final inspection outcome determination remains pending.

3. Soo-Churl Cho, M.D.

a. What was inspected:

- Records review: sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records review: subject eligibility, informed consent, randomization, study blind, treatment compliance, and major data verification
- Data verification: primary and major secondary efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 031-KOA-0703, Site 001: 14 subjects were screened, 12 were enrolled, and 12 completed the study. Records were reviewed for nine enrolled subjects, including detailed review for five subjects. The primary CI at this study site served as the principal CI for Study 031-KOA-0703.

No significant deficiencies were observed and a Form FDA 483 was not issued. The sponsor's study monitoring appeared adequate. All subjects signed the informed consent document. Drug accountability was well documented. Source records were well organized and readily available and appeared complete and accurate. All audited study data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: Data from this study site appear reliable.

Note: These observations are based on preliminary communication with the field investigator. The EIR has not been received and the final inspection outcome determination remains pending.

4. Han-Ik Yoo, M.D.

a. What was inspected:

- Records review: sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records review: subject eligibility, informed consent, randomization, study blind, treatment compliance, and major data verification
- Data verification: primary and major secondary efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 031-KOA-0703, Site 002: 12 subjects were screened, 10 were enrolled, and nine completed the study. Records were reviewed for the 10 enrolled subjects, including detailed review for six subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. The sponsor's study monitoring appeared adequate. All subjects signed the informed consent document. Drug accountability was adequately documented. Source records were well organized and readily available and appeared adequately complete and accurate. All audited study data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: Data from this study site appear reliable.

Note: These observations are based on preliminary communication with the field investigator. The EIR has not been received and the final inspection outcome determination remains pending.

5. Yoo-Sook Jeong, M.D.

a. What was inspected:

- Records review: sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records review: subject eligibility, informed consent, randomization, study blind, treatment compliance, and major data verification
- Data verification: primary and major secondary efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 031-KOA-0703, Site 003: 17 subjects were screened, nine were enrolled, and all nine completed the study. Records were reviewed for the nine enrolled subjects, including detailed review for five subjects. A Form FDA 483 was issued for the following deficiencies:

- Subject 09: Screening source records conflicted with the CRF regarding the use of the concomitant medication NeuraMed® (oxiracetam). This subject with hydrocephalus and a recent history of neurosurgery was given oxiracetam either for five months to suppress seizures (source records) or for one week as a cognitive nutraceutical supplement (CRF).

  Reviewer Comments:

  *Oxiracetam is a nutraceutical not approved as a drug (for seizure suppression or for any indication) and does not appear important as a concomitant medication. Pre-existing hydrocephalus was reported as a serious AE (**SAE**) at subject screening, and the apparently inaccurate information about oxiracetam use was obtained from the subject's caregiver at subject screening.*

  More importantly, as an uncited review observation, this subject does not appear to be eligible for the study . Subject selection criteria specify exclusion for serious cephalic damage, symptomatic neurological disorder except TD, or any condition which complicates study conduct or data interpretation. The subject eligibility criteria appear to include exclusion for hydrocephalus and recent neurosurgery. This subject was randomized to aripiprazole.

  This concern about subject eligibility may be relevant to data interpretation. The reporting of pre-existing hydrocephalus as a serious AE at subject screening is also inappropriate, but this mis-reporting (not cited or discussed as an uncited deficiency observation) appears unlikely to be important. Significant AEs were not observed for this subject.

- Subject 08: The study medication dose was increased four times at Visits 3 through 6 in response to a TSS-CGI of 2, in deviation from the protocol which specifies no dose increase for this TSS-CGI.

  Reviewer Comments: Dose adjustment inconsistent with the protocol may complicate the eventual writing of the dosing instructions (for inclusion in the product label) only if the dosed subject had been randomized to the active drug. This subject was randomized to placebo, and this deficiency does not appear important.

The overall study conduct at this site appears GCP-compliant. All subjects signed the informed consent document. Drug accountability was adequately documented. Source records appeared complete and accurate. All audited study data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data for Subject 09 may not be reliable based on subject eligibility concerns as discussed above. The data from this study site otherwise appear reliable.

Note: These observations are based on preliminary communication with the field investigator. The EIR has not been received and the final inspection outcome determination remains pending.

6. Jeong-Seop Lee, M.D.

a. What was inspected:

- Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records review: subject eligibility, informed consent, randomization, study blind, treatment compliance, and major data verification
- Data verification: primary and major secondary efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 031-KOA-0703, Site 004: 19 subjects were screened, 14 were enrolled, and 13 completed the study. Records were reviewed for 17 subjects, including complete review for the 14 enrolled subjects. A Form FDA 483 was issued. The major cited and uncited (verbal) observations are described below.

Cited on Form FDA 483:

- PE findings (including vital signs, BW, and WC) were corrected on CRFs without an explanation or an audit trail, and unsupported by other study records.
- CRF data entry dates for ECG and laboratory tests preceded (by 4-5 days) source data review dates. Per CI explanation (at inspection and at post-inspection correspondence), all dates are presumably accurate and consistent with the operating procedures at this site, where CRF data entry typically preceded confirmation of data accuracy by supervisory source records review. The CI's explanation appears to be acceptable. Data discrepancies or corrections suggestive of inaccurate CRF data were not observed in the audited subject records (Subject 05, Visit 7; Subject 06, Visits 1 and 2; Subject 07 Visit 1; Subject 09, Visits 1 and 7).
- Dosing data were discrepant between source records (Investigational Product Administration Form) and CRFs. For the following five subjects (eight visits), a total of 12 missed doses were not reported on the CRFs (up to two missed doses per visit): Subject 01 (Visits 4-6), Subject 02 (Visits 3 and 5), Subject 05 (Visit 3), Subject 08 (Visit 2), and Subject 09 (Visit 3).
- Subject 07 (aripiprazole): missed 16 non-consecutive doses of the study medication, no explanatory documentation, overall treatment compliance < 80%, missed doses reported to sponsor
- Subject 13 (placebo): missed nine (six consecutive) doses of the study medication, no explanatory documentation, missed doses reported to sponsor
- Subject 14 (aripiprazole): study medication dose not increased at Visit 3 for TSS-CGI $\geq$ 3 per protocol, no explanatory documentation
- Others: ECG and WC measurement not specified in the informed consent document; first dose of study medication not documented for all subjects; one subject with unclear history of asthma enrolled without adequate evaluation for asthma

Not cited on Form FDA 483 (verbal discussion or EIR review):

- For three subjects, inadequate recordkeeping included inadequate audit trails for CRF corrections for TTS-K-YGTSS at Visits 1 or 2. The corrected TTS-K-YGTSS are reported in the NDA.

Subject	Group	Visit	TTS-K-YGTSS Correction
Subject 03	Placebo	Visit 1	24 to 31, increase by 7
Subject 05	Placebo	Visit 2	26 to 22, decrease by 4
Subject 12	Aripiprazole	Visit 1	23 to 26, increase by 3

- Minor deficiencies in documentation of non-critical information (nearly all subjects): incomplete, inconsistent, illegible, inadequately corrected, or otherwise unclear

Subject 02	aripiprazole	K-YGTSS (Visits 1, 2, 4, 6); ECG (Visit 1)
Subject 04	aripiprazole	K-YGTSS (Visits 5, 6); ECG (Visit 1)
Subject 06	aripiprazole	K-YGTSS (Visits 2, 5-7); TSS-CGI (Visits 2, 4-7); AIMS (Visits 2, 7)
Subject 07	aripiprazole	K-YGTSS (Visits 4, 5, 7); K-SADS-PL-K, DSM (Visit 1)
Subject 09	aripiprazole	K-YGTSS (Visits 2-7); TSS-CGI , K-SADS-PL-K (Visit 1)
Subject 10	aripiprazole	K-YGTSS (Visit 5); TSS-CGI (Visit 3); K-SADS-PL-K, DSM (Visit 1)
Subject 11	aripiprazole	K-YGTSS (Visit 7); K-SADS-PL-K (Visit 1)
Subject 12	aripiprazole	K-YGTSS (Visits 6, 7)
Subject 14	aripiprazole	K-SADS-PL-K (Visit 1)
Subject 01	placebo	K-YGTSS (Visits 1, 3, 4, 6)
Subject 03	placebo	K-YGTSS (Visits 4, 7)
Subject 05	placebo	K-YGTSS (Visits 1, 2, 7)
Subject 08	placebo	TSS-CGI, K-SADS-PL-K (Visit 2)
Subject 13	placebo	K-YGTSS (Visit 2); K-SADS-PL-K (Visit 1)

Reviewer Comments: Subjects were to be randomized in equal ratio. The observed 9/5 ratio appears to be chance occurrence; evidence of incorrect or biased randomization was not observed.

- Others: staff training limited to self-training; study visits not always within protocol-specified timeframe; laboratory testing not always complete prior to subject enrollment

The observed deficiencies appear minor, isolated, or otherwise unlikely to favor NDA approval. For example, a missed placebo dose appears inconsequential for data interpretability, and a missed aripiprazole dose may decrease the apparent efficacy of aripiprazole (unfavorable for demonstration of superiority). The CI provided adequate explanations for most of these deficiencies in response to Form FDA 483. Many of these deficiencies were reported in the NDA as protocol deviations.

Overall, all deficiency observations (cited and uncited) appear to be consistent with inexperienced but acceptable study conduct. Evidence of unblinding or biased study conduct was not observed. All subjects signed the informed consent document. Study records appear adequate, with the observations about corrections interpreted as unskilled recordkeeping. Other than as noted above, all audited study data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

7. Dong-Ho Song, M.D.

a. What was inspected:

- Records review: IRB oversight and monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records review: subject eligibility, informed consent, randomization, study blind, treatment compliance, and major data verification
- Data verification: primary and major secondary efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 031-KOA-0703, Site 005: 13 subjects were screened, nine were enrolled, and seven completed the study. Records were completely reviewed for all 13 subjects. A Form FDA 483 was issued. The major cited (Form FDA 483) and uncited (verbal) observations are described below.

Cited on Form FDA 483:

- ECG and WC measurement not specified in the informed consent document
- Lab results for Visits 1 and 2 sometimes used interchangeably for subject selection
- Screening K-SADS-PL-K not consistently complete and available for review
- Source records for PE (including vital signs) typically not available for review
- Febrile seizure history not documented on screening CRF (Subject 02)
- Updated informed consent document not signed at earliest opportunity (Subject 03)
- ECG and lab tests performed four days after ETV (Subject 05)
- Akathisia on BARS not reported as an AE, recorded as an AE 10 months later (Subject 06)
- Tablets dispensed/returned: 14/4 on CRF discrepant with 15/3 on source record (Subject 06, Visit 5)
- Study medication dose of 15 mg inconsistent with per-protocol dose of 10 mg (Subject 07, Visit 4)
- First dose of study medication not administered at Visit 2 (Subjects 02, 06)
- Abnormal insulin result not noted as abnormal (Subjects 03, 04, 06, 08)
- ECG and lab tests: CRF entry dates preceding source review dates (Subjects 02, 03, 05, 06, 08, 09)

Not cited on Form FDA 483 (verbal discussion):

- No documentation of CI review, screening K-YGTSS
- No documentation of subject education, including about per-protocol treatment compliance
- Incomplete screening K-SADS-PL, some with score corrections (three subjects)

Reviewer Comments: The observed randomization ratio is consistent with the intended 1/1 ratio, five for aripiprazole (Subjects 01, 03, 07, and 09) and four for placebo (Subjects 02, 04, 05, 06, and 08). Each deficiency observation was examined for its potential impact on the primary efficacy endpoint (either for aripiprazole or placebo, as randomized) and on the apparent aripiprazole efficacy. Inadequate randomization, incorrect treatment, or noteworthy trends were not observed.

The observed deficiencies (cited and uncited) appear to be consistent with inexperienced but acceptable study conduct. Evidence of unblinding or biased study conduct was not observed. All deficiency observations appear minor, isolated, or otherwise unlikely to be significant. All subjects signed the informed consent document. Study records appear acceptable, with inadequate audit trail for corrections interpreted as unskilled recordkeeping. All audited study data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: Data from this study site appear reliable.

8. Young-Sik Lee, M.D.

a. What was inspected:

- Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject records
- Subject records review: subject eligibility, informed consent, randomization, study blind, treatment compliance, and major data verification
- Data verification: primary and major secondary efficacy endpoints, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 031-KOA-0703, Site 006: eight subjects were screened, seven were enrolled, and seven completed the study. Records were completely reviewed for all eight subjects. A Form FDA 483 was issued. The major cited (Form FDA 483) and uncited (verbal) observations are described below.

Cited on Form FDA 483:

- ECG and WC measurement not specified in the informed consent document
- Source records for PE (including vital signs) typically not available for review
- Urinalysis not performed, no explanatory documentation (Subject 03, Visit 7)
- Adequate medication washout not verifiable (Subject 04)
- Minor corrections in subject records, including CRF corrections (Subject 06)
- Days with missed doses discrepant between source and CRF (Subject 07; Visits 2, 4, and 6)
- Lab tests: CRF entry dates preceding source record review dates (Subjects 01, 02, and 04)
- ECG not performed at Visits 2 and 7 (Subjects 05 and 06)

Not cited on Form FDA 483 (verbal discussion):

- No documentation of CI review, screening K-YGTSS
- Inadequate documentation of follow up evaluation (phone calls or visits)
- Enrollment despite missing or abnormal laboratory results (Subject 01)
- No documentation of follow up for abnormal insulin result (Subject 01, Visit 7)
- Corrections (Subject/Visit): TSS-CGI (03/6), TTS-K-YGTSS (04/5), and TSS-CGI (07/7)
- Corrections for baseline TSS-CGI, WC, and BW (Subject 05)
- Incorrect treatment, inconsistent with randomization (Subject 06)

*Reviewer Comments: Subject 06 was randomized to placebo (randomization number 583) but received aripiprazole (incorrect randomization number 586). An examination of the efficacy data shows that the TTS-K-YGTSS decreased by 18 (from 29 to 11), an outcome consistent with (incorrect) aripiprazole treatment. The error was reported in the clinical study report, in which the sponsor states that Subject 06 was included in the as-randomized (i.e. placebo group) intent-to-treat (**ITT**) population for efficacy analysis and in the as-treated (i.e. aripiprazole group) ITT population for safety analysis.*

The observed deficiencies appear minor, isolated, or otherwise unlikely to favor NDA approval. All deficiency observations (cited and uncited) appear to be consistent with inexperienced but acceptable study conduct. Evidence of unblinding or biased study conduct was not observed. Study records often lacked an adequate audit trail for data corrections but otherwise appeared acceptable overall. The deficiency observations appear to be consistent with unskilled recordkeeping under potentially inadequate sponsor monitoring, including monitoring for adequate recordkeeping. Other than as noted above, all audited study data were verifiable among source records, CRFs, and NDA data listings.

c. Assessment of data integrity: The data from this study site appear reliable.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

In this orphan indication NDA, the sponsor reports statistically significant aripiprazole efficacy for TD (relative to placebo) as demonstrated in two pediatric pivotal studies: (1) Study 031-KOA-073, in which aripiprazole therapy reduced the TTS-K-YGTSS by 5.6 ($p = 0.03$), and (2) Study 31-12-293, in which (a) low-dose aripiprazole therapy reduced the TTS-YGTSS by 6.3 ($p = 0.002$), and (b) high-dose aripiprazole therapy further reduced the TTS-YGTSS by 9.9 ($p < 0.0001$). As reported by the sponsor, the demonstration of aripiprazole efficacy in Study 031-KOA-073 appears to be marginally significant. Many GCP deficiencies (primarily recordkeeping) were seen mostly for Study 031-KOA-073.

For these superiority studies of aripiprazole relative to placebo, unbiased deficiencies in study conduct may decrease the demonstrable statistical significance. The inspectional findings suggest less experienced study conduct for the earlier, smaller, and apparently more exploratory Study 031-KOA-073 conducted exclusively in one foreign country, relative to the later, larger, and apparently more confirmatory Study 31-12-293 conducted more globally. The six investigators for Study 031-KOA-073 currently hold a total of four US INDs, and none of the six sites have been previously inspected by the FDA. The deficiency

observations indicate inadequate good recordkeeping practice (**GRP**) including GRP for audit trail, a major area of GCP as defined in the US Code of Federal Regulations (**CFR**). Sponsor monitoring may have been inadequate for this Study 031-KOA-073 to help assure adequate GRP as part of GCP.

Relative to Study 31-12-293, the greater number of inspectional observations for Study 031-KOA-073 also likely reflects the greater inspectional rigor: the marginal statistical significance made it important to perform a comprehensive audit, and the small study size made it possible to perform the necessary comprehensive audit. All sites were inspected, and subject records were audited for 58 of 61 subjects (95%), including comprehensive review for 46 of 61 subjects (75%). The comprehensive data audit at inspections of all six sites in Study 031-KOA-073 supports data examination after excluding specific data sets from potentially unacceptable subjects, as identified by inspection and independently by the sponsor, as shown in the table below. The sponsor's reasons for exclusion are not clear (as described in the NDA), as are the acceptability of the reasons for NDA review.

Site	Subject	Treatment Group	Sponsor Reason	Inspectional Concern	TTS-K-YGTSS Reduction
001	12	placebo	not necessary		7 (32 to 25)
002	01	aripiprazole	not elig ble		9 (23 to 14)
002	06	placebo	not elig ble		2 (33 to 31)
004	13	placebo	not necessary		9 (27 to 18)
004	14	aripiprazole	not necessary		3 (22 to 19)
005	01	aripiprazole	not treated		no data
005	09	aripiprazole	not necessary		13 (23 to 10)
006	07	aripiprazole	not necessary		15 (23 to 8)
003	09	aripiprazole		subject elig bility	10 (25 to 15)
004	03	placebo		unverifiable CRF data	3 (32 to 29)
004	05	placebo		unverifiable CRF data	10 (22 to 12)
004	12	aripiprazole		unverifiable CRF data	25 (25 to 0)

TTS-K-YGTSS Reduction: reduction in TTS-K-YGTSS for aripiprazole relative to placebo from Visit 2 to Visit 7

For Subjects 03 and 12 at Site 004, the unverifiable CRF data were the corrected data for Visit 1 (screening) TTS-K-YGTSS, not Visit 2 (baseline) scores that directly impact the primary efficacy endpoint. However, the Visit 1 score corrections remain inadequately explained, at inspection and at post-inspection correspondence. The Visit 1 score corrections may prove to be indirectly significant, and Subjects 03 and 12 at Site 004 are included as part of an exploratory examination.

The impact of removing these data sets (subjects shown above) on the apparent aripiprazole efficacy is explored in the second table below. Two of the eight sponsor-identified subjects (without Visit 7) are not included (Subject 14, Site 004; Subject 01, Site 005). Rows with no subjects removed are shown in grey. Shown for each site in Study 031-KOA-073 and for the overall study (column 1) are:

- Reduction in TTS-K-YGTSS from baseline to Visit 7 for aripiprazole (column 2)
- Reduction in TTS-K-YGTSS from baseline to Visit 7 for placebo (column 3)
- Reduction in TTS-K-YGTSS with and without removing selected subjects (column 4)
- Apparent placebo-adjusted aripiprazole efficacy (column 5)
- Impact of subject removal on the apparent aripiprazole efficacy (column 6)

1. Site (subjects n)	2. Aripiprazole (n)	3. Placebo (n)	4. Subjects Removed (Reason)	5. Efficacy	6. Impact
001 (9)	17.2 (5)	16.3 (4)	None	0.9	
001 (8)	17.2 (5)	19.3 (3)	Subject 12 (sponsor)	-2.1	-3.0
002 (9)	13.8 (5)	10.8 (4)	None	3.0	
002 (7)	14.8 (4)	13.7 (3)	Subjects 01, 06 (sponsor)	1.1	-1.9
003 (9)	9.0 (5)	11.8 (4)	None	-2.8	
003 (8)	8.8 (4)	11.8 (4)	Subject 09 (inspection)	-3.0	-0.2
004 (13)	21.8 (8)	10.0 (5)	None	11.8	
004 (10)	21.3 (7)	12.3 (3)	Subjects 03, 05, 12 (inspection)	9.0	-2.8
004 (12)	21.8 (8)	10.3 (4)	Subject 13 (sponsor)	11.5	-0.3
005 (7)	11.3 (3)	6.5 (4)	None	4.8	
005 (6)	10.5 (2)	6.5 (4)	Subject 09 (sponsor)	4.0	-0.8
006 (7)	16.7 (3)	12.8 (4)	None	3.9	
006 (6)	17.5 (2)	12.8 (4)	Subject 07 (sponsor)	4.7	+0.8
subject mean (54)	15.8 (29)	11.3 (25)	None	4.5	
subject mean (50)	15.7 (27)	11.7 (23)	Four at S3-4 (inspection)	4.0	-0.5
subject mean (48)	14.8 (26)	11.7 (22)	Six at S1-2/S4-6 (sponsor)	3.1	-1.4
subject mean (44)	16.0 (24)	12.6 (20)	Ten at S1-6 (both)	3.5	-1.0
site mean (6 sites)	15.0 (6)	11.3 (6)	None	3.6	
site mean (6 sites)	14.8 (6)	11.7 (6)	Four at S3-4 (inspection)	3.1	-0.5
site mean (6 sites)	15.1 (6)	12.4 (6)	Six at S1-2/S4-6 (sponsor)	2.7	-0.9
site mean (6 sites)	15.0 (6)	13.0 (6)	Ten at S1-6 (both)	2.0	-1.6

Aripiprazole: reduction in TTS-K-YGTSS from Visit 2 to Visit 7 for aripiprazole
Placebo: reduction in TTS-K-YGTSS from Visit 2 to Visit 7 for placebo
Efficacy: apparent (placebo-adjusted) aripiprazole efficacy (difference in TTS-K-YGTSS, aripiprazole minus placebo)
Impact: Impact of subject removal on apparent aripiprazole efficacy (subjects not removed minus removed)

None = no subjects removed (all subjects with TTS-K-YGTSS at Visits 2 and 7)
Four at S3-4 (inspection) = four (subjects) identified by inspection (site/subject): 003/09; 004/03,05,12
Six at S1-2/S4-6 (sponsor) = six identified by sponsor (site/subject): 001/12; 002/01,06; 004/13; 005/09; 006/07
Ten at S1-6 (both) = ten subjects, both Four at S3-4 (inspection) and Six at S1-2/S4-6 (sponsor)

This exploratory examination shows that: (1) the mean decrease in TTS-K-YGTSS ranges from 4.5 (subject mean, no subjects removed) to 2.0 (site mean, ten subjects removed), and (2) the impact of subject removal on apparent aripiprazole efficacy is consistently unfavorable to NDA approvability, as indicated by less apparent placebo-adjusted aripiprazole efficacy (TTS-K-YGTSS reduction) ranging from -1.6 (site mean, ten subjects removed) to -0.5 (site/subject mean, four subjects removed). These results appear to be consistent with the initial exploratory analyses by the review division at NDA filing, which showed that: (1) the per-protocol result was statistically not significant, and (2) the intent-to-treat result was also statistically not significant without Site 004, Site 005, or any two sites.

Summary

In this NDA 21436 S-38, Otsuka seeks an orphan pediatric indication for aripiprazole in managing TD based on two studies. Both studies were audited at GCP inspections of eight study sites:

- Two sites were inspected for the larger Study 31-12-293 (3% of sites, 25% of subjects). Six sites were inspected for the smaller (and earlier) Study 031-KOA-0703 (all sites, all 61 subjects), a study in which demonstration of aripiprazole efficacy was marginally statistically significant.
- For Study 31-12-293, significant deficiency observations were not observed and all audited data were verifiable as reported in the NDA. The study data appear acceptable as reported in the NDA.
- For Study 031-KOA-073, many GCP deficiencies were observed at Sites 003, 004, 005, and 006 with a combined enrollment of 39 subjects (64%). The deficiencies were typically minor, isolated, or otherwise unlikely to be significant. All observations appear to be consistent with inexperienced study conduct; evidence of unblinding or biased study conduct was not observed. Deficiencies with potential impact on data integrity appear to be limited to two subjects: Subject 09 at Site 003 for inadequate subject eligibility assessment and Subject 05 at Site 004 for improperly corrected efficacy data on CRFs. The data for Study 031-KOA-0703 otherwise appear acceptable as reported in the NDA.

Note: For four inspections (Site 533 in Study 31-12-293, Sites 001-003 in Study 031-KOA-0703), the EIR has not been received from the field office and the final inspection outcome classification remains pending. An addendum to this CIS will be forwarded to the review division if the outcome classification changes or if new observations of clinical or regulatory significance are discovered upon receipt and review of the EIR.

{See appended electronic signature page}

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

/s/

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09/15/2014

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09/15/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 21436/S-038

Application Type: Efficacy Supplement

Name of Drug/Dosage Form: Abilify (aripiprazole) 2 mg, 5 mg, 10 mg, 15 mg, 20 mg & 30 mg tablets

Applicant: Otsuka Pharmaceutical Development & Communications, Inc.

Receipt Date: February 12, 2014

Goal Date: December 12, 2014

1. Regulatory History and Applicant's Main Proposals

Reference is made to Otsuka Pharmaceutical Company Ltd.'s (OPC) approved New Drug Application, NDA 21-436, for Aripiprazole (OPC-14597) Oral Tablets which was approved on November 15, 2002. Further reference is made to IND 116,003 for Aripiprazole Oral Tablets (treatment of (b) (4) Tourette's disorder in children and adolescents) submitted on August 15, 2012.

Pursuant to 21 CFR 314.70, Otsuka is hereby submitting a supplemental new drug application (sNDA) requesting approval to add a new indication, treatment (b) (4) Tourette's disorder in pediatric patients (b) (4) to the labeling for this product. Tourette's disorder is a rare condition primarily affecting children and adolescents. An orphan drug designation application was submitted to the Office of Orphan Product Development on June 25, 2005, and orphan drug designation for the treatment of Tourette's disorder in children and adolescents was granted on January 25, 2006 (designation no. 05-2079).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 16, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *This is an efficacy supplement.*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

NO 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment: *The sponsor used the word "WARNINGS", not "WARNING."*

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *There is no RMC with this efficacy supplement, but the last change appears to be in February, 2012.*

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment: *There is no RMC with this efficacy supplement, but the last change appears to be in February, 2012.*

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *The most recent change occurred in February, 2012.*

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *They currently have Revised: TBD. We will add the date closer to the approval date.*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment: *Have them change Warnings to Warning as prescribed in the HL section.*

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

NO 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment: *The sponsor used the word "WARNINGS", not "WARNING."*

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

WILLIAM H BENDER
04/18/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 21436 BLA#	NDA Supplement #:S- 038 BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Abilify Established/Proper Name: aripiprazole Dosage Form: Tablets Strengths: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg		
Applicant: Otsuka Pharmaceutical Development & Communications, Inc. Agent for Applicant (if applicable): David Goldberger, R.Ph., RAC, Vice President, Global Reg. Affairs		
Date of Application: February 12, 2014 Date of Receipt: February 12, 2014 Date clock started after UN:		
PDUFA Goal Date: December 12, 2014	Action Goal Date (if different):	
Filing Date: April 13, 2014	Date of Filing Meeting: March 25, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Treatment of [redacted] (b) (4) Tourette's Disorder		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 116003	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐	X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☒	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 7 years for orphan drug exclusivity ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	7 years for orphan drug exclusivity
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☐ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒	☐	☐	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☐	☒		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☐	☒	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☐	☒	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	☐	☒	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☐	☒	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☐	☐	☒	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☒	
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☒	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** Pre-sNDA – May 21, 2013 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 03/24/2014

BLA/NDA/Supp #: NDA 21436/S-038

PROPRIETARY NAME: Abilify

ESTABLISHED/PROPER NAME: aripiprazole

DOSAGE FORM/STRENGTH: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg

APPLICANT: Otsuka Pharmaceutical Development & Communications, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of (b) (4) Tourette's Disorder

BACKGROUND: Reference is made to Otsuka Pharmaceutical Company Ltd.'s (OPC) approved New DrugApplication, NDA 21-436, for Aripiprazole (OPC-14597) Oral Tablets which was approved onNovember 15, 2002. Further reference is made to IND 116,003 for Aripiprazole Oral Tablets(treatment of tics associated with Tourette's disorder in children and adolescents) submitted on August 15, 2012.

Otsuka submitted a supplemental new drug application (sNDA) requesting approval to add a new indication, treatment of (b) (4) Tourette's disorder in pediatric patients (b) (4) to the labeling for this product. Tourette's disorder is a rare condition primarily affecting children and adolescents. An orphan drug designation application was submitted to the Office of Orphan Product Development on June 25, 2005, and orphan drug designation for the treatment of Tourette's disorder in children and adolescents was granted on January 25, 2006 (designation no. 05-2079).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Bill Bender	Y
	CPMS/TL:	Paul David/Rimmy Grewal	N
Cross-Discipline Team Leader (CDTL)	Mitchell Mathis		Y
Clinical	Reviewer:	Christina Burkhart	Y
	TL:	Robert Levin	Y
Social Scientist Review (*for OTC*	Reviewer:		

products)			
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Huixia Zhang	Y
	TL:	Hao Zhu	Y
Biostatistics	Reviewer:	Thomas Birkner	Y
	TL:	Peiling Yang	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sonia Tabacova	Y
	TL:	Aisar Atrakchi	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Wendy Wilson	N
	TL:	David Claffey	N
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	John Lee	N
	TL:	Susan Thompson	Y
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes	Y

	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:	Somya Dunn	Y
	TL:	Kimberly Lehrfeld	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	OPDP: Nazia Fatima Orphan Products: James Reese		N N
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Mitchell Mathis, M.D., Acting Director, Division of Psychiatry Products

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): July 9, 2014

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter

☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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/s/

WILLIAM H BENDER
04/18/2014

OSI/DGCPC CONSULT: Request for Clinical Inspections

Date: April 9, 2014

To: Ann Meeker-O'Connell, Acting Division Director, DGCPC
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB*
Susan Thompson, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB
CDER OSI PM Track
Name of DSI Primary Reviewer (if known): John Lee
Christina Burkhart, M.D.
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: Christina Burkhart, M.D., Clinical Reviewer, Division of Psychiatry Products (DPP)
Robert Levin, M.D., Team Leader, DPP
Mitchell Mathis, M.D., Director, Division of Psychiatry Products

From: William Bender, R.Ph., RAC, DPP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 21436/S-038
IND#: 116003
Otsuka
David Goldberger, Vice President, Global Regulatory Affairs, David.Goldberger@otsuka-us.com , 609-524-6797; and Patrick Guinn, Associate Director, Global Regulatory Affairs, Patrick.Guinn@otsuka-us.com , 240-683-3277
Drug Proprietary Name: Abilify
Generic Drug Name: aripiprazole
NME or Original BLA: No
Review Priority: Standard

Study Population includes < 17 years of age: Yes
Is this for Pediatric Exclusivity: No
Proposed New Indication: Treatment of (b) (4) Tourette's Disorder.

PDUFA: 12/12/2014
Action Goal Date: 11/12/2014
Inspection Summary Goal Date: 10/12/2014

OSI/DGCPC Consult
version: 09/12/2013

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Tic Disorder/Tourette & Data Verification
510: Robert Riesenberg, M.D. Atlanta Center for Medical Research 811 Juniper Street Atlanta, GA 30308 US	31-12-293	10 Screened 10 Enrolled	• Selection Criteria • Primary Efficacy Endpoint • Secondary Endpoints • Safety Data • Protocol Violations
533: Sohail Khattak, MD, FRCP Kids Clinic 1615 Dundas Street East, Unit 19 Whitby, ON L1N 2L1 Canada	31-12-293	27 Screened 23 Enrolled	• Selection Criteria • Primary Efficacy Endpoint • Secondary Endpoints • Safety Data • Protocol Violations
001: Seoul University Hospital 28 Yeongeon-Dong, Jongro-Gu, Seoul (Tel: 02-2072-2114)	South Korea 031-KOA-0703	14 Screened 12 Enrolled	• Selection Criteria • Primary Efficacy Endpoint • Secondary Endpoints • Safety Data • Protocol Violations
002: Seoul Asian Hospital 388-1 2-Dong, Poongnap, Songpa-Gu, Seoul (Tel: 1688-7575)	South Korea 031-KOA-0703	Screened 12 Enrolled 10	• Selection Criteria • Primary Efficacy Endpoint • Secondary Endpoints • Safety Data • Protocol Violations
003: Social Welfare Corporation, Samsung Life Public Service Foundation, Samsung Medical Center 50, Ilweon-Dong, Gangnam-Gu, Seoul (Tel: 1599-3114	South Korea 031-KOA-0703	Screened 17 Enrolled 9	• Selection Criteria • Primary Efficacy Endpoint • Secondary Endpoints • Safety Data • Protocol Violations

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Tic Disorder/Tourette & Data Verification
004: Inha University Hospital 7-206, 3-Ga, Shinheung-Dong, Joong-Gu, Incheon (Tel: 032-890-2114	South Korea 031-KOA-0703	Screened 19 Enrolled 14	• Selection Criteria • Primary Efficacy Endpoint • Secondary Endpoints • Safety Data • Protocol Violations
005: Yonsei University Medical School, Severance Hospital (134 Shinchon-Dong) 250 Seongsan-Ro, Seodaemun-Gu, Seoul (Tel: 02-2227(8)-0114	South Korea 031-KOA-0703	Screened 13 Enrolled 9	• Selection Criteria • Primary Efficacy Endpoint • Secondary Endpoints • Safety Data • Protocol Violations
006: Chungang University Hospital 224-1 Heukseok-Dong, Dongjak-Gu, Seoul (Tel: 02-6299-1114)	South Korea 031-KOA-0703	Screened 8 Enrolled 7	• Selection Criteria • Primary Efficacy Endpoint • Secondary Endpoints • Safety Data • Protocol Violations

III. Site Selection/Rationale

The approval of the NDA will rely on two adequate and well controlled trials. One was a large global trial, and one was a relatively small study in South Korea at 6 clinical sites. At this point, the larger study appears to be clearly positive, and we don't have specific concerns about sites. However, the Canadian site is the largest enrolling site. We would like to request inspections of one Canadian site, one U.S. site, and at least 3 South Korean sites. The 6 South Korean sites are in Seoul or near Seoul.

One of the two pivotal studies was conducted entirely in South Korea in a non-IND study. For the Korean study, the sponsor has acknowledged that there were significant protocol violations for individual subjects. The sponsor removed several patients from the primary analysis because of the protocol violations. The protocol violations included failure to meet inclusion criteria, errors in study medication actual exposure (given the incorrect study drug), and unacceptable non-compliance with treatment. The study fails for the Per Protocol Analysis. The study becomes negative if one of two sites is removed separately from the analysis (Sites 004 or 005). In addition, the sponsor did not obtain financial disclosure documents for 15 out of 23 sub-investigators.

Domestic Inspections:

Reasons for inspections (please check all that apply):

X Enrollment of large numbers of study subjects

International Inspections:

Reasons for inspections (please check all that apply):

X Domestic and foreign data show somewhat inconsistent results pertinent to decision-making. One of the pivotal studies was conducted entirely in South Korea in a non-IND study. Please refer to the discussion above.

X Other: Site specific protocol violations. It would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection (international and/or domestic) because of the reasons stated above.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact William Bender, RPM (at 301-796-2145), or Christina Burkhart (Medical Officer) at 301-796-4239, or Robert Levin (Medical Team Leader) at 301-796-1110.

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

/s/

WILLIAM H BENDER
04/11/2014

MITCHELL V Mathis
04/11/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21436/S-38

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA #, supplement #, Trade name (generic name) –

21436/S-038 Abilify (aripiprazole) 2, 5, 10, 15, 20, 30 mg tablets
21713/S-030 Abilify (aripiprazole) 1 mg/mL oral solution
21729/S-022 Abilify (aripiprazole) 10 and 15 mg ODT
21866/S-023 Abilify (aripiprazole) 9.75 mg/1.3 mL inj for IM use

HFD # 130

Applicant Name Otsuka Pharmaceutical Development & Communications, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 years for Orphan Drug Status

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

21436 Abilify (aripiprazole) 2, 5, 10, 15, 20, 30 mg tablets
21713 Abilify (aripiprazole) 1 mg/mL oral solution
21729 Abilify (aripiprazole) 10 and 15 mg ODT
21866 Abilify (aripiprazole) 9.75 mg/1.3 mL inj for IM use

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Trial 31-12-293: A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder

Trial 031-KOA-0703: A Randomized, Double-bind, Dose-adjustment, Placebocontrolled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Trial 31-12-293 and Trial 031-KOA-0703

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 116003 YES ☒ NO ☐
Explain:

Investigation #2

IND # 116003 YES ☒ NO ☐
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐	! NO ☐
Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: William Bender, R.Ph., MSHCA, RAC
Title: Director Regulatory Health Project Manager
Date: 12/10/2014

Name of Office/Division Director signing form: Mitchell Mathis, M.D.
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

WILLIAM H BENDER
12/12/2014

MITCHELL V Mathis
12/12/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 21436; 21713; 21729; 21866 BLA #	NDA Supplement # S-038; S-030; S-022; S-023; S-030 BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Abilify Established/Proper Name: aripiprazole Dosage Form: 2mg, 5mg, 10mg, 15mg, 20mg & 30mg Tablets (NDA 21436), oral solution 1 mg/ml (NDA 21713), orally disintegrating tablet 10 mg, 15 mg (NDA 21729), and injectable formulation 9.75 mg/1.3 mL single-dose vial (NDA 21866)		Applicant: Otsuka Pharmaceutical Development & Communications, Inc. Agent for Applicant (if applicable): David Goldberger, R.Ph.
RPM: CAPT William Bender		Division: Division of Psychiatry Products

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is December 12, 2014	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain ____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Weekly FDA News and Notes; Division of Drug Information listserve
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval: 12/12/2004
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included (attached to the Approval Letterr)
• Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	N/A
• Most-recent draft labeling	☐ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	N/A **N/A**
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None 04/18/2014(SRPI); 12/11/2014RPM Label Review DMEPA: ☒ None 09/19/2014 DMPP/PLT (DRISK): ☒ None 10/24/2014 OPDP: ☒ None 10/24/2014 SEALD: ☐ None CSS: ☐ None Other: ☐ PMHS 10/27/2014
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	04/18/2014 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan Designation	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg May 21,2013
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 12/11/2014
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None
PMR/PMC Development Templates *(indicate total number)*	☐ None 1 PMC-12/03/2014
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	11/12/2014
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Orphan drug designation.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A

❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 08/25/2014; 09/03/2014; 09/03/2014; 09/05/2014; 09/15/2014; 11/06/2014; 12/05/2014 &12/05/2014
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 10/31/2014
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/03/2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 11/20/2014
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	02/12/2014
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

WILLIAM H BENDER
12/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21436/S-038
NDA 21713/S-030
NDA 21729/S-022
NDA 21866/S-023

GENERAL ADVICE

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: David Goldberger, RPh, RAC
Vice President, Global Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Goldberger:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received February 12, 2014 (NDA 21436/S-038), and April 3, 2014 (NDAs 21713/S-030, 21729/S-022, 21866/S-023), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abilify (aripiprazole) tablets 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg (NDA 21436), oral solution 1 mg/ml (NDA 21713), orally disintegrating tablet 10 mg, 15 mg (NDA 21729), and injectable formulation 9.75 mg/1.3 mL single-dose vial (NDA 21866).

Reference is also made to the Agency's approval letter dated December 12, 2014, the Agency's corrected approval letter issued on February 24, 2015, and the Agency's general advice letter dated March 27, 2015.

We also reference receipt of your email communication including a declaration from Dr. Sallee dated March 18, 2015, containing your objection to our February 24, 2015, corrected approval letter for the treatment of Tourette's Disorder, and concerns you have raised in the context of litigation. We are clarifying the scope of approval for Tourette's Disorder as follows:

The Indications and Usage statement is a concise statement consistent with FDA regulations at 21 CFR § 201.57(a)(6), (c)(2). The Dosage and Administration section, Clinical Studies section, and other sections of the Full Prescribing Information for Abilify describe the data supporting the use of Abilify for the treatment of Tourette's Disorder. The labeling describes only pediatric clinical trials, provides instructions only for pediatric dosing in Tourette's Disorder, and describes warnings and adverse reactions only for pediatric patients with Tourette's Disorder. Thus, the approval of Abilify for Tourette's Disorder is only for the pediatric population.

If you have any questions, call CAPT Paul David, Chief, Regulatory Project Management Staff at (301) 796-1058 or email Paul.David@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

MITCHELL V Mathis
04/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21436/S-038
NDA 21713/S-030
NDA 21729/S-022
NDA 21866/S-023

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Reference is also made to the Agency's approval letter dated December 12, 2014, and to the Agency's corrected approval letter issued on February 24, 2015, which was backdated to the original approval date of December 12, 2014.

We acknowledge receipt of your email communication including a declaration from Dr. Sallee dated March 18, 2015, containing your objection to our amended December 12, 2014 approval letter for the treatment of Tourette's Disorder. We have reviewed the referenced material and have the following comments:

1. The Indications and Usage (I&U) statement in the Full Prescribing Information (FPI) of drug labeling often includes only a concise statement of the disease or disorder to be treated, without identifying specific age ranges. See 21 CFR 201.57(a)(6). The I&U statement generally does not include age-specific population information unless a Limitation of Use statement (e.g., a statement describing lack of effect in a particular subpopulation) is warranted. No Limitation of Use statement based on age was included in the FPI for Abilify.[1]
2. You will note that when the approval letter was corrected, the FPI, which describes the scope of the approval, was not amended, and the I&U statement has always listed "Treatment of Tourette's Disorder" as the indication. The indication was thus unchanged

[1] We note that the I&U section for Abilify was simplified in 2014, removing references to specific age ranges where they appeared.

when the approval letter was corrected. As such, the correction was a housekeeping matter and not a change intended to alter the conditions of approval.[2]

3. The text in the original approval letter was not consistent with the I&U statement. The information related to the specific population (i.e., pediatric patients) in the original approval letter implied a Limitation of Use that did not exist, and therefore was deleted.
4. The information in Dosage and Administration, Clinical Studies, and other sections of the FPI describes the data supporting the use of aripiprazole for the treatment of Tourette's Disorder in pediatric patients ages 6-18. The label describes the pediatric clinical trials, and provides instructions for pediatric dosing.
5. Therefore, the corrected approval letter did not broaden the indication or the scope of the underlying approval. The corrected letter simply harmonized the letter with the I&U statement in the FPI.

If you have any questions, call CAPT Paul David, Chief, Regulatory Project Management Staff at (301) 796-1058 or email Paul.David@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

[2] We note that the approval letter itself states that the application was approved "for use as recommended in the enclosed agreed-upon labeling text" See Supplement Approval Letter dated 12/12/2014.

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/s/

MITCHELL V Mathis
03/27/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21436/S-038
NDA 21713/S-030
NDA 21729/S-022
NDA 21866/S-023

GENERAL ADVICE

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Vice President, Global Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Goldberger:

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We also refer to your January 16, 2015, email containing labeling that included pertinent information in section 8.4 (Pediatric Use) under the "Irritability with Autistic Disorder" subsection that was inadvertently omitted in the approval action dated December 12, 2014. We have reviewed your labeling and agree to update said subsection as noted in the attached labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

If you have any questions, please call CAPT William Bender, Senior Regulatory Project Manager, at (301) 796-2145 or via email at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

84 Page(s) of Draft Labeling have been withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

MITCHELL V Mathis
01/23/2015

Bender, William

From: Guinn, Patrick <Patrick.Guinn@otsuka-us.com>
Sent: Friday, January 16, 2015 12:37 PM
To: Bender, William
Cc: Goldberger, David; Prindle, Ann; Guinn, Patrick
Subject: FW: Additional Labeling Changes - Abilify Oral FW: NDA 21436 s-038
Attachments: Aripiprazole - Abilify - Current.pdf; Aripiprazole - Abilify - Current.doc; FDA - nda21436s038finalclean12102014doc - markup.pdf; FDA - nda21436s038finalclean12102014doc - markup.doc

Hi Bill,

Please refer to the attachments for the additional labeling changes you requested on January 7 regarding *Irritability Associated with Autistic Disorder*.
In addition, there were a few minor editorial revisions made.

Please let me know what mechanism you would like us to follow for the formal electronic submission.
In addition, please let me know if it is okay to resubmit the revised SPL to the FDA's eLIST.

Regards, Patrick.

Patrick F. Guinn, RAC
Associate Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.

2440 Research Blvd.
Rockville, MD 20850 USA
Phone: 1-240-683-3277
Mobile: 1-301-335-2967
Email: Patrick.Guinn@otsuka-us.com

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/s/

WILLIAM H BENDER
01/20/2015

February 27, 2015

The below approval letter incorrectly referenced pediatric patients in the indication statement.

The official copy of this letter was mailed to the applicant on December 16, 2014. The communication function of this letter has been changed to Advice. A corrected letter was checked in on February 23, 2015 and backdated to December 12, 2014 to maintain the original action date.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21436/S-038
NDA 21713/S-030
NDA 21729/S-022
NDA 21866/S-023

SUPPLEMENT APPROVAL

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: David Goldberger, RPh, RAC
Vice President, Global Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Goldberger:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received February 12, 2014 (NDA 21436/S-038), and April 3, 2014 (NDAs 21713/S-030, 21729/S-022, 21866/S-023), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abilify (aripiprazole) tablets 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg (NDA 21436), oral solution 1 mg/ml (NDA 21713), orally disintegrating tablet 10 mg, 15 mg (NDA 21729), and injectable formulation 9.75 mg/1.3 mL single-dose vial (NDA 21866).

We acknowledge receipt of your amendments dated March 7, 2014; March 26, 2014; April 30, 2014; June 10, 2014; June 20, 2014; June 26, 2014; August 29, 2014; October 28, 2014; November 14, 2014; November 24, 2014; December 2, 2014, December 8, 2014, and December 9, 2014.

These "Prior Approval" supplemental new drug applications provide for labeling revisions based upon two adequate and well-controlled trials that demonstrate the efficacy for the new indication in pediatric patients with Tourette's Disorder.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment agreed upon in your communication dated November 14, 2014:

2837-1 A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of aripiprazole in the treatment of pediatric patients (6-17 years) Tourette's

Disorder. This trial must include a placebo group and more than one fixed dose and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of aripiprazole. Because it is important to establish the dose-response for maintenance, this trial should randomize patients on stable doses of aripiprazole and different doses of aripiprazole (and to placebo) during the maintenance phase.

The timetable you submitted on November 25, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 01/31/2016
Trial Completion: 07/31/2021
Final Report Submission: 07/31/2022

Submit clinical protocols to your IND 116003 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to this postmarketing commitment should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call CAPT William Bender, Senior Regulatory Project Manager, at (301) 796-2145 or via email at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

92 Pages(s) of Draft Labeling has been withheld in Full as b(4) (CCI/TS) immediately following this page.

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

/s/

MITCHELL V Mathis
12/12/2014

Bender, William

From: Guinn, Patrick <Patrick.Guinn@otsuka-us.com>
Sent: Tuesday, December 09, 2014 5:44 PM
To: Bender, William
Cc: Goldberger, David; Prindle, Ann; Guinn, Patrick
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children
Attachments: CLEAN - nda21436s03812092014cleanWB - Response - 9-Dec-14.doc.doc; nda21436s03812092014cleanWB - Response - 9-Dec-14.doc.doc

Hi Bill,

Please refer to the attachments for revised labeling incorporating the most recent FDA comment sent this afternoon, Dec 9.

> **FDA Comment #3: RECENT MAJOR CHANGES, Warnings and Precautions, Metabolic Changes (5.6) 12/2014 - These are new data for Tourette's patients. The labeling will need to have the black line along the side accordingly.**
> ***Otsuka's Response**: Formatting changes have been addressed.*

These revisions have been incorporated into the label along with previous comments provided by FDA this morning, Dec 9.

> **FDA Comment #1: Page 2, Full Prescribing Information Comments - Please move this horizontal line and FULL PRESCRIBING INFORMATION: CONTENTS* to the top of the next page as you did for your application of Abilify Maintena, NDA 202971.**
>
> ***Otsuka's Response**: Formatting errors have been addressed.*
>
> **FDA Comment #2: Page 47, Section 7.2, Drugs Having No Clinically Important Interactions with ABILIFY - *Based on the labeling and published data, it seems that CYP2C19 contributes more to the metabolism of (es)citalopram, compared to CYP3A4 and CYP2D6.***
>
> ***Otsuka's Response**: FDA edits have been accepted.*

The formal submission will be sent electronically later today.

Regards, Patrick.

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Tuesday, December 09, 2014 11:15 AM
To: Guinn, Patrick
Cc: Goldberger, David; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Hi Patrick,
We have addressed your below comment regarding escitalopram. Also, the "Full Prescribing Information Contents" and horizontal line are still on the first page and not on the TOC page (top of the second page) as you did for your Abilfiy Maintena application. Please edit that part accordingly and let us know if you accept our escitalopram comment. If so, please send back a clean word version and the version addressing our comments as you have been doing. I am suspecting that this can be done by COB today.
Thanks,
Bill

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Monday, December 08, 2014 11:09 AM
To: Bender, William
Cc: Goldberger, David; Prindle, Ann; Guinn, Patrick
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Hi Bill,

Please refer to the attachments for labeling that addresses FDA's comments as well as a clean copy of the labeling as requested.

We accept the revised labeling as requested by FDA on Friday, Dec 5.
We are requesting one clarification regarding the deleted text and the revised text provided by FDA in Section 7.2. It appears that escitalopram (highlighted in the deleted text) was inadvertently omitted from the revised text provided by FDA. Otsuka added escitalopram back into the text for the list of substrates of (b) (4) Please provide confirmation that this is acceptable or any additional FDA comments regarding this matter.

In Section 7.2 Drugs Having No Clinically Important Interactions with ABILIFY

(b) (4)

Regards, Patrick.

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Friday, December 05, 2014 11:33 AM
To: Guinn, Patrick
Cc: Goldberger, David; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Hi Patrick,
We have some very minor edits to the label (attached). Please use this label to address our comments and send back to me (also please include a clean word version).
Thanks and please let me know if you have any questions.
Thanks,
Bill

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Tuesday, December 02, 2014 4:57 PM
To: Bender, William
Cc: Goldberger, David; Guinn, Patrick; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Dear Bill,

Please refer to the attachments for the Cover Letter, marked up labeling, and clean copy labeling, as requested by FDA.

Reference is made to Otsuka Pharmaceutical Company, Ltd.'s (OPC) New Drug Applications (NDAs) 21-436 (aripiprazole tablets), approved on November 15, 2002, 21-713 (aripiprazole oral solution) approved on December 10, 2004, 21-729 for Abilify Discmelt (aripiprazole orally disintegrating tablets) approved on June 7, 2006 and 21-866 (aripiprazole intramuscular injection) approved on September 20, 2006.

Reference is also made to the made to the supplemental new drug application (sNDA) requesting approval to add a new indication, treatment of (b) (4) Tourette's disorder in pediatric patients (6 to 17), to the labeling for this product, which was submitted on February 12, 2014.

Further reference is made to the draft labeling provided by FDA on November 30, 2014, in an email from CDR William Bender, Senior Regulatory Project Manager, request for additional revisions to the overall Abilify package insert.

We have accepted and incorporated all text changes requested by FDA. In addition, there were four comments from FDA included in the draft labeling. Comments made by the FDA are stated in bold and are followed by Otsuka's response.

- **FDA Comment #1: Use this clean label as a base document. Please carefully review this label and correct any formatting errors (including the 42-item checklist) and typos. Address all outstanding requests noted in comments and track all changes. Delete comments, once you have addressed them in labeling.**

  ***Otsuka's Response**: Formatting errors have been addressed and all comments that have been addressed in the past have been deleted at requested.*

- **FDA Comment #2: Edits made for consistency with Abilify Maintena labeling (Section 5.8).**

  ***Otsuka's Response**: FDA edits have been accepted.*

- **FDA Comment #3: Have there been any premarketing cases of rhabdomyolysis that were not associated with neuroleptic malignant syndrome? If yes, rhabdomyolysis should be re-added.**

  ***Otsuka's Response**: Rhabdomyolysis has been re-added.*

- **FDA Comment #4: Please add PK changes for venlafaxine, escitalopram, fluoxetine, paroxetine, sertraline to the forest plot. If cannot be added to the plot, please provide brief description as text (Drug Interaction Studies, Figure 3).**

  ***Otsuka's Response**: The PK data for venlafaxine (CSR CN138462) and escitalopram (CSR CN138463) was added to Figure 3. The text summary was added for other ADTs.*

Regards, Patrick.

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Tuesday, December 02, 2014 7:55 AM
To: Guinn, Patrick
Subject: FW: NDA 21436 s038 Abilify for Tourette's in Children

Good Morning Patrick,
Do you think that you will be able to respond today?
Thanks,
Bill

From: Bender, William
Sent: Sunday, November 30, 2014 9:50 PM
To: Guinn, Patrick
Cc: Goldberger, David; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Hi Patrick,

Attached is hopefully our last labeling negotiation. Please use this clean version as your base label, delete the comments that have been addressed, and track any additional changes (if you have any). Since there are a few comments, please send back to me by COB Tuesday, December 2nd.
Thanks,
Bill

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Friday, November 21, 2014 5:16 PM
To: Bender, William
Cc: Goldberger, David; Prindle, Ann; Guinn, Patrick
Subject: NDA 21436 s038 Abilify for Tourette's in Children

Hi Bill,

Please refer to the attachments for the Cover Letter and responses to FDA comments in the labeling.

- Attachment 1: Cover Letter
- Attachment 2: Labeling with responses to FDA comments

The electronic submission is expected to be sent through the FDA e-gateway tonight.

Regards, Patrick.

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Thursday, November 20, 2014 11:43 AM
To: Guinn, Patrick
Cc: Goldberger, David; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Hi Patrick,
We have some minor changes to the label (attached). Please respond to these changes by Monday, November 24th. Please let me know if you have any questions.
Thanks,
Bill

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Friday, November 14, 2014 2:14 PM
To: Bender, William
Cc: Goldberger, David; Guinn, Patrick; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Dear Bill,

Please refer to the attachments for responses to your e-mail correspondence dated 10 Nov 2014.
The electronic submission is scheduled to be submitted through the FDA e-gateway later today.

- Attachment #1 - Cover Letter (responses)
- Attachment #2 – Draft Clean Word labeling
- Attachment #3 – Draft Marked Up Word labeling

Please let me know if you have any questions.

Regards, Patrick.

Patrick F. Guinn, RAC
Associate Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.

2440 Research Blvd.
Rockville, MD 20850 USA
Phone: 1-240-683-3277
Mobile: 1-301-335-2967
Email: Patrick.Guinn@otsuka-us.com

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Monday, November 10, 2014 8:43 AM
To: Guinn, Patrick; Prindle, Ann; Goldberger, David
Subject: NDA 21436 s038 Abilify for Tourette's in Children

Good Morning Mr. Guinn,

Please refer to your Supplemental New Drug Application (sNDA) for Abilify, s-038 for Tourette's in children. We also refer you to the labeling that was sent to you on October 10, 2014 and your response on October 27, 2014. Additionally, we refer you to our April 24, 2014 "Filing Letter" in which we notified you of our target date of November 21, 2014 form communicating labeling changes and postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures-Fiscal Years 2013 Through 2017."

We have proposed revisions to the label that are attached to this email (both a tracked-changes and clean word version). We request that you resubmit labeling that addresses these issues by COB Friday, November 14, 2014. The resubmitted labeling will be used for further labeling negotiations if needed, therefore, please send both a tracked-changes and clean version in word format.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drugs and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We have the following proposed Postmarketing Commitment:

PMC: A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of aripiprazole in the treatment of pediactric patients (6-17 years) Tourette's Disorder. This trial must include a placebo group and more than one fixed dose and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of aripiprazole. Because it is important to establish the dose-response for maintenance, this trial should randomize patients on stable doses of aripiprazole and different doses of aripiprazole (and to placebo) during the maintenance phase.

Please let me know if you agree with this Postmarketing Commitment and if you have any questions.
Thanks,
Bill

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/s/

WILLIAM H BENDER
12/10/2014

Bender, William

From: Bender, William
Sent: Friday, November 14, 2014 2:31 PM
To: Burkhart, Christina; Ritter, Mark; Mathis, Mitchell; Farchione, Tiffany
Subject: NDA 21436 Abilify s-038 Tourettes in children

Hi Guys,
The sponsor has responded to our PMC email as follows:

FDA Comment #2: We have the following proposed Postmarketing Commitment:
PMC: A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of aripiprazole in the treatment of pediatric patients (6-17 years) Tourette's Disorder. This trial must include a placebo group and more than one fixed dose and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of aripiprazole. Because it is important to establish the dose-response for maintenance, this trial should randomize patients on stable doses of aripiprazole and different doses of aripiprazole (and to placebo) during the maintenance phase.

Otsuka's Response*: We accept FDA's proposal for a Post Marketing Commitment to evaluate the longer-term (i.e., maintenance) efficacy of aripiprazole in the treatment of pediatric patients (6-17 years) in Tourette's Disorder in a placebo controlled long-term efficacy study. We would like to request a meeting with the Division to discuss options for the study design. Please let us know if this meeting should occur prior to the PDUFA Date, 12 December 2014.*

They are requesting a meeting to discuss options for the study design and if this should occur before we take an Action.
I am not sure if we need to get into details before the PDUFA goal date as long as they agree to the PMC but I wanted to find out your thoughts. I could tell them to submit a MR and we could discuss the details with them at a later time if you think that is appropriate.

Please let me know your thoughts,
Thanks,
Bill

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/s/

WILLIAM H BENDER
12/09/2014

Bender, William

From: Guinn, Patrick <Patrick.Guinn@otsuka-us.com>
Sent: Tuesday, November 25, 2014 5:05 PM
To: Bender, William
Cc: Goldberger, David; Prindle, Ann; Guinn, Patrick
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Dear Bill,

Otsuka agrees with the timelines provided by FDA for the requested Post Marketing Commitment.

Final Protocol Submission: 01/2016
Trial Completion: 07/2021
Final Report Submission: 07/2022

In addition, Otsuka plans to discuss the study design and details with FDA as a type C meeting prior to submission of the final protocol.

Regards, Patrick.

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Tuesday, November 25, 2014 11:44 AM
To: Guinn, Patrick
Cc: Goldberger, David; Prindle, Ann
Subject: FW: NDA 21436 s038 Abilify for Tourette's in Children

Hi Patrick,
Also, on a side note, do you agree with the below timelines for our PMC request in the below email. Again, you can submit a MR to further discuss the PMC at a later date. Thanks and Have a Happy Thanksgiving… Bill

Final Protocol Submission: 01/2016

Trial Completion: 07/2021

Final Report Submission: 07/2022

From: Bender, William
Sent: Monday, November 17, 2014 10:47 AM
To: Guinn, Patrick
Cc: Goldberger, David; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Hi Patrick,
Your agreement will suffice for now; we do not need a completely agreed upon protocol at this point. We can meet with you, but it doesn't have to be before the PDUFA date.

Thanks,
Bill

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Friday, November 14, 2014 2:14 PM
To: Bender, William
Cc: Goldberger, David; Guinn, Patrick; Prindle, Ann
Subject: RE: NDA 21436 s038 Abilify for Tourette's in Children

Dear Bill,

Please refer to the attachments for responses to your e-mail correspondence dated 10 Nov 2014.
The electronic submission is scheduled to be submitted through the FDA e-gateway later today.

- Attachment #1 - Cover Letter (responses)
- Attachment #2 – Draft Clean Word labeling
- Attachment #3 – Draft Marked Up Word labeling

Please let me know if you have any questions.

Regards, Patrick.

Patrick F. Guinn, RAC
Associate Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.
Otsuka
2440 Research Blvd.
Rockville, MD 20850 USA
Phone: 1-240-683-3277
Mobile: 1-301-335-2967
Email: Patrick.Guinn@otsuka-us.com

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Monday, November 10, 2014 8:43 AM
To: Guinn, Patrick; Prindle, Ann; Goldberger, David
Subject: NDA 21436 s038 Abilify for Tourette's in Children

Good Morning Mr. Guinn,

Please refer to your Supplemental New Drug Application (sNDA) for Abilify, s-038 for Tourette's in children. We also refer you to the labeling that was sent to you on October 10, 2014 and your response on October 27, 2014. Additionally, we refer you to our April 24, 2014 "Filing Letter" in which we notified you of our target date of November 21, 2014 form communicating labeling changes and postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures-Fiscal Years 2013 Through 2017."

We have proposed revisions to the label that are attached to this email (both a tracked-changes and clean word version). We request that you resubmit labeling that addresses these issues by COB Friday, November 14, 2014. The resubmitted labeling will be used for further labeling negotiations if needed, therefore, please send both a tracked-changes and clean version in word format.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drugs and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We have the following proposed Postmarketing Commitment:

PMC: A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of aripiprazole in the treatment of pediactric patients (6-17 years) Tourette's Disorder. This trial must include a placebo group and more than one fixed dose and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of aripiprazole. Because it is important to establish the dose-response for maintenance, this trial should randomize patients on stable doses of aripiprazole and different doses of aripiprazole (and to placebo) during the maintenance phase.

Please let me know if you agree with this Postmarketing Commitment and if you have any questions.
Thanks,
Bill

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For more information please visit http://www.symanteccloud.com

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/s/

WILLIAM H BENDER
12/09/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Soo-Churl Cho, M.D., Ph.D.
101 Daehak-ro, Jongno-gu
Seoul University Hospital
Seoul, Korea 110-744

Dear Dr. Cho:

This letter informs you of the findings of a U.S. Food and Drug Administration (FDA) inspection conducted at your site on June 16, 2014 to June 19, 2014. Investigator Susan D. Yuscius representing the FDA, reviewed your conduct of the clinical investigation (Protocol **031-KOA-0703**, entitled "A Randomized, Double-Blind, Dose-Adjustment, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder") of the investigational drug Aripiprazole (Abilify®), performed for Otsuka Pharmaceutical Development, Inc.

This inspection was conducted as a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Yuscius during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

LCDR LaKisha Williams-Patterson, USPHS
Regulatory Health Project Manager
Division of Good Clinical Practice Compliance
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993-0000

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/s/

LAKISHA M WILLIAMS
12/05/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Han-Ik Yoo, M.D., Ph.D.
Seoul Brain Research Institute,
4F Guui-dong Gwangjin-Gu,
Seoul, South Korea

Dear Dr. Yoo:

This letter informs you of the findings of a U.S. Food and Drug Administration (FDA) inspection conducted at your site on June 23, 2014 to June 26, 2014. Investigator Susan D. Yuscius representing the FDA, reviewed your conduct of the clinical investigation (Protocol **031-KOA-0703**, entitled "A Randomized, Double-Blind, Dose-Adjustment, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder") of the investigational drug Aripiprazole (Abilify®), performed for Otsuka Pharmaceutical Development, Inc.

This inspection was conducted as a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Yuscius during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

LCDR LaKisha Williams-Patterson, USPHS
Regulatory Health Project Manager
Division of Good Clinical Practice Compliance
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993-0000

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/s/

LAKISHA M WILLIAMS
12/05/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Yoosook Joung, M.D.
Samsung Medical Center
81 Irwon-Ro, Gangnam-Gu
Seoul 135-710, South Korea

Dear Dr. Joung:

Between June 30, 2014 and July 4, 2014, Ms. Susan D. Yuscius representing the US Food and Drug Administration (FDA) investigated your conduct of the clinical study entitled "A Randomized, Double-blind, Dose-adjustment, Placebo-controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder" (Study 031-KOA-0703), a study of Abilify® (aripiprazole) sponsored by Otsuka Pharmaceutical Development.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects have been protected.

At the conclusion of the inspection, Ms. Gaberman presented and discussed with you Form FDA 483, Inspectional Observations. We understand that you did not perform this study under a US Investigational New Drug Application (IND). We have reviewed the Form FDA 483, the establishment inspection report, and the documents submitted with the report. We acknowledge your July 21, 2014 written response to the inspection findings and note that you have implemented corrective actions to prevent the recurrence of the inspectional findings presented on Form FDA 483. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown to Investigator Yuscius during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 51 Room 5328
Silver Spring, MD 20993-0002

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/s/

JONG HOON LEE
11/06/2014

JANICE K POHLMAN
11/06/2014

Bender, William

From: Bender, William
Sent: Friday, October 10, 2014 1:53 PM
To: Prindle, Ann (ann.prindle@otsuka-us.com); Goldberger, David (David.Goldberger@otsuka-us.com); Guinn, Patrick (Patrick.Guinn@otsuka-us.com)
Subject: NDA 21436 s038 Abilify for Tourette's Disorder

Hi Ann,
As promised, attached are our labeling edits/comments regarding s038. The edits/comments that I had sent you on October 1st are also included within this label. I have not included a clean copy of the label as there are sections in which we ask for more information, etc. so I did not think that it made much sense at this point.

Please respond to this labeling communication by October 27th.

Please let me know if you have any questions.

Thank you,
Bill
P.S. I believe that we will have one PMC to relay to you. I will send it to you via email for agreement when the reviewers are finished. Thanks again.

110 Pages(s) of Draft Labeling have been withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

WILLIAM H BENDER
11/10/2014

Bender, William

From: Bender, William
Sent: Monday, November 10, 2014 8:43 AM
To: Guinn, Patrick (Patrick.Guinn@otsuka-us.com); Prindle, Ann (ann.prindle@otsuka-us.com); Goldberger, David (David.Goldberger@otsuka-us.com)
Subject: NDA 21436 s038 Abilify for Tourette's in Children

Good Morning Mr. Guinn,

Please refer to your Supplemental New Drug Application (sNDA) for Abilify, s-038 for Tourette's in children. We also refer you to the labeling that was sent to you on October 10, 2014 and your response on October 27, 2014. Additionally, we refer you to our April 24, 2014 "Filing Letter" in which we notified you of our target date of November 21, 2014 form communicating labeling changes and postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures-Fiscal Years 2013 Through 2017."

We have proposed revisions to the label that are attached to this email (both a tracked-changes and clean word version). We request that you resubmit labeling that addresses these issues by COB Friday, November 14, 2014. The resubmitted labeling will be used for further labeling negotiations if needed, therefore, please send both a tracked-changes and clean version in word format.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drugs and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We have the following proposed Postmarketing Commitment:

PMC: A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of aripiprazole in the treatment of pediactric patients (6-17 years) Tourette's Disorder. This trial must include a placebo group and more than one fixed dose and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of aripiprazole. Because it is important to establish the dose-response for maintenance, this trial should randomize patients on stable doses of aripiprazole and different doses of aripiprazole (and to placebo) during the maintenance phase.

Please let me know if you agree with this Postmarketing Commitment and if you have any questions.
Thanks,
Bill

186 Pages(s) of Draft Labeling have been withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

WILLIAM H BENDER
11/10/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - ODE 4
Division of Pediatric and Maternal Health
Telephone 301-796-2200
Fax 301-796-9744

M E M O R A N D U M

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst
Division of Pediatric and Maternal Health
Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Team Leader
Division of Pediatric and Maternal Health
Office of New Drugs

Lynne Yao, M.D., Acting Director
Division of Pediatric and Maternal Health
Office of New Drugs

To: Division of Psychiatry Products (DPP)

Drug: Abilify (aripiprazole) tablets

Application number: NDA 21436/S-038 (IND 116,003)

Re: Pediatric Labeling Review & Assistance with PMC

Applicant: Otsuka Pharmaceutical Development & Communications, Inc.

Proposed Indication: Treatment of (b) (4) Tourette's disorder in pediatric patients (b) (4) years

Proposed Dosing Regimen: The recommended dosage is once-daily using already approved aripiprazole tablets

Consult request:
DPP requests the Division of Pediatric and Maternal Health (DPMH), formerly PMHS to review the proposed pediatric labeling, in particular the indication. Also, DPP requests DPMH input on a possible PMC for a maintenance trial in the pediatric population and suggestions of trial design. DPP also requests DPMH to provide labeling recommendations for subsections 8.1 Pregnancy, 8.2 Labor and Delivery and 8.3 Nursing Mothers.

Materials Reviewed:

- DPMH Consult Request (July 9, 2014)
- February 12, 2014, submission for NDA 21436/S-038
- Published literature (PubMed)
- July 16, 2012, DPMH (formerly PMHS) Abilify Maintena labeling review
- Aripiprazole published literature regarding lactation (LactMed)

REGULATORY HISTORY

On February 12, 2014, Otsuka Pharmaceutical Company Ltd., submitted supplemental New Drug Application (NDA 21-436) for aripiprazole oral tablets for the indication of treatment of (b) (4) Tourette's disorder in pediatric patients (b) (4) years. The applicant submitted data from two placebo controlled trials to support this new indication:

- Trial 31-12-293: A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in children and Adolescents with Tourette's Disorder
- Trial 031-KOA-0703: A Randomized, Double-blind, Dose-adjustment, Placebo-controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder

Abilify (aripiprazole) is an atypical antipsychotic originally approved on November 15, 2002, for the treatment of schizophrenia in adults. Abilify is also currently approved under NDA 21713 for the 1 mg/ml oral solution; NDA 21729 for the orally disintegrating tablet; and NDA 21866 for the intramuscular injection. Abilify is currently approved for:

- Treatment of Schizophrenia in adults and adolescents ages 13-17 years
- Acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate in adults and pediatric patients ages 10-17 years
- Maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate in adults
- Adjunctive treatment of major depressive disorder (MDD) in adults
- Treatment of irritability associated with autistic disorder in pediatric patients ages 6-17 years
- Acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults

On January 25, 2006, Otsuka Pharmaceutical Development and Communications, Inc., received orphan designation for Abilify (aripiprazole) for the Treatment of Tourette's syndrome in accordance with 21 CFR 315.55(d). Therefore, the sponsor is exempt from the requirement under PREA to submit pediatric data or request a waiver or deferral for all pediatric subpopulations and a Pediatric Study Plan (PSP) is not needed.

BACKGROUND

Tourette's is a neurological disorder with childhood onset characterized by repetitive, involuntary motor and vocal tics.[1,2] Tics vary in type, frequency and severity. It is unknown what causes Tourette's disorder. Tourette's disorder can be accompanied by another neurobehavioral disorder such as attention deficit disorder (ADHD), mood disorder, non-obsessive compulsive anxiety disorders or obsessive-compulsive disorder (OCD).[3] In most individuals, tics resolve themselves in early adulthood and in some cases completely disappear. The onset of Tourette Disorder ranges from 2-21 years with a mean age of 5-7 years. Approximately, 30% of patients diagnosed with Tourette's Disorder alone without any other comorbidities are tic-free by young adulthood.[4] According to the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013) Tourette's Disorder diagnostic criteria is as follows:

A. "Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.

B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.

C. Onset is before age 18 years.

D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis)."

Behavioral therapy is usually first-line recommended treatment for Tourette's disorder and proceeds to medications in more moderate to severe cases.[5] The only FDA-approved treatments for Tourette's disorder are haloperidol and pimozide, both of which are approved in pediatric patients .[6,7] There are currently no atypical antipsychotic medications approved for Tourette's disorder.

[1] Tourette Syndrome Fact Sheet. National Institute of Neurological Disorders and Stroke. National Institutes of Health. Publication date January 2012.
http://www ninds nih.gov/disorders/tourette/detail_tourette htm. Web 28 Aug 2014.
[2] Shaw, Z., Coffey, B. (2014). Tics and Tourette Syndrome. Psychiatric Clinics of North America, 37(3), 269-286. http://dx.doi.org/10.1016/j.psc.2014.05.001
[3] Budman, C., Coffey, B., Shechter, R., Schrock, M., Wieland, N. Spirgel, A., et al. (2008). Aripirprazole in Children and Adolescents with Tourette Disorder with and without Explosive Outbursts. *Journal of Child and Adolescent Psychopharmacology*, 18(5), 509-515. DOI: 10.1089/cap.2007.061
[4] Rizzo, R., Gulisano, M., Valeria Cali, P., Curatolo, P. (2012). Long term clinical course of Tourette Syndrome. Brain & Development, 34, 667-673.
[5] Tourette Syndrome. Centers for Disease Control and Prevention. Facts.
http://www.cdc.gov/ncbddd/tourette/treatments.html#CBIT . Web. 28 Aug 2014.
[6] 9.27.11. Orap (pimozide) approved package insert.
[7] Haloperidol package insert. http://dailymed nlm nih.gov/dailymed/drugInfo.cfm?setid=3e44fed0-6132-4881-a9cd-af6156c7af9c

DISCUSSION

The sponsor submitted two studies to support the new pediatric indication for Tourette's Disorder. One study was a fixed-dose, placebo controlled trial in patients ages 7 to 17 years with a total of 133 subjects. The second study was a dose adjusted, placebo controlled trial in patients 6 to 18 years of age with a total of 61 subjects. After reviewing the submission, The Division of Psychiatry Products (DPP) has concluded efficacy has been established for Tourette's disorder.

DPP requested assistance with the wording of the proposed pediatric Tourette's Disorder indication; specifically, whether the appropriate indication language should read, *for the treatment of* (b) (4) *Tourette's disorder in pediatric patients (*(b) (4) *years)* versus *treatment of Tourette's disorder in pediatric patients (*(b) (4) *years)*. In addition, DPP also requested assistance drafting a post marketing commitment for a randomized-withdrawal maintenance trial in the pediatric population. There is an open-label, 52 week study that is ongoing that will provide further safety and efficacy data and DPP requests input on ethical considerations and the appropriateness of such a randomized withdrawal trial in the pediatric population.

DPP is taking the opportunity during this application review cycle to revise Abilify labeling for conformance and consistency with content and format requirements of the Physician Labeling Rule (PLR). Therefore, DPMH also provided recommendations for labeling revisions for subsections 8.1 Pregnancy, 8.2 Labor and Delivery and 8.3 Nursing Mothers.

Pediatric Use Labeling

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population compared with the adult population. For products granted pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

Specific DPMH labeling recommendations are at the end of this review. DPMH recommends the new pediatric indication be worded, *for the treatment of Tourette's disorder in pediatric patients ages (6-17 years)* for consistency with the DSM-5 definition of Tourette's Disorder. Tourette's Disorder, according to the DSM-5, encompasses the occurrence of vocal and motor tics present during the illness although not necessarily at the same time and for at least 1 year (see full definition in the Background section of this review).[8] Both of the clinical trials submitted to support the indication studied vocal and motor tics in patients diagnosed with Tourette's disorder using DSM 5 criteria. Thus, DPMH recommends that the indication be "treatment of Tourette's disorder" as the study included only patients who fit the DSM-5 diagnosis criteria for Tourette's Disorder. In addition, DPP is not planning to restrict the indication

[8] American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.

to pediatric patients as the available data can be used to extrapolate efficacy to adults with Tourette's Disorder.

Postmarketing Commitment (PMC)

Currently, an on-going, long-term (52-week), open-label safety trial (study 31-12-294) is being conducted which will collect longer-term aripiprazole safety data . No new safety issues have arisen to date in the Tourette's Disorder trials that were not present in the aripiprazole pediatric trials for other indications. DPMH agrees with the proposal of a Post-Marketing Commitment (PMC) for a randomized, withdrawal trial. The randomized withdrawal trial will assess how long a patient may need to be on treatment in order to sustain effect as this question will not be answered in the long-term, ongoing safety trial. DPMH also recommends the randomized, withdrawal trial evaluate adult patients in addition to pediatric patients as the disease often extends into adulthood. DPMH believes such a trial design would be ethical in pediatric patients because Tourette's disorder is not life threatening and symptoms may spontaneously remit..[9] Approximately 30% of patients affected with Tourette's and no other comorbidities are tic-free by early adulthood.[4] In addition, common side effects of Abilify such as weight gain, extrapyramidal symptoms, somnolence, tremor, akathisia, restlessness, nausea, fatigue, dizziness and others often cause patients being treated for other indications to discontinue treatment without detrimental effects.

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, DPMH is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

[9] Duckworth, K., Freedman, J. (2012). Tourette's Syndrome FACT SHEET. National Alliance on Mental Illness. (NAMI). www.nami.org/factsheets/Tourettes_factsheet.pdf.

Pregnancy

A search of published literature was performed regarding the use of Abilify in pregnant women. Limited published case reports were found. Available case reports include a varying range of aripiprazole dosage, treatment length and timing of exposure during pregnancy.[10] There are no reports of fetal malformations; however, these data are too limited to determine fetal risk in humans. Gentile (2014) reviewed multiple pregnancy case reports and concluded that there was no strong evidence of fetal risk with first trimester exposure. Gentile (2014) also reports that limited pharmacokinetic data collected during pregnancy showed a decline in plasma levels of more than two-thirds throughout pregnancy and concluded that dose increases may be needed at the beginning of the third trimester; however, when neonatal outcomes such as cardiac rhythm disturbances, respiratory distress and withdrawal symptoms were increased with third trimester aripiprazole exposure.[11] According to Einarson, et al., (2009), women with antipsychotic illness such as schizophrenia tend to be high risk when pregnant due to poor nutrition, lack of prenatal care, high alcohol consumption, tobacco use and use of illicit drugs. Windhager, et al., (2014) reports on aripiprazole plasma levels measured during and after pregnancy in three women. Aripiprazole plasma levels decreased throughout pregnancy in all three women. In all three patients, doses were increased at the beginning of the third trimester. Before birth another decline in plasma levels were observed however doses remained the same and four to five weeks postpartum plasma levels doubled. The authors concluded that aripiprazole dosage may need to increase throughout pregnancy in order to maintain stable plasma levels to prevent psychotic events and relapse.[12] Furthermore, schizophrenia alone has been associated with poor obstetric outcomes such as low birth rate, hypotonia, lethargy, tremors, higher incidence of infant death, preterm delivery, still birth and extrapyramidal symptoms.[13]

Lactation

The Drugs and Lactation Database (LactMed)[14] was searched for available lactation data on with the use of aripiprazole, and limited information was located and is summarized below. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[10] Gentile S, Tofani S, Bellantuono C. (2011). Aripiprazole and Pregnancy A Case Report and Literature Review [Letter to the editor]. *J Clin Psychopharmacology*, 531.
[11] Gentile, S. (2014). A safety evaluation of aripiprazole for treating schizophrenia during pregnancy and puerperium. *Expert Opin. Drug Saf.* [Early Online], 13(11), 1-10.
[12] Windhager, E., Kim, S., Saria, A., Zauner, K., Amminger, P., Klier, C. (2014). Perinatal Use of Aripiprazole; Plasma Levels, Placental Transfer, and Child Outcomes in 3 New Cases. *Journal of Clinical Psychopharmacology,* 34, 637-641. doi: 10.1097/JCP.0000000000000171
[13] Einarson, A., Boskovic, R. (2009). Use and Safety of Antipsychotic Drugs During Pregnancy. *Journal of Psychiatric Practice,* 15(3), 183-192.
[14] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT

There are limited data available with regard to aripiprazole and human breast milk. Two case reports have been published which demonstrate that aripiprazole levels are present in human milk. Schlotterbeck, et al., (2007) reported that aripiprazole concentrations in breast milk are approximately 20% of the maternal plasma level concentration ratio, which is similar breast milk drug levels measured in other second-generation antipsychotics.[15] Watanabe, et al., (2011) reported measuring 38.7 ng/mL of aripiprazole in human breast milk after the mother had been administered 18 mg/day of aripiprazole.[16] Several other case reports of postpartum women taking aripiprazole were reviewed but did not provide sufficient detail because either the mother decided not to breast feed or breast milk samples were not taken.

RECOMMENDATIONS

Postmarketing Commitment (PMC)

Request a randomized, withdrawal trial to assess length of treatment necessary to sustain effect. Consider enrolling adult patients in this trial to appropriately inform use in adults with Tourette's disorder.

Labeling

DPMH refers to the NDA action for final labeling. DPMH participated in team labeling meetings and conveyed the following pediatric and maternal health recommendations for Abilify labeling. Many of these recommendations are for compliance of Abilify labeling with PLR content and format requirements.

Pediatric Labeling

1 INDICATIONSAND USAGE

- New indication should read: "ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution are indication for the treatment of Tourette's Disorder in pediatric patients ages (b) (4) years." (b) (4) , provide appropriate cross references to data sections of labeling that include efficacy information.

2 DOSAGE AND ADMINISTRATION

- Delete data supporting pediatric dosage and administration information from this section of labeling. Provide cross references to the relevant data sections of labeling.

5 WARNINGS AND PRECAUTIONS

- Delete clinical trial data, and instead, provide a succinct description of the warning and precaution and provide cross-references to the relevant data sections of labeling.

[15] Schlotterbeck P, Leube D, Kircher T, Hiemke C, Grunder G. (2007, February 12). Aripiprazole in human milk [Letter to the editor]. *International J Neuropsychopharmacology*, p. 433.
[16] Watanabe N, Kasahara M, Sugibayashi R, et al. (2011). Perinatal Use of Aripiprazole A Case Report [Letter to the editor]. *J Clin Psychopharmacoogy*, p. 377.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

- Provide the appropriate regulatory statement from 21 CFR 201.57(c)(9)(iv) regarding indications and age groups in which safety and effectiveness have not been established.
- Provide subheadings to separate approved indications.
- The basis for efficacy is provided for all indications. Provide the basis for safety for all indications as well.

Pregnancy and Nursing Mothers Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

- Reformat subsection per the proposed Pregnancy and Lactation Labeling Rule (PLLR) while still complying with the current required regulatory language specified I 21 CFR 201.57(c)(9)(i).
- Add contact information for the National Pregnancy Registry for Atypical Antipsychotics.

Labor and Delivery

- Delete subsection as this drug has no use during labor or delivery and no information is available on potential impact of the drug on labor or delivery.

Nursing Mothers

- The current nursing mothers regulatory statement is incomplete. Revise to include the complete regulatory statement specified in 21 CFR 201.57(c)(9)(iii): "Because of the potential for serious adverse reactions in nursing infants from ABILIFY, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

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/s/

CARRIE M CERESA
10/23/2014

JEANINE A BEST
10/23/2014

HARI C SACHS
10/24/2014
I agree with these labeling recommendations

LYNNE P YAO
10/27/2014

Bender, William

From: Bender, William
Sent: Wednesday, October 01, 2014 10:51 AM
To: Prindle, Ann (ann.prindle@otsuka-us.com)
Cc: Goldberger, David (David.Goldberger@otsuka-us.com); Guinn, Patrick (Patrick.Guinn@otsuka-us.com)
Subject: NDA 21436- s038 Abilify for Tourette's Disorder

Hi Anne,

We are making substantial labeling edits to your label, and we wanted to send you Section 14 first to give you time to review our requests.

We have another labeling meeting on October 8th and I will be sending more edits shortly after this said meeting. Just to be clear, we are in the process of improving all our labels but we will not miss any PDUFA dates as a result of this effort.

Please let me know if you have any questions.

Thanks,

Bill

(b) (4)

12 Pages(s) of Draft labeling have been withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

WILLIAM H BENDER
10/06/2014

Bender, William

From: Bender, William
Sent: Monday, August 11, 2014 1:58 PM
To: Prindle, Ann (ann.prindle@otsuka-us.com)
Cc: Goldberger, David (David.Goldberger@otsuka-us.com); Guinn, Patrick (Patrick.Guinn@otsuka-us.com)
Subject: Abilify

Good Day,

We request you convert the current text to describe the PK changes under Section 7 (Drug Interactions) and 8 (Use in specific population) of the label into forest plots and relocate the forest plots into Section 12. Please note that the "dose adjustment recommendation" column should not be included in the forest plots.

Please provide a table for the original PK information in Sections 7 and 8 in the label associated with forest plots for the label in the format below.

Factor (e.g. age, gender, renal impairment, inhibitors of CYP3A4, etc	Type (e.g. female under gender, and mild under renal impairment, etc)	Moiety	PK (Cmax and AUC)	Geometric Mean Ratio*	90% CI	
					Lratio	Uratio

*Change relative to the reference

Using forest plots in drug labeling may communicate more effectively intrinsic and extrinsic factors effects on pharmacokinetics than using texts. For information on the use of Forest plots in Drug label please refer to the following article: Essential Pharmacokinetic Information for Drug Dosage Decisions: A Concise Visual Presentation in the Drug Label, Clinical Pharmacology and Therapeutics, 2011: 90(3):471-4.

You are requested to submit the requested information within 3 weeks upon the receipt of this email. Should you have any questions please contact us via the Regulatory Project Manager for this submission.

Thanks,
Bill

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/s/

WILLIAM H BENDER
09/19/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Jeong-Seop Lee, M.D.
Inha University Hospital
7-206, 3-Ga, Shinheung-Dong, Joong-Gu
Incheon, South Korea

Dear Dr. Lee:

Between June 16, 2014 and June 20, 2014, Ms. Irina Gaberman, representing the US Food and Drug Administration (FDA) investigated your conduct of the clinical study entitled "A Randomized, Double-blind, Dose-adjustment, Placebo-controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder" (Study 031-KOA-0703), a study of Abilify® (aripiprazole) sponsored by Otsuka Pharmaceutical Development.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects have been protected.

At the conclusion of the inspection, Ms. Gaberman presented and discussed with you Form FDA 483, Inspectional Observations. We understand that you did not perform this study under a US Investigational New Drug Application (IND). We have reviewed the Form FDA 483, the establishment inspection report, and the documents submitted with the report. We acknowledge your July 11, 2014 written response to the inspection findings and note that you have implemented corrective actions to prevent the recurrence of the inspectional findings presented on Form FDA 483.

At the conclusion of the inspection, Ms. Gaberman also discussed with you inspectional observations not presented on Form FDA 483. The discussion included the following three inadequately explained changes for the total tic score on the K-YGTTS case report form: (1) Subject 0003 Visit 1, score changed from 24 to 31; (2) Subject 0005 Visit 2, score changed from 26 to 22; and (3) Subject 0012 Visit 1, score changed from 23 to 26. Please explain why these scores were changed. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown to Investigator Gaberman during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations, Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Building 51, Room 5328
Silver Spring, MD 20993-0002

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/s/

JONG HOON LEE
09/04/2014

JANICE K POHLMAN
09/05/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Dong-Ho Song, M.D.
Yonsei University Medical School
134 Shinchon-Dong, 250 Seongsan-Ro
Seoul, South Korea

Dear Dr. Song:

Between June 23, 2014 and June 26, 2014, Ms. Irina Gaberman, representing the US Food and Drug Administration (FDA) investigated your conduct of the clinical study entitled "A Randomized, Double-blind, Dose-adjustment, Placebo-controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder" (Study 031-KOA-0703), a study of Abilify® (aripiprazole) sponsored by Otsuka Pharmaceutical Development.

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We appreciate the cooperation shown to Investigator Gaberman during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 51 Room 5328
Silver Spring, MD 20993-0002

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/s/

JONG HOON LEE
09/03/2014

JANICE K POHLMAN
09/04/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Young-Sik Lee, M.D.
Chungang University Hospital
224-1 Heukseok-Dong, Dongjak-Gu
Seoul, South Korea

Dear Dr. Lee:

Between June 30, 2014 and July 3, 2014, Ms. Irina Gaberman, representing the US Food and Drug Administration (FDA) investigated your conduct of the clinical study entitled "A Randomized, Double-bind, Dose-adjustment, Placebo-controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder" (Study 031-KOA-0703), a study of Abilify® (aripiprazole) sponsored by Otsuka Pharmaceutical Development.

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Sincerely,

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 51 Room 5328
Silver Spring, MD 20993-0002

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/s/

JONG HOON LEE
09/03/2014

JANICE K POHLMAN
09/03/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Robert A. Riesenberg, M.D.
811 Juniper Street, N.E.
Atlanta, GA 30308

Dear Dr. Riesenberg:

This letter informs you of the findings of a U.S. Food and Drug Administration (FDA) inspection conducted at your site from June 9, 2014 to June 23, 2014. Investigator Myla D. Chapman, representing the FDA, reviewed your conduct of a clinical investigation (**Protocol 31-12-29, entitled** "A Multicenter, Randomized, Double-Blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder"), of the investigational drug Aripiprazole (Abilify®), performed for Otsuka Pharmaceutical Development, Inc.

This inspection was conducted as a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Chapman during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,
{See appended electronic signature page}

LCDR LaKisha Williams-Patterson, USPHS
Regulatory Health Project Manager
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5374
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

LAKISHA M WILLIAMS
08/25/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**PEDIATRIC AND MATERNAL HEALTH STAFF REQUEST FOR CONSULTATION**	
TO: CDER Pediatric and Maternal Health Staff *(please check)* Pediatrics X Maternal Health ☐ Both ☐			FROM *(Name, Office/Division, and Phone Number of Requestor)*: FD-130 (Division of Psychiatry Products); CAPT Mitchell Mathis, M.D.	
DATE 07/09/2014	IND NO.	NDA/BLA NO. 21436/S-038	TYPE OF DOCUMENT sNDA	DATE OF DOCUMENT 02/12/2014
NAME OF DRUG Abilify (aripiprazole) 2 mg, 5 mg, 10 mg, 15 mg, 20 mg & 30 mg tablets	NAME OF FIRM Otsuka Pharmaceutical Development & Communications, Inc.		CLASSIFICATION OF DRUG Atypical Antipsychotic	PDUFA Goal Date 12/12/2014
Requested Consult Completion Date: 10/01/2014	☐ Urgent* (< 14 days)		☐ Priority (14-29 days)	X Routine > 30 days
*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.				

REASON FOR REQUEST

Pediatrics:	Maternal Health Team:
X Labeling Review ☐ Written Request/PPSR ☐ PREA PMR/General Regulatory Question ☐ SPA ☐ Action Letter Review ☐ 30-day IND Review ☐ Other Protocol Review Meeting Attendance ☐ PeRC Preparation Assistance X Other (please explain): see below	☐ Labeling Review ☐ Pregnancy Exposure Registry (protocol or report) ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ 30-day IND Review ☐ Risk Management – Pregnancy Prevention and Planning ☐ Evaluation of possible safety signal ☐ Guidance development ☐ Other (please explain):
Link to electronic submission (if available): Gateway Location: \\CHDC9681\CDERESUB\inbound\ECTD\ci1392253606932.88912@fdsul08620te2 Global Review Summit: \\CDSESUB1\evsprod\NDA021436\021436.enx EDR Location: \\CDSESUB1\evsprod\NDA021436\0045	

1. Please briefly describe the submission including drug's indication(s):
Reference is made to Otsuka Pharmaceutical Company Ltd.'s (OPC) approved New Drug Application, NDA 21-436, for Aripiprazole (OPC-14597) Oral Tablets which was approved on November 15, 2002. Further reference is made to IND 116,003 for Aripiprazole Oral Tablets (treatment of (b) (4) Tourette's disorder in children and adolescents) submitted on August 15, 2012.

Pursuant to 21 CFR 314.70, Otsuka is hereby submitting a supplemental new drug application (sNDA) requesting approval to add a new indication, treatment of (b) (4) Tourette's disorder in pediatric patients (b) (4), to the labeling for this product. Tourette's disorder is a rare condition primarily affecting children and adolescents. An orphan drug designation application was submitted to the Office of Orphan Product Development on June 25, 2005, and orphan drug designation for the treatment of Tourette's disorder in children and adolescents was granted on January 25, 2006 (designation no. 05-2079).

2. Describe in detail the reason for your consult. Include specific questions:
We would appreciate CDER Pediatric Health Staff's input on the proposed labeling, in particular the indication [*treatment of* (b) (4) *Tourette's disorder in pediatric patients (*(b) (4) *years)* versus *treatment of Tourette's disorder in pediatric patients (*(b) (4) *years)]*.

We would also appreciate your input on possible postmarketing commitments: whether a maintenance trial in the pediatric population should be required and suggestions on design of this trial if indicated. Currently, an open-label, long-term (52-week) study (31-12-294) is ongoing. This will provide further safety data and some data on efficacy (YGTSS and CGI-TS will be assessed throughout the study). Would a randomized withdrawal trial be indicated or ethical? Would a randomized withdrawal design using a low dose of aripiprazole (e.g., 2 mg) in place of a placebo arm be a viable option and provide useful information?
4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years):
Not Applicable.

Review team:
Project Manager: CAPT Bill Bender
Clinical reviewer & Team Leader: Christina Burkhart, M.D., & Mark Ritter, M.D.
Pharmacology/Toxicology reviewer & Team Leader: Sonia Tabacova, Ph.D., & Aisar Atakchi, Ph.D.
Clinical Pharmacology reviewer & Team Leader: Huixia Zhang, Ph.D., & Hao Zhu, Ph.D.

Other:

PRINTED NAME or SIGNATURE OF REQUESTOR:	METHOD OF DELIVERY (Please check)
CAPT Mitchell Mathis, M.D., Division Director	X DARRTS ☐ EMAIL ☐ HAND ☐ OTHER

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/s/

WILLIAM H BENDER
07/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)

HFD-130/Division of Psychiatry Products
William Bender, RPh., RPM(ext. 2145)
Through:
Mitchell Mathis, M.D., Division Director

REQUEST DATE:

04/30/2014

NDA/BLA NO.:

21436

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NDA/S-038 Submission with Proposed Labeling

NAME OF DRUG:

Abilify (aripriprazole) 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg tablets

PRIORITY CONSIDERATION:

Standard

CLASSIFICATION OF DRUG:

(b) (4)
Tourette's Disorder in Pediatric patients (b) (4)
(b) (4)

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)

September 26, 2014

SPONSOR:

Otsuka Pharmaceutical Development & Communications, Inc.

PDUFA Date: December 12, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PATIENT PACKAGE INSERT (PPI)
☒ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☒ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission: \\CDSESUB1\evsprod\NDA021436\0045

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS: Otsuka Pharmaceuticals submitted this supplemental application for the treatment of Tourette's Disorder in pediatric patients (b) (4). We are requesting your input regarding the sponsor's proposed labeling. Their draft/ proposed labeling (FPI) can be found at the following EDR link: \\CDSESUB1\evsprod\NDA021436\0045 The Global Review Submit can be found at: \\CDSESUB1\evsprod\NDA021436\021436.enx

The medical officer is Christina Burkhart, M.D., and her team leader is Robert Levin, M.D. The OCP reviewer is Huixia Zhang, Ph.D. and her team leader is Hao Zhu, Ph.D. We will invite you to our meetings. Please let me know if you have any questions.
Thank you,
Bill

Mid-Cycle Meeting: July 9, 2014

Labeling Meetings: To be scheduled.
Wrap-Up Meeting: To be scheduled.

SIGNATURE OF REQUESTER	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL (BLAs Only) ✓ DARRTS

Version: 12/9/2011

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/s/

WILLIAM H BENDER
04/30/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-OPDP-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

HFD-130/Division of Psychiatry Products
William Bender, RPh., RPM(ext. 2145)
Through:
Mitchell Mathis, M.D., Division Director

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
04/29/2014		21436	NDA/S-038 with proposed labeling

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Abilify (aripriprazole) 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg tablets	Standard	(b) (4) Tourette's Disorder in peds patients (b) (4) (b) (4)	September 26, 2014

NAME OF FIRM:

Otsuka Pharmaceutical Development & Communications, Inc.

PDUFA Date: December 12, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

EDR link to submission: \\CDSESUB1\evsprod\NDA021436\0045

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS: Otsuka Pharmaceuitcals submitted this supplemental application for the treatment of Tourette's Disorder in pediatric patients (b) (4). We are requesting your input regarding the sponsor's proposed labeling. Their draft/ proposed labeling (FPI) can be found at the following EDR link: \\CDSESUB1\evsprod\NDA021436\0045 The Global Review Submit can be found at: \\CDSESUB1\evsprod\NDA021436\021436.enx

The medical officer is Christina Burkhart, M.D., and her team leader is Robert Levin, M.D. The OCP reviewer is Huixia Zhang, Ph.D. and her team leader is Hao Zhu, Ph.D. We will invite you to our meetings. Please let me know if you have any questions.
Thank you,
Bill

Mid-Cycle Meeting: July 9, 2014
Labeling Meetings: To be scheduled.
Wrap-Up Meeting: To be scheduled.

SIGNATURE OF REQUESTER

CAPT Bill Bender, RPh.
Senior Regulatory Project Manager; 301-796-2145
William.bender@fda hhs.gov
301-796-2145

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ✓ eMAIL ☐ HAND

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/s/

WILLIAM H BENDER
04/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21436/S-038
NDA 21713/S-030
NDA 21729/S-022
NDA 21866/S-023

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Otsuka Pharmaceutical Development & Communications, Inc.
Attention: David Goldberger R.Ph., RAC
Vice President, Global Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Goldberger:

Please refer to your Supplemental New Drug Application (sNDA) dated and received on February 12, 2014, submitted under section 505(b)of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abilify (aripiprazole) 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg tablets.

We also refer to your amendments dated March 5, 2014, March 7, 2014, and March 26, 2014.

This supplemental application proposes the following change(s): the new indication for the treatment of (b) (4) Tourette's disorder in pediatric patients (b) (4)

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is December 12, 2014.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 21, 2014.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

HIGHLIGHTS DETAILS

Highlights Heading

Boxed Warning (BW) in Highlights

1. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment: *The sponsor used the word "WARNINGS," not "WARNING."*

FULL PRESCRIBING INFORMATION DETAILS

2. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment: *The sponsor used the word "WARNINGS," not "WARNING."*

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by May 16, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

If you have any questions, please email CAPT Bill Bender, Senior Regulatory Project Manager, at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

MITCHELL V Mathis
04/24/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21436/S-038

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Otsuka Pharmaceutical Development & Communications, Inc.
Attention: David Goldberger R.Ph., RAC
Vice President, Global Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Goldberger:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21436

SUPPLEMENT NUMBER: 038

PRODUCT NAME: Abilify (aripiprazole) 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg

DATE OF SUBMISSION: February 12, 2014

DATE OF RECEIPT: February 12, 2014

This supplemental application proposes to add a new indication, the treatment of (b) (4) Tourette's disorder in pediatric patients ((b) (4) years of age).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 11, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, please email me at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

William Bender, R.Ph., RAC
CAPT, USPHS
Senior Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

WILLIAM H BENDER
02/20/2014